TRADITIONAL KNOWLEDGE AND ITS EXPERIMENTAL VALIDATION THROUGH IN-VITRO ENZYME ASSAY AND PHYTOCHEMICAL SCREENING OF ANTIDIABETIC PLANTS OF KATHUA DISTRICT, J&K

Thesis Submitted for the Award of the Degree of

DOCTOR OF PHILOSOPHY
in
Botany

By

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LOVELY PROFESSIONAL UNIVERSITY, PUNJAB

2024

DECLARATION

I, hereby declare that the presented work in the thesis entitled **"Traditional Knowledge and Its Experimental Validation through Invitro enzyme assay and phytochemical screening of antidiabetic plants of Kathua District,J & K"** in fulfillment of the degree of **Doctor of Philosophy (Ph. D.)** is an outcome of research work carried out by me under the supervision **Dr. Devendra Kumar Pandey** working as Professor, in **School of Bioengineering and Biosciences** of Lovely Professional University, Punjab, India. In keeping with the general practice of reporting scientific observations, due acknowledgments have been made whenever the work described here has been based on the findings of other investigators. This work has not been submitted in part or full to any other University or Institute for the award of any degree.

Madhvi Parasher

Registration No:41800711

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CERTIFICATE

This is to certify that the work reported in the Ph. D. thesis entitled **"Traditional Knowledge and its experimental validation through Invitro enzyme assay and phytochemical screening of antidiabetic plants of Kathua District of J & K"** submitted in fulfillment of the requirement for the award of degree of **Doctor of Philosophy (Ph.D.)** in the **Department of Botany**, **School of Bioengineering and Biosciences**, is a research work carried out by Madhvi Parasher, 41800711 is bonafide record of his/her original work carried out under my supervision and that no part of thesis has been submitted for any other degree, diploma or equivalent course.

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ACKNOWLEDGEMENT

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ABSTRACT

Plants are fundamental to life on Earth. Plants serve as nature's pharmacy and their usage for healing is perhaps as old as humankind is and has been testified by fossil records aging 60,000 years ago from the Middle Palaeolithic Age. The traditional system of medicine in India is considered a repository of total well-being. The *Charak Samhita*, an age-old written record of herbal therapy, describes 340 herbal plants and their native uses, clear mention is there in Vedic literature, particularly the Rigveda, *Charak Samhita*, and *Susruta Samhita*. Ethnobotanical investigations inventorize the information on the cultural interaction of local folks with plants. Traditional local communities worldwide have a great deal of knowledge about native plants on which they intimately depend.

The Jammu & Kashmir State (32^{o} 17′ and 36^{o} 58′ N Lat., 72^{o} 35′ and 80^{o} 30′ E Long.) is located mostly in the Himalayan Mountains and Shiwaliks and has Himachal and Punjab states to the south. Because of the wide range of elevations, this region of India has a diverse biogeography and a high diversity of vegetation especially in terms of medicinal plant wealth. A large number of people belonging to various ethnic groups are still practicing their own traditional health care systems. The traditional treatment systems adopted by these ethnic communities are being used generation-wise without any scientific validation. They have vast knowledge about various plants that are used for food and medicine. The trajectory of diabetics and the economic burden of the management thereof in on the increase and Jammu and Kashmir now figures amongst states with high number of diabetics i.e. 29 per 100.A large number of medicinal plants with anti-diabetic properties are available in this region and many of them are also used as food in Dogra, Kashmiri, and other local cuisines. Exploitation of such plant resources for use in alternative treatment of type 2 diabetes can help cut the cost of treatment of this disease and also minimize the side effects caused by available pharmacological drugs.

To document the existing traditional knowledge about antidiabetic plants used in the management of diabetes by locals, tribals, and Traditional Health Practitioners (THPs) and validate of these traditional claims, the present work was carried out.

The proposed research was initiated with five objectives. The validated results of the said five objectives are given as under:

1. A thorough ethnobotanical survey was carried out in different locations of district Kathua from June 2019 to December 2021. A total of 310 informants comprising 16 THPs, 93 tribe informants, and 201 local people from the Dogra community participated in the study. The ethnobotanical study led to the documentation of 63 plant species used for the management of T2DM. These values were higher than the reported range of 14-54 species for earlier ethnobotanical studies carried out on traditionally used antidiabetic species. The higher reporting might be due to rich vegetation as the district houses 22 forest types and the presence of a transmigratory tribal population.

2. The data collected through semi-structured questionnaires, focused group discussions, and informal conversations in the field with informants was quantitatively analyzed by applying indices like Use Value, Disease Consensus index, Informant Consensus, and Preference Ranking. The most useful species to ascertain the most important plant species for type-2 diabetes. *Acacia catechu* (L.f.)Willd.,*Ajuga bracteosa* Wall. ex. Benth., *Bergenia ciliata* (Haw.)Sternb., *Urtica dioica* L. and *Zantoxylum armatum* D.C.

3. Qualitative phytochemical screening of these plants was done by measuring Total Phenolics, Total Flavonoids, and antioxidant capacity. Untargeted metabolomics was done to ascertain quantitative estimation of bio-actives, and the HPTLC method was developed and validated for the simultaneous quantification of polyphenolic compounds Gallic acid and Quercetin in the five most preferred species assessed through quantitative analysis. Moreover, the HPTLC method was found to be simple, specific, and sensitive and can be applied in quality control and standardization of drugs.

4. In vitro antidiabetic activity of the traditionally used plants was determined through alpha-amylase and alpha-glucosidase inhibition assay in aqueous and methanolic extracts. All the plant samples exhibited alpha-amylase and glucosidase inhibition. *Acacia catechu* heartwood aqueous extract showed maximum alpha-amylase inhibition and *Ajuga bracteosa* leaves showed maximum alpha-glucosidase inhibition.

5. Out of the 63 species documented, *Aconitum heterophyllum, Bergenia ciliata, Picorrhiza kurroa, Saussurea costus, and Swertia chairata* were the species facing threats in the wild. In-situ populations can be restored by sensitizing nomadic collectors for sustainable uprooting, locals

should be promoted for cultivation can help to reverse the population status of these highly traded species. Progressive farmer Sh Rajat Sharma from the Bani region is successfully cultivating *Aconitum heterophyllum, Picorrhiza kurroa,* and *Saussurea costus*.

46 species are new record for JKUT and 36 species for the Western Himalayas. *Pilea scripta*, *Rhabdosia rugosa,* and *Skimmia anquetilia* are new additions to the anti-diabetic flora of the world. This is the first exclusive study in UT of Jammu & Kashmir to document and validate indigenous knowledge of hypoglycaemic plants. Quantification of polyphenolics (Gallic acid and Quercetin) and in vitro assay validated the usage of local flora in managing diabetes mellitus.

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ACH	*Acacia catechu* heartwood
AGEs	Advanced Glycation End Products
AMPK	AMP-activated protein kinase
ANOVA	Analysis of Variance
BCR	*Bergenia ciliata* rhizome
CBD	Convention on Biological Diversity
CD2 and CD4	Clusters of Differentiation 2 and 4
COX 1 and COX 2	Cyclooxygenase 1 and Cyclooxygenase 2
DCI	Disease Consensus Index
DCA	Detrending correspondence analysis
DM	Diabetes mellitus
DPHH	2,2-diphenyl-1-picrylhydrazyl.
DPP-4 Inhibitors	Dipeptidyl peptidase 4 (DPP-4) inhibitors
ESI-MS	Electrospray ionization mass spectrometry
FFA	Free Fatty Acids
F_{ic}	Factor informant consensus
GC-MS	Gas chromatography mass spectrometry
GAE	Gallic acid equivalents
GLUT 2 and GLUT 4	Glucose Transporter 2 and 4
HBJU	Herbarium Botany Jammu University
HLA	human leukocyte antigens.
HPLC	High Performance Liquid Chromatography.
HPLC-ESI-QTOF-MS	Electrospray Ionization Quadropole Time-of-Flight Mass Spectrometry
HPTLC	High-performance thin layer chromatography
IC50	Half maximal inhibitory concentration
IL 3,IL 5	Interleukins 3 and 5
INS-1	Rat insulinoma cell line

JKUT	Union Territory of Jammu and Kashmir
LADA	Latent autoimmune diabetes of adults
LC-MS	Liquid chromatography-mass spectrometry
LOD	Limit of Detection
LOQ	Limit of Quantification
MODY	Maturity-onset diabetes of the young
MCF-7	Michigan Cancer Foundation-7
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
NIC	National Informatics Centre
PPARγ	Peroxisome proliferator-activated receptor gamma
OD	Optical Density
QE	Quercetin equivalents
RFC	Relative Frequency of Citation
RINm5F	Rat insulinoma cell line
ROS	Reactive oxygen species
RP-HPLC-DAD	Reversed phase-High Performance Liquid Chromatography-Diode Array Detection
STZ	Streptozotocin
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
TFC	Total Flavonoid Content
THPs	Traditional Health Practitioners
TPC	Total Phenolic Content
TK	Traditional Knowledge
TNF-α	Tumor necrosis factor
UDL	*Utrica dioca* leaves
UV	Use Value
UHPLC-DAD	Ultra-high performance liquid chromatography (UHPLC) coupled with diode array detection
ZAF	*Zanthoxylum armatum* fruits

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QE	Quercetin equivalents
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CHAPTER 1

INTRODUCTION

1. Introduction

1.1Traditional Knowledge (TK) of Medicinal Plants

Traditional knowledge (TK) refers to the wisdom that has been accumulated over generations, by people to effectively utilize their lands, natural resources, and environment. It is reflected in their lifestyles, innovations, and practices (Jain, 2005). The Convention on Biological Diversity (CBD) defines TK as the ideas, skills, and customs of local communities worldwide. It is often associated with groups and assumes forms such as anecdotes, folk songs, aphorism, cultural values, rituals, beliefs, local laws, dialects and agricultural methods including the improvement of plant and animal breeds. TK encompasses the knowledge systems, innovations, and practices of people. It has its genesis through centuries of experience. Adapted to cultures and environments, the transmission of this knowledge primarily occurs orally across the generations vertically within communities. Oral traditions such as dances, paintings, and carvings are a part of cultural heritage that has been passed down for thousands of years. TK plays an instrumental role in shaping identities, cultural legacy and way of life. The transmission of TK across generations is essential for preserving and promoting the cultures and identities of indigenous peoples, as well as for sustaining culturally appropriate economic development and the sustainability of livelihoods. Indigenous peoples' holistic approach to life has stayed fundamental in the evolution of the planet's extant cultural heritage and biological diversity, and TK has played a vital role in it. Johnson (1992) defined TK as a corpus of information developed by a faction of people over generations who lived in close propinquity of the environment. TK was gathered over centuries by observers whose survival relied on the applicability of traditional expertise. It is frequently passed down orally or through shared practical experiences with future generations, verified through incremental accumulation (Ohmagari and Berkes, 1997).

Though records of prehistoric plant-human innovations relationships are scarce; the discovery of 77,000 years old bedding made from sedges and layered with monocot grasses and aromatic leaves of *Cryptocarya woodii* speaks volumes about plant-people interaction at one end and science at the other (Wadley *et al.*, 2011). The leaves were larvicidal and are still used as a mosquito repellent in African societies. TK embraces a collection of empirical observations about the immediate environment and a self-management system that controls resource use (Posey, 1998). The earliest known record of the medicinal plant's usage in the preparation of medications dates back

approximately 5,000 years as revealed from a Sumerian clay slab from Nagpur (Kurhekar, 2021). According to some inscriptions, the Egyptians and Chinese were probably the pioneer humans to use plants as medication, dating back to as old as 27 centuries B.C. (Jamshidi *et al.*, 2017). Ancient Egypt with the Kahun Gynaecological Papyrus marks the origin of ancient medicine in the Middle-Eastern area dating almost 4 million years: 1800 BCE, the Edwin Smith Papyrus: 1600 BCE, and the Ebers Papyrus: 1550 BCE (Lemonnier *et al.,* 2017). Ancient Greeks knew about medicinal aspects of certain medicinal plants; Hippocrates (460-370 BC) is considered the founder of Greek medicine. Theophrastus founded the School of Medicinal Plants followed by Pedanius Dioscorides (40-90 AD) commonly called the "Father of Pharmacognosy" who composed the 5-volume encyclopedia "De Materia Medica", characterizing 600 medicinal plants through a string of scientific studies on medicinal plants (Rios, 2005).

Plants have played a fundamental role in human life on Earth since antiquity. The use of plants to alleviate health is perhaps the greatest benefit natural flora renders (Balandri *et al.,* 1985). Life on the earth is the result of the support system that plant biodiversity creates. Mankind is provided with all essentials such as food, housing, clothing, and importantly, medicine. But, the bounty of plants is much more than the commodities, as the rich diversity of vegetation renders countless ecosystem services (CBD, 2014). Plants are natural pharmacies as they contain a plethora of secondary metabolites like alkaloids, phenolics, terpenoids, and flavonoids, which are bioactive and function in concert to improve human health (Eruygur *et al.,* 2019).

Plant use for healing is perhaps as old as humankind is and has been testified by fossil records aging 60,000 years ago from the Middle Palaeolithic Age (Fabricant and Farnsworth, 2001). It has also been testified in Vedas (4500-600 B.C.) (Pei, 2001), which represent the oldest treasure of mankind's knowledge about plants.

The origin of traditional medical knowledge in the Indian subcontinent is believed to be traced back to the Vedic period (circa 1500–500 BCE), during the first Indo-Aryan settlements in Northwest India and the Ganges plains. This period coincides with the composition of the four Vedas (*Rig-Veda*, *Sama-Veda*, *Yajur-Veda*, and *Atharva-Veda*) and the emergence of Vedic practices. There is a close connection between Indian traditional medicine and Vedas, especially *Atharva-Veda* describing the philosophical and spiritual aspects of Ayurveda (Kessler *et al.,* 2013).

The existence of elaborate documentation as old as 1500 BCE suggests that the origins of this medicinal system could be even older (Pole, 2006).

Since time immemorial, floras have directly or indirectly influenced the majority of human culture. Traditional communities still reside in forest areas, and their lifestyle, traditions, and customs have remained virtually unchanged for centuries. Living in an intimate vicinity to nature, these traditional communities have acquired specialized knowledge regarding the utilization of flora. After years of observation, analysis, and trial-and-error experimentation, or even through the use of intuitive methods, innovative individuals have identified and chosen the beneficial and harmful flora of their environment.

1.2 Ethnobotanical Perspective

Ethnobotany is the natural and traditional associations and subsequent interactions between humans and their environments. It is considered a sub-field of ethnobiology focusing on the study of plant-human interaction at all stages of life and its impact on human society. Prior to the introduction of the term ethnobotany, the study of traditional botanical knowledge almost exclusively concentrated on the applications and economic potentials of plants used by ethnic communities. The study was initially known as "Aboriginal botany" (Power, 1873).

John William Harshberger brought to light the term ethnobotany in 1895 while teaching at Pennsylvania University, and it is derived from two Greek syllables "Othnikos" or "Ethnos" meaning country or race; "Botanikos" or "Botane" referring to vegetation. He defined ethnobotany as the study of plants explored and utilized by aboriginal people. He proposed the word "ethnobotany" as a field that interprets the cultural status of the tribes who entirely relied on plants for food, habitation, or clothing (Harshberger, 1896). After the coinage of ethnobotany, this field diversified to encompass a pragmatic relationship with symbolic, ecological, and cognitive connections and the human-plant relationship in the contemporary setup (Schultes and Von Reis, 1995; Alexiades, 1996).

Ethnobotany is also defined as the scientific study of the interaction between primitive people and plants, and it is most usually associated with the study of indigenous plant uses (De, 1968). Schultes defined ethnobotany in 1962 as the analysis of the relationships between primordial communities and their plant environments The research focuses on a wide variety of plant-derived products, including food, medicine, plants used in rituals, coloring agents, fiber, musical

instruments, poisons, fertilizers, building materials, and so on. Because plants are indispensable in virtually every aspect of human activity, ethnobotany incorporates numerous disciplines. Botany, pharmacognosy, toxicology, medicine, biochemistry, nutrition, agriculture, ecology, evolution, sociology, anthropology, comparative religion linguistics, cognitive studies, history, and archaeology are included. The multidisciplinary nature of ethnobotany enables a vast array of approaches and applications and opens the door for numerous scientists to investigate plant uses in various ways (Garnatje *et al.*, 2017). However, medicinal plants have always been the primary focus of ethnobotanical research, and the study of these resources has made substantial contributions to the field's theoretical development. It has now evolved into an integrative interdisciplinary field that includes ethnoecology, ethnomedicine, ethnotaxonomy, and the anthropological and botanical study of material culture and subsistence mode (Saha *et al.*, 2014). It investigates all facets of the mutually beneficial connection between plants and traditional peoples regarding biodiversity prospecting, conservation, and vegetation management. In other words, the research necessitates many skills, including botanical training for plant identification and preservation, anthropological training for understanding cultural ideas and plant perception, and linguistic training for interpretation of local terms. While taxonomists focus on plants and their habitat, ethnobotanists also document the relationship of these plant communities with the local people. Ethnobotanical leads were instrumental in contemporary drug development like codeine and papaverine from *Papaver somniferum*, colchicine from *Colchicum autumnale*, taxol from *Taxus brevifolia*, digoxin and digitoxin from *Digitalis purpurea*, artemisinin from *Artemisia annua*, aspirin *Filipendula ulmaria*, capsaicin from *Capsicum* spp. to name a few (Garnatje *et al.*, 2017; Kumar *et al.*, 2021). Ethnobotany has contributed substantially to every traditional system of medicine including Ayurveda, Siddha, Unani, and Chinese medicine, as well as homeopathy and naturopathy, which are predominantly plant-based. For centuries, Indian society has relied on traditional medicinal systems practiced here. Neglect of Indian traditional medicine was witnessed during the colonial period as they were labeled archaic and unscientific by the authorities (Sen and Chakraborty, 2017). With advances in analytical chemistry in the 19th century, scientists began to extract and modify the active medicinal compounds found in plants and use them as ingredients in allopathic remedies, this parallelly witnessed a surge in the use of natural products for relief.

Eventually, chemists began synthesizing these compounds and creating their versions of plant compounds. At a minimum, 25% of allopathic prescription medications contain at least one plant-

derived active constituent (Barrett *et al.,* 1999). Modern research has demonstrated that herbal medicines are just as effective as conventional medicines and are also extremely secure. Only 15% of the approximately 400,000 species of plants have been investigated phytochemically, a meagre 6% have been systematically evaluated for their biological activity, according to estimates (Patwardhan *et al.,* 2005). Over sixty percent of clinically used drugs contain natural compounds or their derivatives, and over one hundred and twenty chemical products/moieties derived from plant sources are used as lifesaving medications (Yuan *et al.,* 2016; PBW, 2018). Traditional medicine remains vital to human health, especially in primary care. Ethnopharmacological knowledge can be a strong discovery tool for new, safe, and sustainable treatments

1.3 Diabetes mellitus

Diabetes mellitus was described by the word '*Prameha'* in ancient India. It stressed the existence of a metabolic state marked by an increased quantity (*Prabhoota mootra*) and clouded urine (*Aavila mootra*). '*Prameha'* originates from '*Pra'* meaning excessive and frequent urination; *'meha'* for profuse watering. '*Madhumeha'* has also been used to describe diabetes wherein '*madhu'* refers to sweet urine and '*meha'* refers to a watery condition (Sarmah and Sharma, 2014). Egyptian manuscripts antedecent to 1500 B.C., do mention a malady characterized by "excessive urination" for the first time (King and Rubin, 2003; Lakhtakia, 2013). Aretaeus, the Cappadocian coined the term diabetes (Greek, 'siphon') and eloquently stated "... no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into the urine," in the first century A.D., as per available historical records (Ahmed, 2002; Sanders, 2002). In "The Canon of Medicine", the famous Persian physician, Avicenna (980–1037 A.D.) referred to abnormal appetite and diabetic gangrene, besides suggesting a concoction of seeds (lupin, fenugreek, zedoary) as a panacea (Lakhtakia, 2013). John Rollo, the British Surgeon devised the word mellitus from Latin meaning "sweet as honey" in 1798 to differentiate Diabetes mellitus from Diabetes insipidus wherein the urine was tasteless (Lakhtakia, 2013).

Charak Samhita (600 B.C.) does contain details of complications, symptomatology, and pathogenesis of the disease. Overnutrition and a sedentary lifestyle were attributed to *Prameha*. Susruta recommended using bitter and astringent things in their diet to manage the disease. This implies that disease knowledge and its management were known (Singh *et al.,* 2023)

Paul Langerhans discovered the "islets of Langerhans" in 1869. de Mayer and Schaefer named the islet secretions insulin (Latin, insula = island) to lower blood glucose levels. Joseph von Mering and Minkowski deciphered that pancreatic removal caused diabetes in 1889 (Lasker *et al.*, 2005). In 1921 Banting, Best, destroyed the exocrine pancreas except the islet region (Buse *et al.*, 2017). They used an extract of islets to reverse induced diabetic conditions and subsequently purified insulin in collaboration with **Bertram Collip**, a biochemist. The emergence of insulin to treat diabetes gave life to millions of type-I patients besides lending newer insights into diabetes pathogenesis.

1.3.1 Classification of Diabetes: Depending upon the different underlying causes, diabetes is mainly classified into the following types:

Type 1 Diabetes Mellitus (T1DM): It results from an auto-immune response destroying the insulin-secreting pancreatic β cells leading to no insulin generation. The pathogenesis of T1DM is believed to involve T-cell mediated loss of beta cells (Illonen *et al.*,2019). Oral supplementation of insulin is required. Generally, it develops in children and adolescents. CD 4 and CD 8 are mainly involved in the destruction of beta cell mass. Genetic susceptibility is there and HLA locus has been evidenced to be involved. Environmental variables that alter immune response like gut microbiota, viral infections (enterovirus, mumps, etc.), and nutrition influence the onset and development of disease (Katsarou *et al.*, 2017). Insulin antibodies or autoantibodies of glutamic acid decarboxylase are the pioneer ones showing the onset of disease. Diabetic ketoacidosis (DKA) is major metabolic manifestation of the T1DM (Bonnet-Serrano *et al.*, 2018).

Latent Autoimmune Diabetes of Adults (LADA): LADA results from autoimmune elimination of pancreatic β-cells and is accompanied by the appearance of pancreatic autoantibodies but in lesser amounts than Type 1 diabetes (Regnell and Lernmark, 2017). The presence of these antibodies in plasma or serum is a strong indicator that the patient will eventually require insulin therapy to maintain glucose homeostasis (Buzzetti *et al.*, 2017). There is insulin resistance but less pronounced than type 1 (Regnell and Lernmark, 2017).

Type 2 Diabetes Mellitus (T2DM): It distinctly shows persistent hyperglycemia because of insufficient insulin production or a decrease in peripheral tissue response to insulin. Insulin deficiency reduces the availability of glucose to the cell, affecting the hepatic output of glucose of triglycerides and glucose. Polyuria, blurred vision, thirst, weight loss, and ketosis are all symptoms

of T2DM. T2DM complications include nephropathy, retinopathy, neuropathy, and cardiovascular disease (American Diabetes Association, 2019). Oral antidiabetics can manage glycaemic levels if basal insulin production is present and beta cells are not fully compromised otherwise, exogenous insulin is needed, as in T1DM (Kharroubi and Darwish, 2015). T2DM can be managed with an oral hypoglycaemic agent and lifestyle changes.

Maturity Onset Diabetes of the Young (MODY): It is a monogenic diabetes, frequently characterized by the advent of hyperglycemia at a young age (typically before 25 years of age) (Pearson *et al.,* 2006) MODY is reflected by deficient insulin secretion without or with minimal insulin action defects (in the absence of coexistent obesity). MODY accounts for approximately 3% of total diabetic cases (Banday *et al.,* 2020) and 1–6% of all pediatric cases of diabetes It is passed in an autosomal dominant manner, and typically involves the vertical transmission of the disorder through at least across three generations and exhibits a phenotype shared by all family members with diabetes. The abnormalities identified in at least 14 genes on various chromosomes result in MODY (Banday *et al.,* 2020; American Diabetes Association, 2021).

Neonatal Diabetes: An uncommon genetic condition with an incidence of nearly 1 in 90,000 births marked by severe hyperglycemia necessitating treatment. This condition typically manifests between the neonatal period and infancy, generally before the age of 06 months (Beltrand *et al.,* 2020). There is either a problem with the pancreas development or some defect in the functioning of beta cells. The main genetic causes leading to the abnormal pancreas are abnormal expression of the locus 6q24 and mutation in the genes coding for ATP Potassium-dependent ion channels. Mutation in insulin and glucokinase genes also causes this type of diabetes (Busiah *et al.,* 2013).

Gestational Diabetes: It manifests as glucose intolerance apparent or initiates during pregnancy. As per the American Diabetes Association gestational diabetes is "any degree of glucose sensitivity with first detection during pregnancy" (Katra *et al.,* 2016). Hyperglycaemia typically resolves after delivery but they are at an increased risk of progressing into T2DM somewhere later in life (Egen and Dinneen, 2018; Mclntyre *et al.,* 2019). Insulin is administered along with diet and lifestyle interventions throughout to achieve glycaemic targets (McElwain *et al.,* 2021). Women having GDM had seven times increased proneness to T2DM compared to those who had a normal glucose level during pregnancy. Encountering intrauterine hyperglycemia is a strong risk indicator for T2DM (Bellamy *et al.,* 2009). It is a transient form of glucose intolerance due to

insulin resistance and metabolic changes exerting additional stress on beta cells during pregnancy (Mclntyre *et al.,* 2019).

Several exocrine pathologies of the pancreas such as chronic pancreatitis, pancreatectomy, cystic fibrosis, and hereditary hemochromatosis cause damage to islets of Langerhans thereby reducing beta cell mass leading to diabetes. However, pancreatic neoplasia can cause diabetes without reducing beta cell mass (Egen & Dinneen, 2019).

Several endocrinopathies such as Cushing syndrome, pheochromocytoma, hyperthyroidism, and acromegaly involve hormone disorders that are antagonistic to insulin action or secretion and lead to diabetes (Resmini *et al.,* 2009).

1.3.2 Global Prevalence of Diabetes Mellitus (DM):

According to the IDF Atlas (10th edition, 2021), there are 537 million diabetics worldwide, accounting for 10.5% of the total population aged 20 to 79 years in 2021. It will surge to 643 M by 2030 and is projected to touch 783 M by 2045. The economic baggage is estimated to be about 1054 USD by 2045 (Sun *et al.,* 2022). There are about 541 M with impaired glucose tolerance. Epidemiological data predicts that in India, the diabetic population will significantly increase, from 77 million to 124.9 million by 2014 (Raman *et al.,* 2020).

1.3.3 Pathophysiology of Diabetes: Many mechanisms in combination or alone contribute to T2DM progression. Emerging shreds of evidence implicate adipokine dysregulation, inflammation, gut dysbiosis, and immune dysregulation as key pathophysiological elements.

T2DM is an islet paracrinopathy having an obliterated inverse relationship between the glucagon-producing alpha and insulin-producing beta cells diminished (Unger and Orci, 2010; DeFranzo *et al.,* 2015).

β-cell dysfunction leads to decreased insulin secretion. It reduces the body's ability to maintain physiologically required glucose levels. Endoplasmic reticulum (ER) stress, inflammation oxidative stress, and mitochondrial dysfunction, cause glucolipotoxicity, leading to impaired beta cell function. Excess free fatty acids (FFAs) and hyperglycemia cause ER stress through apoptotic unfolded protein response (UPR) pathways. Under pathogenic conditions, outlined above islet integrity of beta cells is lost, and impaired cell-to-cell cross-talk within pancreatic islets exacerbates hyperglycemia (Cerf, 2013; Yamamoto *et al.,* 2019). Obesity-driven glucolipotoxicity

causes metabolic and oxidative stress, damaging the β-cell (Halban *et al.*, 2014). It also triggers Insulin resistance and persistent low-grade inflammation.

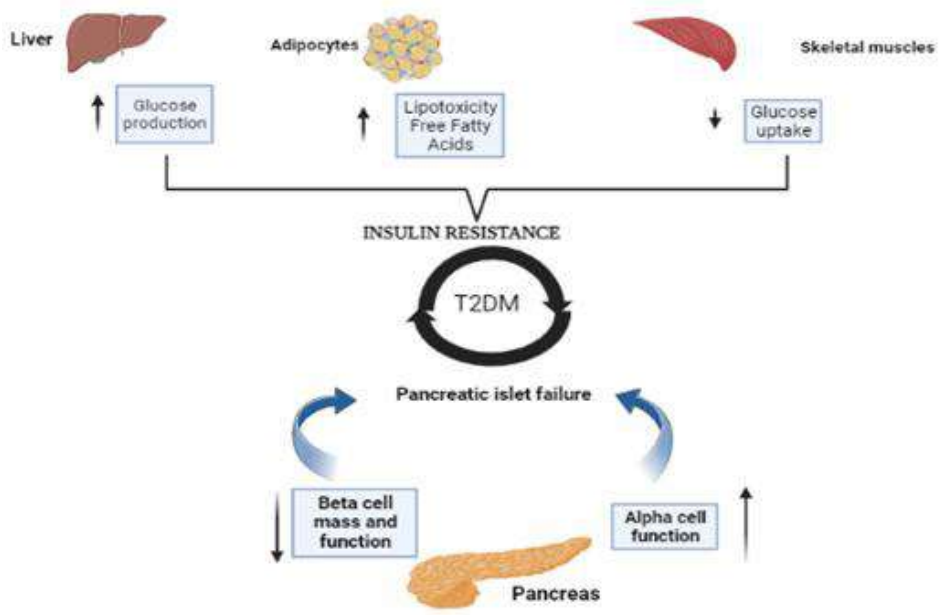


Figure 1.3: Pathophysiology of T2DM mellitus.

Insulin resistance (IR), resulting from enhanced free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat (Schwartz, 2016)

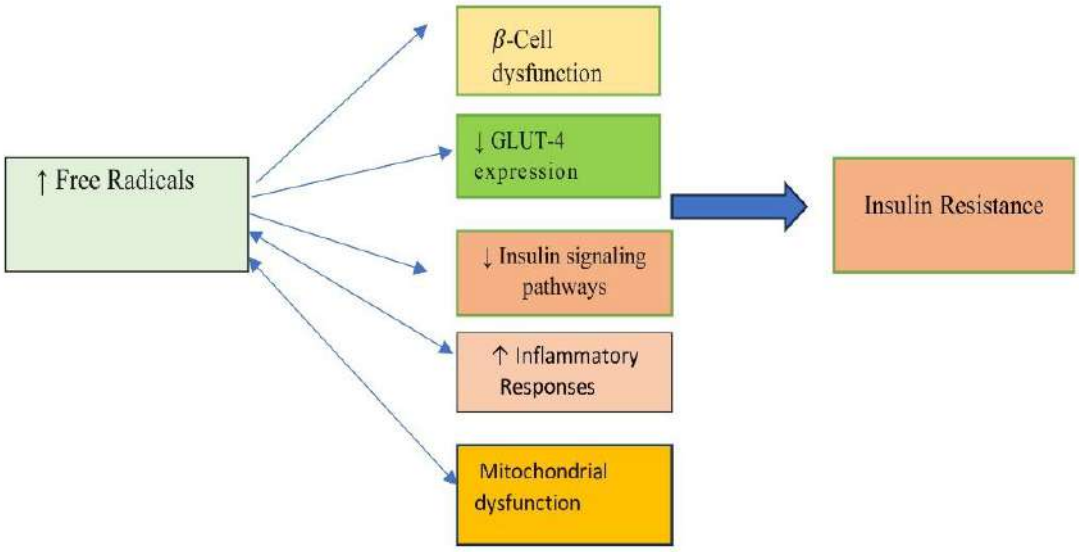


Figure 1.4: Oxidative stress-induced insulin resistance via five major molecular pathways.

Concomitant β -cell dysfunction and IR lead to pronounced hyperglycemia resulting in T2DM progression (Cerf, 2013; Zheng *et al.,* 2018). Reduced GLUT2 glucose transporter expression affects the downstream signalling pathway (Hoang and Thorn, 2015), while defects in proinsulin folding lead to insulin deficiency and T2D progression (Dali *et al.,* 2013; Liu *et al.,* 2018). Adipocytes secrete pro-inflammatory adipokines like TNF-α and IL-6. It attracts macrophages into the adipocytes which may impede beta function (Taylor, 2021). Islet Amyloid Polypeptide (IAPP) hypersecretion promotes the deposition of amyloid fibers on islets; hyperglycemia promotes islet glucotoxicity, and lipo glucotoxicity concomitantly causes beta cell apoptosis. It seems to cause decreases in beta cell mass (Pearson, 2019). Conversely, the hyperglycemic state of diabetic patients hastens the Advanced Glycation End products (AEs) creation. AGE precursors like methylglyoxal and glyoxal; attach to amino moiety of carrier and structural proteins, lipids, and nucleic acids to form irreversible AGEs (Nowotny *et al.,* 2015). The role of the Pylol pathway in T2DM progression is well established as it leads to oxidative stress. Elevated sugar levels funnel into the Pylol Pathway responisible for glucose conversion to sorbitol via reduction by Aldose reductase (AR) using the cytosolic NADPH. Sorbitol is further converted into Fructose by Sorbitol dehydrogenase (Tang *et al.,* 2012; Garg and Gupta, 2022). Under hyperglycaemic conditions, NADPH is decreased due to increased activity of the Polyol pathway, NADPH is required to reduce antioxidant glutathione (GSH). This compromises the antioxidant system leading to more production of reactive free radicals (Quattrini and La Motta, 2019; Garg and Gupta, 2022). Decreased insulin secretion by β-cells, enhanced glucagon secretion by alpha cells, increased glucose production by the liver, increased glucose reabsorption by kidneys, reduced incretin effect in the small intestine, and depressed uptake of glucose by skeletal muscle, liver, and adipose tissue lead to diabetes (Padhi *et al.,* 2019; Galicia-Garcia *et al.,* 2020).

1.3.4 Diabetic Complications

Elevated sugar levels for a long duration lead to numerous secondary complications. These are characterized as **Metabolic Acute Complications and Systemic Late Complications.**

Metabolic Acute Complications: They are relatively short-term nature and encompass non-ketonic hyperosmolar state (NKHS) and diabetic ketoacidosis (DKA). Diabetic ketoacidosis is frequent in T1D whereas hyperosmolar non-ketonic coma is observed in aged/elderly T2DM patients (Halim and Halim, 2019). Deficiency of circulating insulin along with decreased insulin

volume is common to both metabolic complications. Too little fluid intake coupled with decreased insulin levels causes these metabolic disruptions. Insulin deficit induces hyperglycemia, leading to osmosis-driven excess urination and low body fluids. Orthostatic hypotension, seizures, and obtundations are associated symptoms (Pinhas *et al.,* 2007; Halim and Halim, 2019).

Systemic Late Complications: These are chronic and can be microvascular (Retinopathy, neuropathy, nephropathy) or macrovascular (cardiovascular diseases) depending upon the type of vessels involved.

Diabetic nephropathy: A lethal complication affecting 30% of T2DM patients (Samsu, 2021). In renal cells (podocytes, mesangial cells, endothelial cells, and epithelial cells), the renin-angiotensin-aldosterone system (RAAS), AGEs, and epithelial-mesenchymal transition (EMT) cause inflammation, oxidative stress, apoptosis and autophagy in the Diabetic Nephropathy state.

Diabetic neuropathy: It encompasses a distinct group of neurodegenerative changes affecting primarily peripheral sensory and autonomic nerve fibers, motor fibers are involved at later stages (Kim *et al.,* 2012). Chronic high sugar levels and dyslipidemia associated with disturbed insulin signaling result in changes in glial cells, vascular cells, and neurons leading to nerve dysfunction. It often coexists with pain. Deficiency in the blood supply to peripheral nerve fibers is viewed as a plausible additional mechanism of neuropathy (Kim *et al.,* 2012; Feldman *et al*., 2017).

Diabetic retinopathy: Changes in retinal microvasculature, such as destroyed blood-retinal barrier (BRB), loss of vascular endothelial cells, pericytes, glial cells, neurons inside the retina, thickened vascular basement membrane coupled with capillary occlusion leads to DR. It is non-proliferative initially and proliferative at later stages characterized by neovascularisation of the retina (Rodríguez *et al.,* 2019). Inflammation, AGEs, and ROS are concomitant with the overproduction of vascular endothelial factors leading to fragile, immature new vessels causing vitreous hemorrhage. It is followed by a loss of sight completely (Kang and Yang, 2020)

Cardiovascular disease: It embraces an array of heart and blood-vessel-related conditions and a key reason behind morbidity as well as mortality in diabetics (Amiel *et al.,* 2019). The basic underlying reason for CVD is atherosclerosis (deposition of fatty substances on the inner walls of arteries). Elevated glucose damages the endothelial lining of blood vessels and is prone to atherosclerosis. Chronic low-grade inflammation and increased reactive oxygen species further hasten damage to blood vessels. Persistent high glucose levels lead to the narrowing of large

arteries and veins resulting in Coronary Artery Disease, Myocardial Infarction, Stroke (due to damage to vessels in the brain), and Peripheral Artery Disease (narrowing of arteries in limbs) are the main clinical complications because of damage to the blood vascular tree of the body (Leon and Maddox, 2019).

Besides, Non-alcoholic fatty liver disease, Erectile dysfunction in men, Sleep Apnea, and depression are other clinical manifestations of chronic hyperglycemia.

1.3.5 Management of T2DM

The cornerstone of diabetes management is to achieve a euglycemic index that can reduce mortality, delay the advent of disease complications, and impede the disease's progression. The binding capacity of hemoglobin is used to analyze glycemic control. Recommended glycosylated hemoglobin HbA1c levels should be less than 7% in diabetic patients (Copur *et al.,* 2020). Glycemic management and a patient-centered approach in self-care activities are required to prevent diabetic complications. Clinical data suggest that adopting a healthier lifestyle, maintaining an ideal body weight, and indulging in physical activity can help prevent the development of T2DM. Furthermore, lifestyle adjustment has a limited time to manifest its benefits on diabetes, and it is difficult to maintain the new lifestyle (Copur *et al.,* 2020). Nowadays, combined therapy with multiple oral hypoglycemic medications is an effective treatment for glycemic control in diabetes management, but the various combinational therapies also have numerous side effects (Table 1.1).

Non-pharmacological Interventions:

1) Awareness
2) Diet modification
3) Physical exercise

Pharmacological Intervention:

1) Insulin
2) Oral Hypoglycemic Drugs
3) Combinational Therapies

Oral Hypoglycemic Drugs: A huge number of oral synthetic molecules are generally used to ensure normal sugar levels. These include biguanides, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, Sodium Glucose co-transporter-2 inhibitors, α-glucosidase inhibitors, and non-sulfonylurea secretagogues (DeFronzo, 1999; Mayerson and Inzucchi, 2002; DeFronzo and Ghani, 2019). The mechanism of action is different for each class of drugs. Attaining an euglycemic index entirely by either insulin or oral antidiabetic drugs results in enhanced lipid reserves, hypoglycemic episodes, and gastrointestinal disturbances.

Table 1.1 Common Conventional Drug Therapy for T2DM

Oral Anti-diabetic Molecule	Drug Molecule	Mechanism of action	Adverse effects reported	Reference
Sulfonylurea	Gliclazide, Gliclazide, Glimepiride, and Glyburide	Stimulates the opening of Calcium channels in beta cells leading to a surge in insulin secretion	Hypoglycemic episodes, cardiovascular risk, upset stomach	Sola *et al.*, 2015
Meglitinides	Nateglinide, Repaglinide	Enhances the release of insulin Hypoglycemia	Hypoglycemia especially in patients with nephropathy	Guardado *et al.*, 2013
Bi-guanides	Metformin	Selective inhibition of mitochondrial glycerophosphate dehydrogenase leads to decreased gluconeogenesis in the liver, increased insulin sensitivity	Gastrointestinal distress, diarrhea, cramps, nausea, flatulence. decreased absorption of vitamin B12	Sanchez, and Inzucchi, 2017
Thiazolidinedione	Pioglitazone, Rosiglitazone	Sensitize insulin by PPARs leading to elevated adiponectin levels, decreased gluconeogenesis, and an increase in glucose uptake by	low blood sugar levels such as dizziness, sweating, hunger, weight gain, skin reaction, stomach	

		muscle cells and adipocytes	upset, and dark-colored urine	
α-Glucosidase inhibitors	Acarbose, Voglibose and Miglitol	Delay absorption of disaccharides in the lower gastrointestinal tract by inhibiting carbohydrate metabolizing enzymes	Bloating, flatulence, gastrointestinal irritation	Derosa and Maffioli, 2012
DPP-4 inhibitors	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin and Omariglipti	Inhibit the degradation of incretins and Glucagon-like Peptide stimulating insulin secretion	Nasopharyngitis, skin lesions and headache	Gallwitz, 2019
Glucagon-like peptide (GLP) agonist	Dulaglutide, Exenatide, Liraglutide,	Trigger synthesis and secretion of insulin from beta cells inhibits glucagon synthesis	Nausea, vomiting, mild tachycardia	Trujillo *et al.*, 2015.
Sodium-glucose co-transporter 2 (SGLT2) antagonists/ inhibitor	Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin and Tofogliflozin	Inhibit glucose reabsorption in the kidney	Ketoacidosis, Increased cholesterol, Urinary tract Infections	Pittampalli *et al.*, 2018

Combinational Therapy: The pathogenesis of T2DM is complicated, and achieving glycemic control necessitates addressing more than one of the various processes involved in hyperglycemia (Del Prato, 2019). The progressive and complex nature of T2DM impels multiple hypoglycemic drugs even at the time of diabetes diagnosis. Monotherapy provides transient benefits. Various studies support the benefits of using more than one drug (Padhi *et al.*, 2019).

1.4 Role of Plants and Phyto-constituents against T2DM

Botanicals contain numerous phyto-constituents exerting synergistic effects on glucose homeostasis and concomitant diabetic complications. These bioactive molecules show a wide variety of chemical structures and functions.

Flavonoids: They are polyphenolic and present ubiquitously in the plant kingdom. They consist of 02 aromatic rings designated A and B linked by a 3-C chain that forms a heterocyclic ring moiety (C) that contains 4 carbon and 01 oxygen atom. The (-OH) group number and position in the flavonoid rings are responsible for their polarity and solubility. Flavones, flavanols, flavanones, and anthocyanins are different flavonoids. Flavonoids are reported to act as alpha-glucosidase inhibitors and delay glucose absorption (Sok *et al.*, 2021). Quercetin, Rutin, Nargenin, Kaempferol, Fisten, Morin, Apigenin, Luteolin, and Chrysin have exhibited remarkable antioxidant and metal chelation and thus, ameliorate diabetic complications (Testa *et al.*, 2016; Wang *et al.*, 2022).

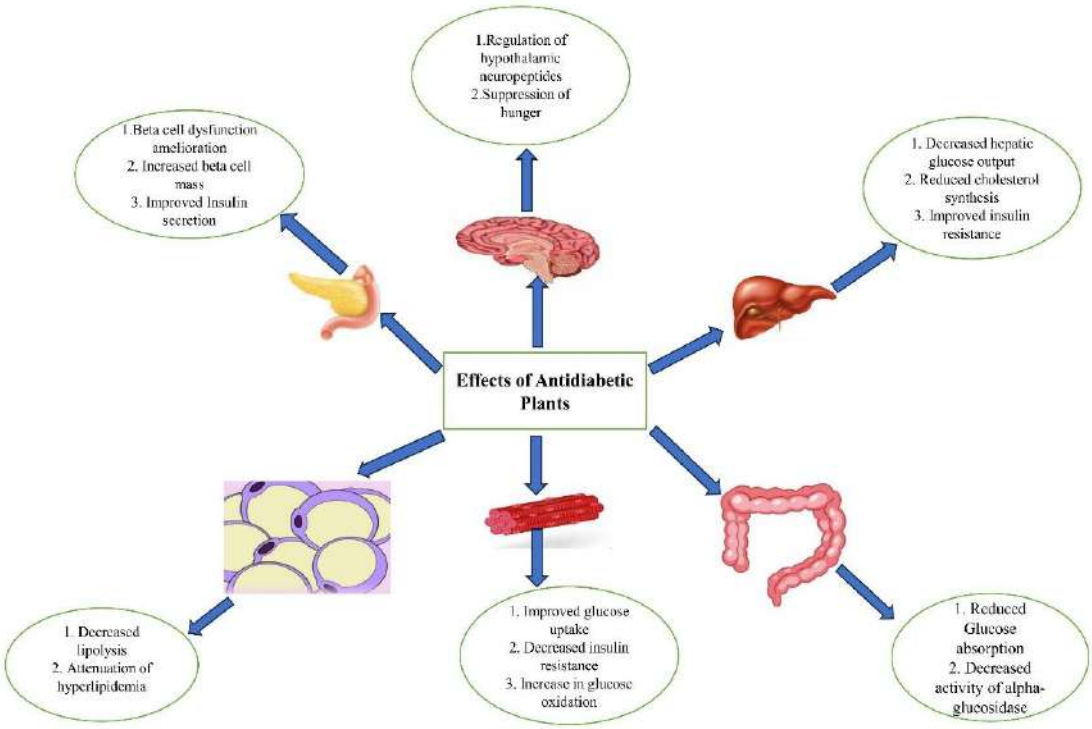


Figure 1.5: Effects of antidiabetic plants against in management of T2DM.

Morin improves serum insulin levels, decreases SOD, catalase, and glutathione (Kapoor, 2012; Abuohashish *et al.*, 2013). Apigenin raises serum insulin levels, Rutin improves IR and glucose

uptake, and quercetin reduces diabetes by stimulating insulin secretion and inhibiting aldolase (Ghorbani, 2017). A biologically active polyphenolic molecule Resveratrol, present in various plant species, benefits diabetic amelioration (Spatelzkudelski and Szkudelska, 2015). Thus, flavonoids and anthocyanins appear to mitigate diabetes through a combination of antioxidant and uncharacterized qualities.

Alkaloids: A diverse and large assemblage of phytocompounds containing Nitrogen with prominent pharmacological activities. They are found extensively in the plant kingdom; about 14-20% of plants contain alkaloids, Avarol, Casuarinra 6-o-a-glucoside, Calysteine B2, Magnoflorine, Jatrorrhizine, Palmitine have shown alpha-glucosidase, and amylase inhibition. Lupanine and trigonelline enhance insulin secretion by suppressing ATP-dependent Potassium channels. Berberine inhibits the DPP-4 enzyme and reduces advanced glycation product formation, also controls oxidative stress (Tan *et al.,* 2017). Harmane, Norharmane, and Pinoline improve insulin secretion by binding at the imidazole site of beta cells. Carbazole alkaloids like mahanimbine, koenimbine, and murrayazoline enhance glucose absorption and translocation of GLUT-4 (Salehi *et al.,* 2019). Thus, plant-derived alkaloids repair and promote pancreatic beta-cell proliferation, stimulate insulin secretion, suppress the Aldose reductase enzyme, Protein Tyrosine Phosphatase–1B increase sensitivity, reduce resistance, increase glycogenesis and inhibit gluconeogenesis (Adhikari, 2021) promotes the glucose uptake by muscle cells (Rasouli *et al.,* 2020)

Saponins: These are naturally present glycosides having surface activity; typically consist of a sugar moiety like glucose, galactose, rhamnose, or xylose glycosidically attached to a triterpenoid or steroidal aglycone. Saponins have a wide array of ethnobotanical uses but are pharmacologically relevant also. Saponins showing promising antidiabetic activities include astragaloside IV, diosgenin, arjunolic acid, platyconic acid, charantin, christinin-A`, elatosides G, H, I, ginsenosides, prototinosaponins AIII and pseudoprototinosaponins AIII, momordin Ic, 28-O-monoglucosides, E- senegasaponins A, B and C (Elekofehinti *et al.,* 2015). Saponins inhibit free radical generation and decrease insulin resistance by repressing apelin levels in adipose tissue (Choudhary *et al.,* 2021).

Tannins: Tannins are high molecular weight polyphenolic compounds and are abundantly present in fruits, green tea, nuts, grains, spices, and beverages. Various studies have shown compounds

like catechin, epicatechin, gallic acid, ellagic acid, and procyanidins (Laddha and Kulkarni, 2019) from plants decrease the progression of T2DM and its resultant complications. They attenuate the overexpression of NF-kβ, AMPK, TGF-β, PARP, and IL-6, which are the key pathways involved in the progression of diabetic neuropathy and retinopathy (Aba and Asuzu, 2018).

Triterpenes: A heterogeneous group of bioactive molecules derived from 02 active isoprene units having 30 carbons (Shibuya *et al.*, 2007). Two C_{15} units bind to form squalene or related acyclic 30-carbon precursors; cyclization and oxidation lead to various structures formed (Tang *et al.*, 2018). Studies have implicated the potential of triterpenes like p-coumaroyl, Oleanolic acid, and ursolic acid as alpha-glucosidase and amylase inhibitors (Teng *et al.*, 2018). Also been reported to inhibit the Advanced Glycation of biomolecules.

Cucurbitacin-B -B promotes translocation of the GLUT4 transporter and improves insulin sensitivity. Uavenoic acid ameliorates insulin resistance in INS-1 cells by upregulating PPAR gene expression. Dihydroxygraphonolide from *Andrographis paniculate* was also found to improve GLUT-4 movement on the cell surface and activate AMPK signaling (Arha *et al.,* 2015). Ginsenoside Rb1 also sensitizes insulin by enhancing the translocation of GLUT4 and leptin receptors (Tabandeh *et al.*, 2017).

Polysaccharides: These are polymeric carbohydrates made up of large monosaccharide units linked together by glycosidic bonds that, when hydrolyzed, yield monosaccharides or oligosaccharides (Zheng *et al.,* 2019). Xylo-oligosaccharide, Fructooligosaccharide (FOS) (oligofructose and short chain FOS) Galactooligosaccharide (GOS), Soybean oligosaccharide (SBOS), Isomaltose, Lichen's β-oligosaccharide, Icodextrin, Konjac glucomannan, ganoderans A, B, isomaltose, laminarin, lichen's β-oligosaccharide, lithosperman, moran, panaxan, pachymaran,trichosan, saciharan, soybean oligosaccharide, and Xylo oligosaccharide (Sajadimajd *et al.*, 2019) are few such therapeutic polysaccharides. Mainly exerts a hypolipidemic effect, modulates gut microbiota, and alpha-glucosidase inhibitors, and increases beta-cell mass (Chen *et al.*, 2018; Xu *et al.*, 2019).

Miscellaneous: Resveratrol, a stilbenoid enhances GLUT-4 translocation and improves insulin sensitivity (Bagul and Banerjee, 2015; Ozturk, 2017). Piceatannol derived from resveratrol restores impaired insulin signaling by enhancing AMPK expression. Embelin and Butein inhibit Interleulin-6 and NF-kB inflammatory pathways, and restore glucose homeostasis (Nayak *et al.,* 2013; Yu *et al.,* 2019).

Herbal medicines possess a diverse group of phytochemicals that exert synergistic effects in combination to alleviate disease complications (Gaonkar *et al.,* 2020). Since time immemorial, they have been relied on as safe, and efficacious with meager side effects. Hence, natural products, especially plant-based ones, are preferred over synthetic ones due to low cost and availability (Jeeva and Anlin, 2014; Oh, 2015).

1.5 Problem Envisaged

The Union Territory (UT) of Jammu and Kashmir (32°17′ and 36°58′ N Lat., 72°35′ and 80°30′ E Long.) is located mostly in the Himalayan Mountains and the states of Himachal and Punjab to the south. Because of extensive elevations, this region of India has a diverse biogeography and a high diversity of vegetation especially in terms of medicinal plant wealth. Many medicinal plant species having industrial potential are growing wild in this region. The area is rich in biological as well as cultural diversity. The considerable population of the UT belonging to diverse ethnicities still upholds its traditional healthcare systems. The traditional medicine systems adopted by these ethnic people are being utilized generation-wise without any scientific validation. They have immense knowledge about edible and medicinal plants. Besides, numerous valued medicinal plants are also a part of the culinary habits of the local populace of this region. Jammu and Kashmir state was among the only five states with diabetes prevalence below 500 per one lakh men (IIPS and Macro International, 2007) but recent studies have shown that the T2DM in J & K is increasing alarmingly with 4.85% in Jammu region (Singh and Kumar, 2015) and 6.05% in Kashmir (Ahmad *et al.,* 2011). As such the economic burden of the management of this disease in this state is on the rise. With the wealth of natural resources in terms of medicinal plants, one may have the option of following an alternative treatment regimen for diabetes in our state. A large number of hypoglycemic plants are available in this region and many of them are also used as food in Dogra, Kashmiri, and other local cuisines. The exploitation of such plant resources for use in the alternative treatment of T2DM can help cut the cost of treatment of this disease and minimize the side effects caused by available pharmacological drugs.

1.6 Relevance and Objectives of the Study: Species exhibiting a high Use Value, DCI, and Preference Ranking can be potentially subjected to further phytochemical and pharmacological studies. The novel molecules can provide leads for future drug development to manage T2DM. The present study aims documentation of TK of plants for the management of T2DM by the local population. This knowledge is vanishing fast as it is not being passed on from the older generation

to the younger one, moreover, very few people in the community nowadays opt for being Traditional Health Practitioners. This indigenous knowledge needs immediate documentation and possibly be integrated into healthcare systems to make diabetes management cost-effective.

The present research achieved the following objectives:

1. To enlist various plants used by the locals and medicine men against type-2 diabetes.
2. To perform quantitative analysis to ascertain the most important plant species for type-2 diabetes.
3. To perform phytochemical analysis of the most important plants to know the chief chemical constituent responsible for anti-diabetic activity.
4. To assess the antidiabetic activity of selected plants by inhibition assay of key carbohydrate digesting enzymes i.e., alpha-amylase and alpha-glucosidase.
5. To suggest a conservation strategy for the species collected from the wild, if facing threat.

CHAPTER 2

REVIEW OF LITERATURE

2. Review of literature

Plants have always been an integral component of human healthcare. Their continued use and popularity of plant-based traditional medicine require scientific validation of therapeutic properties to contribute more novel molecules for the management of T2DM (WHO, 2016).

Ethnobotanical investigations document information on the cultural interaction of local folks with plants. It also studies the know-how of local people about traditionally used plants and the incorporation of plants into their traditions and religion (Balick and Cox, 1996). Therefore, traditional local communities worldwide have a great deal of knowledge about native plants on which they intimately depend (Langeheim and Thimann, 1982). About 800 ethnobotanical studies have reported about 1200 plants with hypoglycaemic potential.

2.1 Ethnobotanical Studies Documenting Hypoglycaemic Plants Globally

2.1.1 Africa

About 80% of the African population lives in resource-poor areas and depends on medicinal plants for health care including chronic ailments like Diabetes mellitus. Africa is abundant in medicinal plants, and numerous of these local species are employed to treat diabetes and have been documented in many ethnopharmacological studies (Chinsembu *et al.*, 2019). These plants have shown synergistic effects on insulin-regenerating pancreatic beta cells, increased insulin secretion, enhanced glucose utilization by skeletal muscle and adipose tissue, repress glucose synthesis in the liver, and decreased glucose uptake from the gut.

Bouzabata (2013) surveyed herbalists in the East region of Souk Ahras of Algeria. The study recorded 59 species being used for managing Diabetes and hypertension. The most preferred plants for diabetes were: *Olea europaea*, *Ajuga iva, Allium cepa*, *Allium sativum, Myrtus communis,* and *Trigonella foenum-graecum*. Sixteen species were employed for both Diabetes and hypertension.

Telli *et al.* (2016) conducted an ethnobotanical survey with Type I and Type II diabetics, herbalists, and traditional healers in Ouargla, Algeria. The study catalogued 67 species from 32 families. *Matricaria pubescens*, *Rhanterium adpressum,* and *Oudneya africana* were the first reports of hypolycemic properties. About 51 species were used for both diabetes and foot complications. The highest UV, RFC, and Fic were shown by *Citrullus colocynthis*, *Anvillea radiata*, *Ammodaucus leucotrichus,* and *Artemisia herba-alba*.

In Morrocco, a substantial number of ethnobotanical as well as ethnopharmacological studies in the last two decades have been done to document plant species in use to manage diabetes mellitus (Jouad *et al.*, 2001; Eddouks *et al.*, 2002; Tahraoui *et al.*, 2007, Hachi *et al.*, 2016; Barkaoui *et al.*, 2017; Katiri *et al.*, 2017; Laadim *et al.*, 2017; Mrabti *et al.*, 2019; Skalli *et al.*, 2019). There are about 255 plants spread over 70 families being traditionally used to manage hyperglycemia (Idm'hand *et al.*, 2020).

Taharoui *et al.* (2007) assessed traditional hypoglycemic and hypotensive plants through an ethnopharmacological study in the Errachidia Province of Morocco. Only 23% of residents use modern medication and traditional medicine was the first option for a sizable portion of the population (78%). 64 medicinal plants spanning 33 families were documented; 45 were used for T2DM, 36 for hypertension, and 18 species were used for both diseases.

Laleye *et al.* (2015) surveyed plant traders, farmers, and herbalists from different locations of Benin to document indigenous knowledge. They reported 203 plants belonging to 176 genera being used traditionally to manage type 2 diabetes. Fabaceae, Apocynaceae, and Euphorbiaceae were the dominant families. *Citrus aurantifolia, Moringa oleifera, Momordica charantia,,* and *Catharanthus roseus* were the most used plants. The main way of administration was decoction and infusion.

In the Ait Baha Chtouka and Tiznit division of Morocco, 48 plants from 25 families were documented for diabetes (Barkaoui *et al.*, 2017). *Allium sativum* and *Salvia* species were the most cited anti-diabetic plant species. *Lavandula dentata* L., *Marrubium vulgaris,* and officinalis.

In the Tafilalet region, diabetics mainly use medicines sourced from *Allium sativum, Artemisia herba-alba*, *Scoparia dulcis,* and *Trigonella foenum-graecum* (Eddouks, 2017). The antidiabetic plants that were most used in the town of Sidi Slimane were: *Origanum vulgare* and *Salvia officinalis Olea europaea* and vulgare (Laadim *et al.*, 2017).

Mrabti *et al.* (2019) ethnobotanically surveyed 400 traditional healers and aged villagers in the Beni Mellal province of Morrocco. 45 species from 25 families were recorded with *Olea europaea, Allium sativum,* and *Trigonella foenum-graecum* having the highest relative frequency of citation.

Skalli *et al.* (2019) in an ethnobotanical survey with 334 diabetic patients in Rabat, Morocco recorded thirty plants used by diabetic subjects to manage diabetes. As reported by Mrabti *et al.*, 2019, the most preferred species were *Olea europaea*, *Allium sativum*, and *Trigonella foenum-graecum.*

Mechchate *et al.* (2020) surveyed the Fez-Meknes of Morocco and 50 plant species were documented in all, spanning 27 families. Lamiaceae, Apiaceae, and Fabaceae were the dominant families. Six antidiabetic herbs were documented for the first time in Moroccon hypoglycemic flora. *Trigonella foenum graecum* followed by *Olea europaea* and *Prunus amygdalus var. amara* were the most commonly mentioned plants and the findings were in coherence with earlier studies. Nearly 67% of diabetes patients supplement medicinal herbs for their medications. Women used herbals more in comparison to men.

Chetoui *et al.* (2021) performed a cross-sectional study in the Beni Mellal-Khenifra province of Morocco involving 1021 diabetics. Overall, 34.8% of participants reported using herbal medicine. Participants reported the usage of 63 kinds of plants from 32 families. A conviction in Herbal medicine's effectiveness was the most vivid reason for its use.

Jamal *et al.* (2022) assessed the antidiabetic flora of the South-Western village (Madjel Belabbes) of Tunisia, from Marsh to April 2021. Situated near the Chaanbi mountain range and characterized by soaring plant richness, phytotherapy was employed in 55.68% of patients, with 20.41% using medicinal herbs daily. The most commonly utilized anti-diabetic herb was *Trigonella foecum graecum* (71.43%) regardless of the type of diabetes or the existence of related disorders. *Cinnamomum verum, Melissa vulgaris, Artemisia herba alba, Rosmarinus vulgaris*, and *Thymus vulgaris* create a second line of defense in the fight against diabetes.

Mudau *et al.* (2022) assessed traditionally used plants for diabetes by Traditional healers of the Vhembe district from the Limpopo area of South Africa. The study recorded 63 medicinal plants from interviews with sixty herbalists.26 new records for antidiabetic plants *Aloe grandidentata* and *Grewia retinervis* emerged as the first for usage in traditional medicine. *Elephantorrhizae lephantina, Elaeodendron trasvaalense, Brackenridgea zanguebarica* , and *Moringa oleifera* were the most used and cited plants for high sugar levels.

Shinkafi *et al.* (2015) surveyed the Hausa–Fulani community of Sokoto in Nigeria.51 informants from around the state revealed 54 species from 33 families. *Cassia sieberiana* emerged the most

often mentioned (19 times) and placed first (39%). The plant species *Azadirachta indica, Ficus exasperata*, and *Schwenckia americana* placed second (15%), with eight citations.

Katemo *et al.* (2012) documented antidiabetic flora of Kisanani, the Democratic Republic of the Congo. They recorded 31 anti-diabetic plant remedies from interviews with 55 Traditional healers. Decoction with water as the sole solvent was the dominant way of administering plants used.

Asase and Yohonu (2016) surveyed 40 herbalists in the Dangme West area of southern Ghana. The study observed that herbalists were well-versed in Diabetes-associated complications like slow-healing wounds, abrupt weight loss, sweetened urine, changes in skin texture, genital pain, and impotency in men. *Aloe vera, Launaea taraxacifoli*a and *Vernonia amygdalina* were most often recommended to control high sugar.

Naceiri *et al.* (2021) carried out a quantitative ethnobotanical survey involving 193 healers of the Tathe zo region of Morocco. A total of 46 plants effective against hyperglycemia were recorded. *Salvia officinalis, Ajuga iva,,* and *Marrubium vulgare* were most frequently cited along with *Cystisus battandieri, Urgenia maritime, Plantago ovate,* and *Zizyphus jujube* as new antidiabetic species from the region.

Ajao *et al.* (2023) reported 39 plants from 24 families used by inhabitants of Ede, southwestern Nigeria. *Crinum jagus* was the species with the highest fidelity level. About 87% of the plants reported were assessed for hypoglycemic activities rendering support to their usage by ethnic populace.

Obakiro *et al.* (2023) documented 61 plants from 59 genera being utilized by traditional healers of 08 districts of Eastern Uganda for diabetes mellitus. *Kigelia africana, Aloe vera, Entada abyssinica, Tamarindus indica, Carica papaya,* and *Maytenus senegalensis were the most used plants. Decoctions were commonly given in herbal recipes and plants were collected from the wild.*

2.1.2 South America

Giovannini *et al.* (2016) cataloged 104 species used to control T2DM from Central American nations viz. Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Pana.In vitro as well as in vivo preclinical experiments for the hypoglycemic effects of 16 species out of the 20 species were recorded by a minimum of two independent sources. Seven species have been documented in more than 03 studies; *Momordica charantia, Neurolaena lobata, Tecoma stans,*

Persea americana, Psidium guajava, Anacardium occidentale, and *Hamelia patens*. Leaf extracts enriched in Sesquiterpene lactone-rich of *Neurolaena lobata* dramatically reduce blood glucose.

In Guatemala, T2DM results in nearly 33% of deaths, because of low earnings; the indigenous population relies on traditional medicine. Cruz and Andrade–Cetto (2015) carried out an ethnopharmacological study amongst the Cakchiquels group in Guatemala to determine the most utilized plants in traditional medicine to treat T2-DM. The study documented *Croton guatamalensis, Hamelia patens, Neurolaena lobata, Solanum americanum,* and *Quercus peduncularis* as the most preferred species against diabetes. About 11 species have a Use Value higher than 0.5 and high DCIs; 64% of plants reported having hypoglycemic effects stood tested clinically; this finding thus, supports the traditional selection of Cakchiquels to manage type 2 diabetes.

Belhaj *et al.* (2021) evaluated ethnobotanical perspectives of folkloric-used antidiabetic plants in the High Atlas Central area of Mexico. The study involved 834 interviews and quantitatively revealed 144 plants used against Type 2 diabetes. The survey was novel as it incorporated toxicology studies. 32 species were the first-time reports from the region for diabetes management.

2.1.3 Europe

There is a revival of herbal medicine in the Western world. Traditional knowledge among Cree of Eeyou, Istcee in Northern Quebec of Canada was assessed and documented 17 species used by aboriginal people. *Abies balsamea, Alnus incana, Gaulteria hispidula, Juniperus communis, and Kalmia anustifolia* are the most common plans used by Creec people. 17 plants were subjected to bioassay-guided antidiabetic potential (Haddad *et al.*, 2012).

Dalar (2018) documented herbals used in the Van area of Turkey against diabetes. A survey spanning 03 years with 600 informants revealed 69 plant species, there were 35 species with no earlier record of antidiabetic use in the scientific literature for Turkey. Five taxa were endemic and one was rare to Turkey. High Use values of *Rheum ribes, Scutelleria orientalis, Urtica dioica, Diplotenia cachrydifolia,* and *Teucrium polium,* indicated potential leads for pharmaceutical agents for diabetes.

2.1.4 Asia

Diabetes is the biggest economic and healthcare burden, according to the WHO (Kumar *et al.*, 2019) India, Maldives, Nepal, Mauritius, Bangladesh, and Sri Lanka are the diabetes capital of the

world, with 84 million diabetics forming one-fifth of the total diabetics globally. Many ethnobotanical studies have been done in these countries to explore and document indigenous knowledge to manage hyperglycemia and related complications.

Ahmadi *et al.* (2016) documented indigenous plants utilized by locals of the Shiraz region of southwest Iran. The information divulged from 25 herbalists revealed 24 species from 19 families, Compositae the leading one (13%). About 45% of the reported species were ascertained to be approved for pharmaceutical activity in animal models.

Nowbandegani *et al.* (2015) surveyed in Fasa and Shiraz regions of Iran to document traditional antidiabetic plants used there. 50 informants divulged 39 plant species recommended by traditional healers. The most recommended species was *Trigonella foenum-graceum.* About 44% of species were also used for obesity management. Clinical studies have approved anti-diabetic properties in 23% of these species and 61% were approved in animal models.

Bahmani (2014) documented traditional knowledge of plants used for treating Type 2 diabetes in the Urmia region of Northwest Iran. Direct observation and interviews with 35 traditional healers revealed about 30 plant species from 17 families used for treating diabetes.

Yaseen *et al.* (2015) in the ethnomedicinal survey in Islamabad, Khyber-Pakhtunkhwa, and Sindh regions of Pakistan documented 120 plant species used as a remedy for diabetes mellitus. 113. Quantitative data was collected involving Traditional Medicine men and diabetic patients via open-ended and semi-structured questionnaires. The leaves with 56 use reports were the preferred plant part and the common mode of administration was recorded to be decoction. RFC ranged from 14-42 and DCI varied from 0.15 to 0.74. Upon comparison, to older studies, it was revealed that 64 species were never reported in diabetes management, 40 spp. lacked pharmacological studies and 3 were not explored for phytochemical profiling. This type of indigenous knowledge will serve to design pharmacological and clinical trials to manage the disease.

Ullah *et al.* (2019) reported 31 species from the Khyber Pakhtunkhwa region, *Momordica charantia, Caralluma tuberculate* and *Citrullus colocynthis* were the most important.

Ali *et al.* (2022) documented traditional plants used to treat hyperglycemia in the Maidan Valley of the Dir district of Khyber Pakhtunkhwa, Pakistan. Ethnopharmacological data was analyzed quantitatively using Relative Frequency of Reference and Use Value. 42 plants from 36 genera

and 27 botanical families were cataloged. The Poaceae was the most represented family. *Ziziphus nummularia* had the greatest RFC value at 0.47, while *Sarcococca saligna* had the highest UV at 0.97. This distant region's reliance on plant species to treat diabetes demonstrates the significance of herbal formulations in addressing fundamental human health concerns.

Truong *et al.* (2022) investigated Vietnam's Mekong Delta traditional health care system. The study focused on how Traditional Vietnamese medicine healers address type-2 diabetes, a new condition in Vietnam (T2D). 36 plants are used to cure T2D, with individuals utilizing between one and seven plants. *Vernonia amygdalina* and *Momordica charantia* specifically garden variety was the most reported species reported by nine healers (45%). According to healers, the wild populations have greater bioactivity. Prescribing polyherbal (multi-species) preparations was a norm for T2D treatment.

Neamsuvan *et al.* (2015) qualitatively documented folk knowledge about antidiabetic plants of the Songkhla Province (Chana and Nathawee) of Thailand. The survey reported 38 species from 28 families. In contrast to many studies, root (8 species; 21.05%), the *Lagerstroemia speciosa* was most common in usage (0.83 use value).

Wasana *et al.* (2022) explored the Galle District of Srilanka flora for antidiabetic species used to treat by Ayurveda and Traditional Healers. It was the pioneer quantitative ethnobotanical study and the plant inventory included 28 species of medicinal plants. The highly cited medicinal plants were *Salacia reticulate* (RFC = 0.55) and *Coccinia grandis* (RFC = 0.48). Celastraceae and Cucurbitaceae were the most utilized family in therapeutics. *Aerva javanica* had the highest used and most popular species (UV = 1.67; RPL = 0.75) among anti-diabetic medications.

Kadir *et al.* (2012) conducted an ethnobotanical survey spanning two years in 15 districts of Bangladesh with 1060 participants. The study included Traditional healers, Traditional drug manufacturers, and locals. 83 species were reported to be used and Euphorbiaceae was the dominant family. *Asparagus racemosus, Azadirachta indica, Momordica charantia, Moringa oleifera Lamk., Terminalia chebula, Justicia adhatoda, Allium cepa, Cassia fistula , Ocimum sanctum,* and *Trigonella foenum-graecum.*

Rehman (2015) documented 33 species used ethnobotanically by the Santal tribe of Joyphurat in Bangladesh. The most used species were *Ageratum conyzoides, Andrographis paniculata, Annona squamosa, Argemone mexicana, Azadirachta indica, Centella asiatica, Coccinia cordifolia, Ficus*

racemosa, Momordica charantia, Moringa oleifera, Syzygium cumuni, Tinospora cordifolia, and *Xanthium indicum.*

2.1.5 India

Several ethnobotanical explorations have been carried out in India as well in the last twenty years bringing antidiabetic flora of various parts into documentation. Most of the studies are qualitative. In recent years, the incorporation of quantitative indices has been witnessed. Nagarajan *et al.* (1982) reviewed 75 medicinal plants utilized for Type 2 Diabetes whereas Handa *et al.* (1990) listed 150 medicinal plants used as a treatment for diabetes. Rai (1994) in a review reported 56 anti-diabetic plants from India. In addition to this, he reviewed five plants viz. *Syzygium cumini, Pterocarpus marsupium, Melia azadirachta*, *Momordica charantia* and *Gymnema sylvestre***.**

2.1.5.1 Himalayas

Himalayas have a rich and varied history of traditional knowledge and practices. The region has remarkable biodiversity (Pei, 1995). The Hindu-Kush-Himalayan region is house to the rich diversity of genes, species, tribes, and ecosystems (Chhetri *et al.*, 2008). A rich repository of medicinal plants exists which is used by inhabitants for ameliorating different ailments (Pandey *et al.,* 2022). Since, relentless want of progress as driven ecosystem canes, the existing pool of Traditional Knowledge is in jeopardy leading to many ethnobotanical studies to record and assess it (Tali *et al.*, 2018).

Chhetri *et al.* (2005) explored indigenous knowledge about hypoglycemic plants among local healers, and tribal healers such as Jhankris, Bijuwas, Bongthings, and Lamas of Sikkim and Darjeeling Himalayas. In total, 37 antidiabetic species were documented.

Ryakala *et al.* (2010) carried out extensive ethnobotanical surveys of varied ethnic groups in biodiversity-rich North-east India. The study yielded 52 species being used in the management of diabetes. Interviews with 340 THPs also revealed that 26 herbal treatments involved the decoction of one or more plants in combination.

Namsa *et al.* (2011) inventorised 21 plant species across 20 families employed for diabetes mellitus treatment by rural folks of the Dhemaji district of Assam. The maiden survey for traditional know-how of antidiabetic flora revealed *Amomum linguiforme, Cinnamomum*

impressinervium, Dillenia indica, Garcinia pedunculata, Solanum indicum, Sterculia viliosa, and *Tabernaemontana divaricata* as first reports in global antidiabetic flora.

Tag *et al.* (2012) quantitatively studied the Khamptis "Chau ya" traditional healers' ethnobotanic management of T2DM in the Lohit district of the eastern Himalayan province of Arunachal Pradesh. Because of their perceived efficacy, assumed safety with minimal side effects, and affordability, the local populace relies heavily on the wisdom of traditional local healers and plants to address their healthcare requirements. Tai Khampti traditional healers used polydrug therapy and thus, prescribed recipes having two or three plant parts and appropriate dietary combinations (beans, fruits, and vegetables) accompanied the antidiabetic therapy. The belief in synergistic interactions may account for the prevalence of multicomponent recipes found in this research. It was thought that polyherbal prescriptions contain a variety of bioactive molecules and more effective healing power than mono-molecule treatment. Eleven plants viz. *Begonia roxburghii, Calamus tenuis, Callicarpa arborea, Cuscuta reflexa, Dillenia indica, Diplazium esculentum, Lectuca gracilis, Millingtonia hortensis, Oxalis griffithii, Saccharum spontaneum*, and *Solanum viarum* were reported for hypoglycemic effects for the first time from this region. A four-year survey in this remote area revealed 42 species in usage. The study recommended further ethnopharmacological research on the novel use of report plants like *Dillenia indica, Diplazium esculentum,* and *Solanum viarum*. Traditional healers frequently used *Clerodendrum colebrookianum, Momordica dioica, Annona squamosa*, and *Coptis teeta*; these plants can be analyzed for further ethnopharmacological studies to discover potential new anti-diabetic drugs.

Tarafdar *et al.* (2014) surveyed ethnic communities inhabiting the Unakoti area in Tripura, India. The quantitative assessment revealed 39 species from 28 families and substantial FL, and UV values (50%) were found for 05 plant species: *Scopaia dulcis, Syzygium cumini, Cicca acida, Cassia fistula,* and *Carica papaya*. whose further pharmacological research was recommended. Among the above, three species viz. *Scoparia dulcis, Syzygium cumini* , and *Cicca acida* demonstrated substantial (50%) RFC values. *Scoparia dulcis* L. was the most used plant among the Darlong and Halam communities for treating diabetes (whole plant decoction) with UV (2.64), RFC (0.57), and FL (100%). This herb is also used by Caribbean cultures in the same way.

Laha *et al.* (2016) documented the indigenous use of plants for diabetes management by the ethnic populace of Mizoram, India. The study discovered 53 antidiabetic plant species in 32 families; Leguminosae was the dominant family in the said study with 7 species.

Kalita *et al.* (2017) assessed the folklore knowledge of the antidiabetic plants in Aptani tribe from Ziro, Lower Subansiri district Arunachal Pradesh, and reported 30 plant species known to have anti-diabetic properties.

Gupta *et al.* (2017) assessed the antidiabetic flora of Una, Himachal Pradesh wherein 84 plant species were reported.

Daimari *et al.* (2019) recorded the plants traditionally utilized by the Bodo tribals in the traditional management of DM in the Kokrajhar district of Assam. Interviews with 54 informants divulged the usage of 37 species from 24 families. *Hodgsonia heteroclita* and *Andrographis paniculata* were the most used species by locals.

Kumar *et al.* (2019) documented the plants utilised by the Jaunsari Tribals of the Chakrata in Jaunsar–Bawar Hills of Uttarakhand in India to treat diabetes. A thorough field survey revealed the traditional knowledge of tribal elders and folk healers.54 plants (representing 47 species and 30 families) were identified as anti-diabetic plants in traditional medicine. The most anti-diabetic herbs belong to Lamiaceae followed by Zingiberaceae, Amaryllidaceae, Apocynaceae, and Compositae.

Sarna (2020) surveyed the rural populace and herbal medicine men of Nalberi, Barpeta, Udalguri, and Kamrup districts of Assam and documented 41 plant species possessing hypoglycemic activity indicating a sound indigenous knowledge base about antidiabetic plants.

Singh *et al.* (2020) gathered information from 201 indigenous medicine men from Mizoram, India .14 genera across 72 families were documented for cancer and diabetes. The antidiabetic potential of *Phlogacanthus thysiformis, Solanum gilo,* and *Lobelia angulate* was recorded for the first time. *Dillenia* scabrella, *Circium sinesis, Eupatorium nodiflorum, Pratia begonifolia, Vernonia teres*, and *Plantago erosa* were also reported first for the anticancer and antidiabetic effects.

Bahayut and Bag (2022) updated traditional knowledge on hypoglycemic plants employed by 23 communities in Sikkim's East and South regions. Chhetri *et al.* (2005) had earlier reported 37 species from the same region, it was updated to 50 plants from 36 different families to manage

diabetes by this study. This revised study reported plants that had not previously been documented in this area, such as *Smallanthus sonchifolius*, *Nyctanthes arbor-tristis*, and *Abelmoschus esculentus.* For species *Ageratina adenophora*, *Equisetum debile*, *Ficus auriculata, Nephrolepis cordifolia*, and *Tupistra clarkei*, no scientific validation has been reported. *Ficus auriculata, Nephrolepis cordifolia*, and *Tupistra clarkei* were cited frequently, and evaluation of antidiabetic potential of these was recommended.

2.1.5.2 Rest of India

Jayakumar *et al.* (2010) surveyed Thiruvananthapuram and Kollam district of Kerala for traditional antidiabetic species and reported 45 plants used. Study divulged tat 30% people interviewed relied completely on botanicals whereas rest used along with conventional medicine.

Rajendran and Manian (2011) reported 16 species from Koli Hills of Eastern Ghats.

Basha *et al.* (2011) reported 21 genera across 13 families used by ethnic Sungli tribe of Yerramalais of Eastern Ghats in Andhra Pradesh.

Deokar *et al.* (2012) documented 42 antidiabetic plants from Chandoli, Dist. Sangli, (M.S.)

Thirumalai *et al.* (2012) documented the usage of 40 traditional plants for managing diabetes by natives of Javadhu Hills in the ethnobotanical survey involving 312 locals.

Kumar and Janardhna (2012) surveyed the Wayanad district of Karnataka for traditional knowledge of diabetes. Interviews with 120 healers resulted in 44 species and 23 formulations in vogue for diabetes management.

Shrivastava and Kanungo (2013) surveyed the Surguja district of Chhattisgarh and inventorised 15 species used by the Uraon tribals for treating diabetes.

Kalimurthi *et al.* (2014) documented 33 species from the coastal village of Kodiyampalayam (Southeast coast of India). *Bruguiera cylindrica Coccinia grandis*, *Rhizophora apiculata, Rhizophora mucronata, Excoecaria agallocha*, and *Andrographis paniculata* were frequently in use.

Goyal (2015) surveyed the traditional anti-diabetic plants in Jodhpur emphasizing on cultural significance of the plants followed by the determination of the Disease Consensus Index of the reported hypoglycemic plants used traditionally by communities here. The study reported the use

of more than one species by individuals. Botanicals were used in many oral forms. 62% of diabetic preparations were in the form of aqueous extract, or juice, or ingested with water if the preparation is powdered. 17% of preparations were eaten as raw salad and 21% were cooked. It was also reported that after incorporating these plant-based preparations there was no need to increase allopathic drug dose. Respondents reported a decrease of symptoms which was because of a decrease in blood glucose levels. Plants having the highest DCI in this study were *Momordica charantia, Azadirachta indica*, *Trigonella foenum-graecum, Capparis deciduas, Gymnema sylvestre, Syzygium cumini,* and *Withania coagulans,*. The study recommended further phytochemical and pharmacological exploration of *Capparis deciduas*, *Withania coagulans,* and *Gymnema sylvestre* because of DCI and unexplored status.

Maina *et al.* (2015) evaluated biodiversity and endemic regions of Andaman and Nicobar Islands flora. They documented about 50 antidiabetic species.

Patekar and Jaiswal (2017) reported 18 hypoglycemic plants from the Amboli region of Maharashtra. *Salacia chinensis, Salacia macrosperma, Alstonia scholaris, Tinospora cordifolia, Gymnema sylvestris, Andrographis paniculata,* and *Curcuma longa* were the most frequently used plants.

Aadhan and Anand (2017) reported 65 plants known to the Paliyar Tribe inhabiting the Sadhuragiri hills of Tamil Nadu.

Mishra *et al.* (2019) reported 40 antidiabetic plants from Khurda, Orissa. Trees (47.5%), shrubs (32.5%), and herbs (20%) dominated the flora. Leaves were used most. *Gymnema sylvestre* was the most utilized species reported in this study.

Dixit and Tiwari (2020) explored and quantitatively assessed the Kanpur Forest division for hypoglycemic species used by ethnic groups.44 Kanpur healers recommended 35 plant species from 24 families. The observed plants had FL, UV, and RFC values of 0.97–0.23, 82.7%–24.1%, and 0.327 to 0.067. Leguminosae led with 14.28% of plants. Trees (43%) and leaves (30.6%) were the most used living forms. *Aloe vera* (0.97), *Syzygium cumini* (82.7%), and *Momordica charantia* (0.327) had the greatest UV, FL, and RFC.

Reena *et al.* (2020) documented folklore knowledge corpus of plants used as antidiabetics by ethnic people of Devendra Kula in the Pudukkottai district of Tamilnadu. They reported a total of

22 medicinal plants known to possess hypoglycemic potential. *Syzygium cumini* was the most commonly mentioned medicinal plant species for diabetes control, with a use value of 1.44.

Hazarika *et al.* (2020) conducted an ethnopharmacological survey in Kamalabari and Garamur, Majuli in Assam. The study documented 52 species of anti-diabetic plants from 33 angiospermic families. In coherence with earlier studies, *Andrgraphis paniculata, Azadirachta indica, Coccinia indica, Dillenia indica*, and *Trigonella foenium graecum* were recorded as very common plant species among the local medicine men utilized for control or treatment of diabetes.

Most of the ethnobotanical studies conducted in India have not been quantitatively assessed have been. Quantitative techniques are of great relevance and scientific interest as they indicate the cultural importance of the species. As research into botanicals grows, the framework of ethnobotanical studies provides better insights into utilizing medicinal plants (Jain, 2007; Souza *et al.*, 2018).

2.2 Validation of Traditional Knowledge

Traditional indigenous knowledge has frequently been deemed unscientific due to its claimed lack of consistency and failure to provide data for quantifiable analysis (Ragupathy and Newmaster, 2009). Despite the absence of recognition of customary indigenous knowledge, a growing corpus of scientific study is enhancing its credibility (Luzuriaga *et al.*, 2018). Confirmation of local knowledge may employ either quantitative, qualitative (Fassil, 2003; Ragupathy and Newmaster, 2009), or both techniques along with using analytical tools to substantiate the basis of their use.

Botanicals comprise of numerous bioactive molecules with variable chemistry and thus modulate multiple targets, genes, and ailments in a composite and safe manner; a synergistic polypharmacology. It renders support to the holistic system of traditional and complementary medicine across cultures

Characterization of the complete set of metabolites present in plants and extracts can potentially enhance our understanding of how a particular botanical works through a network of multiple mechanisms. Few reports on the metabolic profiling of some Indian medicinal plants, such as the extract of Banana fruit (Fahim *et al.*, 2019), Gudmar (*Gymnema sylvestre*) leaf extract (Parveen *et al.*, 2019), *Butea monosperma* flowers (Khan *et al.*, 2017), Makoi (*Solanum nigrum*) fruit extract (Chester *et al.*, 2017), Kutki extract (Zaheeruddin *et al.*, 2017), and Brahmi (*Bacopa monnier*i)

extract (Mallick *et al.*, 2017). These reports have validated the traditional claims about these medicinal plants.

2.2.1 In-vitro Antidiabetic Potential Assessment *via* Enzyme Inhibition Assay

The use of medications depressing glucose absorption is another method of controlling diabetes. Important digestive enzymes participating in carbohydrate degradation include α -amylase and α -glucosidase enzymes. Starch and complicated carbs are hydrolyzed by α- amylase into disaccharides, which are then hydrolyzed by isomaltase into free glucose that can be ingested. The primary enzyme for digestion in humans is α -glucosidase, also known as α -D-glucoside glucohydrolase, secreted by brush border cells of the small intestine. It is bound to the membranes of the brush-bordered cells of the small intestine. To liberate unbound glucose, α-Glucosidase hydrolyzes terminal, non-reducing (1- 4)-linked glucose residues. Since α -glucosidase eventually regulates how much glucose is released from polysaccharides in the intestines, inhibiting this enzyme's activity is one of many well-established medicinal methods for treating T2DM. It is proposed as an efficient method for reducing the polysaccharide substrate supply for glucose release in the gut is mild alpha-amylase suppression with high alpha-glucosidase inhibition (Kajaria *et al.*, 2013; Gutierrez and Martha, 2016)

Many alpha-amylase and glucosidase inhibitors are present in natural products. Earlier studies showed that many diet chemicals block starch-digesting enzymes. Some glycosides, peptides, and lipids isolated from food raw materials inhibited α-amylases and α-glucosidases (Zhang *et al.*, 2020). Many inhibition studies have been carried out in plants to assess their antidiabetic potential in vitro and are summarized in Tables 2.1 and 2.2.

Table 2.1: Alpha-amylase inhibition studies on antidiabetic plants

Plant Name	Plant part used	Extract type	Enzyme source	Inhibition/ IC-50	Reference
Aloe vera (L.) Burm. f.	Leaf gel Raw	Aqueous	Porcine Pancreas	23.3% at 2.5 mg/ml	Sudha *et al.*, 2011; Shah *et al.*, 2013; Mahomoodally *et al.*, 2016
		Cyclohexane	Porcine Pancreas	15.8 % at 2.4 mg/ml	

Amaranthus spinosa L.	Leaf	Methanol	NS	46.02 µg/ml	Rahmatullah *et al.*, 2009; Kumar *et al.*, 2011
Ancusa officinalis L.	Leaves	Polypenolic fraction	Hog Pancreas	954.16±7.46µg/ml	Paun *et al.*, 2020
Artocarpus heterophyllus Lam.	Flower, Leaf	Methanol extract of flowers	Wheat	70.58±9.66 µg/ml	Nair *et al.*, 2013; Mahomoodally *et al.*, 2016
Bixa orellana L.	Leaf	Methanol	Human	5049 µg/ml	Ponnusamy *et al.*, 2011; Ezuruike and Prieto, 2014
			Porcine	50 µg/ml	
Camellia sinensis L. Kuntze	Leaf	Ethanol	NS	1.54 mg/ml	Nickavar and Yousefian, 2011; Mahomoodally *et al.*, 2016
		Ethyl Acetate	NS	0.53 mg/ml	
		Dichloromethane	NS	20.7 mg/ml	
Capparis spinosa L.	Bud (fresh)	-	Porcine Pancreas	0.210±0.01 mmol AE/G extract	Shah *et al.*, 2013; Dalar *et al.*, 2015; Mollica *et al.*, 2017
		-	Porcine Pancreas	0.171±0.01 mmol AE/G extract	
		-	Porcine Pancreas	0.190±0.01 mmol AE extract	
Centella asiatica (L.) Urb.	Leaves	Aqueous	NS	20.2±0.32%	Odhav *et al.*, 2013
	Stem	Aqueous	NS	24.2±0.23% mg/ml	
Cinnamomum verum J.S. Presl	Leaf	Isopropanol	Porcine	40 µg/ml	Ponnusamy *et al.*, 2011; Telli *et al.*, 2016
			Pancreas	1 µg/ml	
Cinnamomum zeylanicum Blume.	Bark	Dichloromethane	Human Pancreas	46.1±1.0 µg/ml	Ali-Shtayeh *et al.*, 2012; Salehi *et al.*, 2013
		Ethyl acetate	Porcine Pancreas	40.1±0.9 µg/ml	

Cistus salviifolius L.	Aerial Part	Aqueous	*Bacillus lichenifor mis*	311.20±1.38 µg/ml	Sayah *et al.*, 2017
Coriandrum sativum L.	Fruit	Ethanol	NS	33.6% ±2.304 mg/ml	Nickavar and Yousefian, 2011; Narkhede, 2012; Mahomoodally *et al.*, 2016
	Leaves	Ethanol	NS	18.8% at mg/ml	
				20.9±0.81% at 2.304 mg/ml	
Curcuma longa L.	Rhizome decoction	Acetone	Porcine pancreas	30 µg/ml	Ponnusamy *et al.*, 2011
		Isoprop			
Cynura cardunculus L.	Leaf, stem	Methanol	Porcine pancreas	9.09±0.11 mg/ml	Mootoosamy and Mahmoodally, 2014; Spínola and Castilho, 2017
Cyperus esculentus L.	Tuber	Aqueous	Porcine pancreas	5.19 mg/ml	Khan and Yadava 2010; Sabiu *et al.*, 2017
Ficus benghalensis L.	Bark	Cold water	Porcine pancreas	270 µg/ml	Ponnusamy *et al.*, 2011; Ocvirk *et al.*, 2013
		Hot water	Human pancreas	4.4 µg/ml	
			Porcine pancreas	130 µg/ml	
			Human pancreas	125 µg/ml	
Ficus racemose L.	Bark, Fruit	Aqueous	Porcine pancreas	742.7±95.0 µg/ml	Ocvirk *et al.*, 2013, Trinh *et al.*, 2016
		Ethanol	Porcine pancreas	46.7±23.6 µg/ml	
Ficus religiosa L.	Leaves, fruit	Acetone	Porcine pancreas	35.3±2.8% inhibition at 1mg/ml	Umair *et al.*, 2017

Inula viscose (L.) Aiton.	Leaf, Shrub Boiled	Ethanol	NS	16.56±1.54 % inhibition at 3000 µg/ml	Orhan *et al.*, 2017
Juglans regia L.	Leaf	Ethanol	NS	28.7± 0.15% inhibition at 2.304 mg/ml	Nickavar and Yousefian, 2011
Leucas cephlotes (Roth) Spreng.	Fruit, leaves	Ethanol	NS	92.86 ± 0.89 µg/ml 98.09 ± 0.69 µg/ml	Dua *et al.*, 2011;Verma *et al.*, 2017
Malva neglecta Wall.	Leaf	Ethanol	Porcine pancreas	15.2±0.8 mg/ml	Dalar and Konczak, 2013
Meliolotus officinalis L. (Pall.)	Leaf	Polyphenols	Hog Pancreas	1.32± 0.08 µg/ml	Paun *et al.*, 2020
Mimosa pudica L.	Whole plant	Acetone	Porcine pancreas	15.6 ± 5.55%	Ocvirk *et al.*, 2013; Tunna *et al.*, 2015
		Ethanol	Porcine pancreas	18.7 ± 6.83 at 1mg/ml	
Momordica balsamia	Leaf	Aqueous	NS	8.9±0.07%at 1mg/ml	Odhav *et al.*, 2013
Momordica dioca Roxb. ex. Wild	Fruit	Methanol	NS	IC= 8 µg/ml	Roa and Mohan, 2017
Morus alba L.	Leaves	Isopropanol	Porcine pancreas	60.5% at 1.8 mg/ml	Sudha *et al.*, 2011
		Methanol	Porcine pancreas	15.1 % at 3.9 mg/ml	
Murraya koengii	Leaves	Ethanol	NS	63.3% at 1 mg/ml	Ponnusamy *et al.*, 2011; Narkhede, 2012
		Isopropanol	Porcine pancreas	10 µg/ml	

			Human pancreas	127 µg/ml	
Ocimum tenuiflorum L.	Leaves	Isopropanol	Porcine pancreas	53.4% inhibition at 0.0094 mg/ml	Sudha *et al.*, 2011; Mahomoodally *et al.*, 2016
Parkia roxburghii G.Don	Pods	Aqueous	Porcine pancreas	7.09±0.65 µg/ml	Sheikh *et al.*, 2015
		Butanol	Porcine pancreas	8.93±0.32 µg/ml	
Phyllanthus amarus Sch. and Thonn.	Whole Plant	Dichloromethane	NS	10.44 µg/ml	Tamil *et al.*, 2010
		Methanol	NS	44.62 µg/ml	
		Aqueous	NS	62.49 µg/ml	
Punica granatum L.	Leaves	Ethyl acetate	NS	187.82 µg/ml	Patel *et al.*, 2014
Rubus fruticosus L.	Leaves	Methanol	Porcine	53.7±2.0 µg/ml	Salehi *et al.*, 2013
Scoparia dulcis L.	Whole Plant	Methanol	NS	65.91 µg/ml	Mishra *et al.*, 2016
Senna occidentalis L.	Leaves	Aqueous	NS	5.8±0.09% at 1 mg/ml	Odhav *et al.*, 2013
	Stem	Aqueous	NS	27.6±0.09% at 1 mg/ml	
Stevia rebaudiana (Bertoni)	Leaf	Aqueous	Porcine Pancreas	198.40 µg/ml	Ruiz *et al.*, 2015
Syzgium cumini (L.) Skeels.	Seeds	Cold Water	Human Pancreas	42.1 µg/ml	Ponnusamy *et al.*, 2011; Mahomoodally *et al.*, 2016; Shaheen *et al.*, 2017
			Porcine Pancreas	10 µg/ml	
		Hot Water	Human Pancreas	50 µg/ml	

			Porcine Pancreas	4.1 µg/ml	
Tribulus terrestris L.	Seeds	Acetone	Porcine Pancreas	250 µg/ml	Ponnusamy *et al.*, 2011; Nowbandegani *et al.*, 2015
			Human Pancreas	511 µg/ml	
Trigonella-foenum-graceum L.	Leaves Seeds	Ethanol	NS	31.3% at 1 mg/ml	Narkhede, 2012
		Aqueous	Porcine, pancreas	1.92 mg/ml	Sudha *et al.*, 2011
		Cyclohexane	NS	13.4 % at 1.5 mg/ml	
		Methanol	Porcine, pancreas	1.87 mg/ml	
Urtica dioca L.	Leaves	Ethanol	NS	1.89 mg/ml	Barkoui *et al.*, 2017
Vaccinium arctostaphylos L.	Fruit	Methanol	Porcine	57.0 ±0.5 µg/ml	Salehi *et al.*, 2013; Nowbandegani *et al.*, 2015
	Leaves	Methanol	Pancreas	0.53 mg/ml	
Zataria multiflora Boiss.	Leaves	Butanol Fraction	NS	47.2±1.2% inhibition at 7.4 mg/ml	Nowbandegani *et al.*, 2015; Moein *et al.*, 2017
Zea mays L.	Corn silk	Aqueous	Porcine Pancreas	5.89 mg/ml	Sabiu *et al.*, 2016

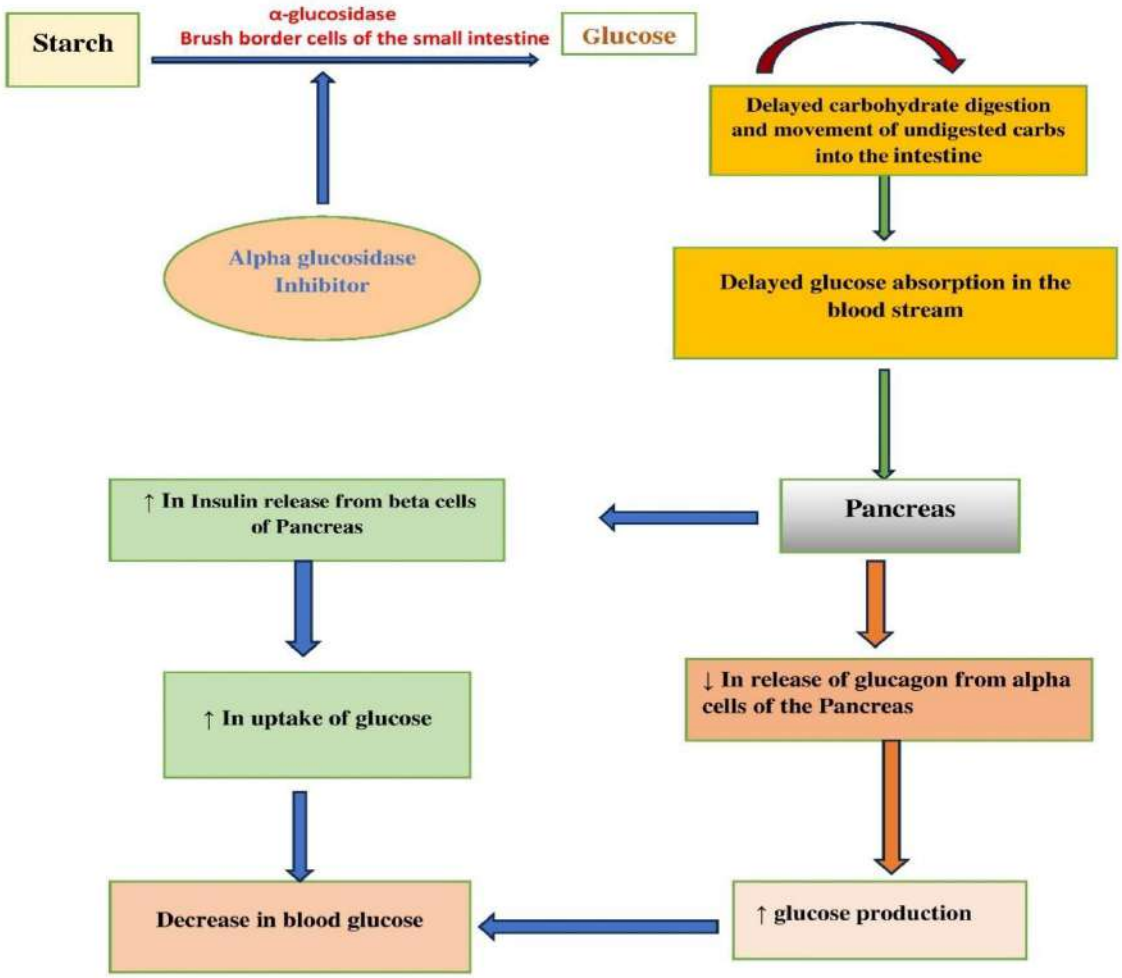


Figure 2.2: Mechanism of action of Alpha Glucosidase Inhibitors

Table 2.2: Alpha-glucosidase inhibitors from antidiabetic plants

Plant Name	Plant Part used	Type of extract	Enzyme source	IC50 extract (mg/mL)	References
Adenosma bracteosum Bonati.	Aerial parts	Ethanolic extract	NS	0.027	Nguyen *et al.*, 2020
		Aqueous extract		0.043	
Andrographis paniculate (Burm. f.) Wall. ex Nees	Leaves	Ethanolic extract	NS	17.2±015 mg/mL	Subramanian *et al.*, 2008

Annona senegalensis Pers.	Leaves	Ethanolic extract	Yeast	0.097	Onwusonye *et al.*, 2014; Ibrahim *et al.*, 2019
Camellia sinensis (L.) Kuntze	Leaves	Aqueous extract	Yeast	2.47 ±0.30 mg/ml	Li *et al.*, 2016
Chrysophyllum cainto L.	Stem bark	Aqueous extract	Yeast	0.0012	Shailajan and Gurjar, 2014; Doan *et al.*, 2018
Conyza canadensis (L.) Cronquist	Whole plant	Methanolic extract	NS	107 µg/mL	Aslam *et al.*, 2018
Cinnamomum zeylanicum Blume.	Bark	Methanolic extract	NS	5.83 µg/mL	Shihabudeen *et al.*, 2013
Cyclocarya paliurus (Batalin) Iljinsk	Leaves	Plant extract	NS	31.5±1.05 µg/mL	Ning *et al.*, 2019
Cerasus humilis (Bunge.) S. Ya. Sokolov	Leaves	70% methanolic extract	NS	36.57 µg/mL	Li *et al.*, 2022
Crataegus pinnatifida Bunge	Fruits	Acetone extract	NS	42.35 ± 2.48 µg/mL	Chen *et al.*, 2022
Ensete superbum (Roxb.) Cheesman	Seeds	Methanolic extract	Yeast	0.0018	Ganesan and Natesan, 2017; Habtemariam and Varghese, 2017
Evodiae fructus (polysaccharides)	Fruits	Water extract	NS	84.6% at 4 mg/mL	Xiong *et al.*, 2022
Ganoderma hainanense	Fruiting body	Chloroform residue	NS	0.409± 0.041 mg/mL	Ma *et al.*, 2019
Gymnanthemum amygdalinum (Delile) Sch. Bip.	Flower	Ethyl acetate fraction	NS	19.24 ± 0.12 µg/mL	Vonia *et al.*, 2022

Hertia cheirifolia (L.) Kuntze.	Flower	Petroleum ether,	Yeast	0.242	Bouriche *et al.*, 2016; Majouli *et al.*, 2017
		Ethyl acetate,	Yeast	0.437	
		Butanol extract	Yeast	0.421	
Homalium ceylanicum (Gardner.) Benth.	Bark	Ethanolic extract	NS	0.019	Sahoo *et al.*, 2017
Hypericum hircinum L.	Aerial parts	Ethanolic extract	NS	0.014	Mandrone *et al.*, 2017
Hypericum scruglii Bacch., Brullo and Salmeri	Aerial parts	Ethanolic extract	NS	0.00725	Mandrone *et al.*, 2017
Lepisanthes fruticose (Roxb.) Leenh.	Seeds	Ethanolic extract	NS	1.873 ± 0.421 mg/mL	Salahuddin *et al.*, 2020
Liquidambar formosana Hance.	Leaves	Ethanolic extract	Yeast	0.0059	Zhang *et al.*, 2017
Mallotus japonicas (L.f.) Müll. Arg.	Leaves	Methanolic extract	Yeast	0.0084	Ndrianingsih *et al.*, 2015
Meliolotus officinalis L. (Pall.)	Leaves	Polypenols	Yeast	146.64±3.64 µg/ml	Paun *et al.*, 2020
Mentha arvensis L.	Leaves	Methanolic extract	Ns	68% at 50 µg/µl	Agawane *et al.*, 2019
Nelumbo nucifera (total flavonoids)	Leaves	Leaf flavonoids	Yeast	1.86±0.018 g/mL	Liu *et al.*, 2013
Oryza sativa L. (*Black rice*)	Black Rice bran	Ethyl acetate extract	NS	47.79±2.28µg/mL	Bhuyan *et al.*, 2022
		Methanolic extract		48.50±0.83 µg/mL	
		Hexane extract		52.80±1.65 µg/mL	

Podocarpus macrophyllus (Thunb.) Sweet	Leaves	Methanolic extract	Yeast	0.045	Ndrianingsih *et al.*, 2015
Potentilla anserine L.	Rhizome	Butyl alcohol fraction	NS	14.18±0.95 µg/mL	Yang *et al.*, 2021
Paliurus spina-christi Mill	Fruit	n-hexane extract	NS	445.7 ± 8.5 µg/mL	Yucca *et al.*, 2022
Quercus dentaa Thunb.	Leaves	Mathanolic extract	Yeast	0.042	Ndrianingsih *et al.*, 2015
Quercus gilva Blume.	Leaves	Mathanolic extract	Yeast	0.11	Ndrianingsih *et al.*, 2015
Quercus glauca Blume.	Leaves	Mathanolic extract	Yeast	0.0447	Ndrianingsih *et al.*, 2015
Quercus phillyraeoides A.Gray	Leaves	Methanolic extract	Yeast	0.0098	Ndrianingsih *et al.*, 2015
Samanea saman (Jacq.) Merr.	Leaves	Methanol extract	Yeast	172.25 (50% inhibition)	Vinodhini and Rajeswari, 2019
Bound phenolic acid *Free phenolic acid*	Naked oats	Plant extract	NS	0.580±0.010 mg/mL 0.721±0.014 mg/mL	Yang *et al.*, 2019
Symplocos cochinchinensis (Lour.) S.Moor.	Bark	Ethanolic extract	NS	82.07 ± 2.1 µg/mL	Antu *et al.*, 2014
Washingtonia filifera H.Wendl.	Seeds	Methanolic extract	NS	0.53 ± 0.014 µg/mL	Floris *et al.*, 2021
Xylosoma congestum (Lour.) Merr.	Leaves	Methanolic extract	Yeast	0.1823	Ndrianingsih *et al.*, 2015
Zanathoxylum armatum D.C.	Leaves	Crude extract	Ns	79.82% at 0.8 mg/mL	Rynjah *et al.*, 2018

NS: Not Specified

2.3 Review of five most preferred traditional species from Kathua District

***2.3.1 Acacia catechu* (L.f.) Willd.**

2.3.1.1 Taxonomic Position

Kingdom: Plantae

Superdivision: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida

Order: Fabales

Family: Fabaceae

Genus: *Acacia*

Species: *catechu*

2.3.1.2 Vernacular Name

English: *Black catechu*

Hindi: *Khair, Pyor, Gayatrin*

Gujrati: *Khair*

Assamese: *Kher*

Malyalam*:* *Kadiram, Cutch Tree*

Kannada: *Kadira, Kadu*

Nepali: *Khyar*

2.3.1.3 Distribution: *Acacia catechu* is a deciduous thorny tree up to 15–17 m tall. A native of central and east Africa, South Asia, Bhutan, China, India, northern and north-western Pakistan, Myanmar, and Nepal (Patel *et al.*, 2009). Found extensively at an elevation of 1200 meters throughout India in lower Shiwaliks of Assam,, Jammu and Kashmir, Punjab, Haryana, Himachal Pradesh, Uttar Pradesh, West Bengal, and Sikkim.

2.3.1.4 Plant Morphology: Medium-sized tree with dark greyish-brown barks, and brown slender branches which are slender, Bark exfoliates in rectangular strips.; leaves petiolate, alternate and bipinnately compound; leaflets oblong and glabrous, whitish to pale yellow 5–10 cm-long axillary spikes; 1–1.5 mm-long campanulate calyx, 2.5–3 mm long corolla, and pods with ovoid seeds (Bhattarai *et al.*, 2020). Flowering from July to August and fruiting occurs from August to December (Patel *et al.*, 2009; Adhikari *et al.*, 2021)

2.3.1.5 Traditional ethnomedicinal uses: Bark decoction is used against cough, cold, and diarrhea (Singh and Lal, 2006); in livestock for broken horns (Sunial *et al.*, 2019). Khoyer is used for pain relief and blood glucose control (Rahmatullah *et al.*, 2013). Ayurvedic skin tonic Khadira Rishta is prepared from heartwood. Chinese use heartwood extracts 'Ercha' for cough, diarrhea, skin ulceration, and lesions (Shen *et al.*, 2006). Soft branches as chew sticks globally owing to antibacterial properties (Shen, 2006; Sharma and Lingha, 2021). Used in asthma, mouth sores, chest pain, bronchitis, cancer, diarrhea, sore throat, ulceration, healing of wounds, and vitiligo. Known to exert antifungal, spasmolytic, and antiviral (Alamabayan *et al.*, 2015).

2.3.1.6 Biological activities: The important biological activities of *Acacia catechu* are listed in Table 2.3.

Table 2.3: Important biological activities of *Acacia catechu*

Biological Activity	**Part Used of *Acacia catechu***	**Type of Extract Used**	**Experimental findings**	**Reference**
Antibacterial	Heartwood	Ethyl acetate extract	Inhibited *Staphylococcus aureus*	Patel 2009; Joshi *et al.*, 2011
	Resin part (*Katha*) Methanol Chloroform Petroleum ether Bark	Aqueous fraction	Inhibited *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis*	Aryal *et al.*, 2021
Anticancer	Bark	Methanol, ethyl alcohol, n-butanol and aqueous	Effective against MCF-7 cell line with IC50 of 137.5 µg/ml.	Kumar *et al.*, 2019
	Bark	Bark Ethanolic extract	Cytotoxic at low concentrations Induced apoptosis	

			of MTT assay SCC-25 cell line	
	Fruits	95% ethanolic extract (100 µg/mL)	Antiproliferative in MTT assay SCC-25 cell line	Isemura, 2019
	Seed	Seed Ethanolic extract	IC50: 52.09 µg/mL Induced apoptosis of SCC-25 cells, HL-60 cell line	Bhandari *et al.*, 2015
Antidiabetic	Bark, seed	Ethanol extract	α-Glucosidase 10.3 µg/mL; α-Amylase: 67.8 µg/mL	Lakshmi *et al.*, 2015; Aryal *et al.*, 2021
	Wood extract	Methanolic extract	α-Glucosidase: 187.80 µg/mL; α-amylase: 341.20 µg/mL	Rahmatullah *et al.*, 2013
Antiulcer	Root	Ethanol and aqueous extracts (0.2 and 0.4 g/kg b.w.orally Wistar albino rats 60)/24 h	67.87% and 71.14% inhibition were observed in two groups of animals	Alambayan *et al.*, 2015

2.3.2 *Ajuga bracteosa* Wall. ex. Benth.

2.3.2.1 Taxonomic Position

Kingdom: Plantae

Superdivision: Spermatophyta

Division: Magnoliophyta

Class: Magnoliosida

Order: Lamiales

Family: Lamiaceae

G**enus:** *Ajuga*

species: *bracteosa*

2.3.2.2 Vernacular Names

Sanskrit: *Nilkanthi*

English: Bungle, Copal tree.

Punjabi: *Khurbanti*.

Kashmir: *Jan-i-adam*

Hindi: *Kori booti*

Others: *Lilkounthe, Ratpacho, Kwaga Bootei*.

2.3.2.3 Distribution: Commonly called kauri booti, *Ajuga bracteosa* is a perennial herb found in the plains of Punjab, the upper Gangetic plains, and Kashmir Himalayas to Nepal in Western Himalaya.

2.3.2.4 Plant Morphology: *A. bracteosa* is a perennial, aromatic, villous, delicate, and prostrate herb that ranges in height from 10 to 30 cm; Roots are fibrous; Leaves obovate to elliptical, around 2-6 cm, and serrated margins. The leaf base is oblanceolate in shape (Gohain *et al.*, 2021). Inflorescence spike with whorls of flowers present along the stem. Flowers tubular with two-lipped corolla; blue-purplish, Calyx (4.5-6 mm) campanulate. Fruit is a nutlet; oblong to obovoid with adaxial side swelled. Grows mostly on grassland, exposed slopes, and open fields in temperate and subtropical areas at an elevation between 1,300 and 2,000 meters (Hussain *et al.*, 2016)

2.3.2.5 Traditional Ethnomedicinal Uses: *Ajuga bracteosa* roots have been utilized in folkloric medicine for fatigue, diarrhea, and dysentery. An alternative to quinine, the leaves are used for fevers; as an astringent, crushed leaves stop hemorrhaging (Khare, 2007). A leaf infusion containing honey and ginger juice treats elevated fever and congestion in the respiratory tract. In Taiwan, *Ajuga bracteosa*, roots, and leaves are utilized to cure various inflammatory conditions, including hepatitis. In Ayurveda also, it is recommended for treating rheumatism, gout, ataxia, and amenorrhea. It is also used as a malaria treatment. In Asian countries, it is a folk remedy for gout, pneumonia, hepatitis, rheumatism, and other neuro-inflammatory conditions (Jan *et al.*, 2014). In India, leaves, flowers, and bark decoction is used against cancer, diabetes, malaria, and inflammation (Qureshi *et al.*, 2009).

2.3.2.6 Biological activities: The important biological activities of various plant parts of *Ajuga bracteosa* are listed in Table 2.4.

Table 2.4: Important biological activities of *Ajuga bracteosa*

Biological Activity	Part Used	Type of Extract Used	Experimental findings	Reference
Anti-tumor	Aerial Parts	Crude methanolic extracts and aqueous	IC50 values lower than 5 µg/ml and 10 µg/ml against two cell lines (MCF-7 and Hep-2)	Pal *et al.*, 2014
Anti-tumor	Leaves	Methanolic, Hexane and crude	0.41µg/mL of IC50 for tumor necrosis factor (TNF), activated NF-κB activity	Ghufran *et al.*, 2009
Antimicrobial	Leaves	Ethanolic extract	Maximum 68.8% chemo suppression in the respiratory tract and 77.7% chemo-suppression recorded. ED50 of ELEAB was 300 mg/kg b/w of mice[	Chandel *et al.*, 2010.
Antibacterial	Leaves	Methanolic Acetone	Inhibited *Staphylococcus aureus* and acetone extract active against *Escherichia coli*	Vohra and Kour, 2011
Hypoglycemic	Leaves	Hydroalcoholic extract (80:20)	Significant lowering of glucose concentration in the *A. bracteosa* treated group on 14th day	Singh *et al.*, 2016
Anti-inflammatory	Whole Plant	70% Ethanolic extract	COX-1 and COX-2 inhibitory activity at 25 and 50 µg/mL concentration.	Gautam *et al.*, 2011
Anti-arthritic	Whole Plant	70% Ethanolic extract	20 mgk/kg (68.31%) as compared with aspirin (60.49%).	Kaithwas *et al.*, 2012

2.3.3 Bergenia ciliata (Haw.) Sternb.

2.3.3.1 Kingdom: Plantae

Super-division: Spermatophyta

Division: Magniliophyta

Class: Magnoliopsida

Order: Saxifragales

Family: Saxifragaceae

Genus: *Bergenia*

Species: *ciliata*

2.3.3.2 Vernacular Names:

Amchi: *Khadhur*

Engligh: Hairy bergenia

Sanskrit: *Amabhedaka,*

Urdu: *Zahkm -e -Hayat*

Bengali: *Patharkuchi,*

Gujrati: *Pashanbheda, Pakhanbheda*

Kashmiri: *Pashanbhed*

Pahadi: *Satopdi*

Hindi: *Pakhanabheda, Silpbheda, Sadpottar*

Tamil: *Sirupilai*

Telugu: *Kondapindi Pashto Kamargul, Ghat pana*

2.3.3.3 Distribution: *Bergenia ciliata*, or hairy Bergenia, is a perennial herb found from Central Asia, Afghanistan to China, Himalayan region from the altitude range (1800–3000 m). In India, it is recorded from Arunachal Pradesh, Meghalaya, West Bengal, north-west Himalayas, Kyongnosla, Karponanag, Gangtok in Sikkim (Chauhan *et al.*, 2012; Hasan *et al.*, 2013; Kumar *et al.*, 2015).

2.3.3.4 Plant Morphology: About 50-centimeter-tall perennial herb with a similar spread. Root rhizomatous with suborbicular leaves; 10-30 cm. in lent and 5-15 cm in width; rounded at the apex and base. Leaf margin: finely denticulate and lined with soft hairs. Leaves; opposite and alternate; ex-stipulate, green, turn bronze during cooler temperatures. Pinkish-white flowers with ovate

petals, and lobes are acute and denticulate near the apex and are hermaphrodite, calyx;5 sepals adnate to the ovary, corolla 4 or 5, perigynous and imbricate, stamens indefinite, ovary 4 or 5 and united, fruit is capsule-shaped or occasionally baccate, seeds are numerous (Amad *et al.*, 2018) It blooms in the spring from February to April and the fruiting season is March to July. Seeds 1-2 mm (Akiyama *et al.*, 2012)

2.3.3.5 Ethnomedicinal uses: Since antiquity, *Bergenia ciliata* used in folkloric, Ayurveda, and Unani to treat gastric, kidney, bladder stones, and wounds (Asolkar *et al.*, 1992; Ahmad *et al.*, 2018). Rhizome paste is applied on burns, and wounds. Mixed with honey and administered to women for post-partum recovery, to cure diarrhea, and fever (Chowdhary *et al.*, 2009). In rural and ethnic Himalayan communities, used to treat pulmonary infections, piles, bladder and kidney stone dissolution, and leucorrhea (Kumar and Tyagi, 2013). Leaves are commonly called 'Pasenbeda' because of their lithotrypic properties (Ahmad *et al.*, 2018).

2.3.3.6 Biological activities: Important biological activities shown by *Bergenia ciliata* have been summarized in Table 2.5.

Table 2.5: Important biological activities of *Bergenia ciliata*

Biological Activity	Part Used	Type of Extract Used	Experimental findings	Reference
Antimicrobial	Rhizomes	Methanolic extract	Maximum inhibition against *Staphylococcus aureus* at 1000 µg/disc	Sinha *et al.*, 2001
	Rhizomes	Aqueous, 50% ethanolic and methanolic crude extracts	At 50 mg/ml, the effect was most significant	Sajad *et al.*, 2010
Anti-fungal	Root, leaves	Ethanol, hexane, Ethylacetate, Chloroform, Butanol	Effective against *Microspoum canis*, *Candida albicans*, and *Pleuroetus oustreatus*	Azhar *et al.*, 2002
	Leaves	Ethanol, Ethylacetate aqueous	Effective against *Microspoum canis*	
Antitussive	Rhizome	Methanolic and Ethanolic extract	Ethanolic, aqueous, chloroform extract lowered glucose by 70.13%,71.34%, and	Sinha *et al.*, 2001

			42.23% resp. in STZ diabetic mice	
Antidiabetic	Rhizome	50% aqueous-methanol extract	Dose-dependent inhibition against α-amylase and glucosidase enzyme	Bhandari *et al.*, 2008
Anti-ulcer	Rhizomes	Aqueous and methanolic extract	Aqueous extract decreased ulceric lesions more than methanolic extract	Kakub and Gulfraz, 2007
Antimalarial	Leaves	Ethanolic extract	Significant chemo suppression on day 7, in a dosage-dependent manner; max. 87.50 % at 1,000 mg/kg	Walter *et al.*, 2013
Antilithiatic	Rhizomes	Crude Extract	Less as compared to *Dolichos biflorus*	Garrimella *et al.*, 2001

2.3.4 *Urtica dioica* L.

2.3.4.1 Kingdom: Plantae

Super-division: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida

Order: Rosales

Family: Urticaceae

Genus: *Urtica*

Species: *dioica*

2.3.4.2 Vernacular names

English: Stinging nettle

Hindi: *Bichhu-buti, Kali-kaundali*

Assamese: *Chorat*

Kannada: *Churachi*

Sanskrit: *Vrscikali, Vrishchhiyaa – shaaka*

Unani: *Anjuraa*

2.3.4.3 Distribution: It is ubiquitously present worldwide native to Europe, temperate North America, Asia, and Western Africa (Jakubczyk *et al.*, 2015). It rows ample in the entire Himalayas at altitudes of 2,100 - and 3,200 m. Also been reported from Rajasthan and Kerala. The stinging nettle grows well in temperate climates having ample sunlight (Joshi *et al.*, 2014).

2.3.4.4 Plant Morphology: *Urtica dioica* L., popularly called, nettle is an erect, perennial, dioecious plant; approximately 2 meters to 6.5 feet in height (Petruzzello, 2022). Diarch roots; stem is quadrangular, green, and contains lacunar collenchyma;12 to 20 fibrovascular bundles (Corsi and Masini, 1997). Leaves dark green; oblong to oval, opposite, base cordate, margin toothed, dark green above and lighter below (Testai *et al.*, 2002). The stinging trichomes on aerial parts contain histamine, acetylcholine, and serotonin-rich fluid (Tuberville *et al.*, 1996; Corsi and Masini, 1997). Flowers are brown to greenish arranged in racemes in the axils of the upper leaves; Flowers; have dioecious separate inflorescences, and flowering begins in May and lasts to September (Corsi and Masini, 1997; Ahmed and Parsuraman, 2014). Fruit small acenes containing tiny dark brown to black seeds.

2.3.4.5 Traditional Ethnomedicinal Uses: Nettle is used as a diuretic, and astringent, for arthritis, anemia, and hay fever. Tea prepared from *U. dioica* leaves has also been utilized as a purifying tonic blood cleanser. The leaves are used externally to address conditions like gout, sciatica, neuralgia, hemorrhoids, hair loss, and skin complaints.

2.3.4.6 Biological activities: The important biological activities of *Urtica dioica* are listed in Table 2.6.

Table 2.6: Important Biological Activities of *Urtica dioica*

Biological Activity	Part Used	Type of extract	Key findings	Reference
Anti-proliferative	Leaves	Dichloromethane extract and aqueous extract 10 ,20 mg/kg/day,	Repression of breast cancer cell line; allograft tumor BALB/c mouse model ↓tumor size and	Mohammadi *et al.*, 2017; Rizk *et al.*, 2017

		respectively for 28 days	weight. ↑apoptosis, ↓proliferation. ↑caspase.	
		Methanolic extract, oxylipins	Significantly decreased the cell proliferation of acute myeloid leukemia; ↓Proliferation ↑ Apoptosis extrinsic pathway ↑ caspase	D'Abrosca, 2019
Anti-endometriosis	Aerial parts	Hexane, ethyl acetate, and methanol extract 100 mg/kg Orally for 4 weeks to Surgery-induced endometriosis rat model	↓implant volumes, ↓adhesion scores ↓TNF-α, ↓VEGF, ↓IL-6;	Ilhan *et al.*, 2019
Anti-inflammatory	Leaves	Hydroalcoholic extract to Wistar rats	400 mg/kg considerably decreased the paw edema by 26%.	Hajhashemi *et al.*, 2013
	Aerial Parts	Carrageenan-induced paw edema in essential oil	100 mg/kg reduced paw edema by 44.08%	Chira *et al.*, 2023
Antidiabetic	Leaves	Hydroalcoholic extract at conc. of 50, 100, and 200 mg/kg/day for 2 weeks to insulin resistance Wistar rats	↓ in serum glucose, low-density lipoprotein, insulin resistance	Ahangarpour *et al.*, 2012
			Significantly reduced the blood glucose concentration.	Golalipour and Khori, 2007
	Leaves	0.1 g/kg/day for 5 days in STZ-diabetic rat	Increased serum insulin, number of beta cells and volume of islet	Gohari *et al.*, 2018

Cardiovascular	Leaves	Leaves extract and isolated flavonoids	Reduction in thrombin-induced platelet aggregation (IC50 was 0.25 ± 0.05 and 0.40 ± 0.04 mg/ml)	El Haouari *et al.*, 2006

2.3.5 *Zanthoxylum armatum* DC.

2.3.5.1 Taxonomic Position

Kingdom: Plantae

Super-division: Spermatophya

Division: Magnoliophyta

Class: Magnoliopsida

Order: Rutales

Family: Rutaceae

Genus: *Zanthoxylum*

Species: *armatum*

2.3.5.2 Vernacular Names

English: Prickly Ash

Nepali: *Timur, Nepali peeper*

Oriya: *Tundopoda*

Bengali: *Gaira, Tambul*

Manipuri: *Mukthrubi*

Hindi: *Tejphal, Nepali dhaniya*

Trade name: *Timru*, *Timur* (Phuyal *et al.*, 2019).

2.3.5.3 Distribution*: Z. armatum* is distributed from subtropical valleys to temperate valleys of the Himalayas. Found in Jammu & Kashmir and north-east India, Pakistan, Thailand, China, Japan, South Korea, North Vietnam, Taiwan, Philippines, and Sumatra (Nair and Nayar, 1997).

2.3.5.4 Plant Morphology: Small aromatic tree up to six meters high. Glabrous branches bear erect reddish-brown stipular spines. Imparipinnate, sessile leaves having entire margins; 3-5 pairs of leaflets. The inflorescence is terminal panicles on short lateral shoots. The male flower has 6-8 stamens and the female flower has 1 to 3 ovoid globose carpels. The fruit is a s drupe, red in colour, ovoid, glandular warted contains 2 shiny black seeds (Nair and Nayar, 1997; Phuyal *et al.*, 2018). The flowering initiates on 05-year-old plants; begins in April-May and fruits in August-October (Kunwar *et al.*, 2013).

2.3.5.5 Traditional Ethnomedicinal Uses

Fruits are given against fever, indigestion, cold, cough, and as a tonic (Anonymous, 1970). The bark and pericarps are utilized in fish poisoning (Joshi, 2004; Kunwar *et al.*, 2009, 2013; Malla *et al.*, 2014). The seeds relieve toothache. The liquid obtained by fermenting seeds cures tuberculosis and alleviates edema (Subedi, 2017) powdered seeds with lukewarm water improve liver functions (Rai and Pokharel, 2006). The dried seeds of *Zanthoxylum armatum* along with leaves of *Artemisia vulgaris* are used for repelling termites and wood-eating insects (Turin, 2003). Fruits are used to relieve toothache, dyspepsia, and stomachache. Seeds are used as condiments and flavoring agents (Anonymous, 1970; Abbasi *et al.*, 2013). The whole plant parts used as a carminative, stomachic, and anthelmintic. Toothbrushes are made from fresh twigs In Nepal, fruit decoctions are recommended against rheumatism, cholera, diabetes, and asthma (Balami, 2004; Malla *et al.*, 2014; Singh *et al.*, 2016). The main biological activities of *Zantoxylum armatum* have been summarized in Table 2.7.

Table 2.7: Important Biological Activities of *Zanthoxylum armatum*

Pharmacological Activity	Plant Part Used	Type of Extract Used	Experimental findings	Reference
Antihyperglycemic	Bark	Aqueous-alcohol extract to STZ-induced diabetic rats	↓fasting blood glucose levels by 43% 400 mg/kg	Karki *et al.*, 2014
	Bark, leaves, and fruits	Methanol extract,	↓ glucose levels, ↑insulin secretion via the K-ATP channel Inibited β-glucosidases; 94% by bark extract, 97%	Alam *et al.*, 2018

			by leaf extract, and 84% by fruit extract.	
	Leaves	Aqueous extract	50 % inhibition for amylase at 7.40 mg/ml and 0.30 mg/ml α-glucosidase	Rynzah *et al.*, 2019
Antioxidant	Leaves	Crude methanol extract, Essential oil and ethyl acetate fraction of the crude extract.	Significant ferric reducing and divalent metal chelating potentials.	Negi *et al.*, 2012
		Essential oil	Good DPPH radical scavenging activity (IC50 = 27 µg/mL) relative to ascorbic acid (IC50 = 15.0 µg/mL)	Guleria *et al.*, 2013
Anti-inflammatory	Stem bark	Ethanol extract	Carrageenan-induced paw edema method in male Wister rats.An inhibition of 19.12%, at 250 mg/kg dose after 4 h of administration. control.	Sati *et al.*, 2011
Anti-spasmodic	Fruit, bark and leaves	Methanol extract	Inhibited butyrylcholinesterase activity by 83% and potentially relaxed precontracted muscles	Alam *et al.*, 2019
		Crude extracts	20% protection from diarrhea at 300 mg/kg and 60% protection at 1000 mg/kg.	Gilani *et al.*, 2010
Anti-viral/anti-protozoal	Leaves	Aqueous extract	Effective against *Giardia lamblia* and *Plasmodium berghei*	Goel *et al.*, 2002

	Fruits	Methanolic extracts	Active against HSV-1 and influenza virus A	Rajbhandari *et al.*, 2009
Hepatoprotective	Leaves Fruit	Methanolic	Regulated liver enzymes, and total bilirubin. Vit. C quantity in serum and non-protein thiols in the liver	Talluri *et al.*, 2019
	Bark	Ethanolic extract	400 mg/kg once daily for seven days decreased liver enzymes as compared to silymarin.	Ranawat *et al.*, 2010

2.4 Quantification of Bioactive Molecules

Phyto-compounds are central in Traditional Medicine; thus, it is crucial to identify, characterize, and standardize these compounds to improve treatment outcomes (Vighnesh *et al.*, 2022). High-Performance Liquid Chromatography (HPTLC) is a popularly used technique nowadays to analyze phytochemicals. HPTLC is preferred as it is sensitive, accurate, and precise. Besides, it offers versatility, cost-effectiveness, high throughput, consumption of less solvent, and maximum optimization. All these aspects render it an advanced analytical technique possessing a quality level at par with High-Performance Liquid Chromatography and Gas Chromatography. Currently, it is extensively employed for analysis of phytochemicals. It provides faster identification and precise quantification of phytochemicals. So, many studies are using it to validate the usage of traditional plants and active principles ameliorating the ailment (Srivastava, 2011). Several analytical techniques with different settings have been put into use for qualitative and quantitative evaluation of phytochemicals (Table 2.8).

Table 2.8: Quantification techniques used in *Ajuga bracteosa, Acacia catechu, Bergenia ciliata, Urtica dioica* and *Zanthoxylum armatum*.

Plant Name	**Plant Part Used**	**Technique**	**Major compound detected/quantified**	**Reference**
Acacia catechu	Bark	UHPLC	Polyphenol viz. Catechin, Rutin,	Kumar *et al.*, 2019

			Quercetin, Kaempferol	
	Bark	HPLC	Epicatechin	Lakshmi and Rajendran, 2012
	Heartwood	HPLC/Photo Diode Array	Gallic acid, Quercetin, 3-rhamnoside, Quercetin 3-glucuronide, Epicatechin, Protocatechuic-acid-4-glucoside	Kumar *et al.*, 2018
	Heartwood	HPTLC	Catechin	Bhardwaj *et al.*, 2020
	Leaves	UHPLC	Ellagic acid, Quercetin, Rutin	
	Leaves	UHPLC	Ellagic acid	Kumar *et al.*, 2017
	Leaves	HPLC coupled with ESI-MS	Catechin, Epicatechin, epicatechin-3-*O*-gallate, and epigallocatechin-3-*O*-gallate	Shen *et al.*, 2006
	Seeds	HPLC/UV detector	Catechin, Quercetin	Thangavelu *et al.*, 2020
Ajuga bracteosa	Aerial Parts	HPTLC	B-sitosterol	Pal, 2014
	Whole Plant	RP HPLC-DAD	Hydroquinone, Pyrocatechol, Catechin, Chlorogenic acid, Caffeic acid, Vanillic acid, *p-coumaric* acid, Ferulic acid, Sinapic acid, Coumarin, Salicylic acid, Trans cinnamic acid, Rutin, Quercetin,	Zahra *et al.*, 2017

			Ellagic acid (17) and Kaempferol	
	Roots	HPTLC	Dehydrocostus lactone	Tesemma *et al.*, 2023
Bergenia ciliata	Rhizome	HPTLC	Bergenin,(+)-Catechin, Gallicin and Gallic acid; and β-Sitosterol	Dharmender *et al.*, 2010
	Leaves	RP-HPLC	Bergenin, Gallic acid, and Arbutin	Boros *et al.*, 2014
	Rhizome	HPLC	Bergenin, Epicatechin, Catechin, and Gallicin	Srivastava *et al.*, 2015
	Rhizome and Leaves	RP-HPLC	Bergenin	Ali *et al.*, 2021
Urtica dioca L.	Leaves	RP-HPLC	Isolectins	Ganzera *et al.*, 2003
	Leaves	HPTLC	Ursolic acid	Shailajan *et al.*, 2014
	Leaves	HPLC	Chlorogenic acid and caffeic acid	Nencu *et al.*, 2015
	Whole Plant	HPLC–DAD	Quercetin and isorhamnetin glycosides	Dar *et al.*, 2013
	Roots	GC-MS	Sterols and tri-terpenes	Obranović *et al.*, 2023
Zantoxylum armatum D.C.	Seeds, Bark, and Leaves	HPLC-ESI–QTOF-MS)	Fargesin, Planispine A Planispine B and Asarinin	Guo and Li, 2016
	Leaves, Bark and Seeds	UHPLC-DAD	Asarinin, sesamin, fargesin and kobusin	Kumar *et al.*, 2014
	Whole Pericarps	HPLC	Three sanshools (hydroxy-α-, hydroxy-β- and hydroxy-γ-sanshool) and Prudomestin (3,5,7-	Zhuo *et al.*, 2021

			Trihydroxy-4′,8-dimethoxyflavone)	
	Fruits	PLC	Gallic acid,ombuin, linoleiyl-O-α-D-xylopyranoside, 3,4,3′,4′,5′,5-hexahydroyxy diphenyl ether, tambulin and artifact prudomestin	Nooreen *et al.*, 2017

CHAPTER 3

MATERIAL AND METHODS

3. Materials and Method

3.1 Study site

The study was conducted in the Kathua district of UT of Jammu & Kashmir. The district has geographic coordinates of 32° 14' and 32° 55' N latitude and 75° 70' and 76° 16' E longitude (Fig. 3.1). Kathua district has a forest cover of 1,158 km^2, and elevation extending from 253 to 4162 m (Sharma *et al.*, 2012; Rao *et al.*, 2015). The geographical expanse of the district is 2,502 km^2, having 257 panchayats. Administratively, the Kathua district is divided into four tehsils (Kathua, Basholi, Hiranagar, and Billawar) and 08 Development blocks (Kathua, Lohia-Malhar, Billawar, Basohli, Barnoti, Bani, Hiranagar, and Duggan). Most of the villages are still cut from active transportation in hilly tracts and a day or two is usually required on foot (Rao *et al.*, 2015).

3.1.1 Climate and Rainfall

The average minimum and maximum annual temperatures range from 9 to 23 °C. The annual rainfall ranges from 912 to 1801 mm (Rao *et al.*, 2015). Different parts of the Kathua district experience a diverse array of climates ranging from sub-tropical blocks viz. Barnoti, Ghagwal, Hiranagar, and Kathua to sub-Alpine and temperate in higher reaches of Bani and Lohai-Malhar blocks whereas Basohli and Billawar have the intermediate type of climate. A temperate to Alpine climate exists in the upper elevations of the district i.e. Bani and Lohai-Malhar blocks. The district's two lowland tehsils, Kathua, and Hiranagar, always have different temperatures than its two hilly tehsils, Basholi and Billawar, because of differences in altitude. Plains temperatures reach as high as 48 °C in the summers and as low as 3°C during the winter. In upper mountainous regions, temperatures reach subzero. The highest regions of the two hilly tehsils receive snowfall for the majority of the year. The district receives precipitation during the monsoon season, winter, and early summer. Hills receive more precipitation than plains. The average annual precipitation in the region is 1,360 mm. About 85 % of the annual precipitation occurs in the monsoon season (July to September) and the rest in winter (December to February).

3.1.2 Physiography

The physiography of the region is highly variable. High mountain ranges, gorges, canyons, and valleys dominate the landscape. Southern and south-western portions are plains; the elevations range from 280 and 500 m. Regions in the north and northeast are hilly and mountainous with

elevations between 500 and 3000 m and inter-mountain valleys known as the Dun belt. The predominant physiographic slope is south and south-westward.

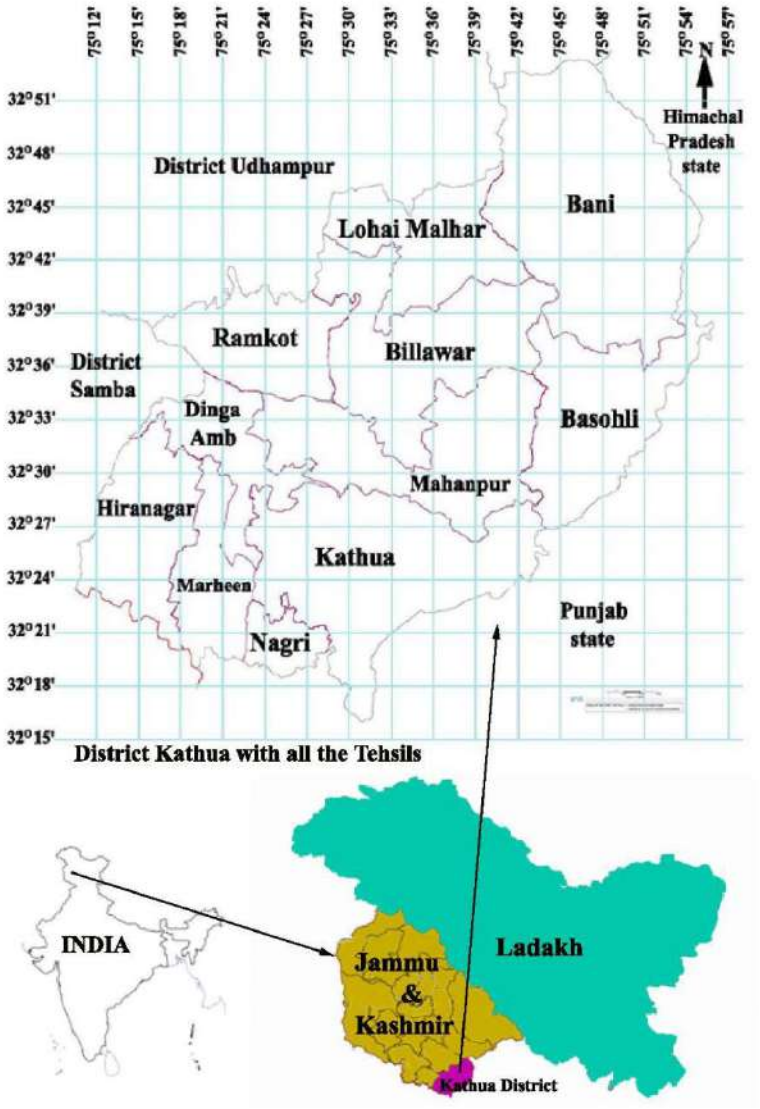


Fig 3.1: Location map of the research site

The Hilly terrain is characterized by steep escarpments and deep valleys. The district is drained by a perennial Ravi River and its tributaries Ujh, Sewa, and Bein. The Ravi River defines the eastern district/state border between Himachal and Punjab State. Additionally, several seasonal streams (*khads*) traverse the entire district.

As per the 2001 population census, the district is inhabited by 5, 50,084 persons with a population density of 207 persons km^{-2}. The men and women population in the district is 2,69,457

and 2,41,998, respectively with a men/women sex ratio of 898. The district has recorded a growth rate of +21.50 % for the population during the years 1991-2001 as compared to 29.98 % at the State level during the same period (NIC, Kathua). As per census 2011, Kathua district has a tribal population of 53307 accounting for 3.57% of the total tribal populace of Jammu & Kashmir.

3.1.3 Types of Forests

Kathua district is one of the districts in India with the highest number of forest types. 22 forest types are found in the study area. The dominant forest type is the Northern Dry Mixed Deciduous Forest covering 25.2% of the total forest area (Ashutosh *et al.*, 2010; Rao *et al.*, 2015). The key tree species of these forests are *Anogeissus latifolia, Bombax ceiba, Acacia catechu, Emblica officinalis, Butea monosperma, Terminalia tomentosa, Acacia modesta* and *Cassia fistula.*The temperate type of forests are located at an altitude of 2100 to 3300 m. The main species of these forests are *Pinus roxburghii, Cedrus deodara, Pinus wallichiana Rhododendron arboreum, Quercus leucotrichophora, Quercus semicarpifolia, Abies pindrow, Picea smithiana*, and *Betula utilis.* The Alpine scrub vegetation starts above 3000 to 3600 m altitude. The region is thus, floristically region is quite diverse encompassing subtropical to temperate and alpine vegetation.

3.2 Methodology for Ethnobotanical Survey

3.2.1 Ethnobotanical Data Collection

Field visits were carried out from April 2019 to November 2022 to collect primary data about various plant species, as an option to conventional medicine, for the management of T2DM. The study area was visited regularly at various locations as tabulated in Table 3.1. To assess traditional knowledge of the antidiabetic plants, field surveys, interviews, and focused group discussions were held with locals, tribal *Gujjars*, and Traditional Health Practitioners (THPs), commonly referred to as *Vaids* or *Hakeems*. Through the use of signs, questions from the community, and herbal market vendors, the THPs were consulted. After a thorough explanation of the study's goals, Pre-Informed Consent (PIC) was acquired from all the participating informants (Plate 1(a-h)).

Plate-1(a-h): Photographs of the scholar interacting with the informants.

Local dialects such as *Dogri*, *Gojri*, and Hindi were used to interview participants. Semi-structured questionnaires were used to conduct interviews. The questionnaire consisted of two parts. The first part comprised questions related to demographic information such as gender, age, level of education, and the experience of informants in the context of disease. The second part contained ten (10) informative questions about (1) the local name of the plant referred, (2) the plant description in general, (3) the preparation method (4) the route of administration, (5) "Organoleptic" attributes such as taste, flavor, and texture, (6) main indications after consuming the plant, (7) number of times of plant medicine to be administered, (8) did the patient feel improvement after using the plant species, (9) basic knowledge about the site of gathering and information about cultivation of the plant species used, (10) whether the patient suggested the plant species to other members of the community. The data was analyzed using a binary assessment - (1) for "yes" indicating knowledge, or (0) for "no" indicating a lack of knowledge. Each instance focuses on a single question, allowing for a mathematical examination of the outcomes.

The predominant causes of T2DM like obesity, sedentary lifestyle, family history, age factor, alcohol, and smoking along with symptoms used for the diagnosis of diabetes like polydipsia, polyphagia, polyuria, fatigue, weakness, and sudden weight loss were also canvassed with the participants. They were asked to rate comparable causes and symptoms on a scale of 1 to 5, with 5 representing the most important element and 1 representing the least reliable attribute.

The acquired data was compared with previously published ethnobotanical and pharmacological studies of anti-diabetic plants reported, from all over the globe through different databases available as PubMed, Science Direct, Google Scholar, and Scopus.

Table 3.1: Details of the villages/areas involved in the ethnobotanical survey

S.No.	Location/Village	Geographical coordinates	Population (As per 2011 census)
1	Budhi	32.4494°N, 75.4490°E	4254
2	Baial	32.43°N, 75.43°E	807
3	Barwal	32.429°N, 75.474°E	3922
4	Sher kotla	32.455°N, 75.504°E	1175
5	Uttri	32.409°N, 75.528°E	1157
6	Jakbhar	32.382°N, 75.456°E	2504
7	Jagatpur	32.376°N, 75.588°E	1494

8	Kathera	32.460°N, 75.529°E	429
9	Bhoond	32.624°N, 75.266°E	1403
10	Thein	32.591°N, 75.405°E	625
11	Mathrachak	32.387°N, 75.474°E	347
12	Forelain	32.434°N, 75.420°E	6462
13	Mahanpur	32.54°N, 75.64°E	1554
14	Mehtabpur	32.418°N, 75.578°E	1334
15	Amala	32.458°N, 75.382°E	1076
16	Taraf Sanji	32.420°N, 75.330°E	354
17	Hiranagar	32.434°N, 75.420°E	304
18	Dhaman	32.709°N, 75.708°E	642
19	Bani	32.707°N, 75.815°E	2093
20	Basholi	32.503°N, 75.810°E	5433
21	Sermuni	32.500°N, 75.816°E	1525
22	Phinter	32.582ºN, 75.543ºE	1811
23	Hutt	32.620°N, 75.894°E	2343
24	Siyara	32.639°N, 75.870°E	521
25	Darun	32.592°N, 75.508°E	2231
26	Derli	32.591°N, 75.431°E	850
27	Karroh	32.393°N, 75.662°E	950
28	Khanpur	32.419°N, 75.444°E	1461
29	Khokhyal	32.367°N, 75.523°E	1759
30	Chack Desa	32.374°N, 75.502°E	2727
31	Plassi	32.522°N, 75.789°E	482
32	Saladi	32.510°N, 75.543°E	474
33	Thanoon	32.439°N, 75.457°E	431
34	Banjal	32.529°N, 75.789°E	643
35	Bhed-bhalod	32.459°N, 75.518°E	1214
36	Tridwan	32.367°N, 75.523°E	1523
37	Chack Prothan	32.394°N, 75.231°E	328
38	Fatehpur-Bani	32.707°N, 75.815°E	2057
39	Parnala	32.559°N, 75.593°E	2269

40	Uchapind	32.631°N, 75.443°E	2507
41	Beral	32.569°N, 75.564°E	1069
42	Dewal	32.594°N, 75.567°E	2042
43	Dhanore	32.394°N, 75.680°E	1374
44	Amwala	32.620°N, 75.303°E	1602
45	Sukrala	32.652°N, 75.588°E	717

3.2.2 Collection of Reported Plant Specimens

During field visits, plant specimens were collected based on information gathered from informants. Each plant specimen was given a voucher number, and its information was recorded in the field notebook. Field data attributes like the site of collection, altitude, time and date, field accession number, color of the flower, fragrance, and other attributes liable to be lost on pressing were recorded for each plant specimen collected. Herbs were gathered as a whole; in the case of shrubs and trees, only young, tender twigs bearing flowers and fruit were collected. They were cut with the aid of secateurs and a pruning knife. The collected plants were immediately pressed in old newspapers and blotters. For the next 24 hours (sweating period), the press was locked. Then it was opened, blotters changed, and wherever necessary, plant parts were rearranged to bring them to the desired position. The process of changing blotters was done every 24-36 hours for 3-4 days to reduce discoloration of foliage and flowers and to avoid rotting.

3.2.3 Preparation of Herbarium

The plant specimens were pasted on herbarium sheets as per the protocol outlined by Forman and Bridson (2004). Polyvinyl alcohol (PVA) glue was used to mount the specimens on the herbarium sheets. Excess adhesive was removed with soft damp blotting paper. The thoroughly blotted specimens were housed in a wooden tray, covered with thick sheets of blotting paper, and pressed with a heavy book to exert pressure. Stems, flowers, and leaves were stitched with white cotton thread; knotted on the back. Stitches at intervals of 8–10 cm were made for woody stems. Printed labels were pasted in the right corner of herbarium sheets. The labels contained all the information about the dried collected specimens as sheet number, collection date, the botanical and local name of the plant species, family name, flower color, fragrance if any, habitat, altitude, name of the collector, and the person who identified the specimen. A solution of mercuric chloride was used

to protect Herbarium specimens against damage from insects. Naphthalene balls were placed to repel the insects from the herbarium sheets.

3.2.4 Plant identification and description

The specimens were authenticated employing standard taxonomic identification keys. Each plant species was designated with a valid botanical name, authority, and family. The updated nomenclature as per the latest version of ICBN (Vienna code, 2006) was assigned to the identified specimen. Local names were assigned to each plant. Local floras of the Jammu division (Sharma and Kachroo, 1981; Swami and Gupta, 1998) along with floras of temperate zones of the erstwhile state of J & K (Singh and Kachroo, 1976, 1994) were reviewed for the identification, description, and nomenclature of the species. The taxonomic databases of the Botanical Survey of India (www.efloraindia.nic.in,www.flowersofindia.net) and www.ipni.org were also consulted. The plant specimens were validated by Dr. R.K. Manhas, Associate Professor in Botany, Govt. Degree College, Kathua, and Mr Nitin Katoch, Curator, Herbarium of the Department of Botany, University of Jammu. Specimens were deposited in the herbarium of the Department of Botany, University of Jammu, JKUT, India.

3.2.5 Quantitative Data Analysis

The data collected using semi-structured questionnaires, interviews, and discussions with the local people, tribals, and traditional healers were recorded as use reports.

3.2.5.1 Use Value (UV)

The data collected from the direct interviews with the local people and traditional healers was analyzed by applying the quantitative method 'Use-value' (Phillips *et al.*, 1994). It evaluates the relative significance of species known to the local community or the informants. The use-value (UV) of each species is therefore based directly on the importance ascribed by the informants and bears no relationship with the opinion of the researcher, where '*U*' is the total number of use-reports cited by each informant for a given species and '*n'* is the total informants.

3.2.5.2 Factor Informant Consensus (F_{ic})

Trotter and Logan's (1986) factor informant consensus (F_{ic}) was used to assess the quantum of knowledge homogeneity and information sharing regarding hypoglycemic plant species among the THPs, tribes, and local ethnic people. The F_{ic} was calculated as:

$$F_{ic} = \frac{n_{ur} - n_t}{n_{ur} - 1}$$

where n_t is the total hypoglycemic plants utilized by each informant category and n_{ur} is the summation of citations for a particular class. F_{ic} values are minimum`; approach zero in case of no information exchange among informants about the utilization of anti-diabetic plants found in the community, and they rise to nearly one upon maximum information exchange (Sharma *et al.*, 2012).

3.2.5.3 Disease Consensus Index (DCI)

It is a comparison based on mathematical attributes evaluating the plant knowledge on remedy and the degree of consensus on how people recommend using a plant to treat specific diseases (Type 2 Diabetes in this case). Questions in the second part of the questionnaire will be used for the calculation of this index using the formula given by Andrade-Cetto *et al.* (2006).

where '*x*' is any species, $DCI = \left(\frac{\sum Vxi}{cc} mVx\right) Pm^{-0.1}$ '*Vxi*' is the summation of individual values recorded for one plant species within the community and assesses the knowledge of and the number of mentions for a plant, '*mVx*' is the statistical mean of the individual values for one plant and assesses the knowledge of that plant, and '*Cc*' is the correlation coefficient, and is the maximum number of informants whom can refer to a plant and evaluates the number of mentions of that plant. '*Cc*' is also the number of interviewed informants. $Pm^{-0.1}$ is the compensation factor, and analyses the dispersion for one plant, considering the mode of administration, preparation, and parts used. With the DCI, we can evaluate the knowledge about one plant, the plant knowledge as a remedy (for the specific disease), and how much the people appreciate the plant and its remedy (Andrade–Cetto *et al.*, 2006; Cruz and Andrade–Cetto, 2015).

Ethnobotanical questions specifically asked to calculate the index were: (1) plant name, (2) plant general description, (3) where they acquired the plant, (4) availability of the plant (rare/abundant), (5) plant part used, (6) preparation method, (7) form of consumption, (8) duration of plant use, (9) who recommended the plant, (10) relief symptoms after plant use, (11) whether they found the plant useful, (12) whether they recommend the use of the plant to others, (13) whether they know

if the plant can cause any damage, and (14) whether they knew another use for the plant (modified from Cruz and Andrade–Cetto, 2015).

3.2.5.4 Informant Preference Ranking

It was determined following Martin (1995), to analyze the top five important plants used to manage hyperglycemia in the study site. Informants who were experienced were asked to name the best-preferred plants for the control of high blood sugar. The informants were asked to order the reported anti-diabetic plants based on their potency by giving the highest value (10) to the most preferred; the lowest value (1) for the least preferred plant and the value in between for the rest of the plants. Then, the results were summed for all respondents and ranked based on the overall scores received for each medicinal plant (Goonfa et al., 2020).

3.2.5.5 Statistical analysis

ANOVA was used to analyze the informants' characteristics in terms of their age, education, and knowledge of anti-diabetic plants. Data normalization was done via log transformation. The Fisher's Least Significant Difference (LSD) multiple range test was performed to compare the mean values of age, education level, and anti-diabetic plants known for men and Women informants, where the value of the ANOVA was significant at $P < 0.05$. The analysis was carried out Microsoft Excel software.

3.2.6 Chemical analysis of most preferred Plants for validation of their Traditional Use

3.2.6.1 Collection of plant material

Plant parts used viz. bark of *Acacia catechu* (ACB), leaves of *Ajuga bracteosa (ABL)*, rhizomes of *Bergenia ciliata* (BCR), leaves of *Utrica dioca* (UDL) and seeds of *Zanthoxylum armatum* (ZAS). The collection sites with altitudes, coordinates, and accession numbers are presented in Table 3.2.

Table 3.2: Collection spots of plants for analysis of anti-diabetic potential from different sites of Kathua District, UT of Jammu & Kashmir, India

Plant name	Part used	Accession number	Site of collection
Acacia catechu (L.f.) Willd	Bark	HBJU-16704	Kathua, 32.3863 ºN, 75.5173 ºE
Ajuga bracteosa Wall. ex Benth.	Leaves	HBJU-16717	Phinter, 32.5829 ºN, 75.5430 ºE
Bergenia ciliata (Haw.) Sternb.	Rhizome	HBJU-16738	Bani, 32.7079 ºN, 75.8156 ºE
Urtica dioca L.	Leaves	HBJU-16742	Machheddi, 32.7008 ºN, 75.5990 ºE
Zanthoxylum armatum D.C.	Seed	HBJU-16737	Billawar, 32.6136 ºN, 75.6041ºE

3.2.6.2 Sample Preparation

All the plant parts to be used were thoroughly washed to remove any soil and contaminants. Then, they were subjected to shade drying for a few days. Each plant material was air-dried in the shade, finely powdered, and passed through 120 mesh size; subjected to maceration for 48 h in ethanol (Plate 2(a-e)). The said process was carried out for 03 consecutive days; the resultant filtrate was concentrated in a vacuum in the rotary evaporator below 45 °C. 50 g of Crude ethanolic extracts were fractionated by dissolving into distilled water followed by partitioning thrice with hexane, dichloromethane, and ethyl acetate in a row to yield respective solvent-solvent fractions (Bhatia *et al.*, 2019).

3.2.6.3 Phytochemical Analysis

3.2.6.3.1 Total Phenolic Content (TPC)

200 µL of the sample (100mg/mL) plant extracts followed by the addition of 100 µL of Folin-Coicalteu reagent (1: 10; v/v) in a test tube, and initial absorbance was taken (Ainsworth *et al.*, 2007). Then, 800 µL of 1 M Sodium carbonate (Na_2CO_3) solution was added to the above mixture

making a final volume of 2 mL and incubated for 25 minutes. Absorbance was measured at 765 nm by using Lab man 1100 Spectrophotometer. TPC was calculated via a calibration curve with gallic acid, and the results were expressed as milligrams of gallic acid equivalent per gram of dry weight of the extract (mg GAE/g) (Aryal *et al.*, 2021).

3.2.6.3.2 Total Flavonoid Content (TFC)

TFC was determined by the Aluminium chloride ($AlCl_3$) method, which depends on the formation of a complex between Aluminium chloride $AlCl_3$ and flavonoids in the sample. The complex shows maximum absorbance at 415 nm. Precisely, 200 µL of each sample extract (100mg/mL) was mixed with 100 µL ethanol and 50 µL 10% Aluminium chloride ($AlCl_3$) separately followed by the addition of 50 µL of 1 M potassium acetate and 110 µL of distilled water were added to each well. The reaction mixture was made to stand for aboutt 25 minutes (Ahmed *et al.*, 2015). The TFC was determined through a calibration curve with quercetin OD measured at 415nm and results were obtained as milligrams of quercetin equivalents per gram dry weight of extract (mg QE/g).

3.2.6.3.3 Free Radical Scavenging Activity; DPHH (2,2-diphenyl-1-picrylhydrazyl) Assay

The free radical scavenging activity of the plants was assessed using DPPH (2,2-diphenyl-1-picrylhydrazyl) Assay. The reaction was carried out in 02 ml volume; was mixed with 200 µL plant sample extract was mixed with 800 µl 0.1 M Tris HCl buffer (pH7.4). Then, 01 ml of 100 µL DPPH(2,2-diphenyl-1-picrylhydrazyl) (0.1 mM) was added to make a final volume of 02 ml. The mixture was incubated in the dark for 25 minutes and absorbance was recorded at 517 nm (Brand-Williams *et al.*, 1995). The percent scavenging was calculated using the formula: Ascorbic acid was utilized as a reference compound.

$$\% \text{ scavenging} = \frac{\text{Control OD} - \text{Sample OD} \times 100}{\text{Control OD}}$$

Plate 2(a-e): (a) Shade-dried powdered samples of *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata* rhizome, *Urtica dioca*, and *Zanthoxylum armatum* fruits, (b-e) extraction with different solvents

3.2.6.3.4 Alpha -Amylase inhibition assay

The α-Amylase (500 U/ml) was premixed with plant sample extracts at varying concentrations of 100-500 µg/ml. Starch azure (0.5% starch solution) was added as a substrate in the reaction mixture to initiate the reaction. The reaction was done at 37°C for 5 min and was terminated by adding 02 ml of DNSA (3,5-dinitrosalicylic acid) (Kim *et al.,* 2011) The reaction mixture was then subjected to heat at 100°C for 15 min and diluted with 10 ml of distilled water in an ice bath. α-amylase activity was determined by measuring at 540 nm using a spectrophotometer (LABMAN 1900). A control reaction was carried out without the test sample. The results were taken in triplicate. The % α-amylase inhibitory activity is calculated by the following formula;

% enzyme inhibition = Ac – At / Ac × 100,

where Ac is the absorbance of enzyme-substrate reaction with 30% DMSO (dimethyl sulfoxide) and At is the absorbance of enzyme-substrate with plant sample extract. The reaction was carried out in triplicate. The inhibition data was processed using GraphPad Prism 09 software.

3.2.6.3.5 Alpha-Glucosidase Inhibition Assay

80 µL of the α-glucosidase enzyme (500 U/mL) was prepared in 50 mM phosphate saline buffer (pH 6.8). It was mixed with 100-500 µg/ml of plant sample extracts prepared in 30% Dimethyl sulfoxide (DMSO). The initial absorbance was recorded at 410 nm. Then, the reaction mixture was pre-incubated at 37°C for 15 minutes. Then,100 µL of 1.4 mM substrate p-nitrophenyl glucopyranoside (pNPG) was added and the mixture was incubated at 37°C for 25 minutes. Absorbance was measured at 410 nm using a spectrophotometer (LABMAN 1900). Acarbose was used as the reference compound (Bhatia *et al.*, 2019). The percentage inhibition of α-glucosidase by plant extract was calculated by using the following formula:

% enzyme inhibition = Ac – At / Ac × 100,

where Ac is the absorbance of enzyme-substrate reaction with 30% DMSO and At is the absorbance of enzyme-substrate with plant sample extract. The reaction was carried out in triplicate. The inhibition data was processed using GraphPad Prism 09 software.

3.2.7 High-Performance Thin Layer Chromatography (*HPTLC)*

3.2.7.1 Chemicals and reference compounds

All reference compounds viz. gallic acid and quercetin (97% pure) were procured from Sigma Aldrich (USA). All reference compounds were stored at -20 °C. All solvents used in our experimentation were of HPTLC grade that was purchased from S.D. Fine Chemicals, Mumbai, India.

3.2.7.2 High-Performance Thin Layer Chromatography (HPTLC) Instrumentation

HPTLC instrument consisted of Linomat-5 applicator CAMAG (Muttenz, Switzerland) fitted with Linomat-5 automatic sample applicator and CAMAG TLC scanner-3 ("Scanner_180710" S/N 180710 (2.01.02)) run by WinCATS software (version: 1.4.6.2002). The stationary phase consisted of pre-coated silica gel 60 F254 TLC plates (20 × 10 cm, E. Merck, Darmstadt, Germany). Each sample was placed at the plates as bands 6 mm wide, with 13 mm distance between tracks, via a Linomat-5 automatic sample applicator fitted with a 100µl Hamilton syringe. The dosage speed from the Hamilton syringe was 150 nL/s. Conditions desired for densitometric scanning were fixed at 4.00 x 0.30 mm slit dimension with a scanning speed of 20 mm/s and data resolution of 100 µm/step. The HPTLC was performed at 24 ±2 °C temperature with 45% relative humidity in CAMAG twin trough glass chamber (20 cm x 10cm) saturated before for 20 minutes with mobile phase vapor.

3.2.7.3 Simultaneous quantification of gallic acid and quercetin

5 µL of plant samples and reference compounds were applied on an HPTLC plate and were developed in mobile phase-toluene: ethyl acetate: formic acid (13.5:9:0.6 v/v/v). After development up to 75 mm, plates were dried with a hot air dryer, and clear bands were visualized under UV (UV cabinet with dual wavelength UV lamp. Immediately plates were scanned at 254 nm reflectance wavelength.

3.2.8 Liquid Chromatography (Electron spray Ionization Quadropole Time of Flight Mass Spectrometry (LC-ESIQTOF-MS)

The LC-MS analysis of aqueous fraction was performed using a Waters Mass Q-TOF Mass Spectrometer with a diode array detector. Source and scan parameter settings used were gas temp: 30°C, gas flow: 10/min, nebulizer: 50 psi, VCap: 3000. The solvent elution consists of mobile phase A: Acetate buffer and Mobile Phase B: Acetonitrile.0.5 mM acetate buffer, and water at the flow rate of1.5 mL/min. The elution gradient was initiated from 5% acetonitrile for 0.1 min to 30% acetonitrile for 10 min, 80% acetonitrile for 20 minutes, and back to its initial conditions. During

the entire process, the column temperature was kept at 30°C. After passing through the flow cell of the diode array detector, the column elute was directed TOQ-TOF MS. The mass spectrum analysis was performed using positive electron spray ionization (ESI-positive mode) in the mass range of 400-2000 Daltons at a scan rate of 1 (Plate 3(a-f).

3.2.8.1 Data Analysis

Raw data files obtained from the LC-HRMS were processed using MZmine 2 and Mestre Nova 12.0 software. For annotation of molecules segregated, chromatograms were compared with published literature, and structures were drawn using PubChem, and ChemDraw databases.

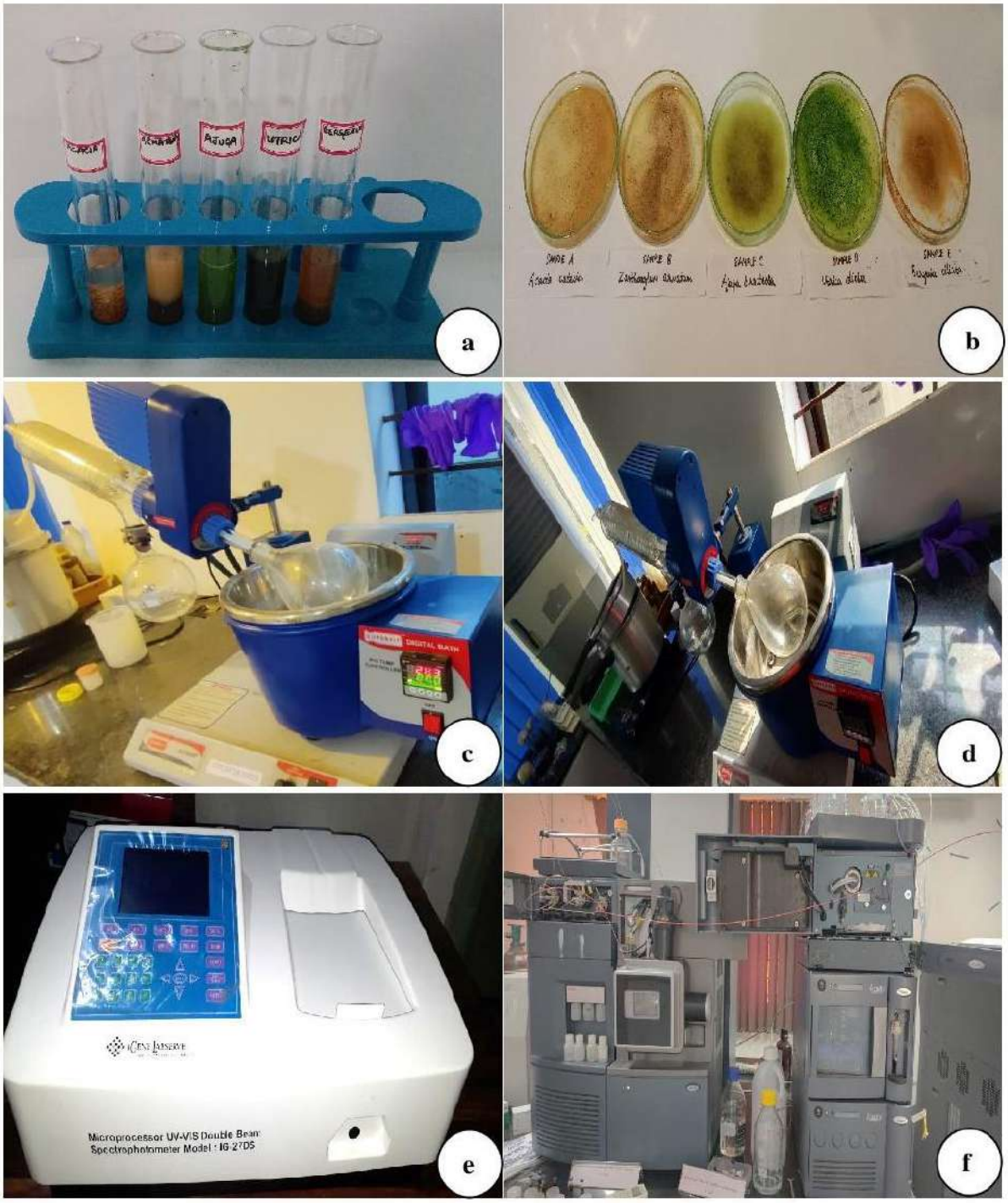


Plate 3(a-f): (a) Liquid-liquid Extraction of sample A- *Acacia catechu*, B- *Zanthoxylum armatum*, C- *Ajuga bracteosa*, D- *Utrica dioica*, and E- *Bergenia ciliata*, (b) extracts of sample A- *Acacia catechu*, B- *Zanthoxylum armatum*, C- *Ajuga bracteosa*, D- *Utrica dioica*, and E- *Bergenia ciliata* (c-d) Rotary evaporator (e) Spectrophotometer, and (f) Waters Mass Q-TQF Mass spectrometer

CHAPTER 4

RESULTS AND DISCUSSION

4. Results and Discussion

4.1 Results

4.1.1 Informants

310 informants participated in the present study. The informants comprised Traditional Health Practitioners (THPs) (15 men; 01 Women), 93 tribals (74 men; 19 Women), and 201 locals from the ethnic *Dogra* community (88 Women and 113 men) were interviewed (Table 4.1).

ANOVA of the age of participants didn't vary significantly (ns); there was significant variation (*P<0.001*) in education level and anti-diabetic plants reported among the three informant groups (THPs, *Gujjar* tribe, and locals). The age of participants in the study ranged between 23 and 88 years. The mean age lay between 53 to 75 years.

Of all the Women THPs, 94.7% of female and 67.6% of male tribal participants, and 36.4% of female and 17.7% of male local *Dogra*s have no formal education background. They have never gone to any educational institutions. The values showed significant differences (*F-value* = 18.68; *P < 0.001*) for the male and female participants, with greater literacy prevalent among males. There were considerable differences in the mean number of anti-hyperglycaemic species reported by the three groups of informants (*F-value* = 27.6; *P <0.001*). THPs recorded a notably higher number of antidiabetic plants among the three informant groups than the tribal and local *Dogra* participants. Women THPs recorded more hyperglycemic plants than their male counterparts. In the context of tribal and local informants. There was an insignificant difference between genders so far as locals and tribals were concerned. The mean number of citations of anti-diabetic plants was significantly (*F-value* = 68.4; *P < 0.001*) higher for THPs (9.1 ± 3.4) than tribe (4.2 ± 1.6), and local (3.6 ± 1.7%) informants.

Table 4.1: Demographic characteristics of informants

Attributes	Informants		ANOVA	
	Women	Men	*F- value*	*P-value*
Age^{ns}				
THPs	75.0 ± 0.0	55.3 ± 2.0	1.94	0.087^{ns}
Gujjar tribe	53.0 ± 2.4	53.0 ± 1.6		
Locals	55.6 ± 1.2	57.5 ± 1.1		

Educational Qualification* **				
Never attended a school				
THPs	1	-	18.68	< 0.001
Gujjar tribe	18	50		
Locals	32	20		
1-7 class				
THPs	-	2		
Gujjar tribe	1	6		
Locals	14	13		
1-8 class				
THPs	-	9		
Gujjar tribe	-	16		
Locals	34	71		
>12 class				
THPs	-	4		
Gujjar tribe	-	2		
Locals	8	9		
Anti-diabetic plants known* **				
THPs	$13.0^{a,a} \pm 0.0$	$8.9^{a,b} \pm 0.8$	27.6	< 0.001
Gujjar tribe	$4.1^{b,a} \pm 0.3$	$4.3^{b,a} \pm 0.2$		
Locals	$3.8^{c,a} \pm 0.2$	$3.7^{c,a} \pm 0.2$		

Values concerning the age of the informants and hypoglycemic plants are mean ± standard error, concerning education, values given in the table are the number of informants. ANOVA was performed to find the significant variation in age, education level, and knowledge of anti-diabetic plants between the men and women informants. Tuckey's LSD was performed when the ANOVA between the type and gender of informants was found significant at $P < 0.05$.

4.1.2 Characteristics of anti-diabetic plants

The present ethnopharmacological survey in Kathua led to the documentation of 63 species spanning 34 families and 58 genera as reported by the informants (Table 4.2; Plates 4-14)).

Table 4.2: Taxonomic attributes, habit, plant part used, mode/method of administration, and use-values of the hypoglycemic plants used in Kathua

Plant Name	Family	Accession no.	Vernacular name	Habit	Plant-part used	Method of administration (use-reports)	UV
Abelmoschus esculentus (L.) Moench.	Malvaceae	HBJU-16721	*Bhindi*	Shrub	Fruits	Cut Fruits are dipped in water for a few hours and then eaten empty stomach (9)	0.03
Acacia catechu (L. f.) Willd.	Fabaceae	HBJU-16704	*Khair*	Tree	Bark	Bark & heartwood is boiled in ample amount of water; reduced decoction consumed empty stomach (56)	0.18
Acacia nilotica(L.) Willd. ex Delile.	Fabaceae	HBJU-16705	*Kikar*	Tree	leaves, stem, flowers, seeds, gum	The Flower, seeds, gum, leaves, and bark are shade dried, coarsely powdered, and dried tubers of *Ipomoea batatas* are added in equal amounts, 10 grams consumed preferably with cow milk two times a day (2)	0.01
Aconitum heterophyllum Wall.	Ranunculaceae	HBJU-16730	*Patrees*	Herb	Roots	Decoction of tubers (18)	0.06
Aegle marmelos (L.) Corrêa	Rutaceae	HBJU-16734	*Bel*	Tree	wood, fruits	Decoction of Heartwood is consumed twice, glasses made of its heartwood are used, people store water overnight, and then consume it empty stomach (54)	0.17
Ajuga bracteosa Wall. ex Benth.	Lamiaceae	HBJU-16717	*Neelkanthi*	Herb	Leaves	Decoction of leaves (36)	0.12

Allium cepa L.	Liliaceae	HBJU-16713	*Payaz*	Herb	leaves, bulb	Fresh leaves are cooked and eaten as vegetables (1), and fresh juice of bulb is consumed (5)	0.02
Allium sativum L.	Liliaceae	HBJU-16714	*Thom*	Herb	Bulb	Fresh Bulb juice (4) and bulb eaten raw empty stomach (2-6 flakes) (16)	0.06
Aloe vera (L.) Burm. f.	Liliaceae	HBJU-16712	*Ghritkumai, aloe*	Shrub	Leaves	Leaves are cut and gel is consumed (5), About 10 ml of juice/pulp is mixed with 10 grams of crushed black pepper (19)	0.07
Amaranthus viridis L.	Amaranthaceae	HBJU-16684	*Chaleri*	Herb	Leaves	Fresh leaves are boiled/cooked and incorporated as vegetables in the diet (4)	0.01
Anethum graveolans L.	Apiaceae	HBJU-16689	*Kale sow*	Herb	Seeds	Seeds are boiled and decoction (about 250 ml)is taken twice a day (13)	0.04
Anona squamosa L.	Magnoliaceae	HBJU-16715	*Seetaphal*	Tree	Leaves	Empty stomach Fresh Leaves are eaten (9)	0.03
Artemisia scoparia Waldst. & Kit.	Asteraceae	HBJU-16692	*Jhau*	Herb	Leaves	Dried leaves are powdered &consumed with lukewarm water (7)	0.02
Azadirachta indica A. Juss.	Meliaceaae	HBJU-16720	*Neem*	Tree	Leaves	Leaf juice is taken; leaves are eaten raw (35)	0.11
Berberis lyceum Royle	Berberidaceae	HBJU-16694	*Kaimlu, daruhridra*	Shrub	Roots	Roots are soaked overnight and boiled; decoction is consumed alone (66) or with powdered seeds of *Zanthoxylum armatum* (17)	0.24

Bergenia ciliata (Haw.) Sternb.	Saxifragaceae	HBJU-16738	*Zakhme-hyat,*	Herb	Roots	Dried rhizome extract is consumed (25)	0.08
Bryophyllum pinnatum (Lam.) Oken	Crassulaceae	HBJU-16695	*Patharkut*	Herb	Leaves	Fresh leaves consumed directly empty stomach (3)	0.01
Cajanus cajan (L.) Huth	Fabaceae	HBJU-16707	*Chane*	Herb	Seeds	Powdered seeds are premixed to flour to lower the glycemic index of Rotis (26)	0.08
Calotropis procera (Aiton) W. T. Aiton.	Ascelpideaceae	HBJU-16745	*Desi ak*	Shrub	Leaves	Leaves are placed beneath feet sole (6)	0.02
Cassia absus L.	Fabaceae	HBJU-16706	*Chaskoo*	Herb	Seeds	Powdered seeds (25 grams) consumed with lukewarm milk (8)	0.03
Catharanthus roseus (L.) G. Don	Apocyanaceae	HBJU-16685	*Sadabhahar*	Herb	Leaves	Fresh leaves (2-4) are directly eaten empty stomach (32)	0.10
Chenopodium album L.	Chenopodiaceae	HBJU-16745	*Bathua*	Herb	Leaves,	Leaves are cooked by boiling and consumed as such (20)	0.06
Cinnamomum tamala (Buch. -Ham.) T. Nees & C. H. Eberm.	Lauraceae	HBJU-16710	*Tejpatta*	Tree	Leaves	Dried powdered leaves are mixed with dried leaves of *Murraya koengii* and *Aegle marmelos* (12)	0.04
Cinnamomum zeylanicum Garcin ex Bl.	Lauraceae	HBJU-16711	*Dalchini*	Tree	Bark	Powdered bark about one teaspoon full is boiled and consumed (12)	0.04
Coccinia indica Wight & Arn.	Cucurbitaceae	HBJU-16699	*Kanuri*	Vine	Fruits	Raw green fruits eaten directly (2) or cooked (10)	0.04

Curcuma longa L.	Zingiberaceae	HBJU-16743	*Haldi*	Herb	Rhizome	Dried powdered rhizome consumed with cow milk (12) and also a constituent of polyherbal formulations (6)	0.05
Datura innoxia Mill.	Solanaceae	HBJU-16740	*Akdatuara*	Shrub	Leaves	Fresh tender leaves are massaged on feet; relieve neuropathic pain (3)	0.01
Emblica officinalis Gaertn.	Euphorbiaceae	HBJU-16702	*Amla*	Tree	Fruits	Powdered dried Fruits with water, raw fruits are eaten (6), pickled (4), cooked as curry (8), and part of *Triphla* (26)	0.11
Gymnema sylvestre (Retz.) Schult.	Apocyanaceae	HBJU-16686	*Gudmar*	Vine	Leaves	Decoction of leaves is consumed (9), dried leaves mixed with *amla, harad,* and *Beda* (2)	0.03
Gynura procumbens (Lour.) Merr.	Asteraceae	HBJU-16693	*Sugar plant*	Shrub	Leaves	Fresh Leaves are chewed directly (15)	0.05
Holarrhena pubescens (L.) Wall.	Apocyanaceae	HBJU-16687	*Inderjau*	Tree	Seeds	Powdered seeds are mixed with seed powder of *Cajanus cajan* and *Hordeum vulgare* in the same amount; mixed with water and consumed before meals (22)	0.07
Hordeum vulgare (L.)	Poaceae	HBJU-16729	*Jau*	Herb	Grains	Seeds are powdered and used as flour (13)	0.04
Isodon rugosus (Wall.) Codd	Lamiaceae	HBJU-16719	*Kothal*	Herb	Leaves	Leaf decoction is taken (10)	0.03

Mangifera indica L.	Anacardiaceae	HBJU-16688	*Aam, amb*	Tree	Old leaves	Older leaves are dried in the shade, coarsely powdered, sieved, and 10 grams taken with water(5)	0.02
Mimosa pudica L.	Fabaceae	HBJU-16708	*Chui-mui*	Herb	Leaves	Fresh leaves are boiled and infusion is consumed (3)	0.01
Momordica charantia L.	Cucurbitaceae	HBJU-16700	*Karela*	Vine	Fruits, leaves	Used as a vegetable; Fresh juice of fruits (48) and leaves is taken empty stomach (12)	0.18
Moringa oleifera Lam.	Morangaceae	HBJU-16722	*Sanjwan*	Tree	Leaves	Leaves are shade-dried, powdered& consumed empty stomach with water (3)	0.01
Murraya koenigii (L.) Spreng.	Rutaceae	HBJU-16735	*Kadi patta*	Shrub	Leaves	Leaves are eaten empty stomach (29)	0.09
Nigella sativa L.	Ranunculaceae	HBJU-16731	*Kali jiri, kalonji*	Herb	Seeds	Seed oil is mixed in tea (1), oil is prepared by addition of castor oil & methi seeds (4)	0.02
Ocimum sanctum L.	Lamiaceae	HBJU-16718	*Tulsi*	Herb	leaves, seeds	Seeds are dried and consumed as decoction (11)	0.04
Pennisetum glaucum R. Br.	Poaceae	HBJU-16728	*Bajra*	Herb	Grains	Used as a wheat substitute for carb source (26)	0.08
Phyllanthus niruri L.	Euphorbiaceae	HBJU-16701	*Bhui amla*	Herb	leaves,	Leaves are eaten directly (5)	0.02
Picrorhiza kurroa Royle	Plantaginaceae	HBJU-16726	*Kutki*	Herb	Roots	Powdered tubers are boiled and decoction used (23)	0.07

Pilea scripta (Buch. - Ham. ex D. Don) Wedd.	Urticaceae	HBJU-16741	*Na*	Shrub	Leaves	Leaves are boiled and consumed (9)	0.03
Psidium guajava L.	Myrtaceae	HBJU-16725	*Amrood*	Tree	leaves, fruits neutraceutical	Leaves and fruits are consumed (13)	0.04
Punica granatum L.	Lythraceae	HBJU-16716	*Druni*	Tree	Leaves	Dried powdered seeds and leaves are consumed with water empty stomach (9)	0.03
Pyrus pashia Buch. - Ham. ex D. Don	Rosaceae	HBJU-16732	*Batungi, mahal molranum*	Tree	fruits, leaves	Fruits are eaten (8), the decoction of leaves as tea (4)	0.04
Saussurea lappa (Decne.) C. B. Clarke	Asteraceae	HBJU-16691	*Kuth*	Herb	Rhizome	Dried rhizome infusion consumed empty stomach with lukewarm water (12)	0.04
Skimmia anquetilia N. P. Taylor & Airy Shaw	Rutaceae	HBJU-16736	*Shidi - gili*	Shrub	Leaves	Fresh leaves are eaten (1)	0.003
Sorghum bicolor (L.) Moench	Poaceae	HBJU-16727	*Charri*	Herb	Grains	Preferred as a carbohydrate source over wheat (12)	0.04
Swertia chirayita (Roxb.) H. Karst.	Gentianaceae	HBJU-16703	*Kariraita, chairaita*	Herb	Roots	Root decoction (32)	0.10
Syzygium cumini (L.) Skeels.	Myrtaceae	HBJU-16724	*Jamum*	Tree	Seeds, fruits	Seeds are dried in the shade, finely powdered, and consumed with water (67)	0.22

Terminalia arjuna (Roxb. ex-DC.) Wight & Arn.	Combretaceae	HBJU-16696	*Arjun*	Tree	Bark	The bark is boiled and the decoction is used as tea empty stomach(23)	0.07
Terminalia bellirica (Gaertn.) Roxb.	Combretaceae	HBJU-16697	*Bheda*	Tree	Fruits	Fruits are used as pickles (2), and to make curries (3), dried fruits are added to *Triphla* (3)	0.02
Terminalia chebula Retz.	Combretaceae	HBJU-16698	*Harad*	Tree	hardwood, fruit	Shade dried fruits pickled (5); powdered and added in *Triphla* (9),	0.04
Tinospora cordifolia (Willd.) Hook. f. & Thomson	Menispermaceae	HBJU-16723	*Guduchi, giloy*	Vine	stem	The bark is stripped off, and shade-dried; 01 kg of stems are coarsely crushed and dipped in 4 lts of water, and the resultant filtrate is taken out and shade-dried for 7-8 hours. The off-white left precipitate is gathered and taken with water empty stomach (51)	0.16
Trachyspermum ammi Sprague.	Apiaceae	HBJU-16690	*Ajwain*	Herb	Seeds	100 grams of powdered seeds are mixed with 03 types of salt i.e. sea, rock, and black salt, *Amla*, *Anardana*, *T. chebula*, and *T. bellirica* (shade dried), filtered 6-7 times, and the extract is taken (5).	0.02
Tribulus terrestris L.	Zygophyllaceae	HBJU-16744	*Gokhru*	Herb	Seeds	Seed Powder consumed with lukewarm cow milk (7)	0.02
Trigonella-foenum-graceum L.	Fabaceae	HBJU-16709	*Methi*	Herb	seeds, leaves	Seeds soaked overnight; water and seeds together consumed empty stomach (52), fresh leaves cooked and eaten (11)	0.18

Urtica dioica L.	Urticaceae	HBJU-16742	*Bichhu buti*	Herb	Leaves	Leaves cooked as vegetables (27)	0.09
Withania somnifera (L.) Dunal	Solanaceae	HBJU-16739	*Ashwagandha*	Herb	seeds, roots	Shade-dried seed powder is taken with water (20), also with seeds of *Ocimum sanctum* (2)	0.07
Zanthoxylum armatum DC.	Rutaceae	HBJU-16737	*Timbre*	Tree	Seeds	Powdered Seeds mixed with powdered berberis roots are consumed once in the morning with water (51)	0.16
Zizyphus jejuba Mill.	Rhamnaceae	HBJU-16733	*Ber*	Small tree	leaves, seeds, fruits	Ripened fruits are consumed; Leaf decoction is also used (6)	0.02

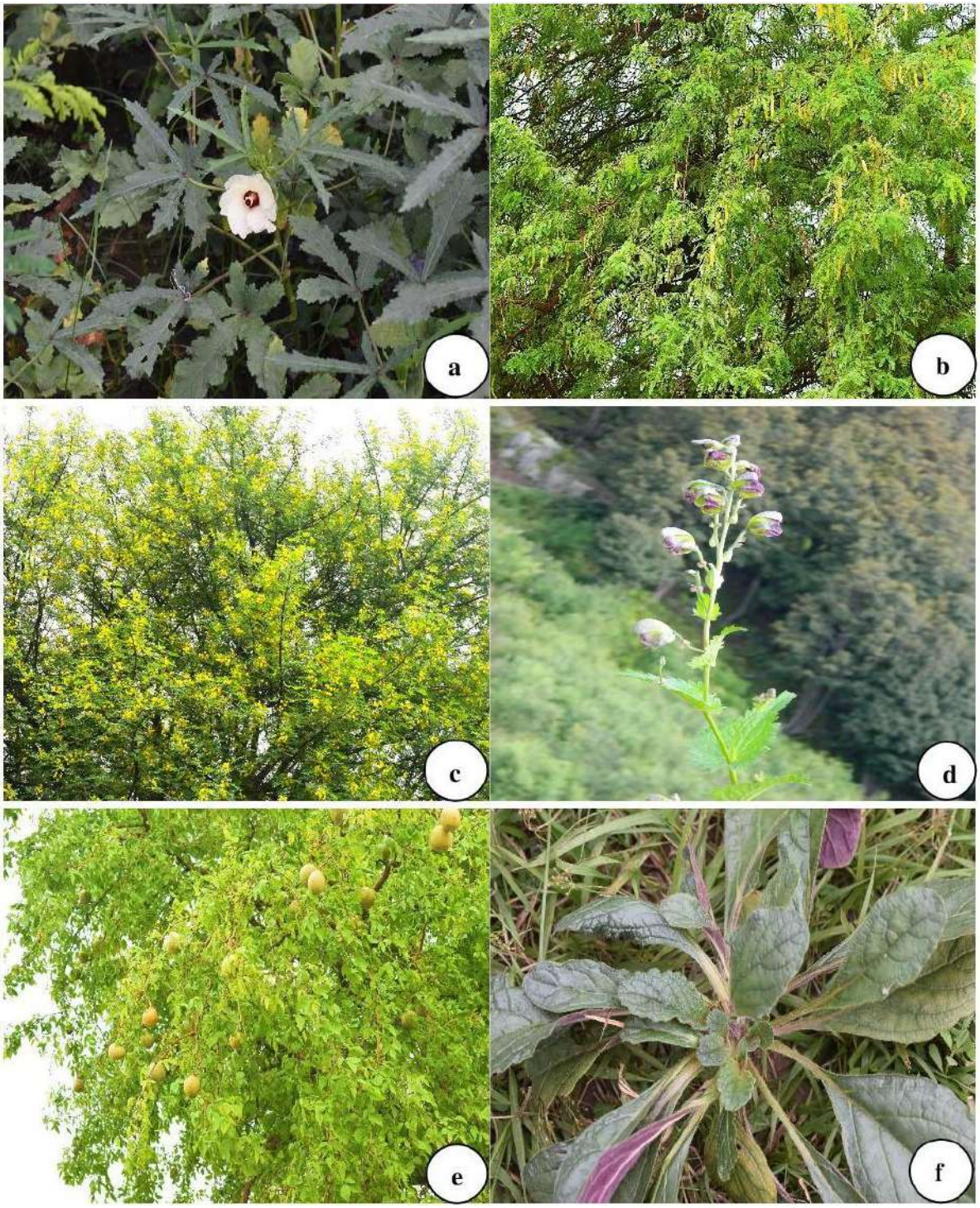


Plate 4(a-f): (a) *Abelmoschus esculentus* (L.) Moench., (b) *Acacia catechu* (L. f.) Willd., (c) *Acacia nilotica* (L.) Willd. ex Delile., (d) *Aconitum heterophyllum* Wall., (e) *Aegle marmelos* (L.) Corrêa, and (f) *Ajuga bracteosa* Wall. ex Benth.

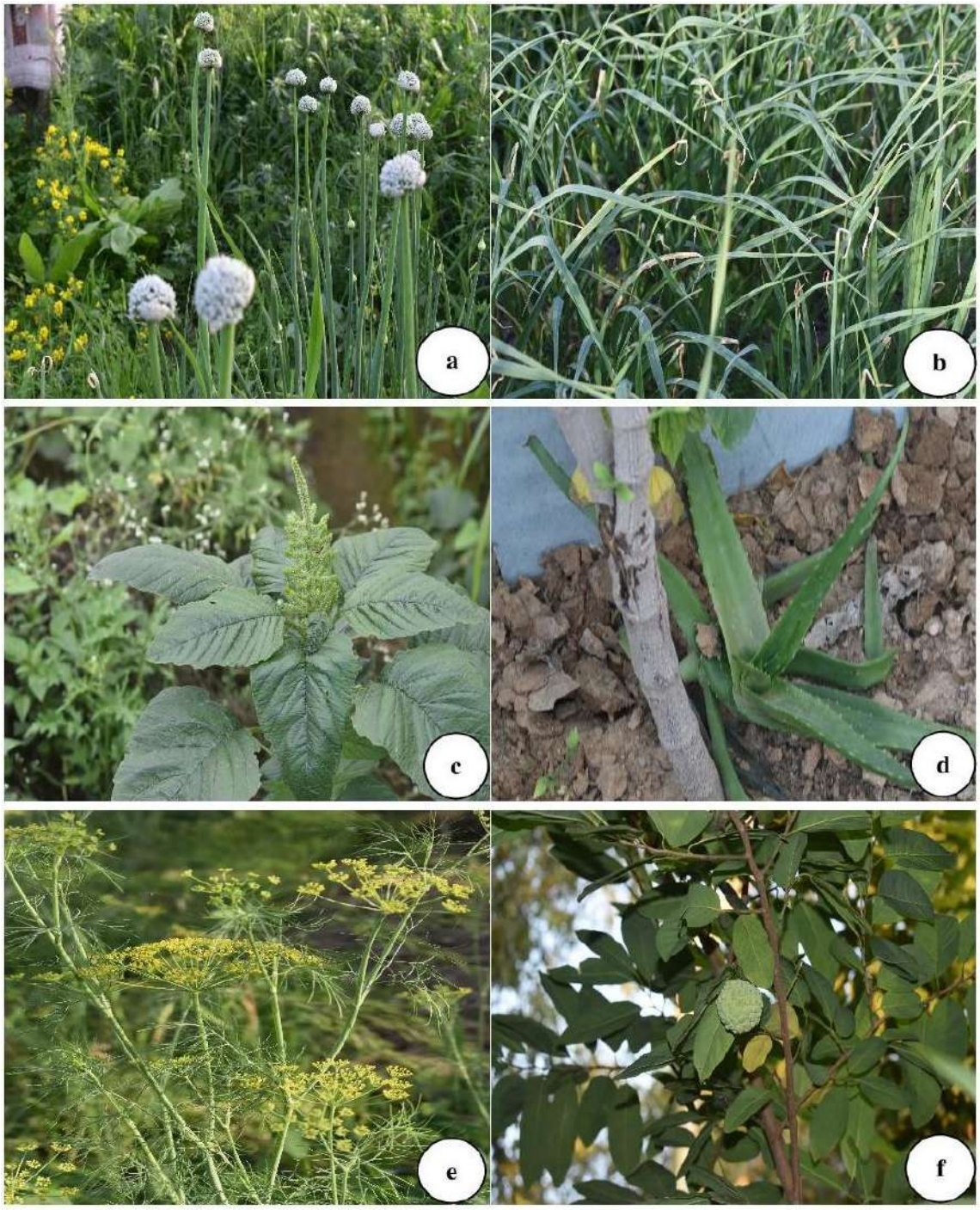


Plate 5(a-f): (a) *Allium cepa* L. (b) *Allium sativum* L., (c) *Aloe vera* (L.) Burm.(d) *Amaranthus viridis* L., (e) *Anethum graveolans* L., (f) *Annona squamosa* L.

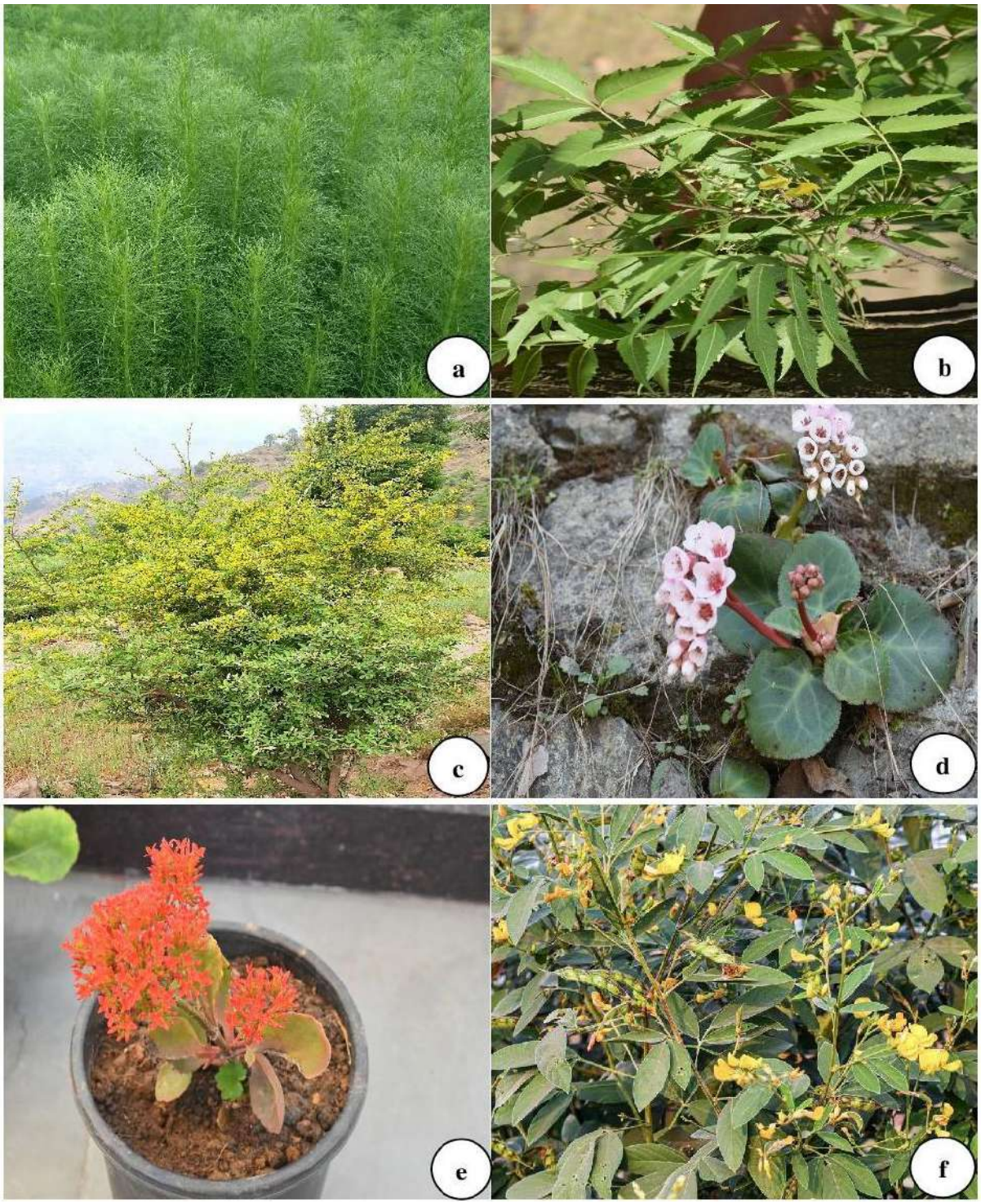


Plate 6(a-f): (a) *Artemisia scoparia* Waldst. & Kit., (b) *Azadirachta indica* A. Juss., (c) *Berberis lyceum* Royle, (d) *Bergenia ciliata* (Haw.) Sternb., (e) *Bryophyllum pinnatum* (Lam.) Oken, and (f) *Cajanus cajan* (L.) Huth.

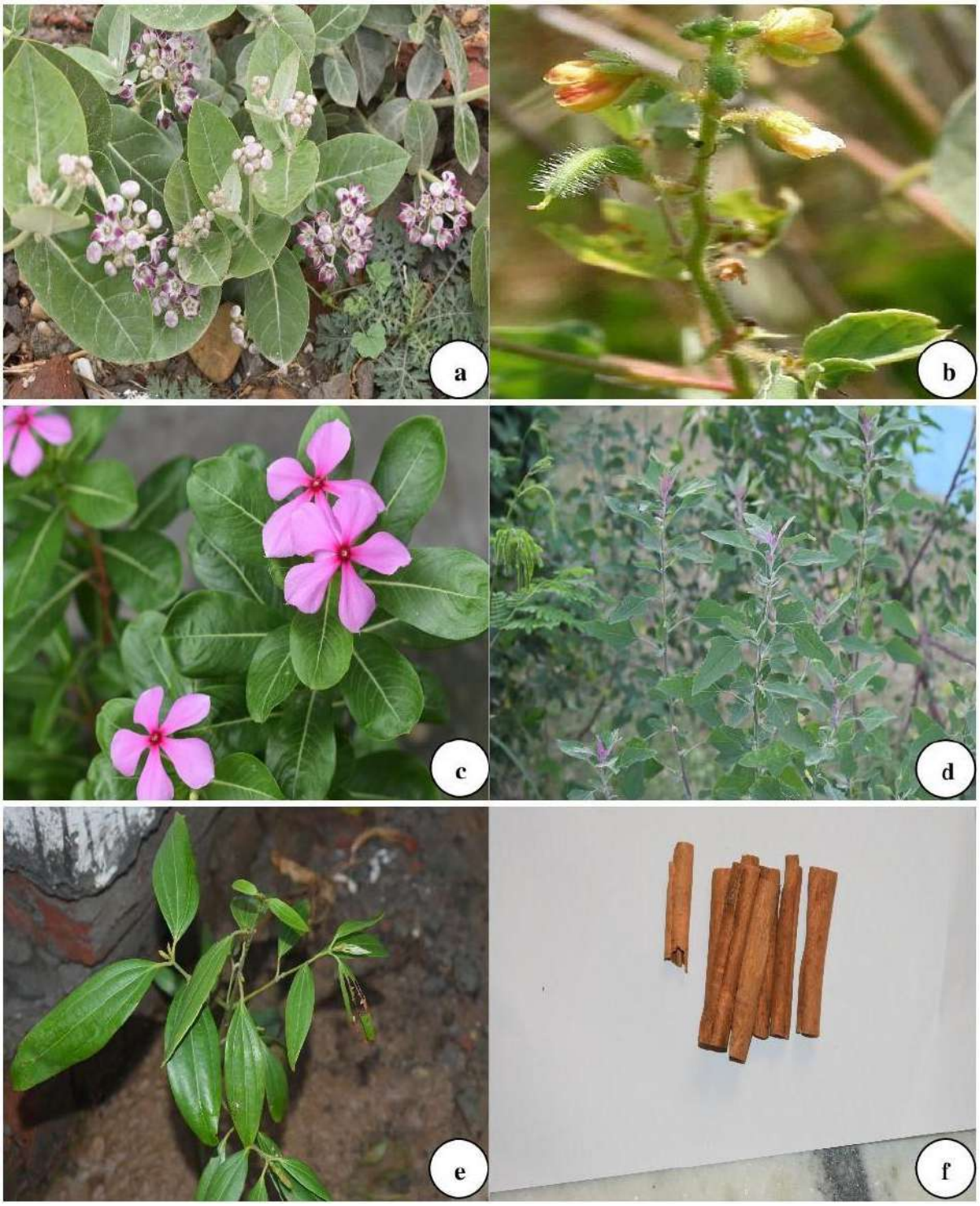


Plate 7(a-f): (a) *Calotropis procera* (Aiton) W.T. Aiton., (b) *Cassia absus* L., (c) *Catharanthus roseus* (L.) G. Don, (d) *Chenopodium album* L., (e) *Cinnamomum tamala* (Buch.-Ham.) T.Nees & C.H.Eberm., and (f) *Cinnamomum zeylanicum* Garcin ex Bl.

Plate 8(a-f): (a) *Coccinia indica* Wight & Arn., (b) *Curcuma lonca* L., (c) *Datura innoxia* Mill., (d) *Eleusine coracana* Gaertn., (e) *Emblica officinalis* Gaertn., and (f) *Gymnema sylvestre* (Retz.) Schult.

Plate 9(a-f): (a) *Gynura procumbens* (Lour.) Merr., (b) *Holarrhena pubescens* (L.) Wall., (c) *Hordeum vulgare* L., (d) *Mangifera indica* L., (e) *Mimosa pudica* L., and (f) *Momordica charantia* L.

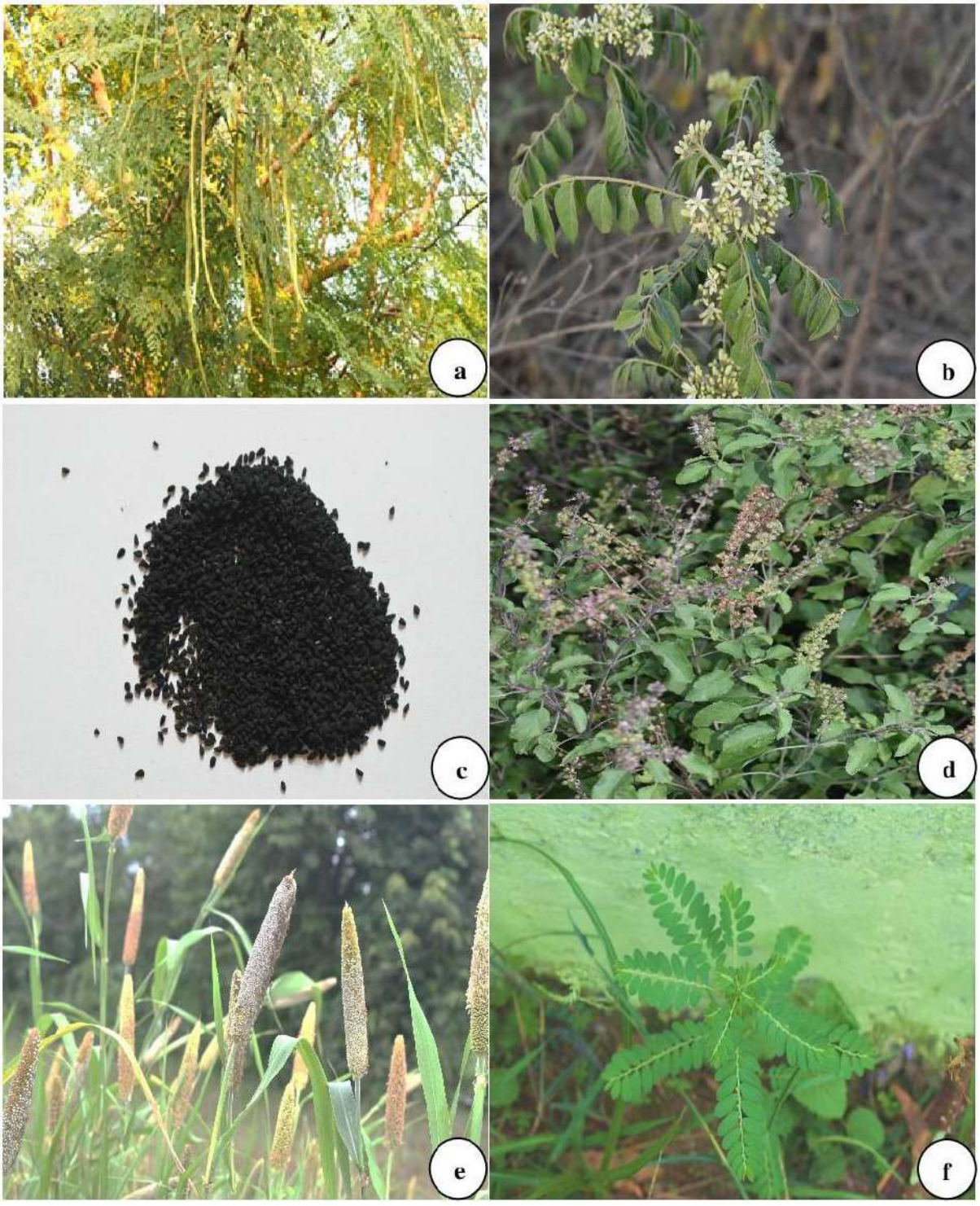


Plate 10(a-f): (a) *Moringa oleifera* Lam., (b) *Murraya koenigii* (L.) Spreng., (c) *Nigella sativa* L., (d) *Ocimum sanctum* L., (e) *Pennisetum glaucum* R.Br., and (f) *Phyllanthus niruri* L.

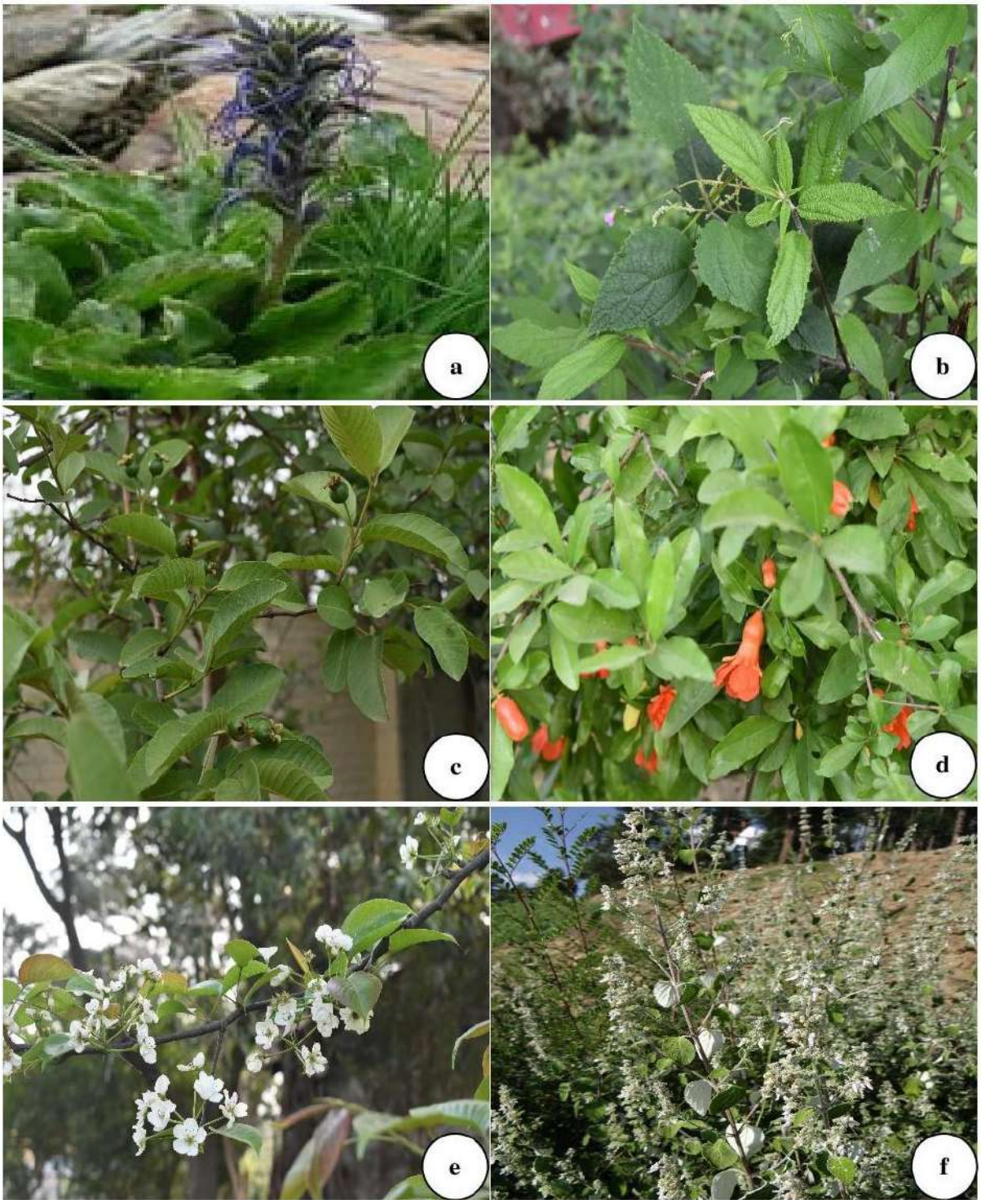


Plate 11(a-f): (a) *Picrorhiza kurroa* Royle. (b) *Pilea scripta* (Buch.-Ham. ex D.Don) Wedd. (c) *Psidium guajava* L. (d) *Punica granatum* L. (e) *Pyrus pashia* Buch.-Ham. ex D.Don(f). *Isodon rugosus* (Wall.) Codd

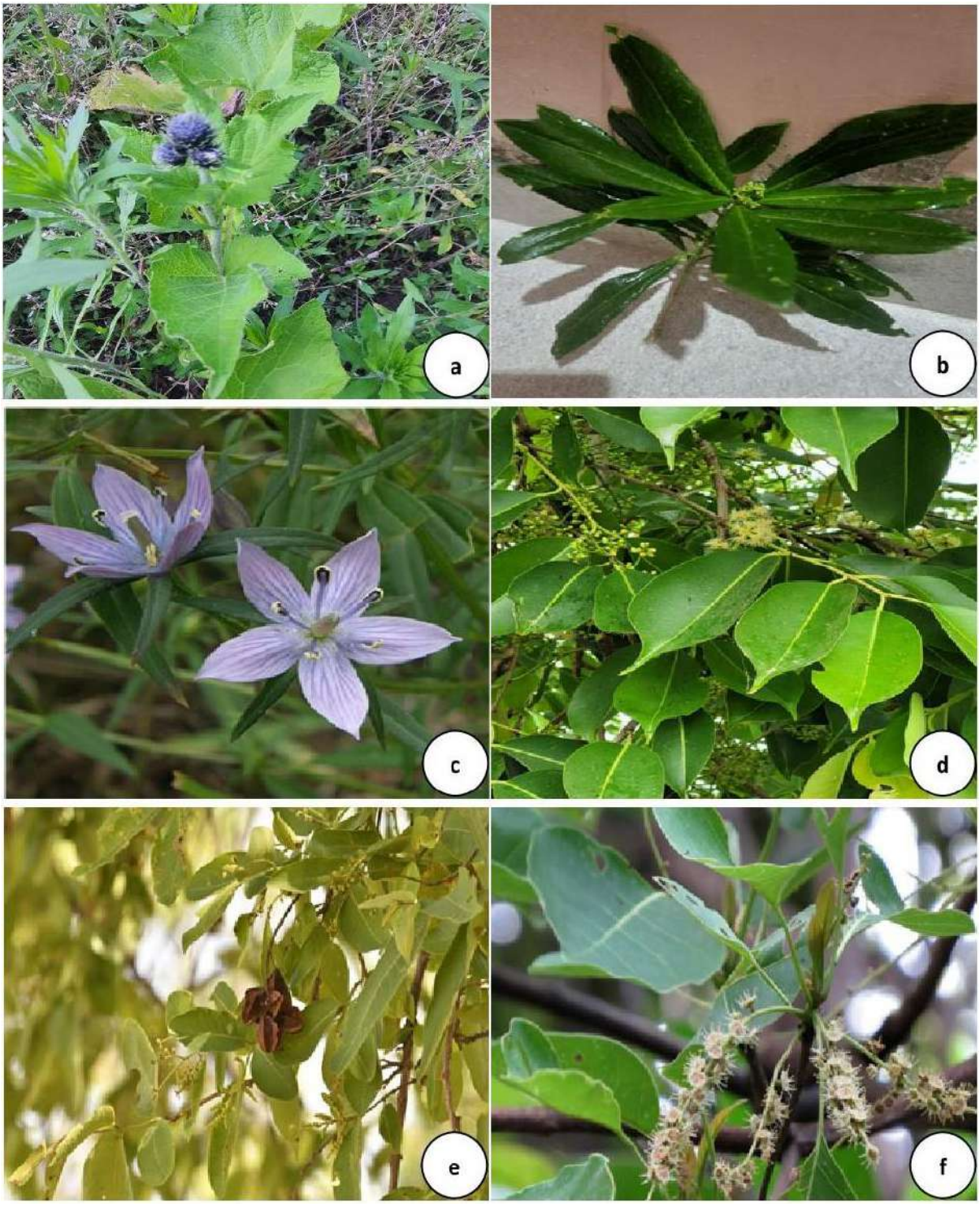


Plate 12(a-f): (a) *Saussurea lappa* (Decne.) C.B.Clarke, (b) *Skimmia anquetilia* N.P.Taylor & Airy Shaw, (c) *Swertia chirayita* (Roxb.) H.Karst., (d) *Syzygium cumini* (L.) Skeels, (e) *Terminalia arjuna* (Roxb. ex DC.) Wight & Arn., and (f) *Terminalia bellirica* (Gaertn.) Roxb.

Plate 14(a-c): (a) *Withania somnifera* (L.) Dunal, (b) *Zanthoxylum armatum* DC., and (c) *Zizyphus jejuba* Mill.

The families representing most in the anti-hyperglycemic flora of the study site were Fabaceae (9.5%; 5 genera & 6 spp), Rutaceae (6.3%; 4 genera & 4 spp), and Apocynaceae, Asteraceae, Lamiaceae, Poaceae, and Ranunculaceae (4. 8%; 3 genera and 3 spp, each) (Fig. 4.1).

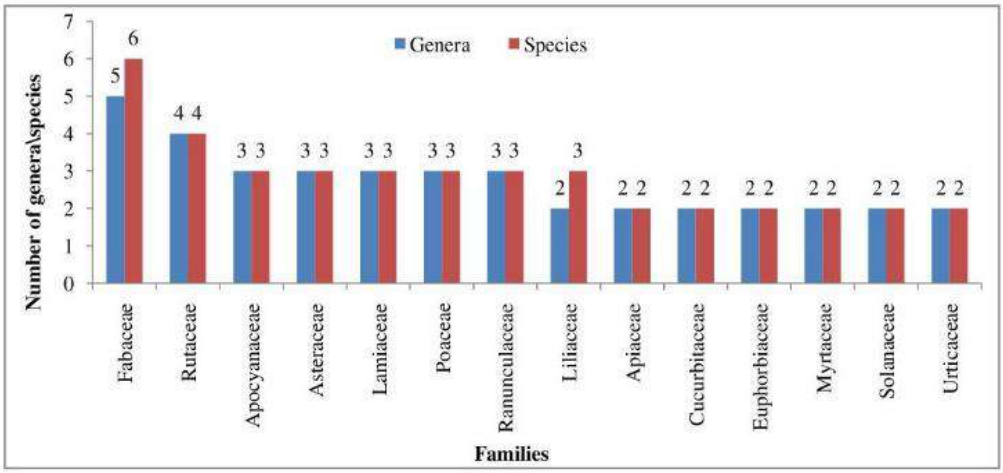


Figure 4.1: Most important plant families used against diabetes

Herbs with a 47.6% contribution were the life forms utilized most (Fig. 4.2) nearly followed by tree forms (31.7%), and shrubs (14.3%).

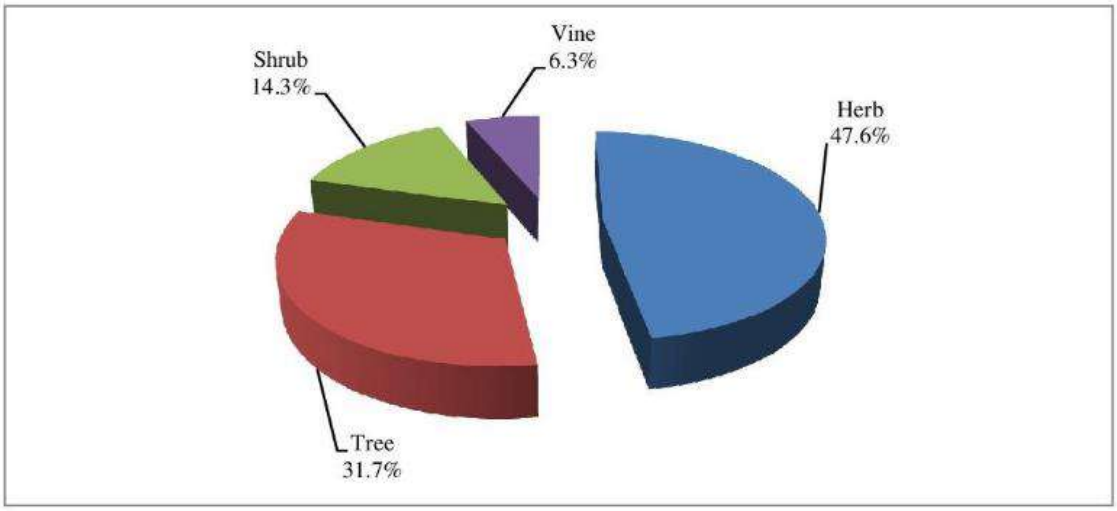


Figure 4.2: Life forms of documented anti-diabetic plants.

The plant parts most commonly utilized were leaves (40%) (Fig. 4.3). Other used plant parts were; Seeds (20%), fruits (12.5%), and roots (7.5%). The main modes of anti-diabetic plant administration were Infusion/decoction (28.6%) and in powdered form (22.2%). Decoctions or

infusions were normally taken. The general dosage quantity ranges from 250 ml to 500 ml, preferably on an empty stomach in the mornings and evenings before supper.

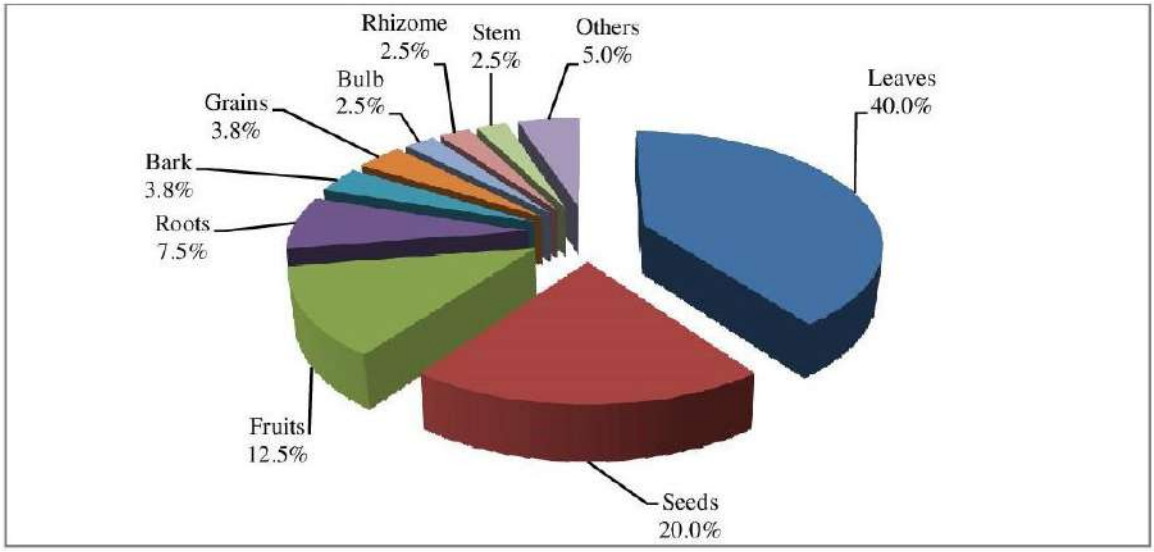


Figure 4.3: Various plant parts used against diabetes

4.1.3 Symptoms and Causes of T2DM as per

According to the informants, the notable metabolic symptoms used for diagnosis of T2DM (Fig. 4.4) included frequent fatigue and weakness (4.9), sudden loss of weight (4.7), and frequent urination, particularly at dusk hours (4.5).

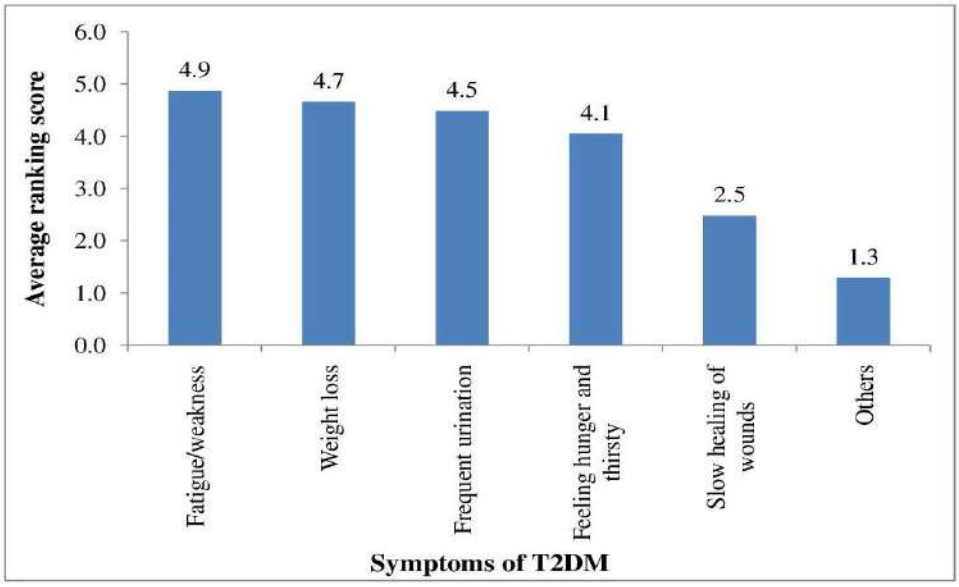


Figure 4.4: Important symptoms used for diagnosing T2DM by the informants

The other symptoms described by the informants were dry, itchy, and flaky skin, depleted immunity, blurring of vision, and pricking needle-like sensation, numbness in extremities (Fig. 4.5) accounting for 1.3. The main underlying reason for diabetes according to informants, was family history (4.6) followed by obesity (3.9). A few other driving reasons like age (3.7), sedentary lifestyle (3.5), high blood pressure, smoking, and alcoholism were also mentioned by informants (1.9).

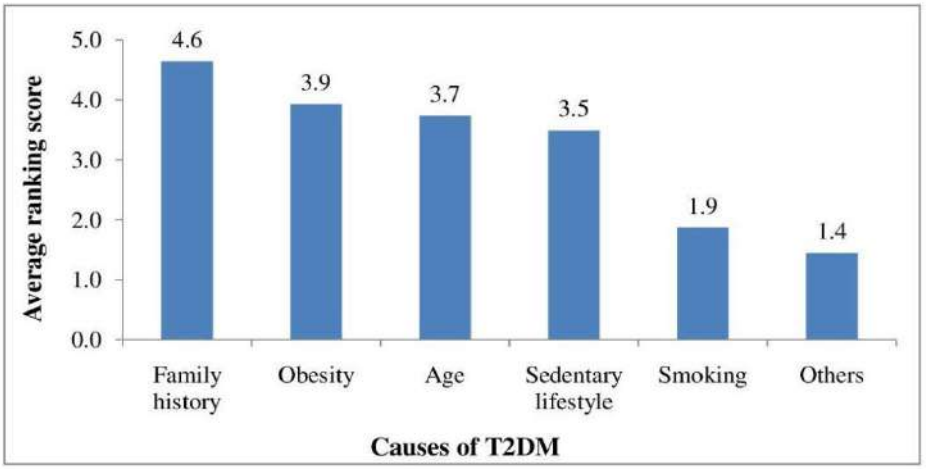


Figure 4.5: The main reasons for T2DM according to the informants

4.1.4 Consensus for reported anti-diabetic plants

Factor informant consensus (F_{ic}) assesses the degree of traditional knowledge-sharing tendency among the three informant groups (Table 4.3). The F_{ic} values indicate that the maximum F_{ic} was shown by local participants (0.92) followed tightly by informants of the *Gujjar* tribals (0.90) and the lowest values were documented for the THPs (0.75). Tribals show a notable tendency to share hypoglycaemic species among community members.

Table 4.3: Factor informant consensus (F_{ic}) for various groups of informants.

Informant group	**N_t**	**N_{ur}**	**Fic**
Gujjar tribals	42	392	0.90
THPs	37	146	0.75
Locals	59	747	0.92
Overall	63	1285	0.95

Abbreviations used: N_t- number of taxa; N_{ur}- number of use reports.

4.1.5 Disease Consensus Index (DCI)

The values of DCI indicate that the most significant plants of the district were *Allium cepa* (DCI, 1.25), *Allium sativum* (1.04), *Psidium guajava* (0.84), *Ocimum sanctum* (0.76), *Momordica charantia* (0.75), *Mangifera indica* (0.74), *Punica granatum* (0.69), *Curcuma longa* (0.66), *Abelmoschus esculentus* (0.64) and *Syzygium cumini* (0.62). The lesser DCI was recorded by *Cinnamomum zeylanicum* (0. 09) closely followed by *Cinnamomum tamala* (0.12), *Mimosa pudica* (0.16), *Anethum graveolens* (0.17), *Chenopodium album* (0.19), *Holarrhena pubescens* (0.19), *Nigella sativa* (0.19), and *Amaranthus viridis* (0.20) (Table 4.4).

Table 4.4: Disease Consensus Index (DCI) of plants used against diabetes in Kathua district

Botanical names of plants	**∑V**	**mVx**	**DCI**
Abelmoschus esculentus	72	8.00	0.64
Acacia catechu	397	7.09	0.50
Acacia nilotica	14	7.00	0.49
Aconitum heterophyllum	114	6.33	0.40
Aegle marmelos	385	7.13	0.51
Ajuga bracteosa	255	7.08	0.50
Allium cepa	67	11.17	1.25
Allium sativum	204	10.20	1.04
Aloe vera	151	6.29	0.40
Amaranthus viridis	18	4.50	0.20
Anethum graveolans	54	4.15	0.17
Anona squamosa	48	5.33	0.28
Artemisia scoparia	44	6.29	0.40
Azadirachta indica	214	6.11	0.37
Berberis lyceum	465	5.60	0.31
Bergenia ciliata	144	5.76	0.33
Bryophyllum pinnatum	19	6.33	0.40
Cajanus cajan	145	5.58	0.31
Calotropis procera	41	6.83	0.47
Cassia absus	38	4.75	0.23
Catharanthus roseus	218	6.81	0.46
Chenopodium album	87	4.35	0.19

Cinnamomum tamala	41	3.42	0.12
Cinnamomum zeylanicum	36	3.00	0.09
Coccinia indica	86	7.17	0.51
Curcuma longa	146	8.11	0.66
Datura innoxia	15	7.50	0.56
Eleusine coracena	68	6.18	0.38
Emblica officinalis	335	7.61	0.58
Gymnema sylvestre	53	4.82	0.23
Gynura procumbens	70	4.67	0.22
Holarrhena pubescens	95	4.32	0.19
Hordeum vulgare	92	7.08	0.50
Mangifera indica	43	8.60	0.74
Mimosa pudica	12	4.00	0.16
Momordica charantia	521	8.68	0.75
Moringa oleifera	20	6.67	0.44
Murraya koenigii	163	5.62	0.32
Nigella sativa	22	4.40	0.19
Ocimum sanctum	96	8.73	0.76
Pennisetum glaucum	175	6.73	0.45
Phyllanthus niruri	28	5.60	0.31
Picrorhiza kurroa	173	7.52	0.57
Pilea scripta	46	5.11	0.26
Rhadosia rugosa	52	5.20	0.27
Punica granatum	75	8.33	0.69
Psidium guajava	119	9.15	0.84
Pyrus pashia	88	7.33	0.54
Saussurea lappa	71	5.92	0.35
Skimmia anquetilia	5	5.00	0.25
Swertia chirayita	197	6.16	0.38
Syzygium cumini	526	7.85	0.62
Terminalia arjuna	189	6.75	0.46
Terminalia bellirica	58	7.25	0.53
Terminalia chebula	71	5.07	0.26
Tinospora cordifolia	392	7.69	0.59

Trachyspermum ammi	29	5.80	0.34
Tribulus terrestris	39	5.57	0.31
Trigonella foenum-graceum	491	7.79	0.61
Urtica dioica	176	6.52	0.42
Withania somnifera	147	6.68	0.45
Zanthoxylum armatum	381	7.47	0.56
Zizyphus jejuba	47	7.83	0.61

4.1.6 Diversity Indices

The perusal of Table 4.5 showed that the maximum richness or number of antidiabetic species was reported by the locals (59), followed by tribes (42) and THPs (37). A similar trend was evident for the number of use reports. Simpson I-D and Shannons's diversity indices recorded the maximum values for locals (1-D, 0.97; H', 3.66) and the minimum for tribes (0.94; 3.22). The highest evenness was found with the information shared by THPs (0.76).

4.1.7 Cluster analysis

Cluster analysis, one of the ordination techniques, was used to classify or group the informants and anti-diabetic plants based on the similarity of information recorded from different informants' groups.

Table 4.5: Variation in species richness, diversity indices, and evenness among the *Gujjar* tribals, THPs, and locals.

Diversity attribute	Tribes	THPs	Locals
Taxa_S	42	37	59
Number of use-reports	392	146	726
Simpson_1-D	0.94	0.96	0.97
Shannon_H	3.22	3.34	3.66
Evenness_e^H/S	0.59	0.76	0.66

The perusal of Fig. 4.6 shows that the cluster analysis grouped the three categories of informants into two groups based on 30 % similarity between group I, comprising tribes and locals, and group II having Tradition Health Practitioners (THPs).

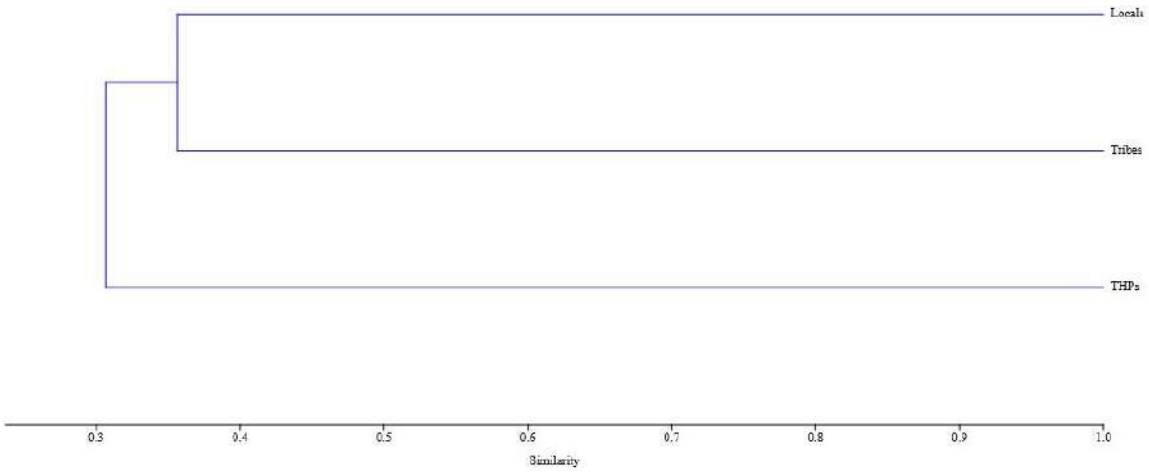


Figure 4.6: Cluster analysis of various informants

The first clustering at 8% similarity, segregated *Skimmia anquetilia* (Group-I) from the rest of the 62 species because it was recorded only by the *Gujjars* and that too with very low use-reports (Fig. 4.7). Further clustering at 45% similarity, divided the species into a total of seven groups. Species found in Group II (7 species) and Group III (7 species) were reported mainly by the *Gujjars*, whereas Groups- IV (13 species), VI (2 species), VII (24 species), and VIII (7 species) were clustered based on their predominant reporting by the tribe informants. Species like *Hordeum vulgare* and *Gymnema sylvestre* were more familiar among the THPs and were segregated into Group-V.

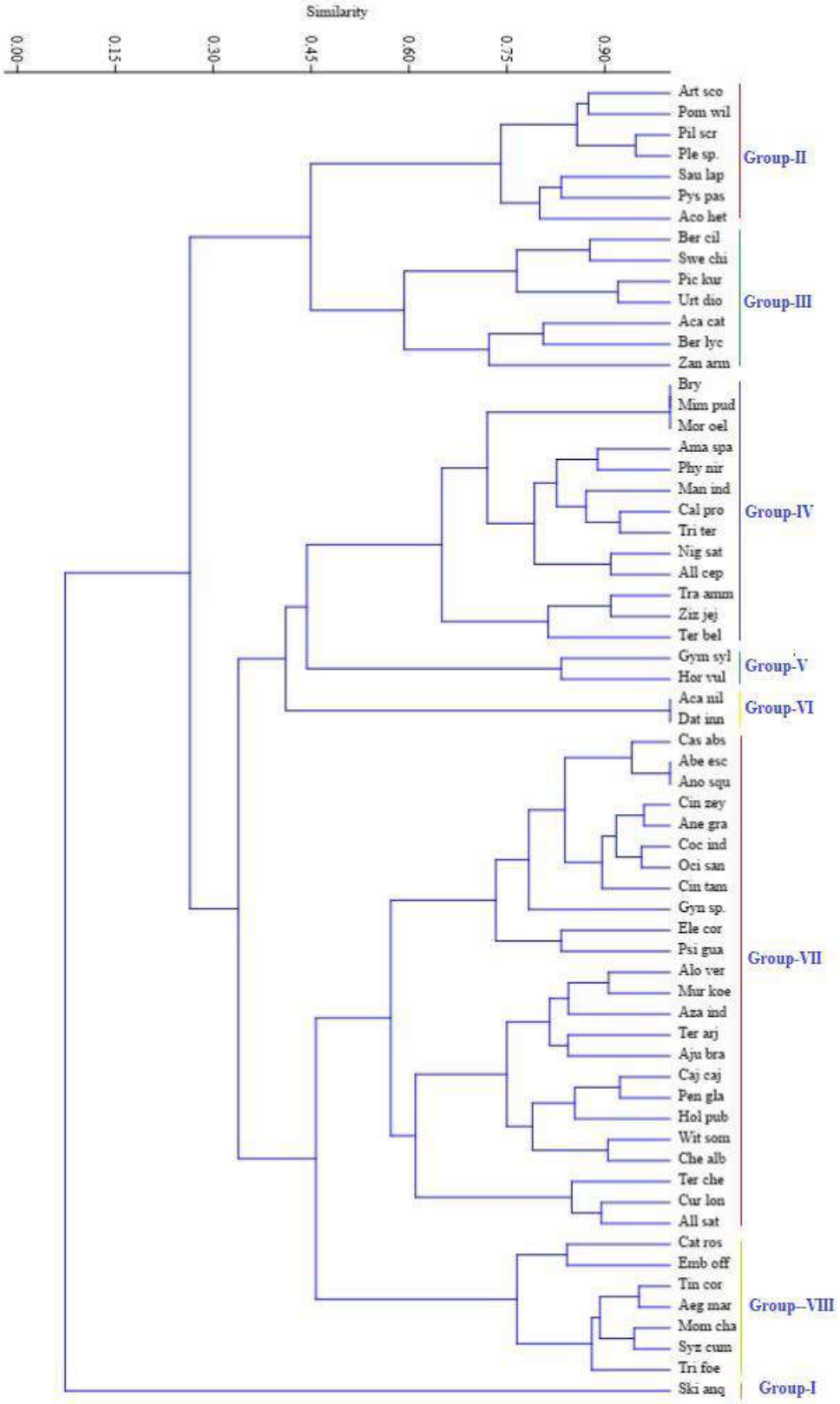


Figure 4.7: Cluster analysis showing the classification of anti-diabetic species

4.1.8 Detrending Correspondence Analysis (DCA)

Further analysis was performed to find the most important or driving species among the 63 anti-diabetic species using Detrending Correspondence Analysis (DCA). The first two axes of the DCA explained all the 100% variation in the data, with Axis-I and II explicated 89.9% and 10.1% variability, respectively. *Gymnema sylvestre* and *Hordeum vulgare* were the driving species for the first axis of the DCA having 3.15 and 3.03 values, respectively. The DCA Axis-II was defined by species like *Abelmoschus esculentus*, *Amaranthus viridis*, *Anona squamosa*, *Bryophyllum pinnatum*, *Cassia absus*, *Catharanthus roseus*, *Gynura procumbens*, *Mimosa pudica*, and *Moringa oleifera*, reported only by the locals (Fig. 4.8).

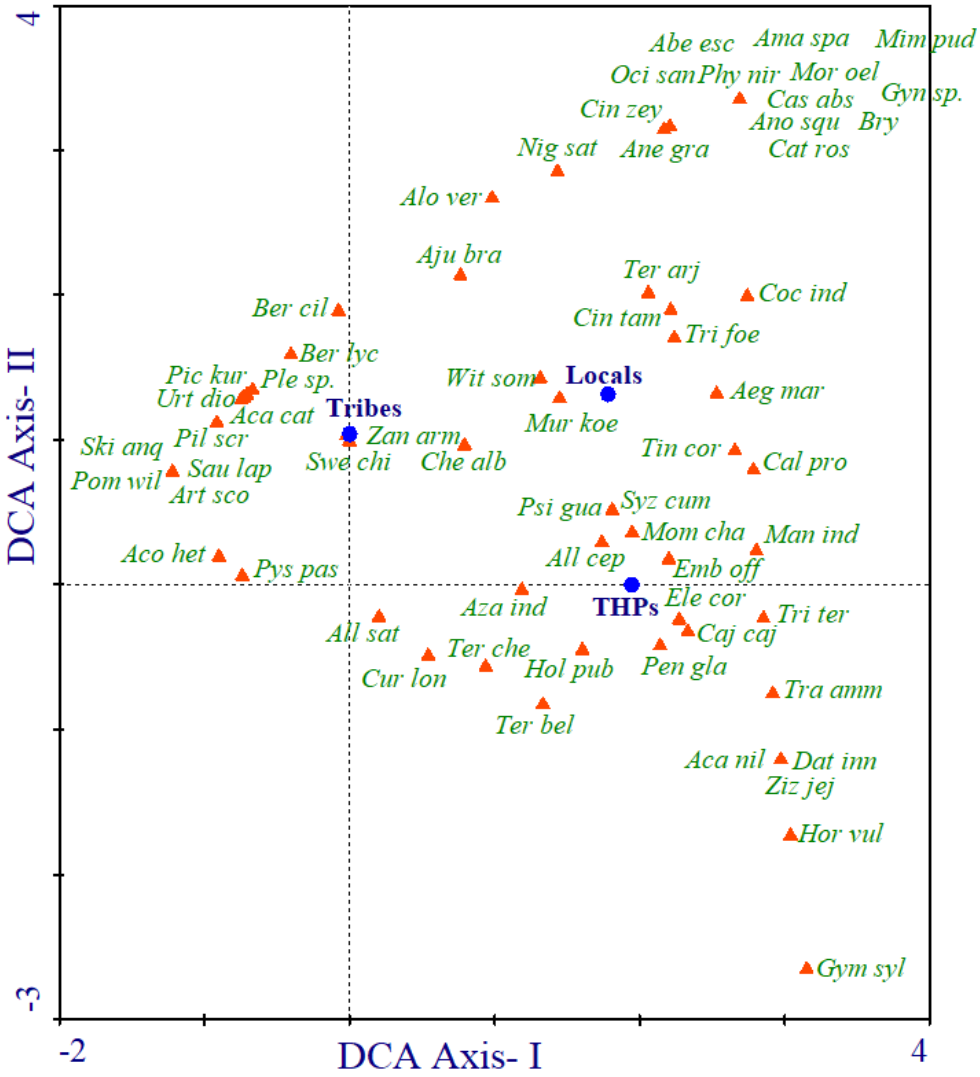


Figure 4.8: Detrended correspondence analysis (DCA) of the plants used against diabetes by the *Gujjar* tribals, THPs, and Locals.

Accordingly, for the classification of the informants, THPs were the most important variable for the DCA Axis-I and locals for the DCA Axis-II (Fig. 4.8).

4.1.9 Preference Ranking

The anti-diabetic species were ranked based on scores assigned by the 34 key informants for the most preferred species to cure diabetes (Table 4.6). The total scores assigned by the key informants show that *Ajuga bracteosa* (3.85), *Urtica dioica* (3.74), *Acacia catechu* (3.65), *Bergenia ciliata* (3.59), *Zanthoxylum armatum* (3.59), *Momordica charantia* (3.53), *Tinospora cordifolia* (3.47), *Emblica officinalis* (3.44), and *Coccinia indica* (3.26) are the ten most preferred plants recommended by informants. Phytochemical analysis of the top five species will be performed to validate their anti-diabetic properties.

Table 4.6: Preference Ranking of Anti-diabetic Species

Botanical names of plants	Score	Ranking
Ajuga bracteosa	3.85	1
Urtica dioica	3.74	2
Acacia catechu	3.65	3
Bergenia ciliata	3.59	4
Zanthoxylum armatum	3.59	5
Momordica charantia	3.53	6
Syzygium cumini	3.53	7
Tinospora cordifolia	3.47	8
Emblica officinalis	3.44	9
Coccinia indica	3.26	10
Pennisetum glaucum	3.26	11
Trigonella-foenum-graceum	3.26	12
Azadirachta indica	3.15	13
Aegle marmelos	3.12	14
Hordeum vulgare	3.03	15
Gymnema sylvestre	3.00	16

Aloe vera	2.94	17
Cajanus cajan	2.85	18
Curcuma longa	2.76	19
Cinnamomum tamala	2.56	20
Berberis lyceum	2.47	21
Swertia chirayita	2.38	22
Terminalia chebula	2.35	23
Psidium guajava	2.26	24
Terminalia arjuna	2.24	25
Allium sativum	2.21	26
Holarrhena pubescens	2.21	27
Withania somnifera	2.12	28
Murraya koenigii	2.06	29
Catharanthus roseus	2.00	30
Aconitum heterophyllum	1.94	31
Terminalia bellirica	1.91	32
Eleusine coracena	1.85	33
Chenopodium album	1.79	35
Picrorhiza kurroa	1.79	34

The values of score are the mean of rank given by the key informants (n = 34)

4.1.10 Phytochemical analysis of the few most preferred anti-diabetic species

Preference Ranking was used to assess the most effective plants in the study area detailed in Table 4.7. Five most preferred plants (Ranked 1 to 5) viz. *Ajuga bracteosa* (3.85), *Urtica dioica* (3.74), *Acacia catechu* (3.65), *Bergenia ciliata* (3.59), and *Zanthoxylum armatum* (3.59) were subjected to further phytochemical investigations.

Preference ranking has been used in several ethnobotanical studies to determine the degree of effectiveness of the species against a particular disease or multiple diseases. The index rests on the paradigm that elder informants possess more corpus of traditional knowledge (Martin, 2010; Tekley *et al.,* 2013; Kidane *et al.,* 2018; Tefera and Kim, 2019; Hu *et al.,* 2020).

Table 4.7: Collection spots of plants used for phytochemical screening

Plant name	Part used	Accession number	Site of collection
Acacia catechu (L.f.) Willd	Bark	HBJU-16704	Kathua, 32.3863 ºN, 75.5173 ºE
Ajuga bracteosa Wall. ex. Benth.	Leaves	HBJU-16717	Phinter, 32.5829 ºN, 75.5430 ºE
Bergenia ciliata (Haw.) Sternb	Rhizome	HBJU-16738	Bani, 32.7079 ºN, 75.8156 ºE
Urtica dioca L.	Leaves	HBJU-16742	Machhedi, 32.701 ºN, 75.5990 ºE
Zanthoxylum armatum D.C.	Seed	HBJU-16737	Billawar, 32.6136 ºN, 75.6041 ºE

4.1.10.1 Total Phenolic Content (TPC)

TPC was estimated using the Folin–Ciocalteu reagent in each extract. The results were calculated via calibration curve of gallic acid (0-100 ul) and equation y = 0.1244x-0.2104, R^2 = 0.9616 (Fig. 4.9) and expressed in gallic acid equivalents (GAE) per gram dry extract weight. The content of phenolic compounds in ethanol extracts ranged from 56.36 ± 2.8 to 134.19 ± 6.70 mg GAE/g. *Acacia catechu* and *Bergenia ciliata* had the highest phenolic contents of 127.28 ± 6.36 mg GAE/g and 134.19 ± 6.70 mg GAE/g, respectively while the smallest TPC was recorded in *Zanthoxylum armatum, Ajuga bracteosa, Urtica dioica* of 80.02 ± 4.0 mg GAE/g, 56.36 ± 2.8 mg GAE/g, & 84.09 ± 4.20 mg GAE/g, respectively (Table 4.8).

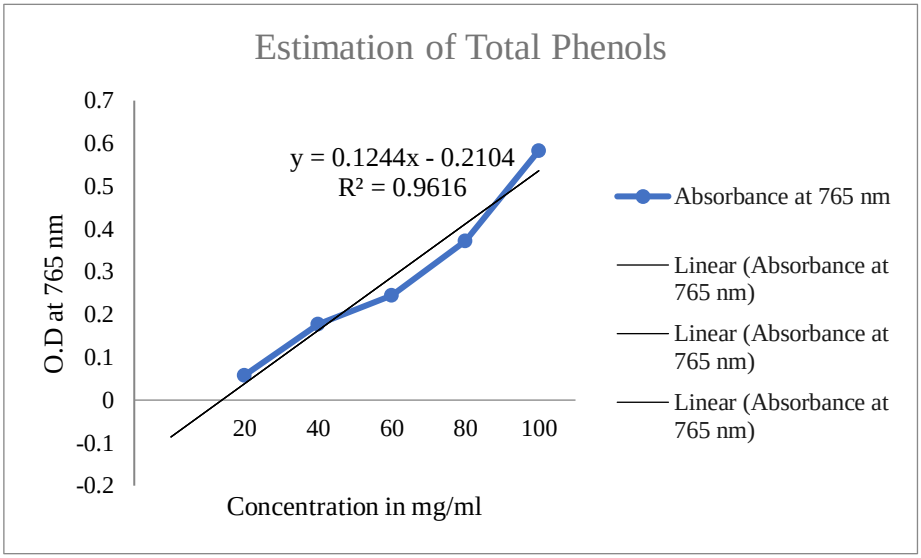


Figure 4.9: Calibration curve of gallic aci

Table 4.8: Total phenolic content *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata* rhizome, *Utrica dioca* leaves, and *Zanthoxylum armatum* fruits.

Plant sample	OD (765 nm)	Concentration (mg GAE/g)
Acacia catechu	1.373 (Df.10)	$127.24^{b} \pm 0.66$
Ajuga bracteosa	1.192 (Df.10)	$56.34^{e} \pm 0.55$
Bergenia ciliata	1.459 (Df.10)	$134.22^{a} \pm 0.55$
Utrica dioca	1.882 (Df.10)	$84.41^{c} \pm 0.35$
Zanthoxylum armatum	1.799 (Df. 10)	$80.08^{d} \pm 0.23$

The values given are mean ± standard deviation. Fisher's LSD was applied as a multiple-range test when the values of one-way ANOVA were significant at $P < 0.05$. The values followed by the same alphabets within a column do not vary significantly as per Fisher's LSD.

4.1.10.2 Total Flavonoid Content (TFC)

The results calculated from the calibration curve of quercetin (y=0.0656x-0.0844 $R^2 = 0.9899$) (Figure 4.10) and expressed in quercetin equivalents per gram dry extract weight. The total flavonoid content in ethanol extracts ranged from 50.36 ± 2.51 to 255.7 ± 12.78 mg QE/g (Table 4.9).

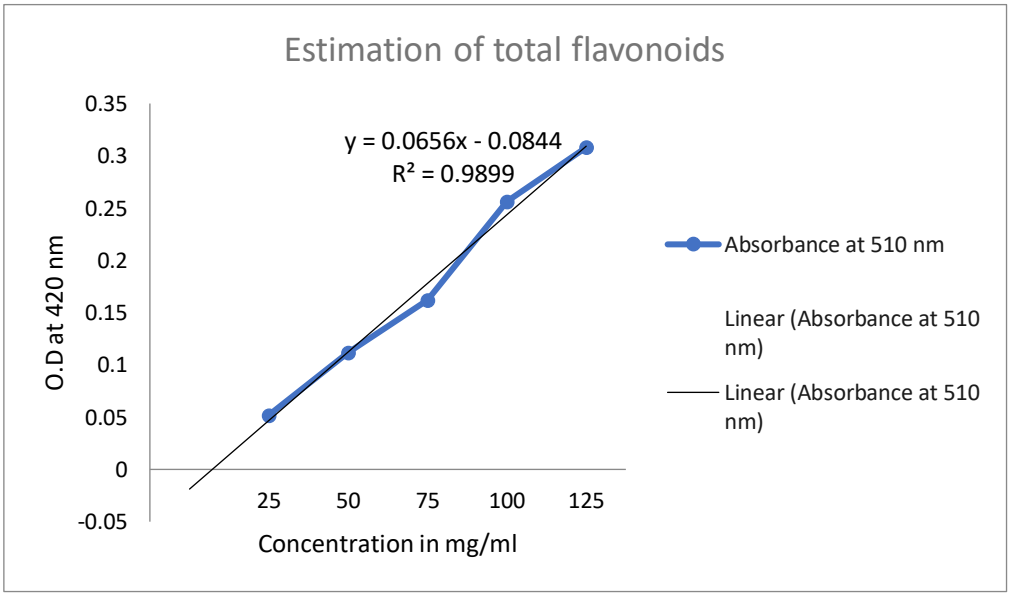


Figure 4.10: Calibration curve of Quercitin

Table 4.9: Total flavonoid content of *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata* rhizome, *Utrica dioca* leaves, and *Zanthoxylum armatum* fruits.

Plant name	OD at 765 nm	Concentration (mg QE/g)
Acacia catechu	1.593 (Df.10)	$256.13^{a} \pm 0.59$
Ajuga bracteosa	1.223 (Df.10)	$199.27^{b} \pm 0.35$
Bergenia ciliata	0.958 (Df 10)	$158.93^{d} \pm 0.45$
Urtica dioca	1.092 (Df. 10)	$179.23^{c} \pm 0.40$
Zanthoxylum armatum	0.246 (Df.10)	$50.35^{e} \pm 0.44$

The values given are mean ± standard deviation. Fisher's LSD was applied as a multiple-range test when the values of one-way ANOVA were significant at $P < 0.05$.

The *Zanthoxylum armatum* fruit extract had the smallest amount of flavonoids (50.36 mg QE/g), while the *Acacia catechu* had the highest flavonoid content (255.7 ± 12.78 mg QE/g). *Ajuga bracteosa*, *Urtica dioca*, and *Bergenia ciliata* showed flavonoid content of 199.29 ± 9.96, 179.32 ± 8.96, and 158.90 ± 7.94 mg QE/g, respectively).

4.1.10.3 DPPH (2,2-diphenyl-1-picrylhydrazyl) assay

The antioxidant potential of the ethanolic extracts of *Acacia catechu* heartwood (ACH), *Ajuga bracteosa* leaves (ABL), *Bergenia ciliata* rhizome (BCR), *Urtica dioica* leaves (UDL), and *Zanthoxylum armatum* fruits (ZAF) were evaluated by the DPPH assay method. The tests were done in triplicate in each concentration, and the mean SD of the three tests was taken. The ethanolic extract of the *Acacia catechu, Ajuga bracteosa, Bergenia ciliata Utrica dioica, and Zanthoxylum armatum* showed 32.566% ± 0.373, 85.23 ± 0.19,73.61 ± 0.34, 39.26 ± 0.16 and 38.015 ± 0.14%, inhibition respectively. The standard Ascorbic acid showed 99.356 ± 0.27 (Table 4.10). *Ajuga bracteosa* leaves showed antioxidant activity as high as standard Ascorbic acid. The high flavonoids and phenol content levels of *Ajuga bracteosa, Bergenia ciliata, Urtica dioica, and Acacia catechu, Zanthoxylum armatum*, plants correspond to their high antioxidant levels. DPPH free radical scavenging assay is a widely employed assay as it is advantageous compared to other laboratory-generated free radicals and is accurate.

Table 4.10: Antioxidant activity of the *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata* rhizome, *Urtica dioica* leaves, and *Zanthoxylum armatum* fruits.

Concentration (mg/mL)	OD at 517nm	%age scavenging
Control	0.972	
Acacia catechu heartwood		
10	0.890	$8.45^{d} \pm 0.27$
20	0.886	$8.86^{d} \pm 0.05$
30	0.782	$19.60^{c} \pm 0.43$
40	0.723	$25.70^{b} \pm 0.28$
50	0.611	$37.25^{a} \pm 3.39$
Ajuga bracteosa leaves		
10	0.421	$56.70^{e} \pm 0.44$
20	0.234	$75.99^{d} \pm 0.22$
30	0.144	$85.23^{c} \pm 0.19$
40	0.111	$88.62^{b} \pm 0.38$
50	0.015	$98.50^{a} \pm 0.34$
Bergenia ciliata rhizome		
10	0.721	$25.80^{d} \pm 0.22$
20	0.651	$33.00^{c} \pm 0.11$
30	0.462	$52.49^{b} \pm 0.10$
40	0.274	$71.86^{a} \pm 0.34$
50	0.256	$73.61^{a} \pm 0.34$
Urica dioca leaves		
10	0.869	$10.70^{e} \pm 0.41$
20	0.673	$30.45^{d} \pm 0.20$
30	0.660	$32.02^{c} \pm 0.36$
40	0.620	$36.62^{b} \pm 0.38$
50	0.588	$39.26^{a} \pm 0.16$
Zanthoxylum armatum fruits		
10	0.907	$6.77^{f} \pm 0.36$
20	0.817	$16.00^{e} \pm 0.21$
30	0.714	$26.55^{d} \pm 0.24$
40	0.651	$33.08^{c} \pm 0.13$
50	0.599	$38.78^{b} \pm 0.06$
Ascorbic acid	0.009	$99.36^{a} \pm 0.27$

The values given are mean ± standard deviation. Fisher's LSD was applied as a multiple-range test when the values of one-way ANOVA were significant at $P < 0.05$. The values followed by the same alphabets within a column do not vary significantly as per Fisher's LSD.

4.1.10.4 Alpha-amylase Assay

The methanolic and aqueous extracts of *Acacia catechu* heartwood (ACH), *Ajuga bracteosa* leaves (ABL), *Bergenia ciliata* rhizome (BCR), *Utrica dioca* leaves (UDL), and *Zanthoxylum armatum* fruits (ZAF) were evaluated for α-amylase inhibition with Acarbose as a positive control (Table 4.11). All the extracts exhibited an inhibition above fifty percent. At a conc. 500 µg/mL, ACH aqueous extract (84.42± 0.51%) followed by methanolic ZAF (75.80 ± 0.11 %), and minimum by exhibited by aqueous BGR (52.16 ± 0.01%**).**

Table 4.11: Alpha-amylase inhibitory effects of *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *B. ciliata* rhizome, *U. dioca* leaves, and *Z. armatum* fruits.

Concentration (µg/ml)	**Percentage inhibition**				**t-values**	**P-values**
	OD at 540nm	**Methanolic extract**	**OD at 540 nm**	**Aqueous**		
Control	1.8028		1.9245			
Acacia catechu heartwood						
100	1.1869	34.16 ± 0.01	0.9873	48.86 ± 0.27	-95.11	< 0.001
200	1.1727	34.84 ± 0.46	0.7762	59.20 ± 0.41	-68.39	< 0.001
300	1.1498	36.99 ± 0.91	0.5692	70.42 ± 0.01	-63.79	< 0.001
400	0.9172	49.74 ± 0.46	0.3729	80.84 ± 0.71	-64.05	< 0.001
500	0.7734	57.59 ± 0.44	0.3028	84.42± 0.51	-68.87	< 0.001
Ajuga bracteosa leaves						
100	1.7334	3.85 ± 0.01	1.6522	15.10 ± 0.09	-222.74	< 0.001
200	1.6788	6.88 ± 0.01	1.5729	18.46 ± 0.37	-53.90	< 0.001
300	1.2238	20.86 ± 0.47	1.4231	22.58 ± 0.01	-6.31	0.003
400	0.9866	45.67 ± 0.46	1.0246	47.19 ± 0.51	-3.83	0.019
500	0.6334	64.82 ± 0.07	0.7998	58.64 ± 0.16	60.71	< 0.001
Bergenia ciliata rhizome						
100	1.5624	13.33 ± 0.01	1.6729	14.04 ± 0.05	-22.41	< 0.001
200	1.3990	22.45 ± 0.11	1.4627	23.99 ± 0.02	-25.00	< 0.001
300	1.2749	29.28 ± 0.01	1.2444	35.52 ± 0.32	-34.09	< 0.001
400	1.0669	40.90 ± 0.29	1.0826	43.87 ± 0.22	-14.33	< 0.001
500	0.8624	65.56 ± 0.48	0.9794	52.16 ± 0.01	47.89	< 0.001

Utrica dioca leaves						
100	1.5643	13.23 ± 0.01	1.7623	8.35 ± 0.13	65.12	< 0.001
200	1.3558	24.79 ± 0.01	1.5627	19.13 ± 0.58	16.77	< 0.001
300	1.1369	37.03 ± 0.19	1.2003	37.96 ± 0.58	-2.64	0.058
400	0.9637	46.54 ± 0.01	1.0994	42.92 ± 0.29	21.80	< 0.001
500	0.7356	59.21 ± 0.02	0.8240	57.75 ± 0.45	5.61	0.005
Zanthoxylum armatum fruits						
100	1.6983	5.80 ± 0.01	1.7844	7.55 ± 0.48	-6.35	0.003
200	1.5842	12.12 ± 0.01	1.7228	10.48 ± 0.01	247.37	< 0.001
300	1.2151	33.60 ± 1.72	1.3217	31.48 ± 0.37	2.09	0.105
400	0.6754	62.11 ± 0.19	1.0006	48.02 ± 0.01	127.80	< 0.001
500	0.4356	75.80 ± 0.11	0.8112	58.19 ± 0.72	42.02	< 0.001

Values given are mean ± standard deviation.

The minimum IC5O value was observed for aqueous ACH (125.40±0.04 ug/mL) followed by methanolic ZAF (358.94 ± 4.25 µg/mL) (Table 4.12). IC50 value of aqueous *Acacia catechu* heartwood extract was lower than acarbose AJL, BGR, and UDL methanolic extracts showed 64.82 ± 0.07%, 65.56 ± 0.48%, and 59.21 ± 0.02% of α-amylase inhibition, respectively. The aqueous extracts of AJL, BGR, and UDL (at a concentration of 500 µg/mL) exhibited 58.64 ± 0.16%, 52.16 ± 0.01 %, and 57.75 ± 0.45% of α-amylase inhibitory activity, respectively. Acarbose (at a concentration of 500 µg/mL) showed α-amylase activity with an IC50 value of 175.39±0.02 µg/mL.

The perusal of t-values(P< 0.05) shows that in case of *Acacia catechu* aqueous solution, recorded significantly higher α-amylase inhibition for all the concentrations. In *Ajuga bracteosa* significant higher α-amylase inhibition was recorded for aqueous solution upto 300 µg/mL. For 400 and 500 µg/mL conc., the significantly higher α-amylase inhibition for methanolic extracts. The aqueous solution of *Bergenia ciliata* recorded significantly higher α-amylase inhibition up to 400 µg/mL conc and upto 500 µg/mL in methanolic extract. The methanolic extract of *Urtica dioica* leaves reported significantly (P< 0.05) higher inhibition at 100,200,400 and 500 µg/mL conc. In *Zanthoxylum armatum* aqueous solution recorded significantly higher inhibition only in case of 100 µg/mL conc. For 200,400 and 500 µg/mL conc., methanolic extract recorded significantly higher inhibition.

Table 4.12: IC 50 values of Alpha Amylase Assay of *Acacia catechu* heartwood (ACH), *Ajuga bracteosa* leaves (ABL), *Bergenia ciliata* rhizome (BCR), *Urtica dioica* leaves (UDL), and *Zanthoxylum armatum* fruits (ZAF).

Plant Sample	Methanolic (µg/mL)	Aqueous (µg/mL)
Acacia catechu heartwood	444.4172 ± 0.07963	125.40 ± 0.0416
Ajuga bracteosa leaves	414.54 ± 0.2996	444.254 ± 0589
Bergenia ciliata rhizome	480.966 ± 0.0844	434.516 ± 0.168
Urtica dioca leaves	423.411 ± 0.503	436.538 ± 0.5847
Zanthoxylum armatum fruits	358.94 ± 4.257	425.881 ± 0.3423
Acarbose (µg/mL)	175.3944 ± 0.0285	

4.1.10.5 Alpha glucosidase Assay

The highest amount of inhibition was exhibited by *Ajuga bracteosa* leaves (ABL) i.e. 85.79 ± 0.078 % and 81.17 ± 0.07 % in methanolic and aqueous extract, respectively. The IC 50 for methanolic extract was 128.89 ± 0.044 ug/mL which was quite lower than standard (162.39 ± 0.0285 ug/mL) and aqueous extract (194.82 ± 0.028 ug/mL) also showed comparable IC-50 with standard (Table 4.13).

Table 4.13: α-Glucosidase inhibitory effects of *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *B. ciliata* rhizome, *U. dioca* leaves, and *Z. armatum* fruits.

Species/ Concentration (ug/mL)	Percentage inhibition				*t-values*	*P-values*
	OD at 410 nm	Methanolic extract	OD at 410 nm	Aqueous		
Control	1.9922			1.9273		
Acacia catechu						
100	1.4485	27.81 ± 0.96	1.3429	30.89 ± 0.40	-5.15	0.007
200	1.2359	37.96 ± 0.01	1.1245	41.81 ± 0.17	-38.73	< 0.001
300	1.1104	44.58 ± 0.56	0.9674	49.84 ± 0.06	-16.10	< 0.001
400	0.8823	55.44 ± 0.63	0.6528	66.12 ± 0.01	-29.38	< 0.001
500	0.6001	69.21 ± 0.56	0.4766	75.83± 0.51	-15.11	< 0.001
Ajuga bracteosa						

100	1.0244	48.58 ± 0.01	1.2844	33.35 ± 0.01	228.80	< 0.001
200	0.8722	57.06 ± 0.14	0.9763	49.38 ± 0.17	59.83	< 0.001
300	0.6234	68.71 ± 0.01	0.8249	57.39 ± 0.33	58.88	< 0.001
400	0.4668	76.33 ± 0.29	0.6720	65.13 ± 0.14	59.98	< 0.001
500	0.2829	85.72 ± 0.14	0.3628	81.55 ± 0.33	20.11	< 0.001
Bergenia ciliata						
100	1.6255	18.41 ± 0.01	1.7622	8.67 ± 0.19	90.56	< 0.001
200	1.4652	26.29 ± 0.26	1.5625	18.99 ± 0.11	44.48	< 0.001
300	1.1907	41.01 ± 0.19	1.0725	44.53 ± 0.31	-16.84	< 0.001
400	0.9725	51.32 ± 0.21	0.9777	49.31 ± 0.03	16.60	< 0.001
500	0.8722	56.16 ± 0.11	0.7624	60.54 ± 0.08	-53.64	< 0.001
Urtica dioca						
100	1.3345	33.86 ± 0.25	1.4625	24.19 ± 0.04	65.44	< 0.001
200	1.1827	40.46 ± 0.30	1.237	35.97 ± 0.14	23.58	< 0.001
300	1.0244	48.72 ± 0.25	1.1107	42.27 ± 0.20	34.97	< 0.001
400	1.0004	49.64 ± 0.46	0.9612	50.27 ± 0.15	-2.30	0.083
500	0.5976	70.03 ± 0.17	0.5623	71.89 ± 0.11	-15.96	< 0.001
Zanthoxylum armatum						
100	1.2958	34.92 ± 0.04	1.2846	14.36 ± 0.14	249.59	< 0.001
200	1.2338	37.40 ± 0.36	0.9765	21.20 ± 0.12	73.70	< 0.001
300	1.1195	43.82 ± 0.08	0.8251	35.40 ± 0.13	94.27	< 0.001
400	0.7765	61.02 ± 0.02	0.675	45.14 ± 0.27	103.19	< 0.001
500	0.5921	70.30 ± 0.03	0.3630	67.22 ± 0.20	25.84	< 0.001

Values given are mean ± standard deviation.

Perusal of t-values in assay reveal in *Acacia catechu* significantly (P<0.05) higher α-glucosidase inhibition was recorded for aqueous solution in all the concentrations, whereas in *Ajuga bracteosa*, the significantly (P<0.05) higher α-glucosidase inhibition was recorded for methanolic extract in all the five concentrations. α-glucosidase inhibition was significantly higher for methanolic extract at 100,200 and 400 µg/mL and for aqueous extract at 300 and 500 µg/mL conc. in *Bergenia ciliata.* In case of *Urtica dioica* the significantly (P<0.05) higher α-glucosidase inhibition was recorded for methanolic extract at 100,200 and 300 µg/mL conc. and for aqueous extract at 500 µg/mL conc. For *Zanthoxylum armatum*, significantly (P<0.05) higher α-glucosidase inhibition was recorded at all the five concentrations in methanolic extracts.

The methanolic extract of ACH, ZAF, UDL, and BGR (at a concentration 500 µg/mL) exhibited 69.21 ± 0.56%, 70.33 ± 0.03%, 70.03 ± 0.17% and 56.16 ± 0.11 % of α-glucosidase inhibition with IC50 values of 365.46 ± 0.46, 352.30 ± 0.1, 128.89 ± 0.04, 385.65 ± 0.004, 404.77 ± 0.43 µg/mL, respectively (Table 4.14). The Aqueous extracts of ACH, BGR, UDL and ZAF (at a concentration of 500 µg/mL) exhibited 75.83 ± 0.51%, 60.54 ± 0.08%, 71.89 ± 0.11%, 67.22 ± 0.20% of α-glucosidase inhibition with an IC50 values of 269.80 ± 0.097, 369.51 ± 0.094, 391.730 ± 0.71 and 416.34 ± 1.01 ug/mL, respectively. Acarbose (at a concentration 500 µg/mL) showed α-Glucosidase activity with an IC50 value of 162.39±0.02 µg/ml. Inhibition in both extracts occurred in a concentration-dependent manner.

Table 4.14: IC 50 Values of Alpha Glucosidase Assay of *Acacia catechu* heartwood, *Ajuga bracteosa* leaves,*Bergenia ciliata* rhizome, *Urtica dioica* leaves and *Zanthoxylum armatum* fruits.

Plant Name	Methanolic	Aqueous	Acarbose
Acacia catechu	365.463 ± 0.4667	269.80 ± 0.0978	162.39 ± 0.0285
Ajuga bracteosa	128.89 ± 0.044	194.82 ± 0.028	
Bergenia ciliata	404.778 ± 0.437	369.51 ± 0.094	
Utrica dioca	385.65 ± 0.004	391.730 ± 0.717	
Zanthoxylum armatum	352.306 ± 0.115	416.34 ± 1.016	

The values given are the mean ± standard deviation.

4.1.10.6 Correlation Analysis

The correlation coefficients determined between phenolics, flavonoids, DPHH, alpha-amylase, and alpha-glucosidase are shown in Table 4.15. In the present study, strong positive correlations were seen between TPC with *α*-amylase and *α*-glucosidase inhibition. However, TFC and *α*-glucosidase inhibition depicted a significant correlation with *α*-amylase inhibition. TFC exhibited a significant positive correlation with alpha-amylase and glucosidase. The *α*-glucosidase inhibition and antioxidant activity depicted a significant linear correlation, indicating that good antioxidant status results in better inhibition.

Table 4.15: Correlation Analysis of TPC, TFC, DPHH, Alpha amylase, and Alpha Glucosidase inhibition.

	Amy_Meth	Amy_Aqu	Glu_Meth	Glu_Aqu	Phen	Flav	DPPH
Amy_Meth	1.00						
Amy_Aqu	0.81***	1.00					
Glu_Meth	0.65***	0.51***	1.00				
Glu_Aqu	0.78***	0.76***	0.91***	1.00			
Phen	0.83***	0.81***	-0.09^{ns}	0.40^{ns}	1.00		
Flav	0.57*	0.78***	0.37^{ns}	0.79***	0.44ns	1.00	
DPPH	0.25*	0.08^{ns}	0.70***	0.58*	-0.07^{ns}	0.22^{ns}	1.00

N=75 for all the parameters except Phenolics and Flavinoids (n=15). The correlation values significant at P<0.05, 0.01, and 0.001 are represented by *, **, and ***.

4.1.11 LC-MS-ESI-QTOF characterization of ethanolic extracts of *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata, Urtica dioica,* and *Zanthoxylum armatum*

All five plant extracts were subjected to untargeted metabolic screening through LC-MS ESI-QTOF.

4.1.11.1: LC-MS Analysis of Acacia catechu heartwood (Fig 4.11)

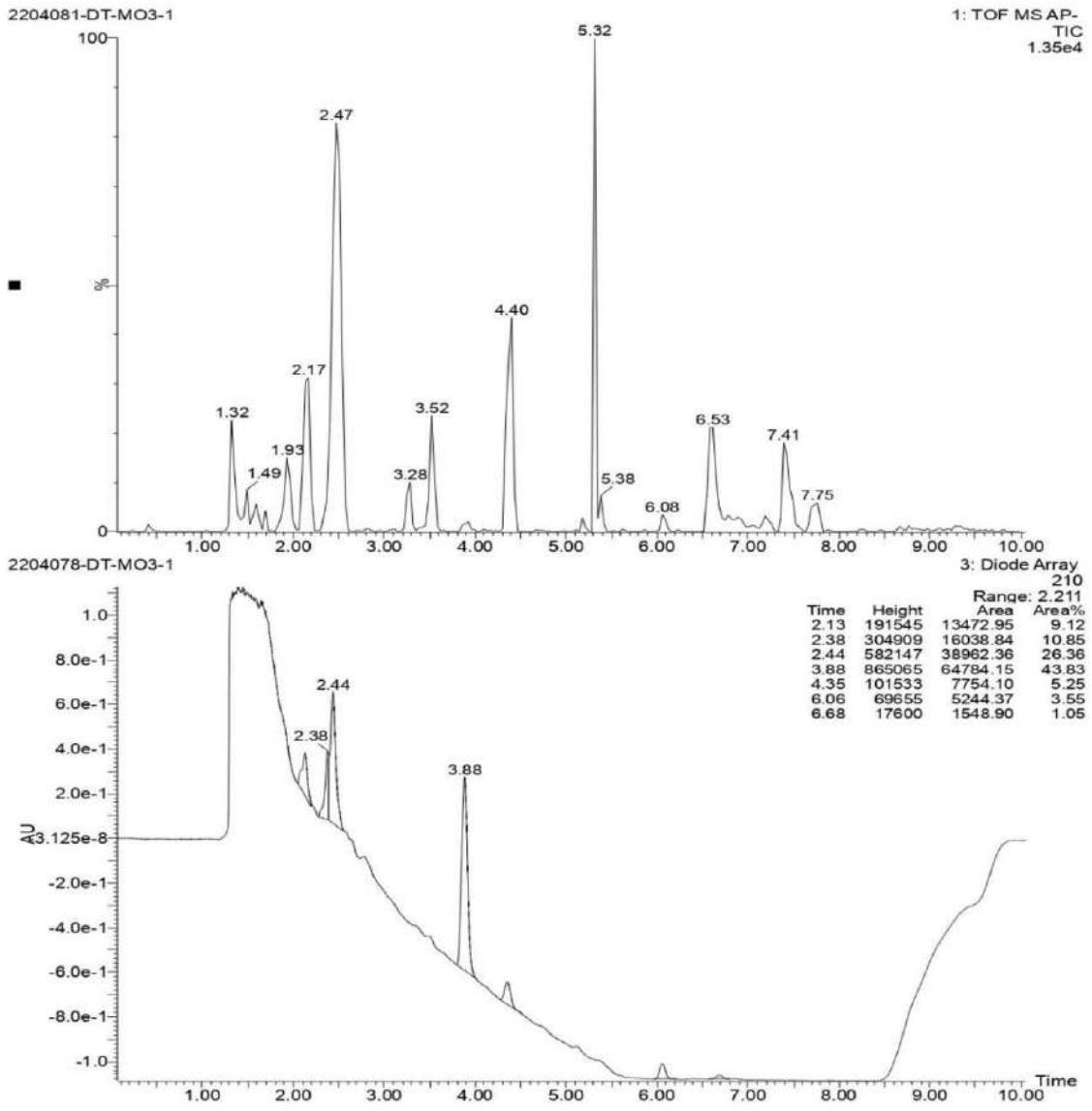
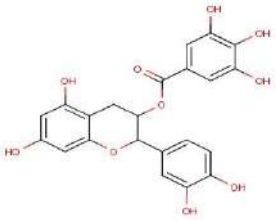
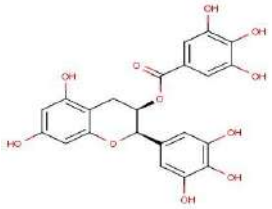
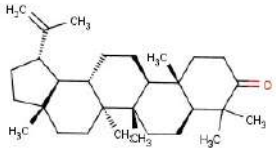
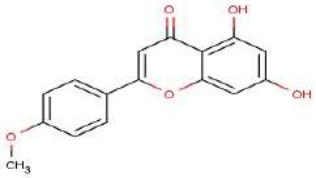
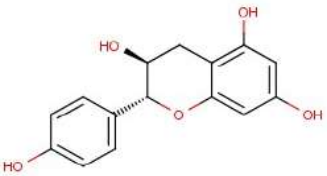
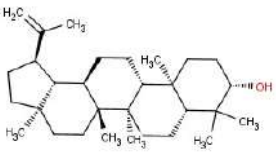
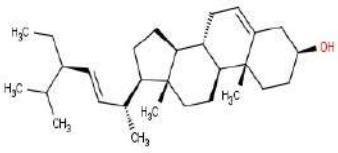
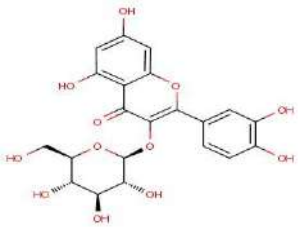
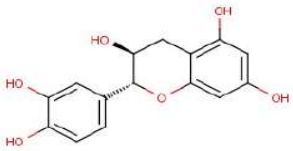
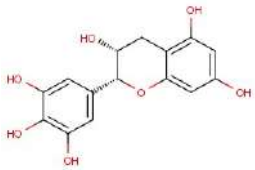
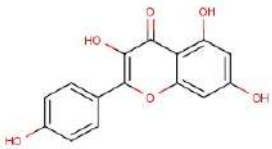
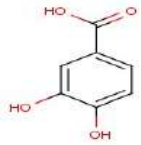
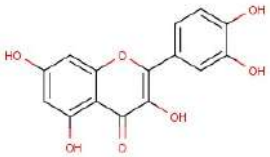
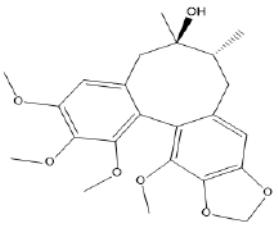


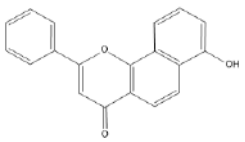
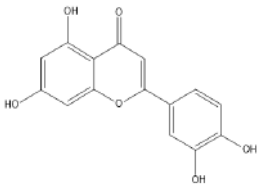
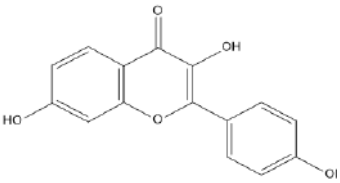
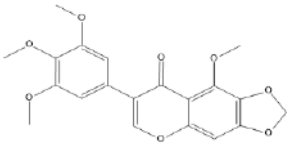
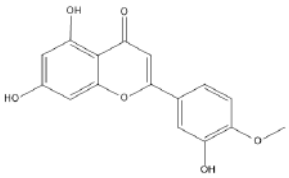
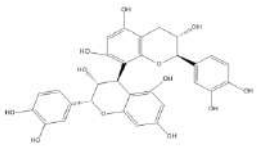
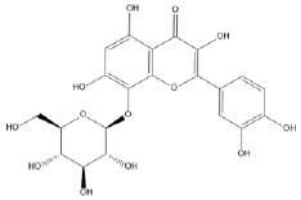
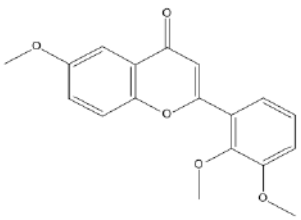
Figure 4.11: Total Ion Chromatogram of *Acacia catechu* LC- MS

About 23 compounds were annotated from the heartwood extract of *Acacia catechu* (Table 4.16 and Fig. 4.12a-n) the potent Epicatechin gallate, Epigallocatechin gallate, Lupenone, Acacetin, Afzelechin, Lupeol, Poriferasterol, Isoquercetin, Catechin, Epicatechin, Epigallocatechin, Kaempferol, Protocatechuic acid, Quercetin and Taxifolin are few metabolites with myriad of bioactivities (Shen *et al.,* 2006; Laxmi, 2017; Panya *et al.,* 2019; Wang *et al.,* 2019; Aryal, 2021)

Table 4.16: Annotated compounds of the *Acacia catechu* -LC-MS -ESI-QTOF analysis

Compound	Mol. Formula	Mol. Weight (m/z)	Retention Time	Structure	Reference
Epicatechin gallate	$C_{22}H_{18}O_{10}$	442.36	1.32		Aryal *et al.*, 2021
Epigallocatechin gallate	$C_{22}H_{18}O_{11}$	458.35	1.49		Aryal *et al.*, 2021
Lupenone	$C_{30}H_{48}O$	424.21	1.93		Aryal *et al.*, 2021
Acacetin	$C_{16}H_{12}O_5$	284.14	2.17		Yin *et al.*, 2019
Afzelechin	$C_{15}H_{15}O_5$	274.01	2.47		Hong *et al.*, 2015; Aryal *et al.*, 2021
Lupeol	$C_{30}H_{50}O$	426.32	3.28		Amoussa *et al.*, 2016
Poriferasterol	$C_{29}H_{48}O$	412.31	3.52		Shen *et al.*, 2006

Isoquercetin	$C_{21}H_{20}O_{12}$	464.12	4.40		Aryal *et al.*, 2021
Catechin	$C_{15}H_{14}O_6$	290.08	5.32		Shen *et al.*, 2006;Shi *et al.*, 2016
Epigallocatechin	$C_{15}H_{14}O_7$	306.07	5.38		Freidrich *et al.*, 2000; Shen *et al.*, 2006
Kaempferol	$C_{15}H_{10}O_6$	286.13	6.08		Santos *et al.*, 2021,Aryal *et al.*, 2021
Protocatechuic acid	$C_7H_6O_4$	154.23	6.53		Singh *et al.*, 2009
Quercetin	$C_{15}H_{10}O_7$	302.21	7.41		Aryal *et al.*, 2021
Taxifolin	$C_{15}H_{22}O_7$	304.01	7.75		Laxmi *et al.*, 2019
Gomisin	$C_{23}H_{28}O_6$	418.196	1.980		Aryal *et al.*, 2021

2'-Hydroxy-a-naphtho-flavone	$C_{19}H_{12}O_3$	287.0937	2.27		Aryal *et al.*, 2021
Luteolin	$C_{15}H_{10}O_6$	285.1135	2.894		Yilmaz *et al.*, 2018
3,7,4'-Trihydroxyflavone	$C_{15}H_{10}O_5$	271.0971	3.6		Li *et al.*, 2011; Aryal *et al.*, 2021
Irisflorentin	$C_{20}H_{18}O_8$	381.1242	3.6		Roger *et al.*, 2012; Aryal *et al.*, 2021
Diosmetin	$C_{16}H_{12}0_6$	301.1111	3.6		Aryal *et al.*, 2021
Procyanidin B1	$C_{30}H_{26}O_{13}$	579.2104	3.6		Shen *et al.*, 2006; Aryal *et al.*, 2021
Gossypin	$C_{21}H_{20}O_{13}$	482.24			Petsalo *et al.*, 2006; Aryal *et al.*, 2021
2',3',6-Trimethoxyflavone	$C_{18}H_{16}O_5$	313.287	4.943		Aryal *et al.*, 2021

LC-MS analysis of *Acacia catechu* (Fig. 4.12a-n)

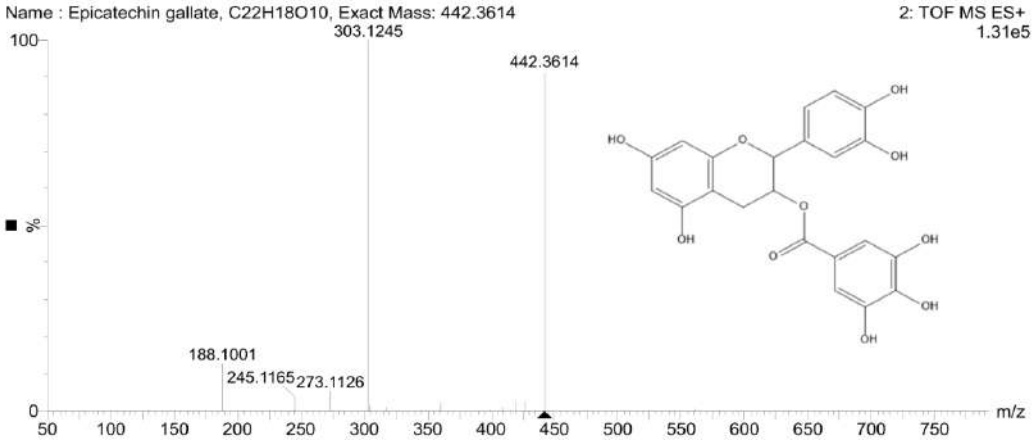


Figure 4.12a: LC-MS Mass spectrum of Epicatechin gallate in *Acacia catechu*

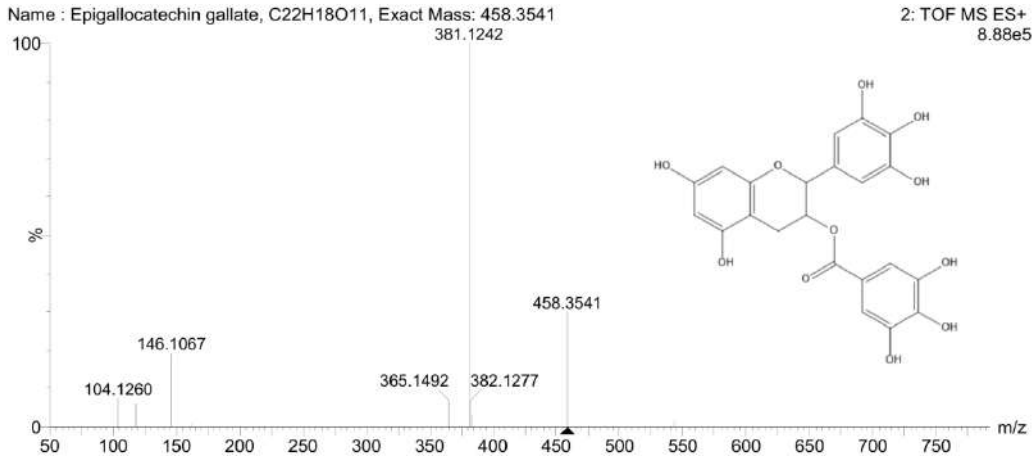


Figure 4.12b: Mass fragmentation of Epigallocatechin gallate in *Acacia catechu*

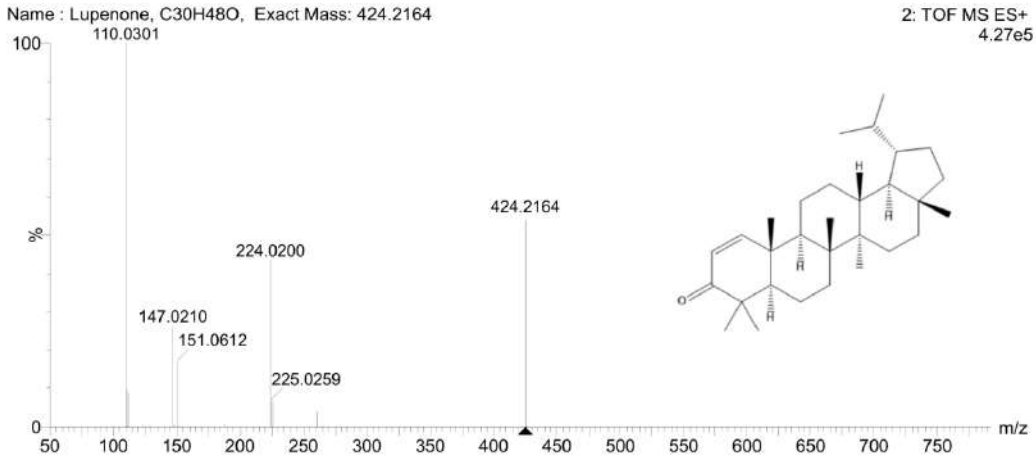


Figure 4.12c: Mass fragmentation of Lupenone in *Acacia catechu*

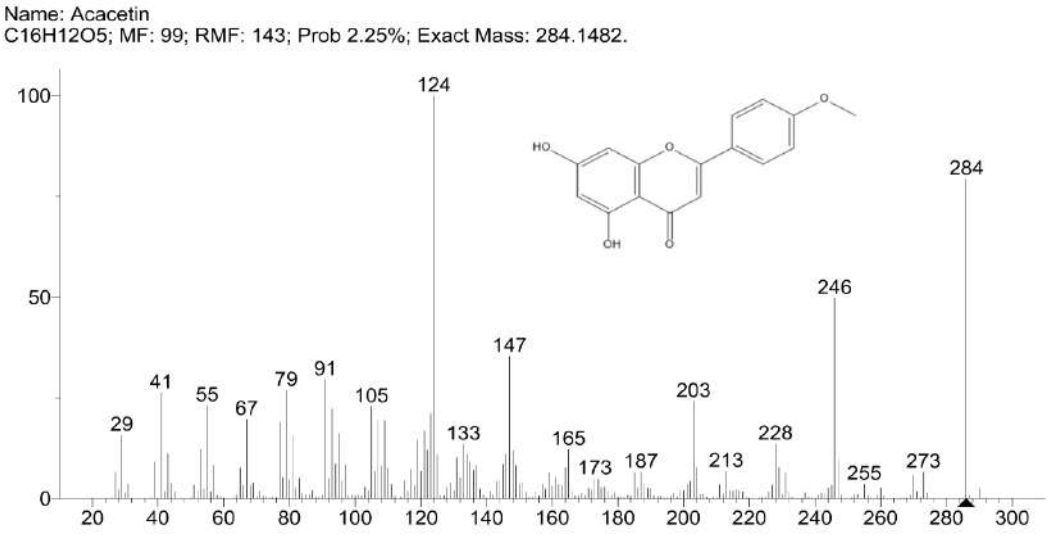


Figure 4.12d: Mass fragmentation of Acacetin in *Acacia catechu*

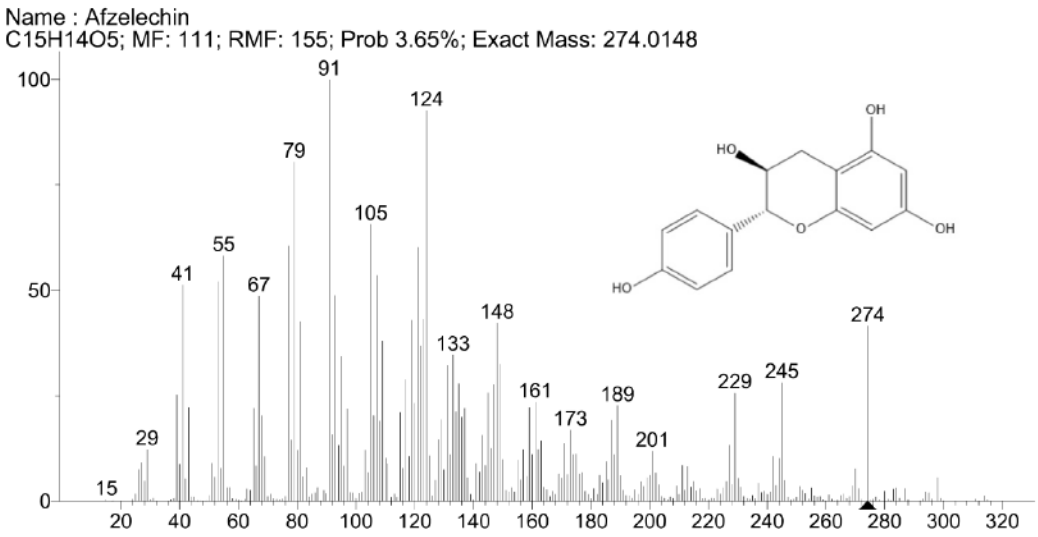


Figure 4.12e: Mass fragmentation of Afzelechin in *Acacia catechu*

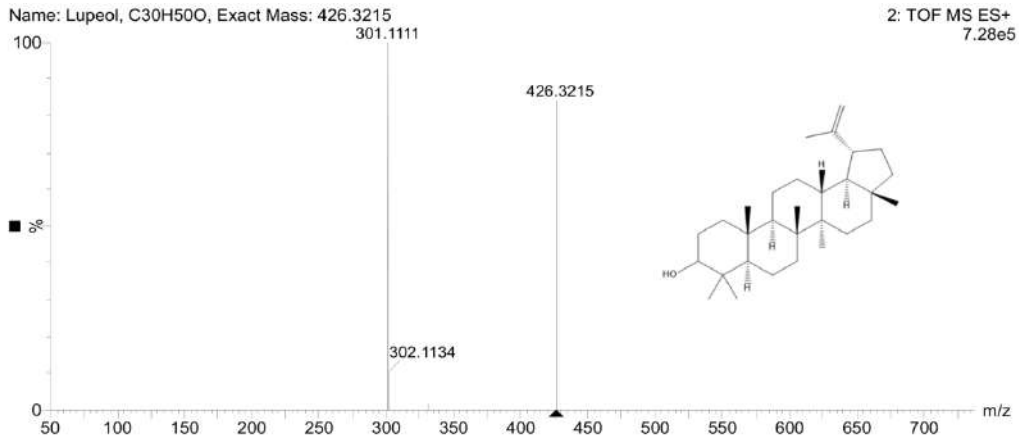


Figure 4.12f: Mass fragmentation of Lupeol in *Acacia catechu*

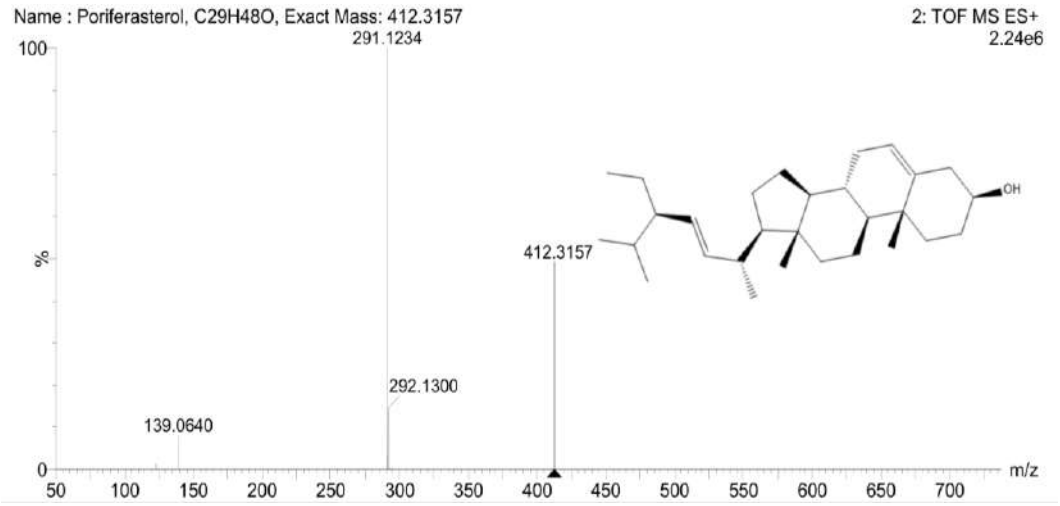


Figure 4.12g: Mass fragmentation of Poriferasterol in *Acacia catechu*

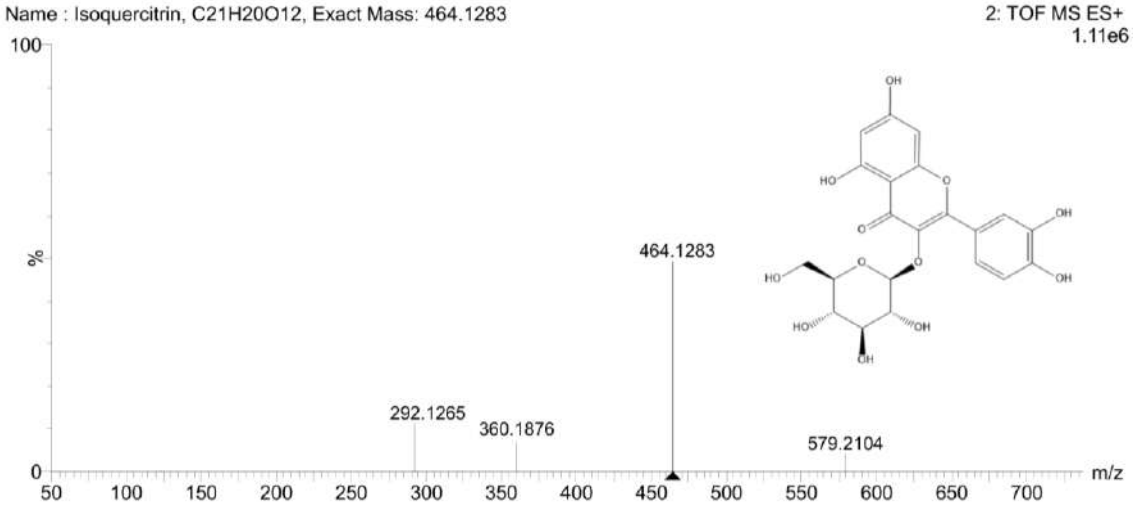


Figure 4.12h: Mass fragmentation of Isoquercetin in *Acacia catechu*

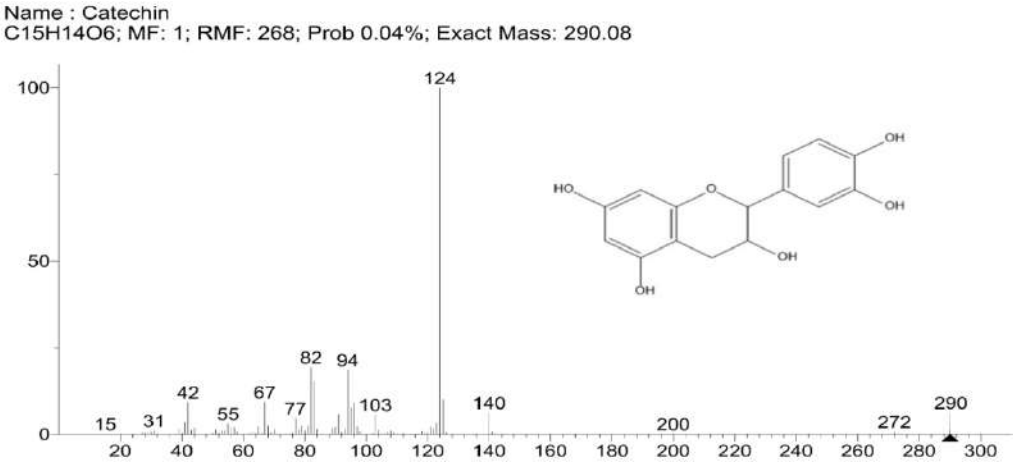


Figure 4.12i: Mass fragmentation of Catechin in *Acacia catechu*

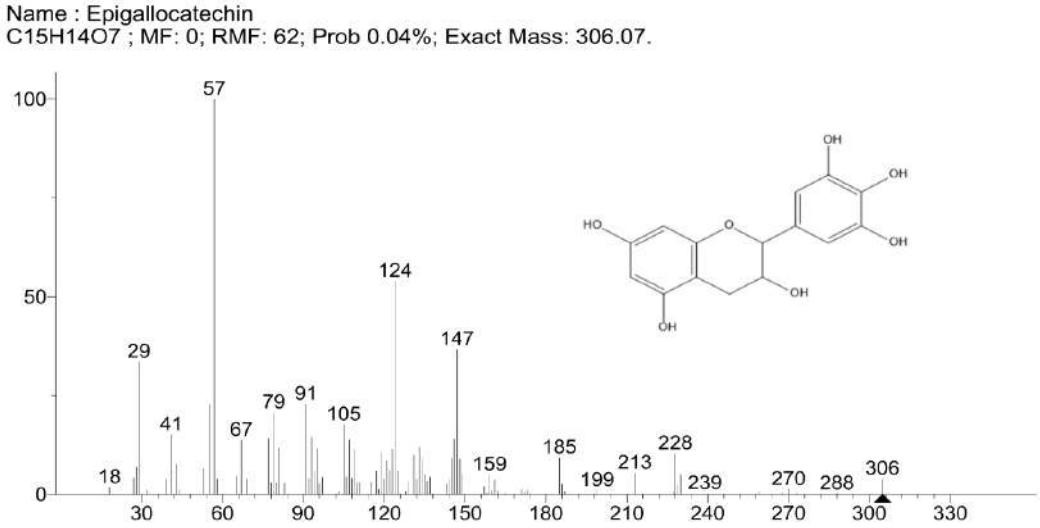


Figure 4.12j: Mass fragmentation of Epigallocatechin in *Acacia catechu*

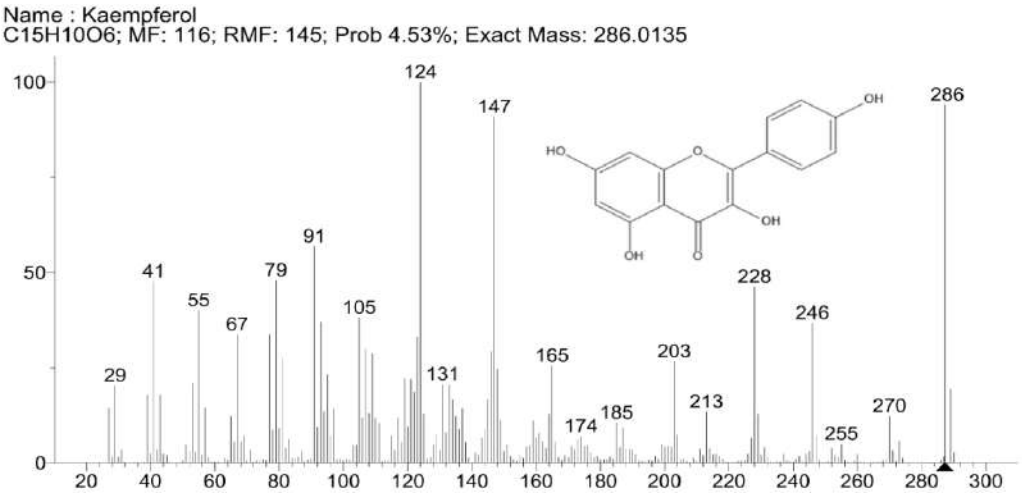


Figure 4.12k: Mass fragmentation of Kaempferol in *Acacia catechu*

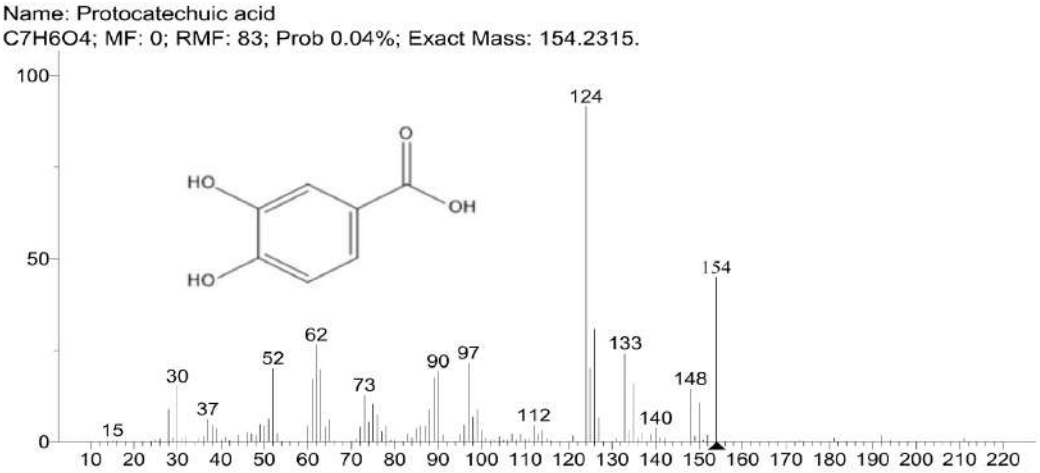


Figure 4.12l: Mass fragmentation of Protocatechuic acid in *Acacia catechu*

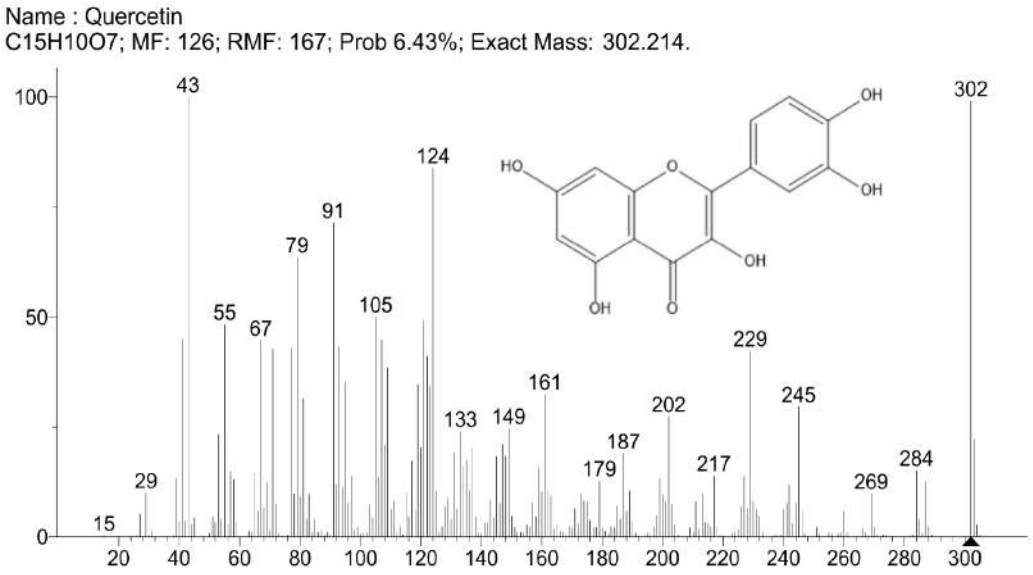


Figure 4.12m: Mass fragmentation of Quercetin acid in *Acacia catechu*

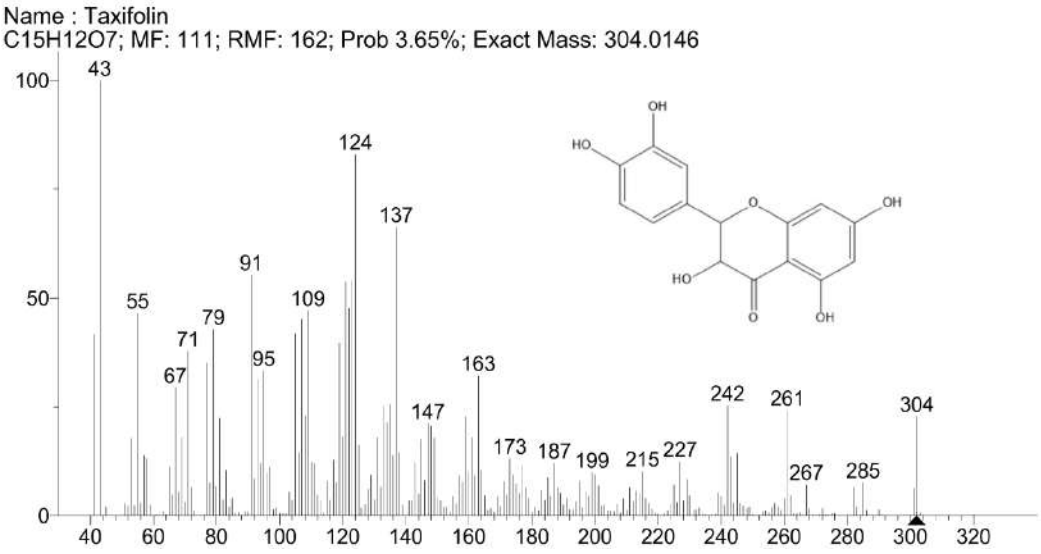


Figure 4.12n: Mass fragmentation of Taxifolin in *Acacia catechu*

4.1.11.2: LC-MS Analysis of *Ajuga bracteosa* Leaves

The LC-MS profiling of *Ajuga bracteosa* leaves led to the isolation of 17 compounds (Table 4.17; Fig. 4.13). The compounds were annotated with a comparison with published literature (Medjeldi *et al.,* 2018; Khatteli *et al.,* 2020; Goger *et al.,* 2021).

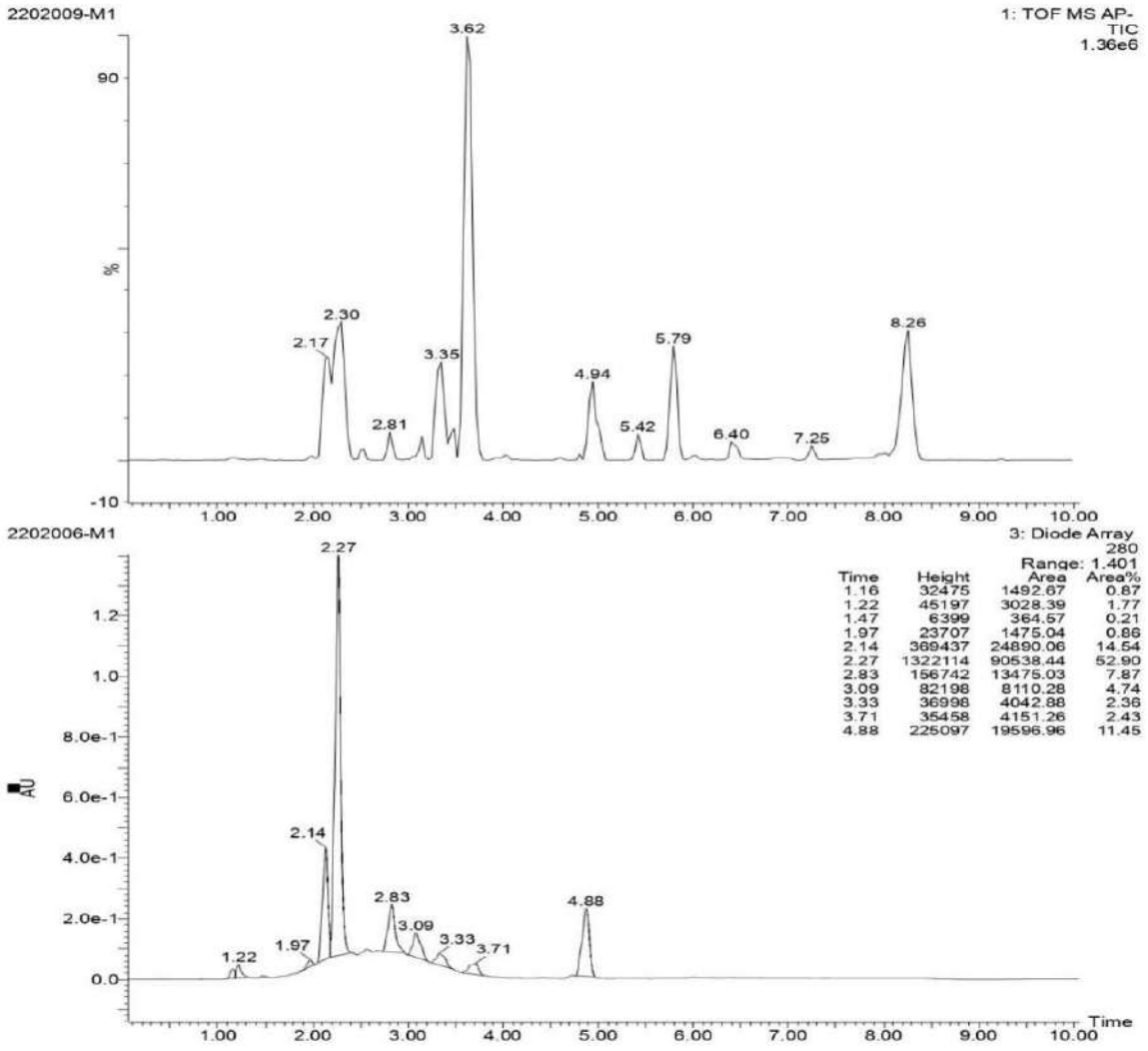
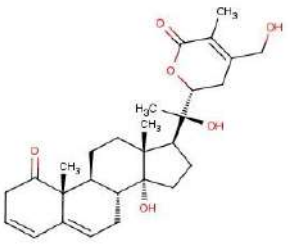
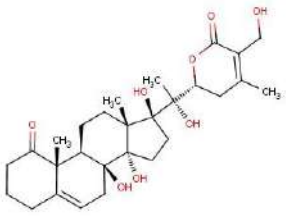
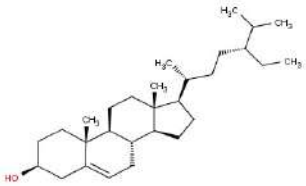
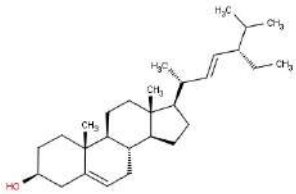
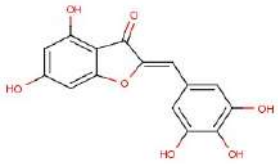
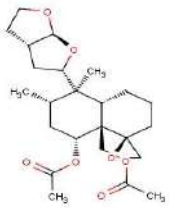
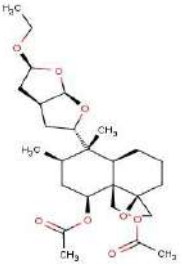
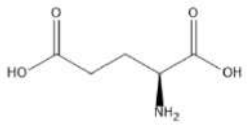
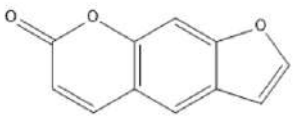
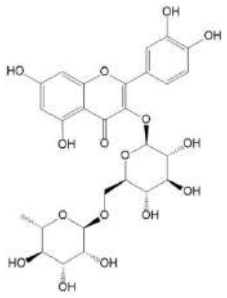
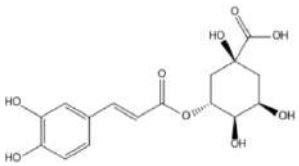
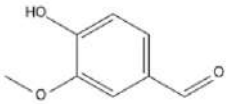
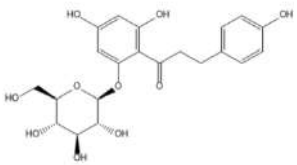
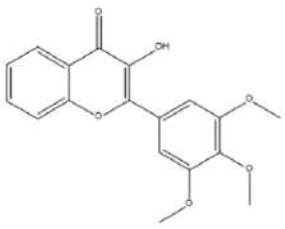


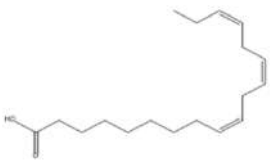
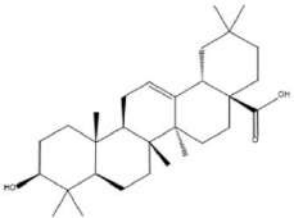
Figure 4.13: Total Ion Chomatogram (TIC) of *Ajuga bracteosa* leaves

Table 4.17: Annotated compounds in *Ajuga bracteosa* leaves

Compound	Mol. Formula	m/z	RT	Structure	Reference
Ajugin A	$C_{28}H_{38}O_6$	470.35	3.33		Kumari *et al.*, 2023

Ajugin D	$C_{28}H_{40}O_8$	504.62	2.14		Kumari *et al.*, 2023
Ajugin E	$C_{28}H_{38}O_7$	486.64	1.97		Kumari *et al.*, 2023
Beta-Sitosterol	$C_{29}H_{50}O$	414.71	3.09		Verma *et al.*, 2002
Stigmasterol	$C_{29}H_{48}O$	412.76	2.27		Verma *et al.*, 2002
Bracteatin	$C_{15}H_{10}O_7$	302.45	2.83		Riaz *et al.*, 2004,Castro *et al.*, 2011
Dihydroclerodin	$C_{24}H_{36}O_7$	436.56	1.22		Riaz *et al.*, 2004
Clerodinin D	$C_{26}H_{40}O_8$	480.63	3.71		Riaz *et al.*, 2004; Castro *et al.*, 2011

Glutamic acid	$C_5H_9NO_4$	149.1	2.082		Goger *et al.,* 2021
Azelaic acid	$C_9H_{16}O_4$	188.1	2.082		Goger *et al.,* 2021
Psoralen	$C_{11}H_6O_3$	186.16	2..082		Tine *et al.,* 2017
Rutin	$C_{27}H_{30}O_{16}$	611.3	2.082		Khatteli *et al.,* 2020
Chlorogenic acid	$C_{16}H_{18}O_9$	482.1	1.304		Khatteli *et al.,* 2020
Vanillin	$C_8H_8O_3$	151.1	151.119		Zahra *et al.,* 2017
Phloridzin	$C_{21}H_{24}O_{10}$	435.3	3.910		Du *et al.,* 2021
3-Hydroxy-3',4',5'-trimethoxyflavone	$C_{18}H_{16}O_6$	327.2	3.824		Hussain *et al.,* 2012

Linolenic acid	$C_{18}H_{30}O_2$	279.2	6.060		Goger *et al.*, 2021
Oleanolic acid	$C_{30}H_{48}O_3$	479.1	3.893		Goger *et al.*, 2021

LC-MS Mass spectrum of *Ajuga bracteosa* (Fig. 4.14(a-h))

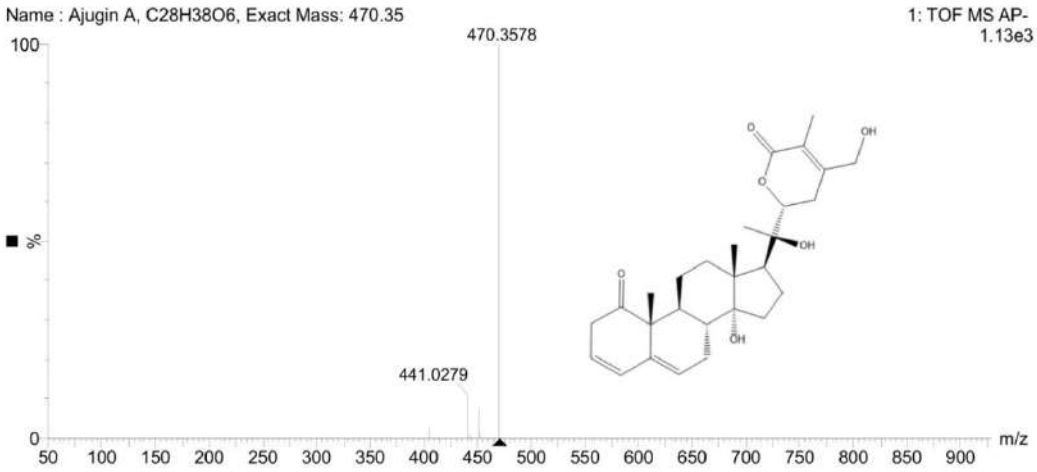


Figure 4.14a: Mass fragmentation of Ajugin A in *Ajuga bracteosa*

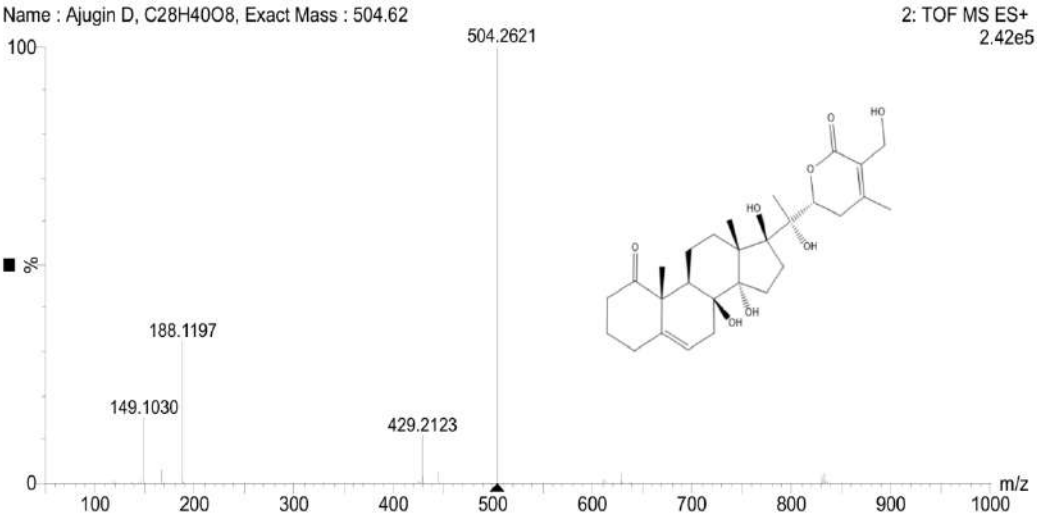


Figure 4.14b: Mass fragmentation of Ajugin D in *Ajuga Bracteosa*

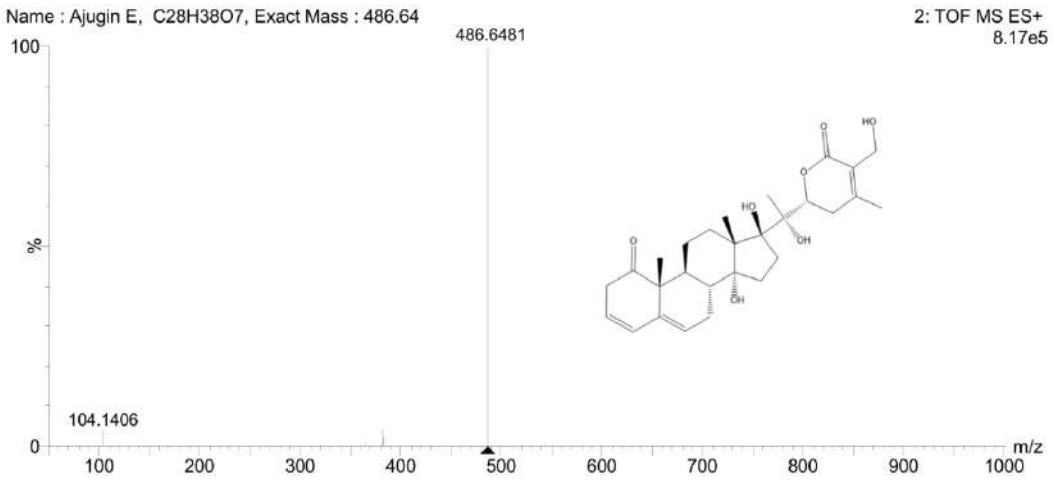


Figure 4.14c: Mass fragmentation of Ajugin E in *Ajuga bracteosa*

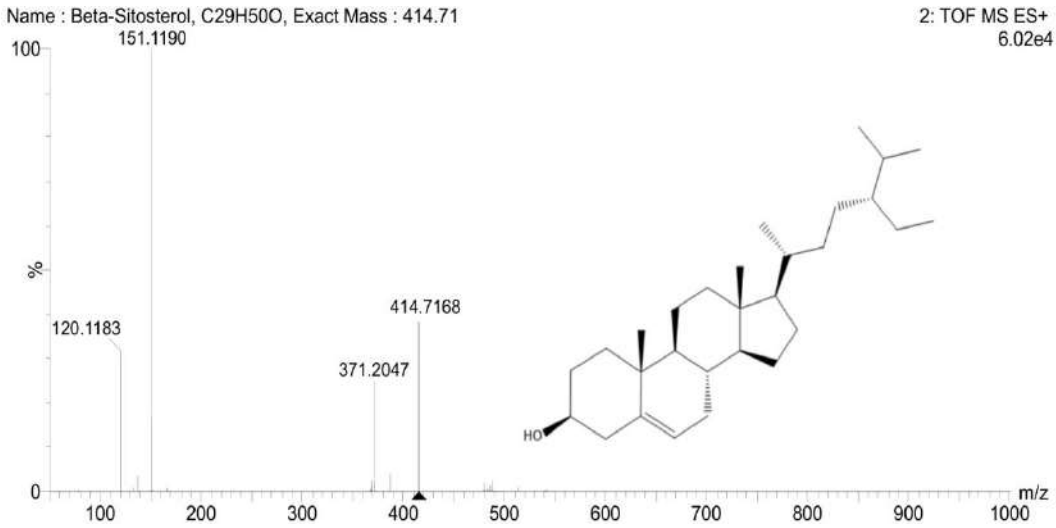


Figure 4.14d: Mass fragmentation of Beta-Sitosterol in *Ajuga bracteosa*

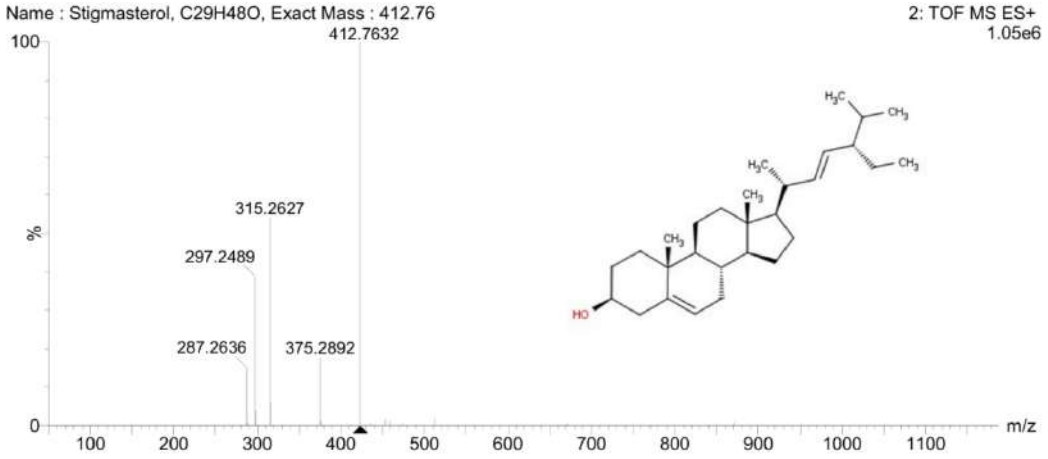


Figure 4.14e: Mass fragmentation of Stigmasterol in *Ajuga Bracteosa*

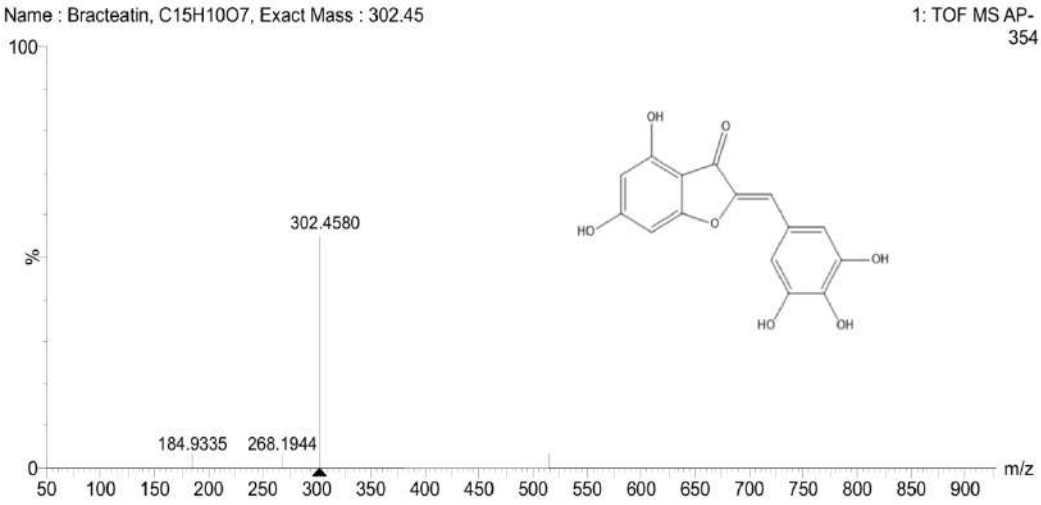


Figure 4.14f: Mass fragmentation of Bracteatin in *Ajuga bracteosa*

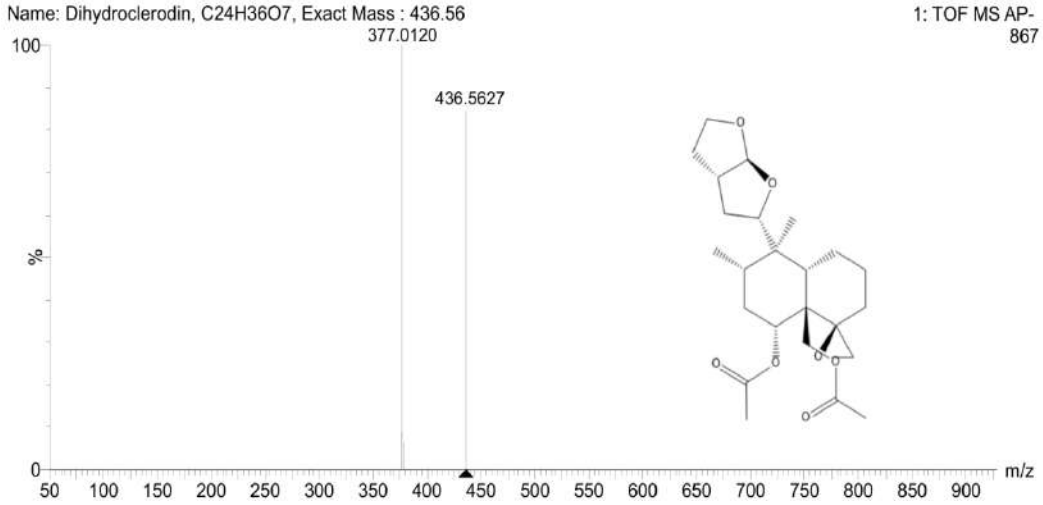


Figure 4.14g: Mass fragmentation of Dihydroclerodin in *Ajuga bracteosa*

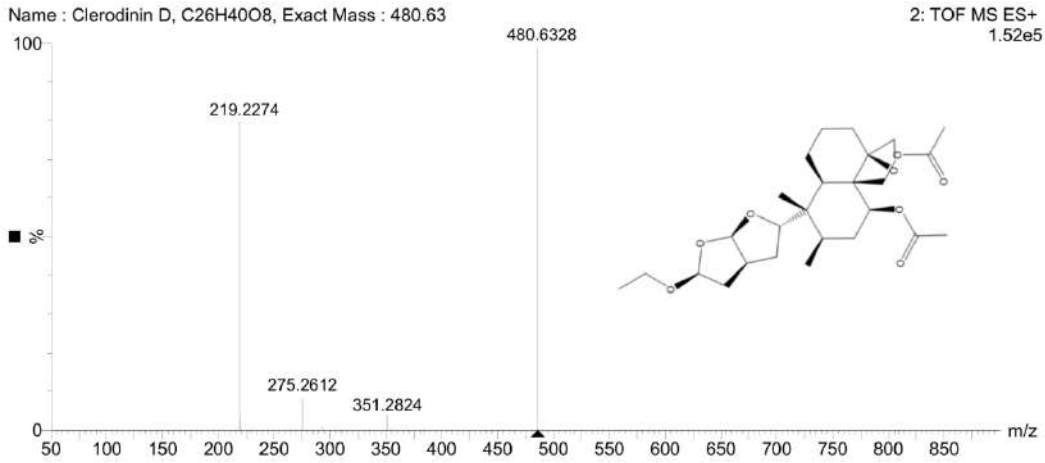


Figure 4.14h: Mass fragmentation of Clerodinin D in *Ajuga bracteosa*

4.1.11.3: LC-MS Analysis of *Bergenia ciliata* rhizome (Fig. 4.15)

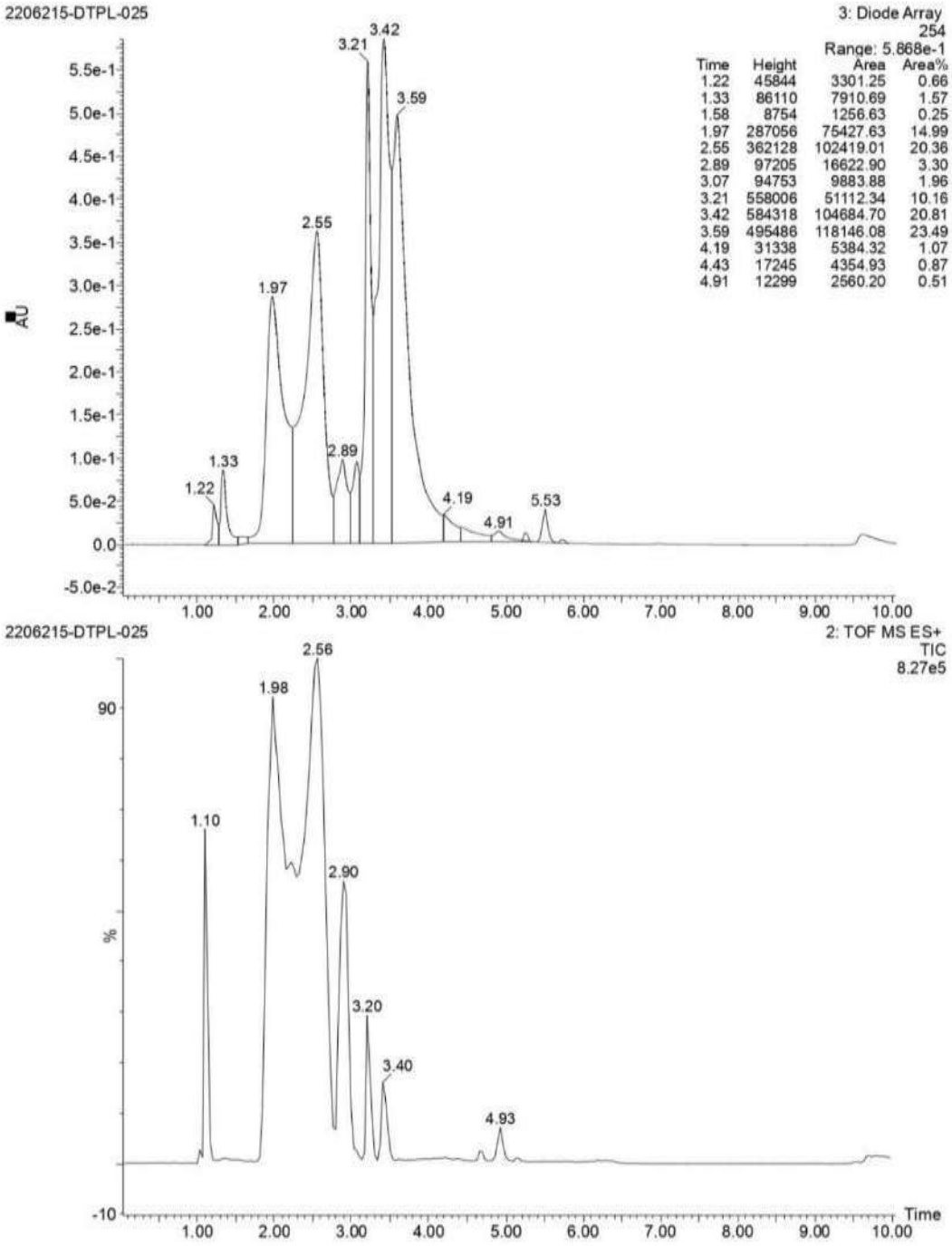


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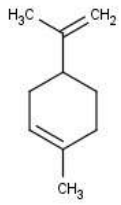
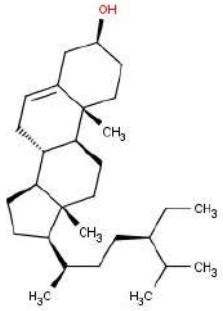
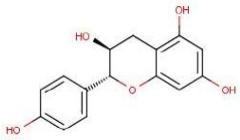
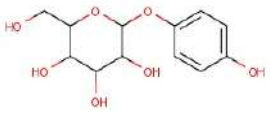
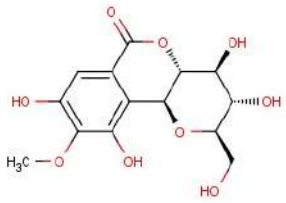
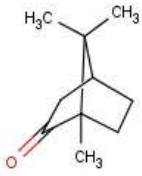
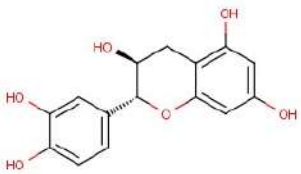
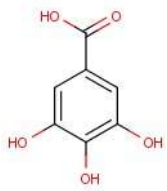
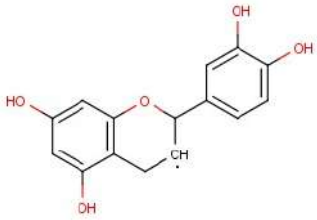
Figure 4.15: Total Ion Chromatogram of *Bergenia ciliata* rhizome

Nine molecules were isolated from *Bergenia ciliata* rhizome extract through LC-MS in 10 minutes run time (Table 4.18; Fig. 4.15).

Table 4.18: Annotated compounds in *Bergenia ciliata* rhizome

Compound	Mol. Formula	m/z	Structure	Reference
Limonene	$C_{10}H_{16}$	136.12		Kashima *et al.*, 2011
Beta-Sitosterol	$C_{29}H_{50}O$	414.38		Dharmender *et al.*, 2010
Afzelechin	$C_{15}H_{14}O_5$	274.08		Sapkota *et al.*, 2022
Arbutin	$C_{12}H_{16}O_7$	272.08		Pandey *et al.*, 2017
Bergenin	$C_{14}H_{16}O_9$	328.27		Sapkota *et al.*, 2022
Camphor	$C_{10}H_{16}O$	152.12		Kashima *et al.*, 2011
Catechin	$C_{15}H_{14}O_6$	290.033		Shen *et al.*, 2006;Pandey *et al.*, 2017

Gallic Acid	$C_6H_2(OH)_3COOH$	170.12		Pandey *et al.*, 2017
Galloylcatechin	$C_{22}H_{18}O_{18}$	273.07		Bhandari *et al.*, 2008

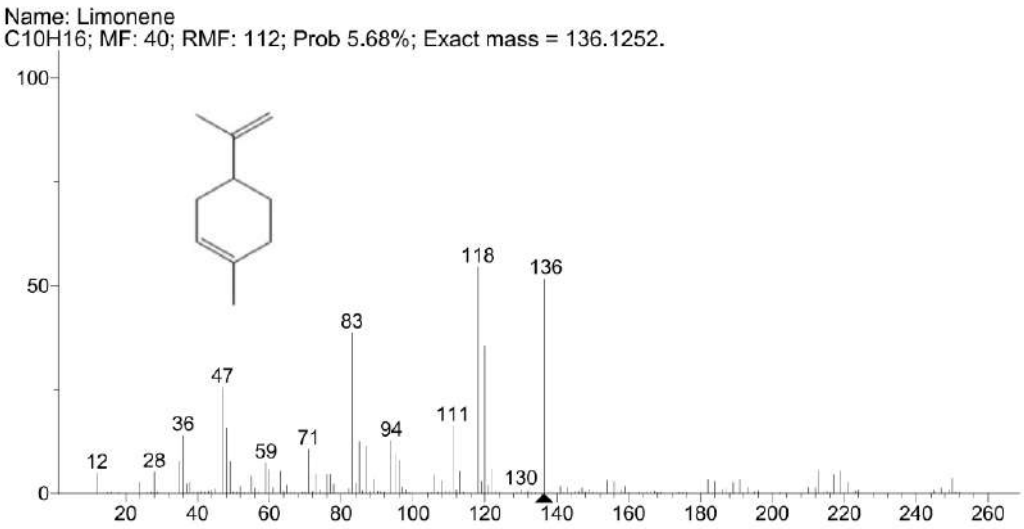


Figure 4.16a: Mass fragmentation of Limonene in *Bergenia ciliata*

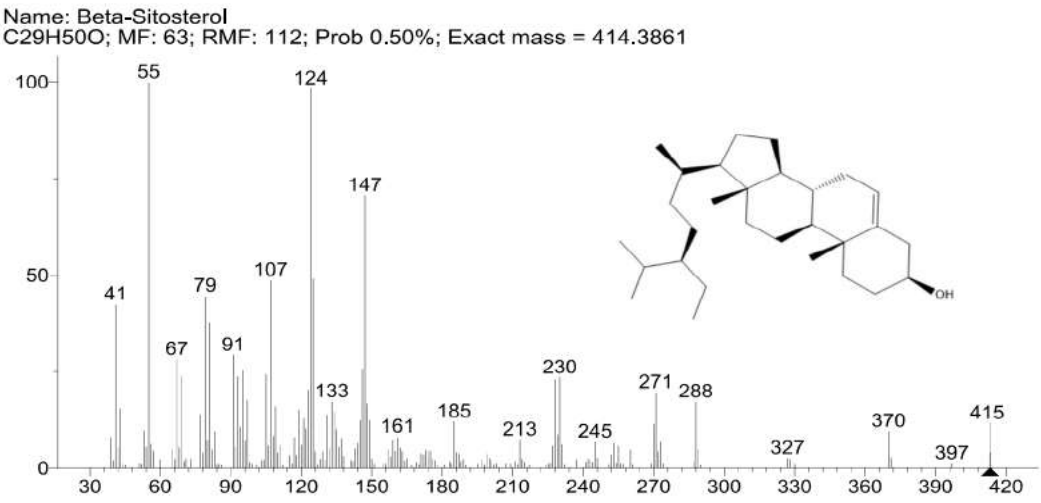


Figure 4.16b: Mass fragmentation of the Beta-Sitosterol in *Bergenia ciliata*

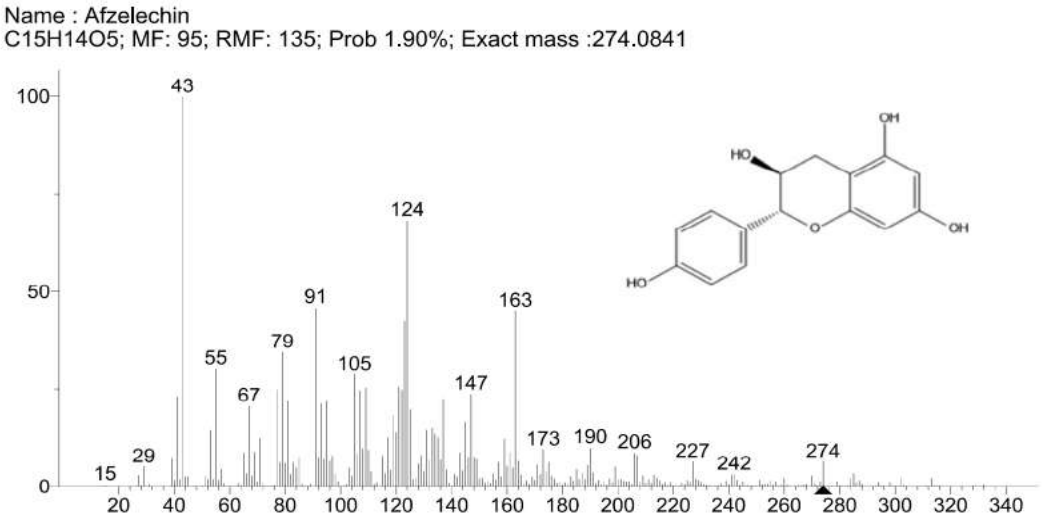


Figure 4.16c: Mass fragmentation of the Afzelechin in *Bergenia ciliata*

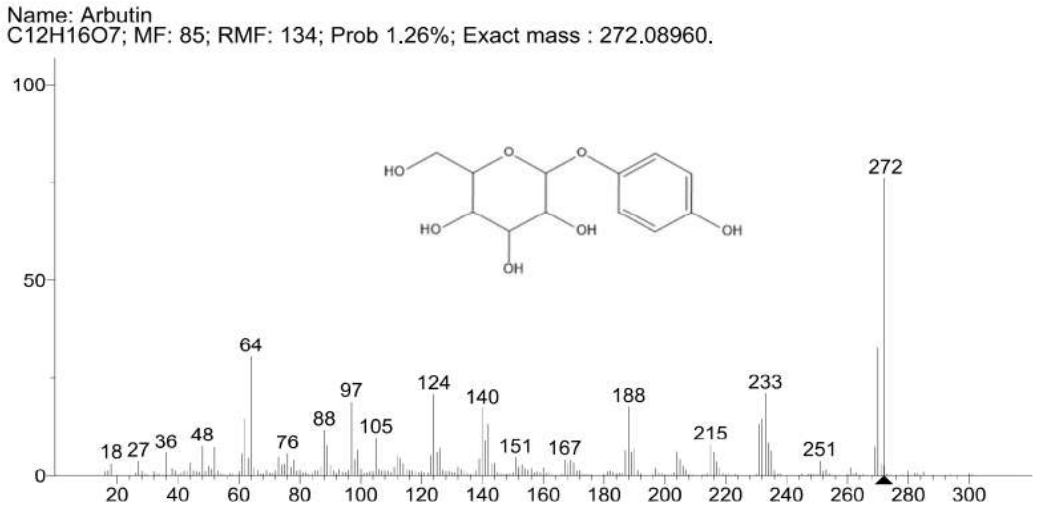


Figure 4.16d: Mass fragmentation of the Arbutin in *Bergenia ciliata*

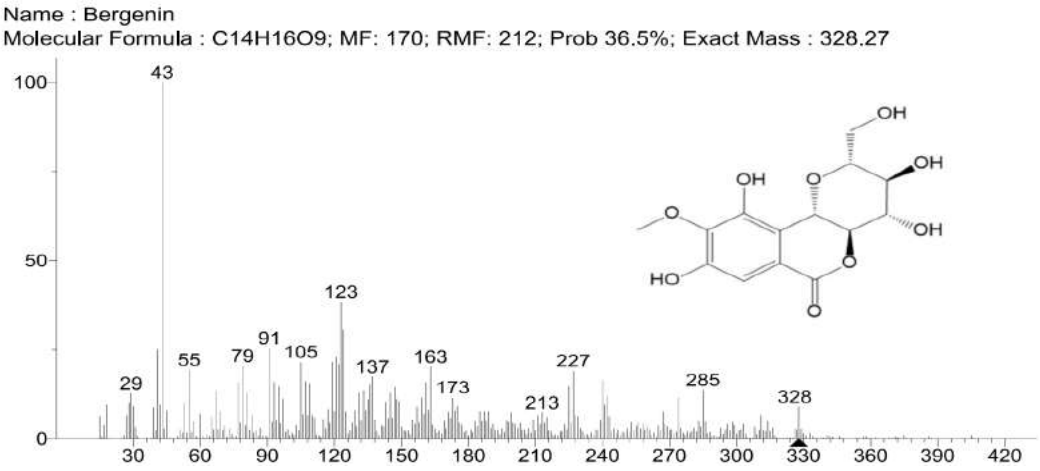


Figure 4.16e: Mass fragmentation of Bergenin in *Bergenia ciliata*

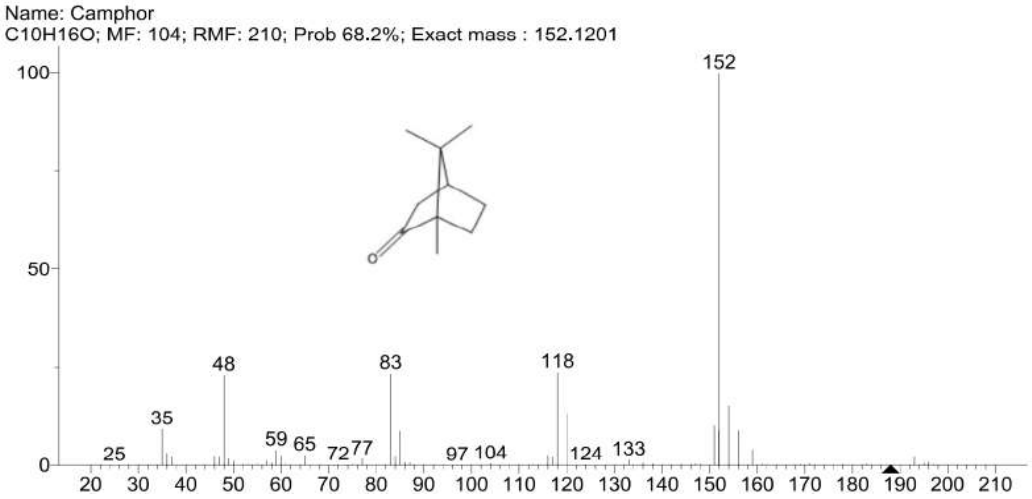


Figure 4.16f: Mass fragmentation of Camphor in *Bergenia ciliata*

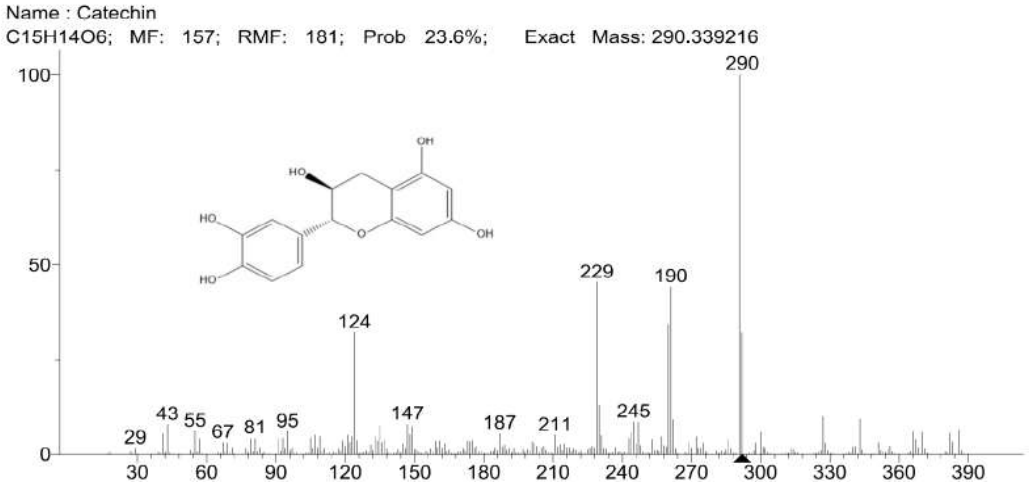


Figure 4.16g: LC-MS Mass Spectrum of Catechin in *Bergenia ciliata*

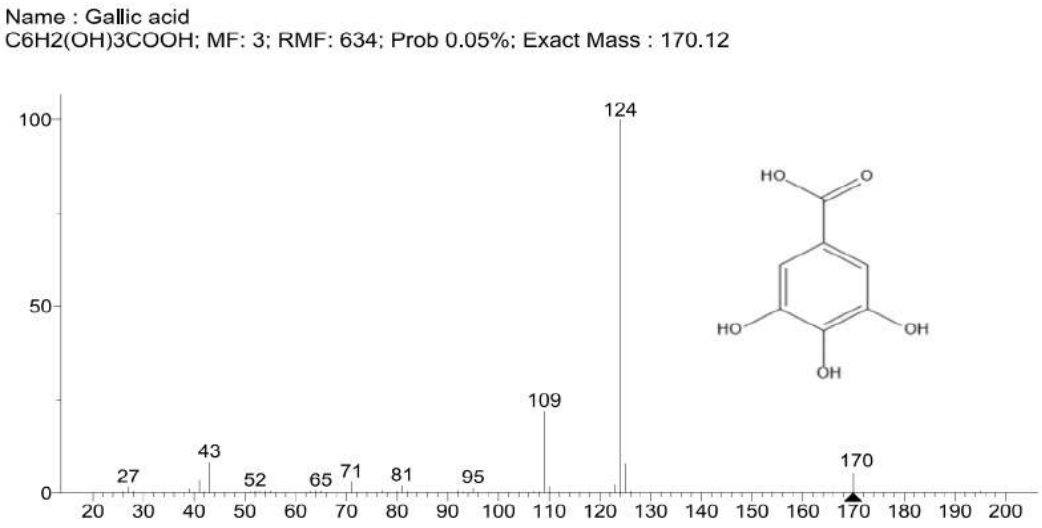


Figure 4.16h: Mass fragmentation of Gallic Acid in *Bergenia ciliata*

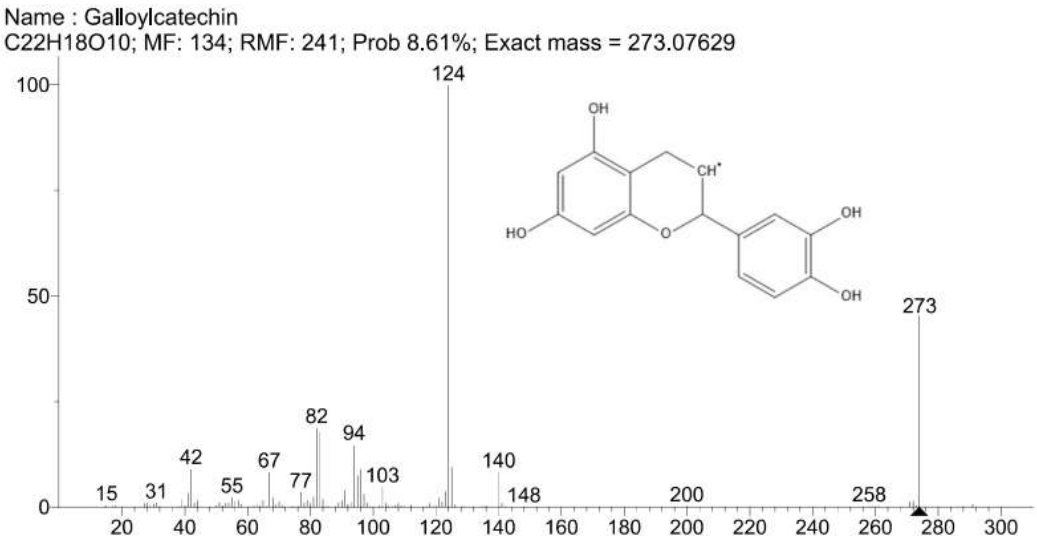


Figure 4.16i: Mass fragmentation of Galloylcatechin in *Bergenia ciliata*

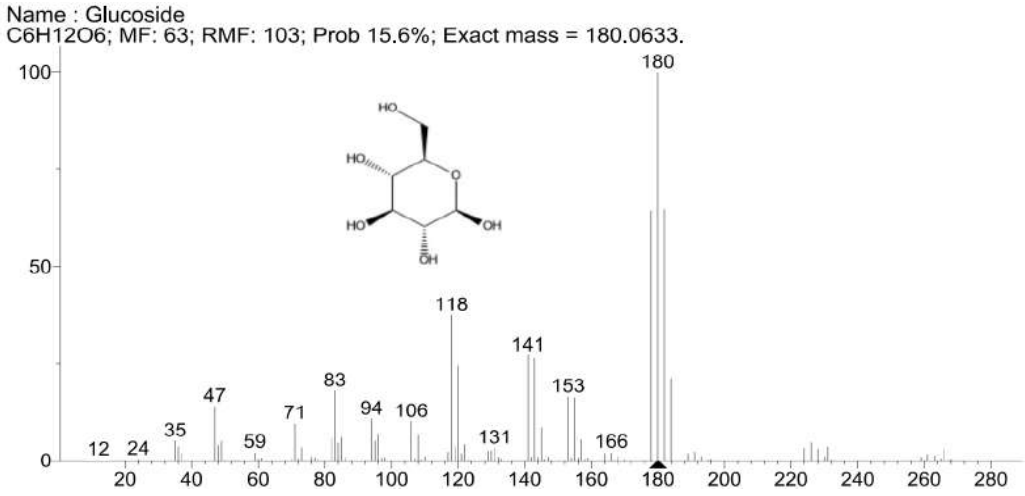


Figure 4.16j: Mass fragmentation of Glucoside in *Bergenia ciliata*

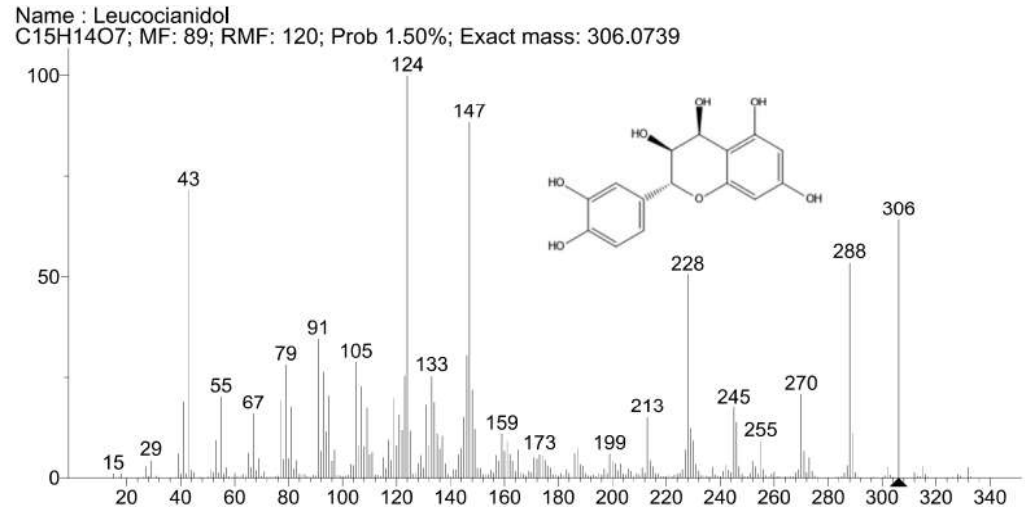


Figure 4.16k: Mass fragmentation of Leucocianidol in *Bergenia ciliata*

4.1.11.4: LC-MS Analysis of *Urtica dioica* leaves (Fig. 4.17)

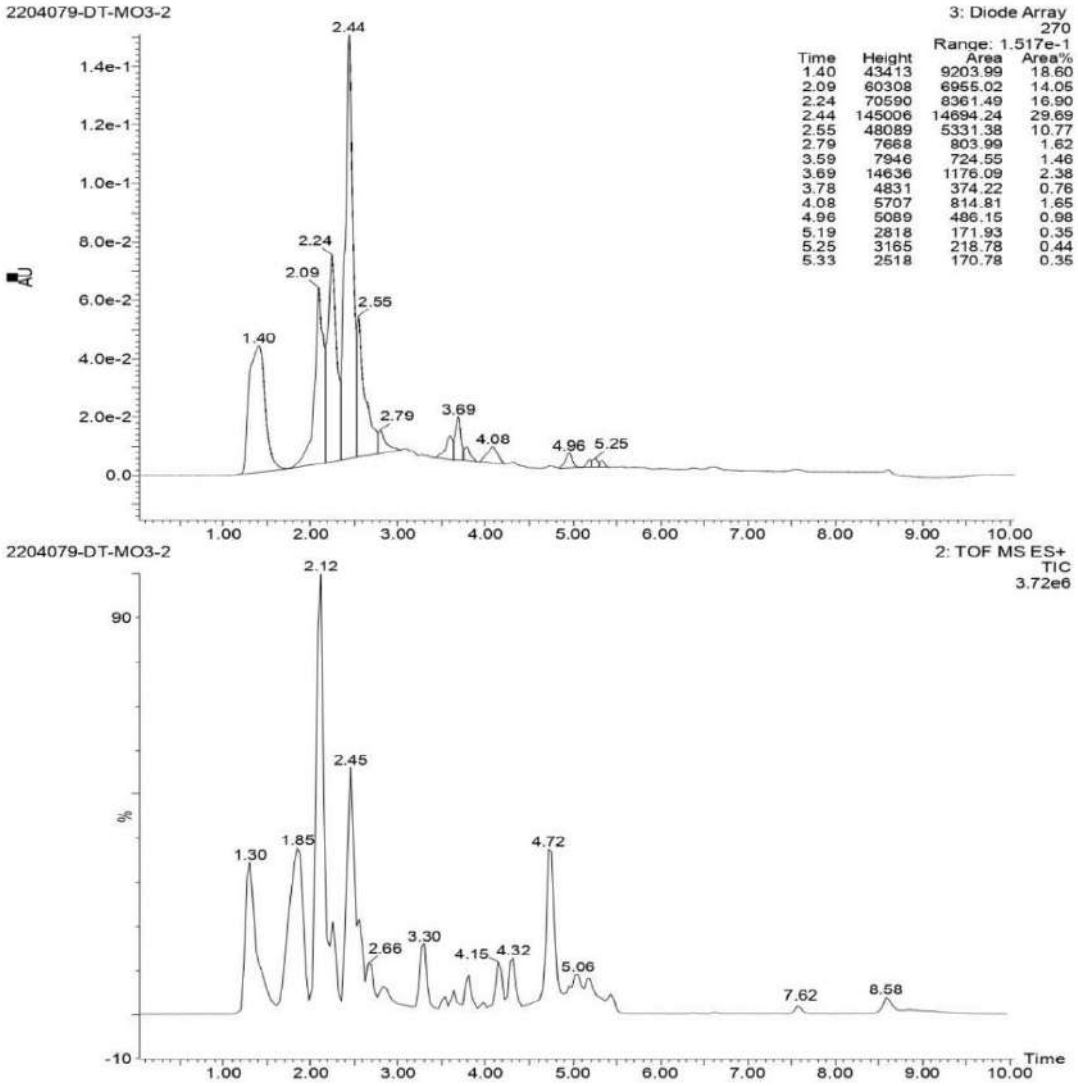
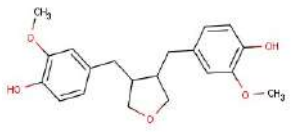
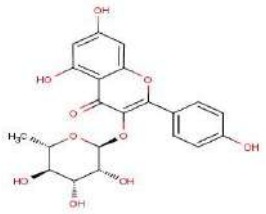
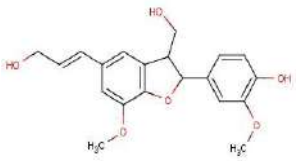
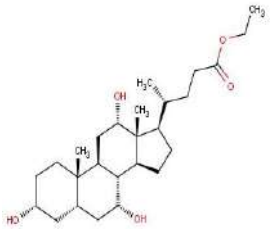
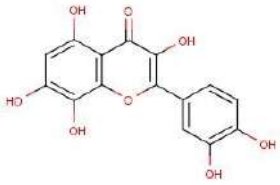
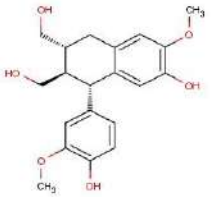
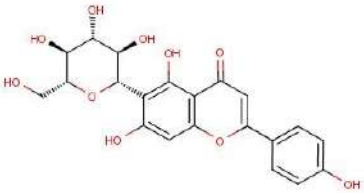
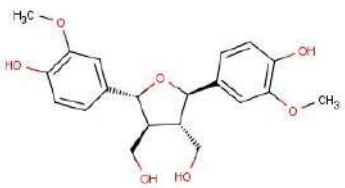


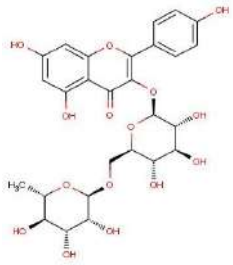
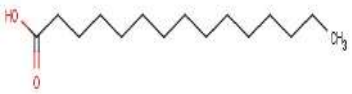
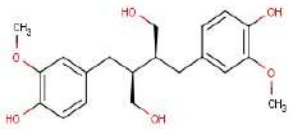
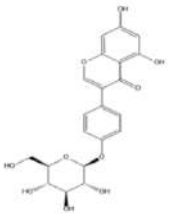
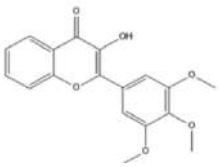
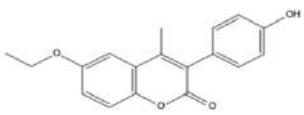
Figure 4.17: Total Ion Chromatogram of *Urtica dioica* leaves

LC-MS of *Utrica dioica* leaves led to the isolation of 14 compounds (Table 4.19, Fig. 4.18a-l).

Table 4.19: Annotated compounds in *Urtica dioica* leaves

Compound	Mol. Formula	m/z	RT	Structure	Reference
3,4-Divanillyltetrahydrofuran	$C_{20}H_{24}O_5$	344.41	4.72		Shan *et al.*, 2016

Afzelin	$C_{21}H_{20}O_{10}$	432.4	1.85		Aisha *et al.*, 2010
Dehydrodiconiferyl alcohol	$C_{20}H_{22}O_6$	358.35	4.15		Taheri *et al.*, 2022
Ethyl cholate	$C_{26}H_{44}O_5$	436.62	5.06		Taheri *et al.*, 2022
Gossypetin	$C_{15}H_{10}O_8$	318.26	1.30		Taheri *et al.*, 2022
Isolariciresinol	$C_{20}H_{24}O_6$	360.85	3.30		Zhou *et al.*, 2013
Isovitexin	$C_{21}H_{20}O_{10}$	432.46	2.12		Orcic *et al.*, 2014, Aisha *et al.*, 2010
Neoolivil	$C_{20}H_{24}O_7$	376.88	2.45		Farag *et al.*, 2013

Nicotiflorin	$C_{27}H_{30}O_{15}$	594.53	8.58		Ilham *et al.*, 2019
Pentadecanoic acid	$C_{15}H_{30}O_2$	242.48	7.62		Farag *et al.*, 2013; Franciskovic *et al.*, 2017
Secoisolariciresinol	$C_{20}H_{26}O_6$	362.46			Franciskovic *et al.*, 2011
Sophoricoside	$C_{21}H_{20}O_{10}$	433.190	2.657		Franciskovic *et al.*, 2017
3-Hydroxy-3',4',5'-trimethoxyflavone	$C_{18}H_{16}O_6$	329.175	3.707		Bhattarai *et al.*, 2022
6-Ethoxy-3 (4'-hydroxyp-henyl) -4-met-hylcoumarin	$C_{18}H_{16}O_4$	295.182	5.061		Orcic *et al.*, 2014

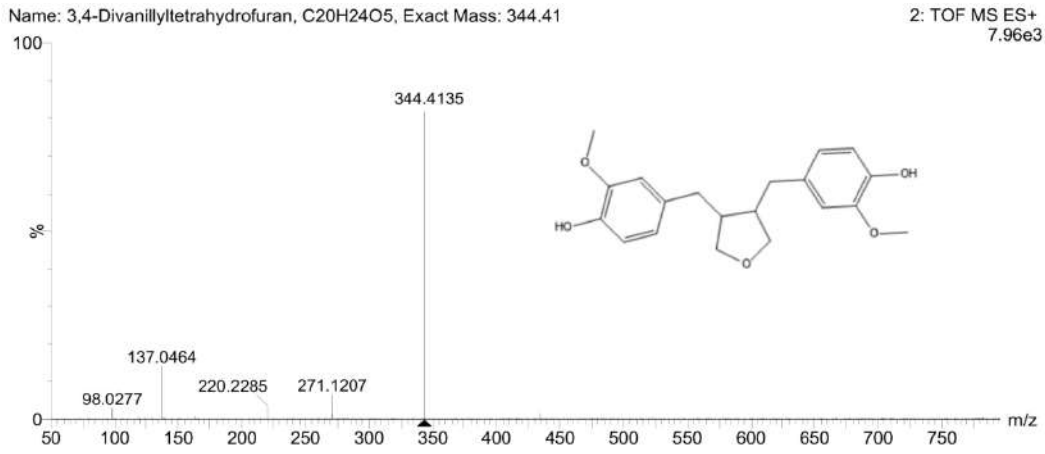


Figure 4.18a: Mass fragmentation of 3,4-Divanillyltetrahydrofuran in *Urtica dioica*

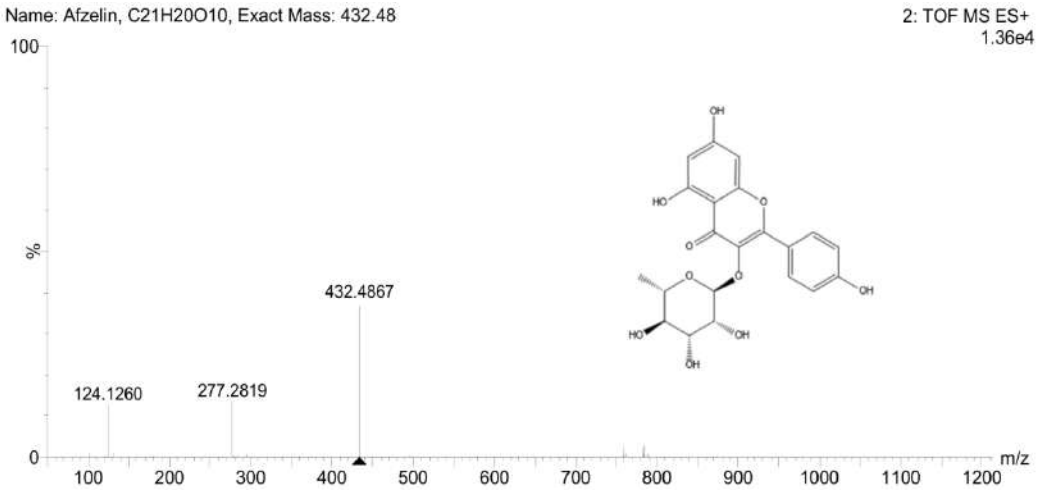


Figure 4.18b: Mass fragmentation of Afzelin in *Urtica dioica*

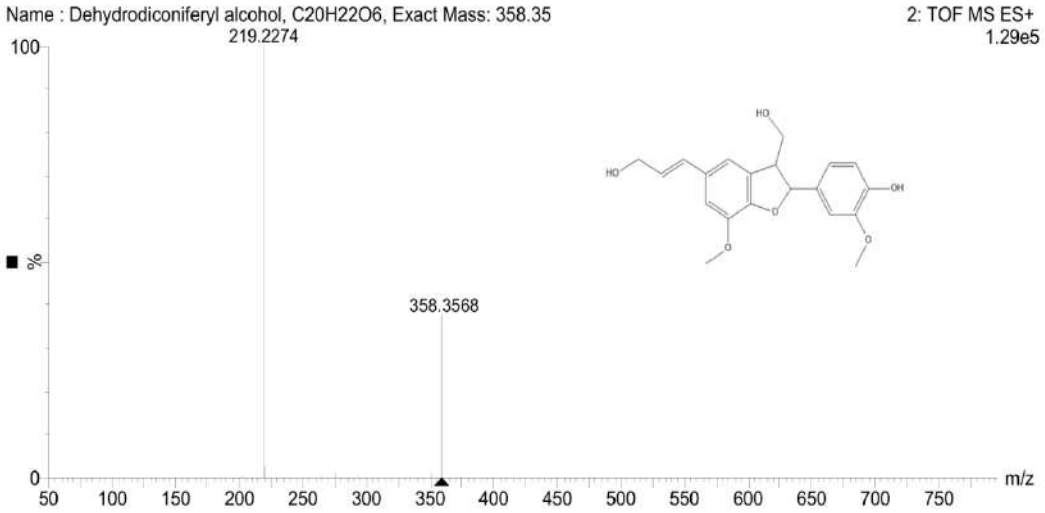


Figure 4.18c: Mass fragmentation of Dehydrodiconiferyl alcohol in *Urtica dioica*

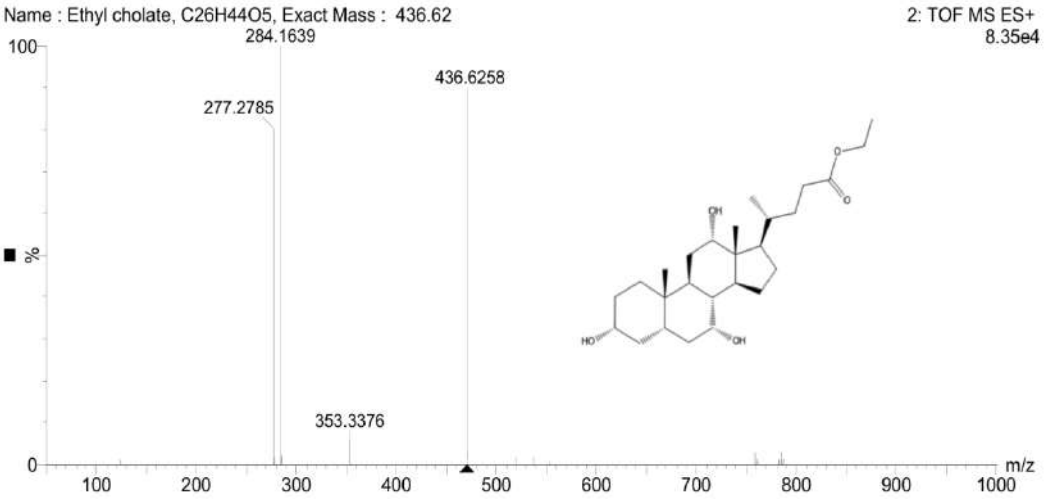


Figure 4.18d: Mass fragmentation of Ethyl cholate in *Utrica dioica*

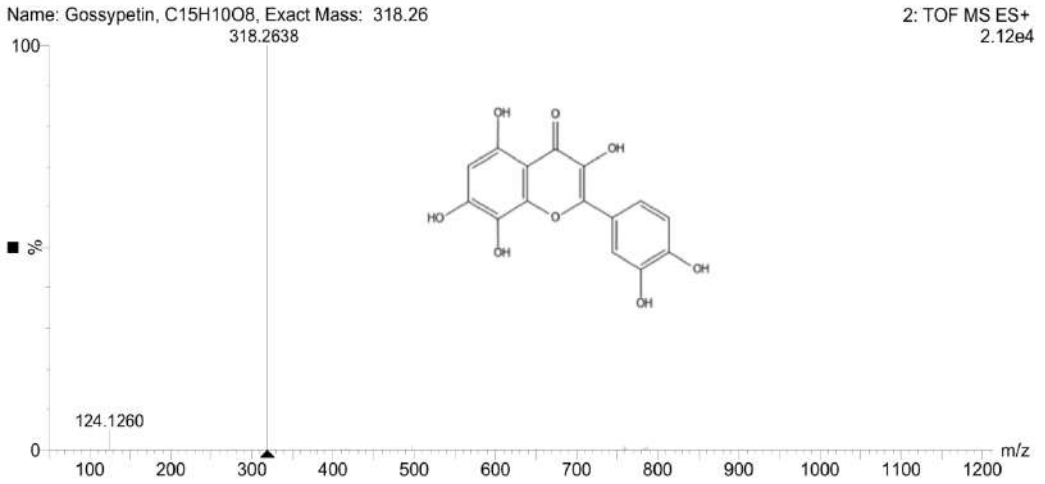


Figure 4.18e: Mass fragmentation of Gossypetin in *Utrica dioica*

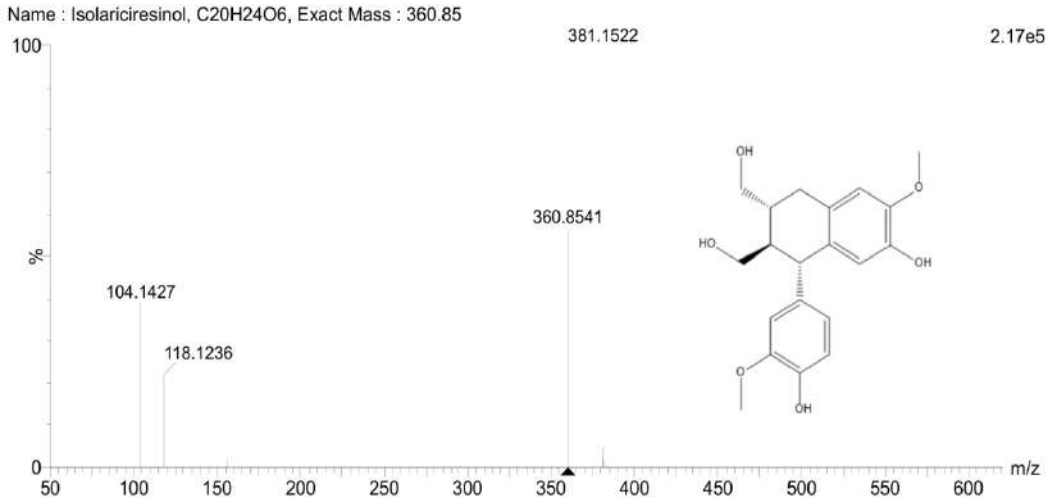


Figure 4.18f: Mass fragmentation of Isolariciresinol in *Urtica dioica*

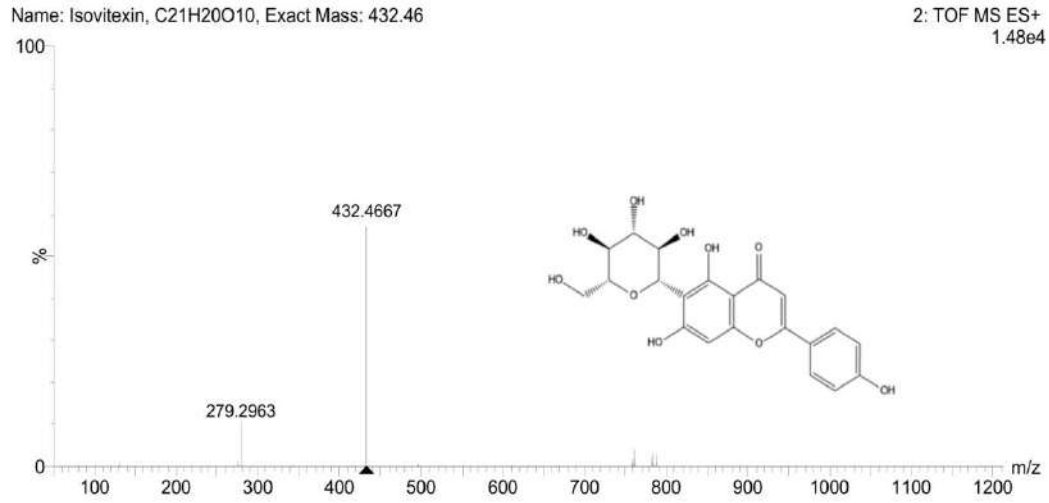


Figure 4.18g: Mass fragmentation of Isovitexin in *Urtica dioica*

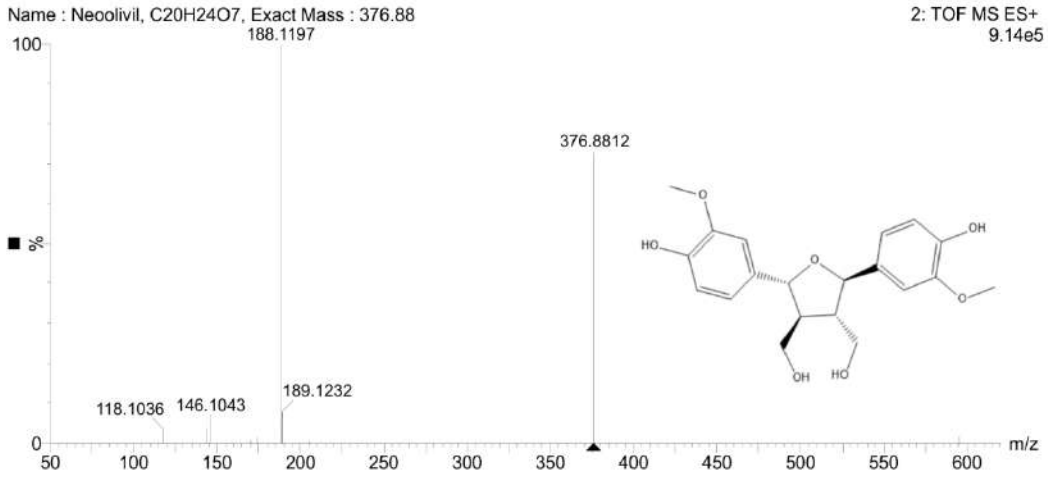


Figure 4.18h: Mass fragmentation of Neoolivil in *Urtica dioica*

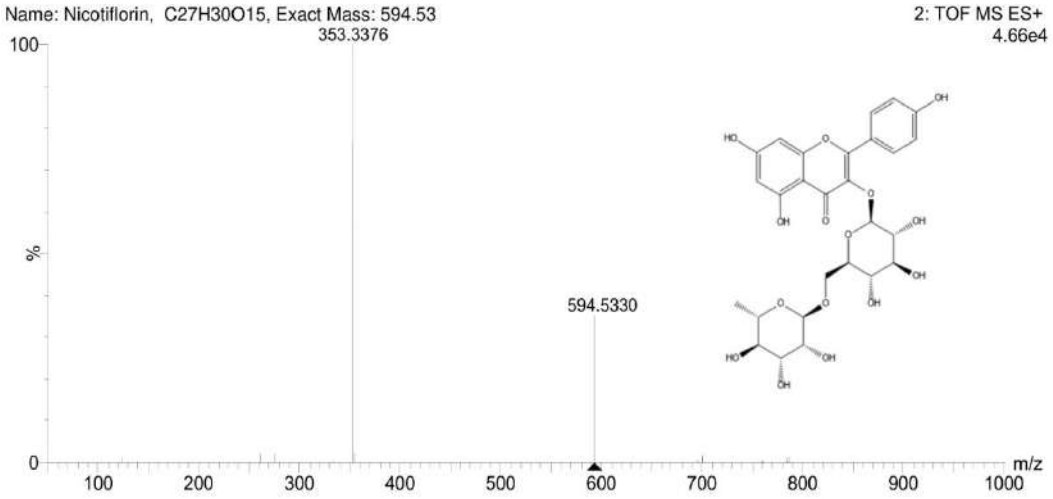


Figure 4.18i: Mass fragmentation of Nicotiflorin in *Urtica dioica*

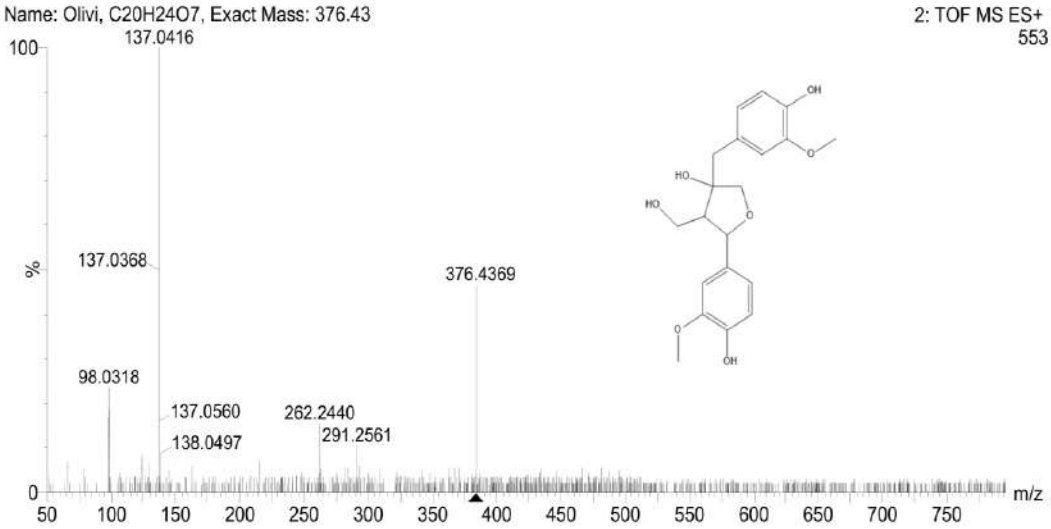


Figure 4.18j: Mass fragmentation of Olivin in *Urtica dioica*

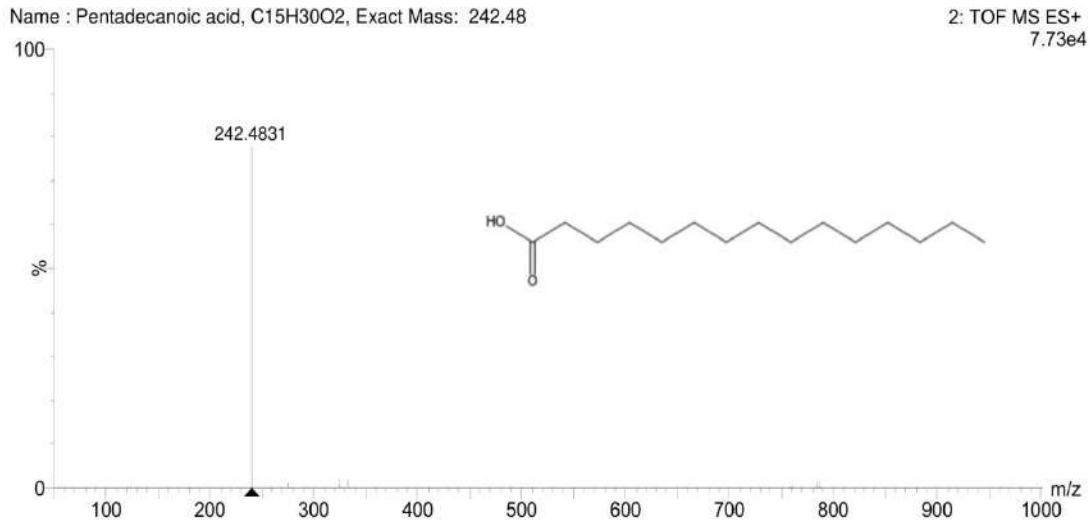


Figure 4.18k: Mass fragmentation of Pentadecanoic acid in *Urtica dioica*

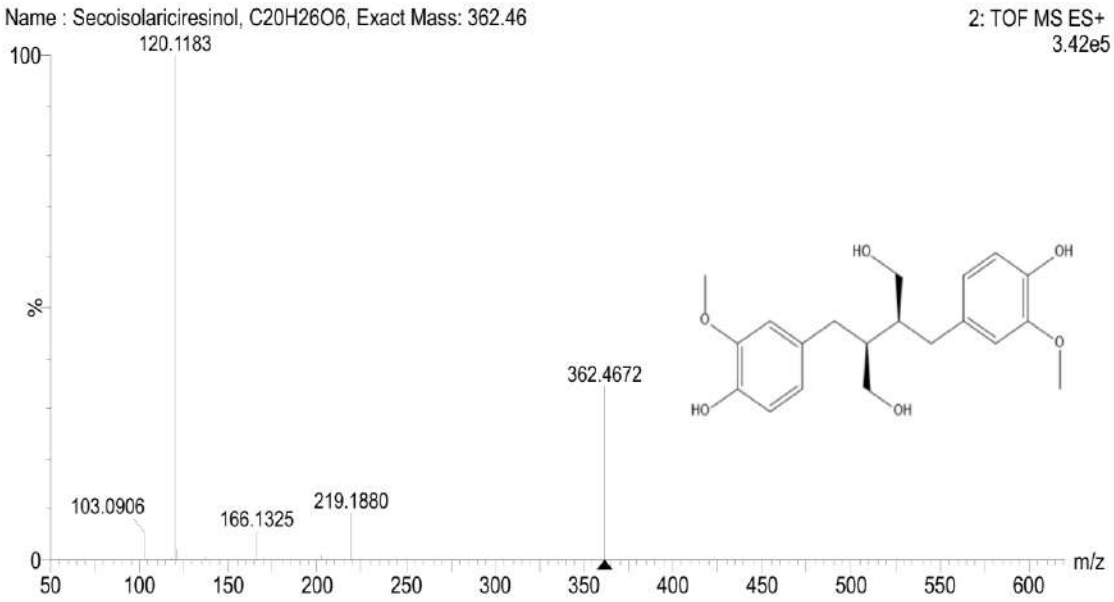
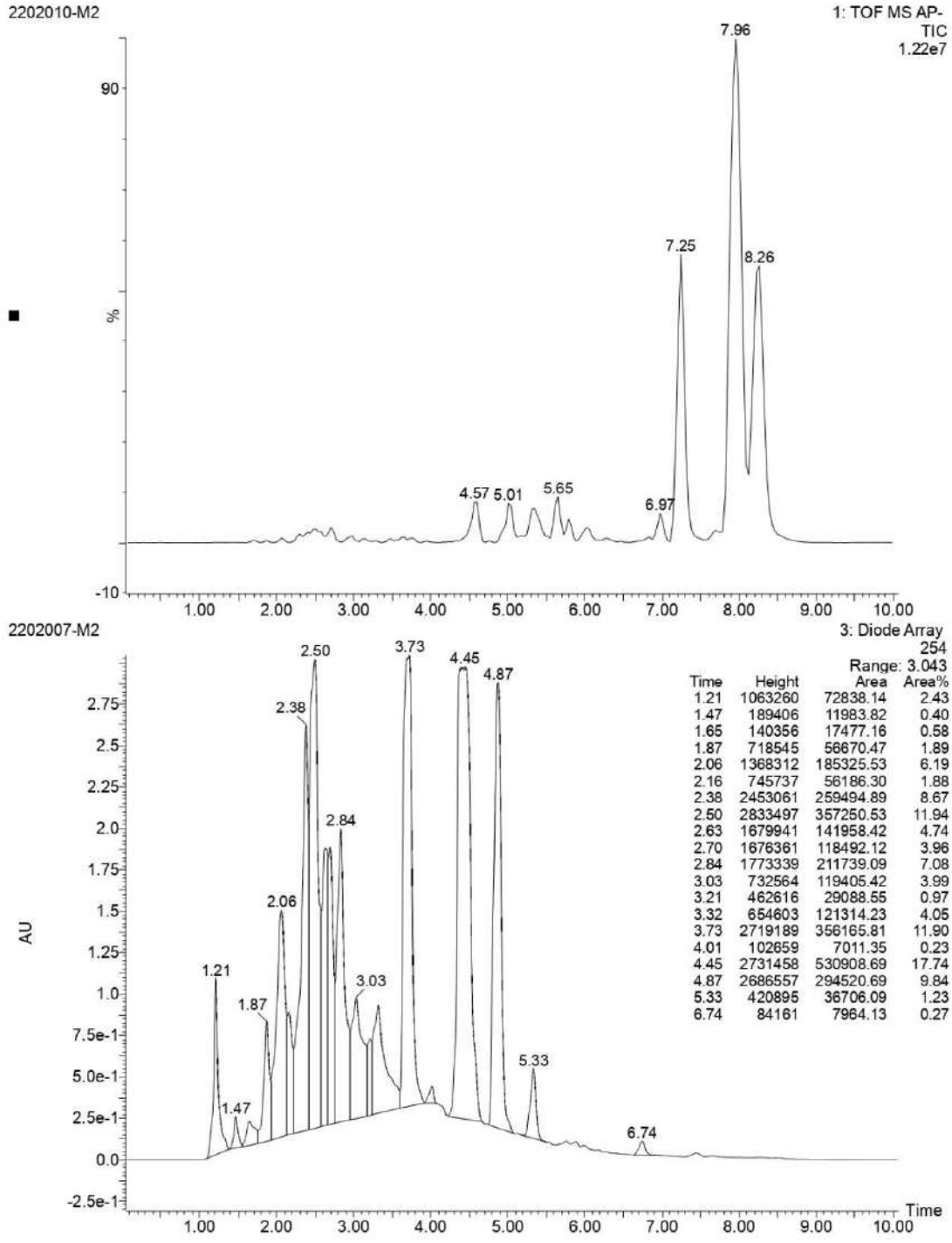


Figure 4.18l: Mass fragmentation of Secoisolariciresinol in *Urtica dioica*

4.1.11.5: LC-MS Analysis of *Zanthoxylum armatum* fruits (Table 4.20; Fig. 4.19)

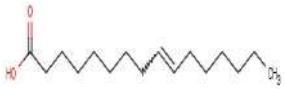
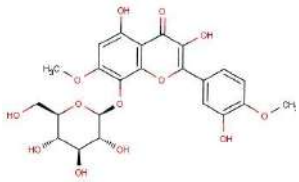
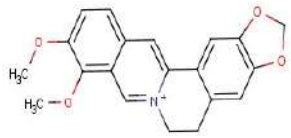
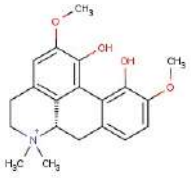
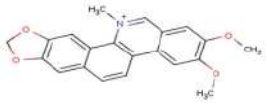
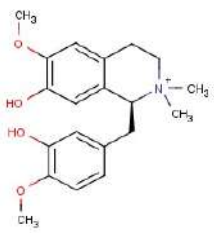


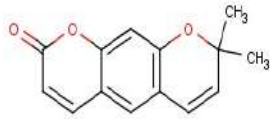
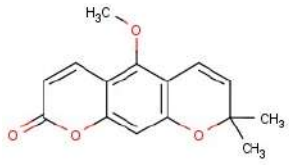
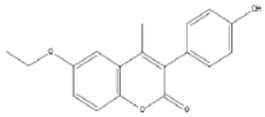
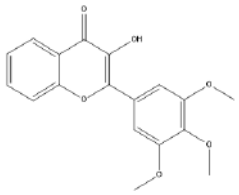
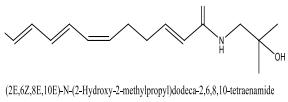
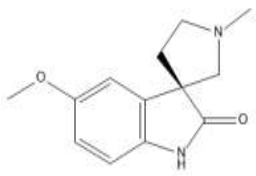
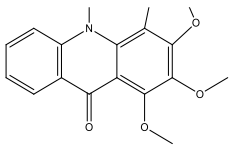
Time	Height	Area	Area%
1.21	1063260	72838.14	2.43
1.47	189406	11983.82	0.40
1.65	140356	17477.16	0.58
1.87	718545	56670.47	1.89
2.06	1368312	185325.53	6.19
2.16	745737	56186.30	1.88
2.38	2453061	259494.89	8.67
2.50	2833497	357250.53	11.94
2.63	1679941	141958.42	4.74
2.70	1676361	118492.12	3.96
2.84	1773339	211739.09	7.08
3.03	732564	119405.42	3.99
3.21	462616	29088.55	0.97
3.32	654603	121314.23	4.05
3.73	2719189	356165.81	11.90
4.01	102659	7011.35	0.23
4.45	2731458	530908.69	17.74
4.87	2686557	294520.69	9.84
5.33	420895	36706.09	1.23
6.74	84161	7964.13	0.27

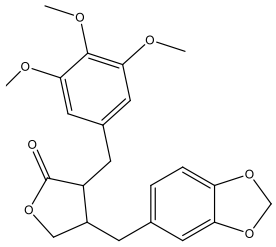
Figure 4.19: Total mass ion chromatogram of Zanthoxylum *armatum* fruits

Fourteen molecules were isolated from *Zantoxylum armatum* fruit extract through LC-MS in 10-minute run time (Table 4.20; Fig. 4.19).

Table 4.20: Annotated compounds in *Zantoxylum armatum* fruits

Compound	Mol. Formula	m/z	RT	Structure	Reference
cis-9-hexadecenoic	$C_{16}H_{30}O_2$	254.15	2.06		Sahu *et al.*, 2021
Tambuletin	$C_{23}H_{24}O_{13}$	508.42	1.21		Muahtaq *et al.*, 2019; Sultana *et al.*, 2023
Berberine	$C_{20}H_{18}NO_4$	336.10	5.33		Wang *et al.*, 2018;Sahu *et al.*, 2021
Magnoflorine	$C_{20}H_{24}NO_4$	342.41	2.84		Bhat *et al.*, 2018
Nitidine	$C_{21}H_{18}NO_4$	348.28	4.45		
Tambetarine	$C_{20}H_{26}NO_4$	344.32	2.50		Nooreen *et al.*, 2017

Xanthyletin	$C_{14}H_{12}O_3$	228.15	1.87		Kumar *et al.*, 2014
Zanthoxyletin	$C_{15}H_{14}O_4$	258.27	1.47		
6-Ethoxy-3(4'-hydroxyphenyl)-4-methyl-coumarin	$C_{18}H_{16}O_4$	296.3	1.6		Tine *et al.*, 2017
3-Hydroxy-3',4',5'-trimethoxyflavone	$C_{18}H_{16}O_6$	328.3	6.74		Zhuo *et al.*, 2021
Hydroxy Alpha-sanshool	$C_{16}H_{25}NO_2$	246.22	5.53	 (2E,6Z,8E,10E)-N-(2-Hydroxy-2-methylpropyl)dodeca-2,6,8,10-tetraenamide	Bhat *et al.*, 2018; Zhuo *et al.*, 2021
Horsfieldin	$C_{20}H_{20}O_6$	356.4	2.556		Zhang *et al.*, 2018
Melicopine	$C_{17}H_{15}NO_5$	313.3	5.045	 -dimethoxy-11-methyl-[1,3]dioxolo[4,5-c]acridin-6-one	Barua *et al.*, 2022

Epiashantin	$C_{22}H_{24}O_7$	400.37	7.46	 4-(1,3-benzodioxol-5-ylmethyl)-3-[(3,4,5-trimethoxyphenyl)methyl]oxolan-2-one	Bhatt *et al.*, 2018

LC-MS Characterization of *Zanthoxylum armatum* (Fig. 4.20a-h)

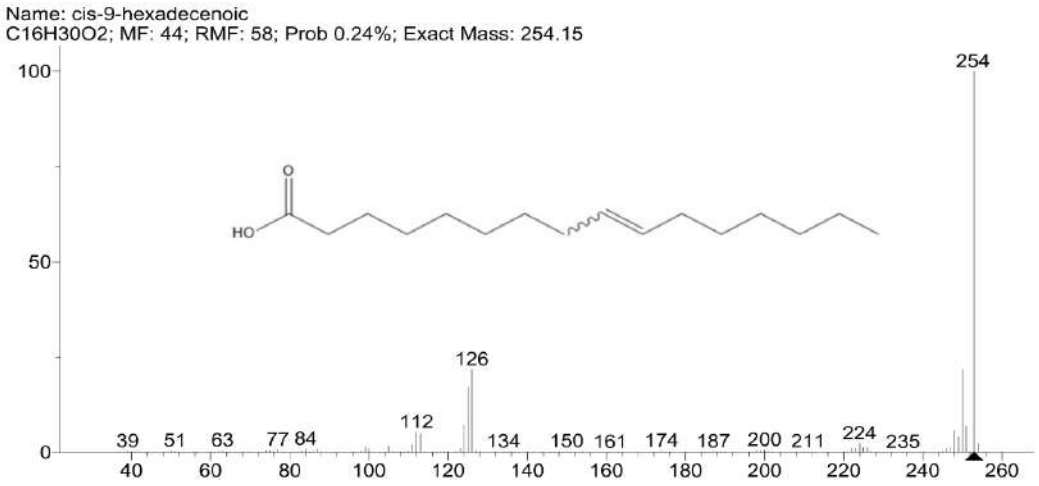


Figure 4.20a: Mass fragmentation of cis-9-hexadecenoic in *Zanthoxylum armatum*

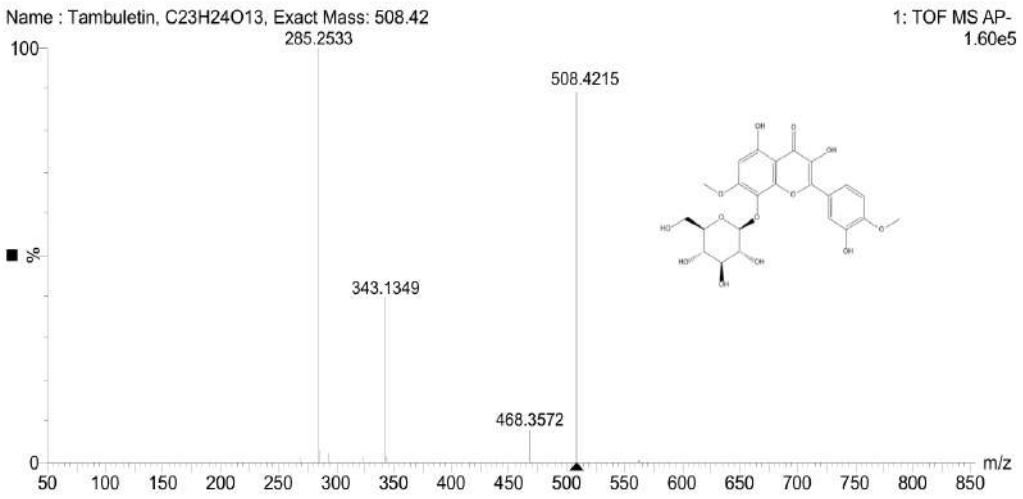


Figure 4.20b: Mass fragmentation of Tambuletin in *Zanthoxylum armatum*

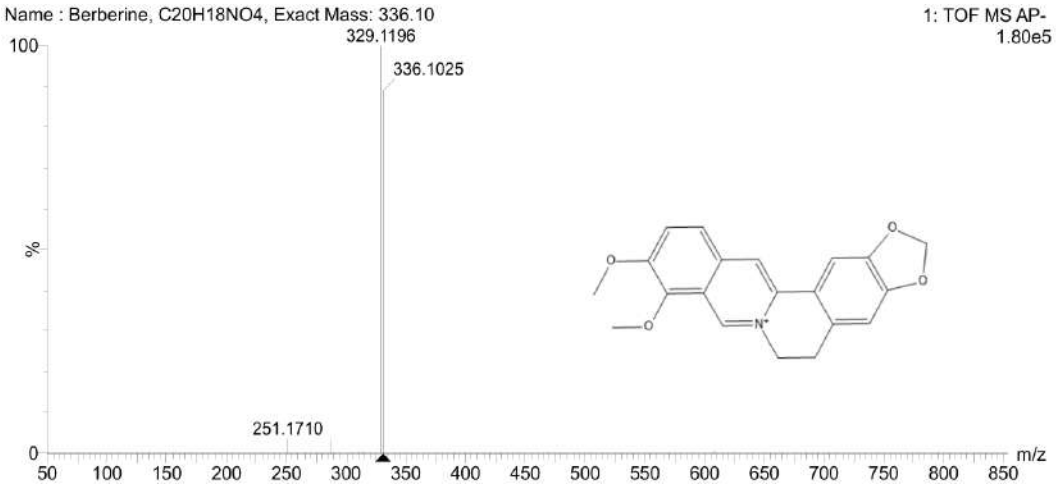


Figure 4.20c: Mass fragmentation of Berberine in *Zanthoxylum armatum*

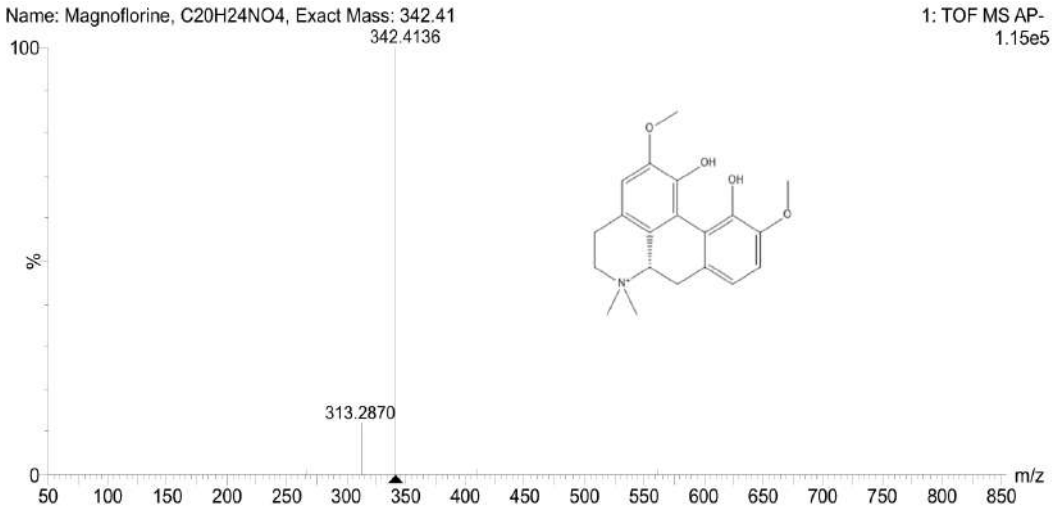


Figure 4.20d: Mass fragmentation of Magnoflorine in *Zanthoxylum armatum*

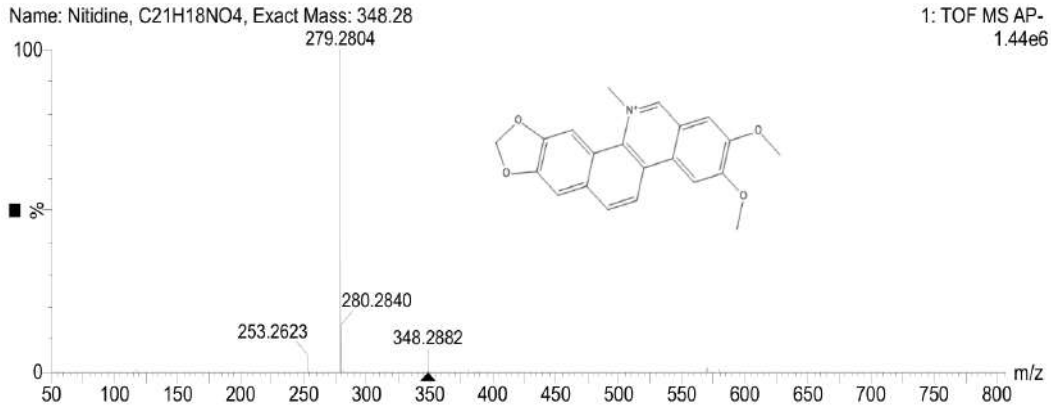


Figure 4.20e: Mass fragmentation of Nitidine in *Zanthoxylum armatum*

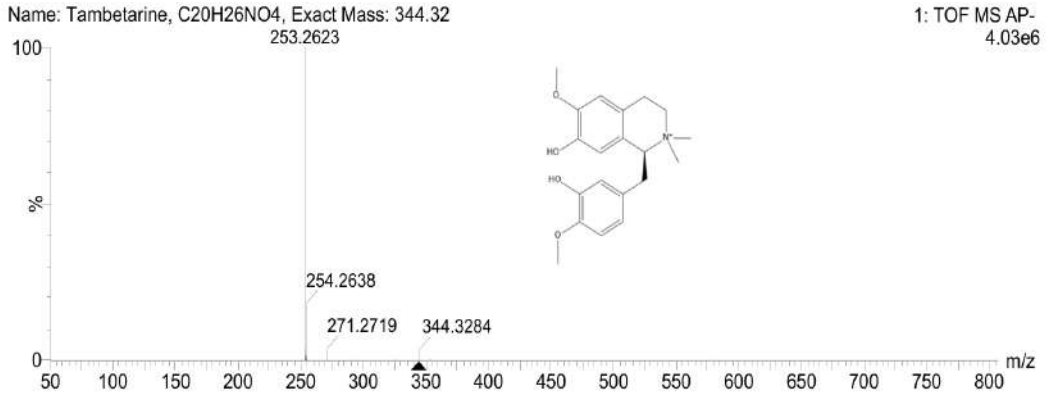


Figure 4.20f: Mass fragmentation of Tambetarine in *Zanthoxylum armatum*

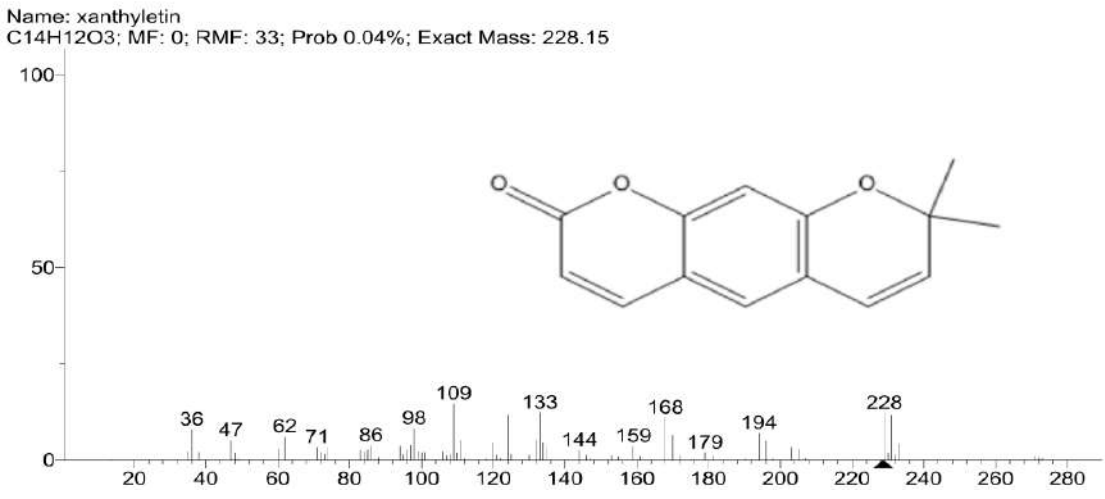


Figure 4.20g: Mass fragmentation of Xanthyletin in *Zanthoxylum armatum*

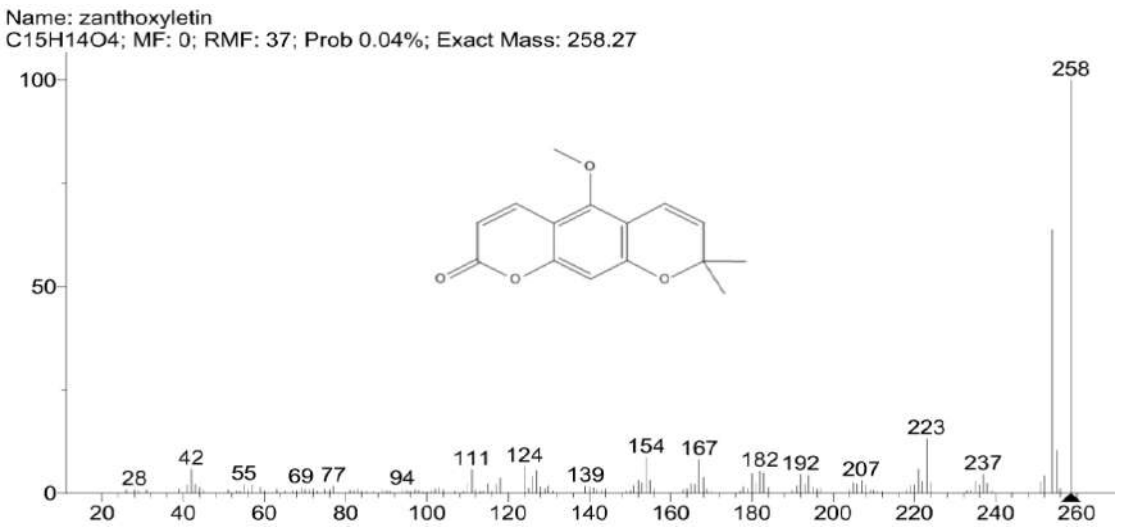


Figure 4.20h: Mass fragmentation of Zanthoxyletin in *Zanthoxylum armatum*

4.1.12 HPTLC method development for simultaneous quantification of polyphenolic compounds (Gallic acid and Quercetin)

4.1.12.1 Validation of HPTLC Methods

HPTLC method validation was performed on parameters such as linearity, limit of sensitivity, specificity, precision, accuracy, recovery and robustness according to the ICH guidelines (International Council for Harmonisation, 2005).

4.1.12.2 Precision

The same spot of gallic acid (500 ng/spot), quercetin (500 ng/spot) withn=6 was used to check the accuracy of the instrument. Repeatability (intraday) and reproducibility (inter-day) of the method were implemented with three different concentration levels of reference compounds on the same day and also analyzed after 3 days, respectively. These analyses were attempted seven times and all the obtained results are represented as mean ± % RSD.

4.1.12.3 LOD and LOQ

Signal-to-noise (S/N) ratios with different concentrations of reference compounds were applied along with methanol as a blank and evaluated LOD and LOQ values.LOD was measured as 3,1 (SD/S), whereas limits of quantification (LOQ) as 10,1 (SD/S), where S represents slope and SD means the standard deviation of the Y-intercept from the regression line.

4.1.12.4 Specificity

Peak purity was assessed by comparing standard reference compounds with that of plant samples at the beginning, peak maxima, and end of the peak. Additionally, Overlaying spectra of the isolated bands from the plant samples were compared with the marker compounds. The segregated bands of each reference standard compound were compared with plant samples and were checked for corresponding Rf values in their scanned densitometric chromatograms.

4.1.12.5 Method Development

HPTLC technique was used for the quantitative assessment of polyphenols i.e. gallic acid and quercetin among all the selected plants. HPTLC studies showed that the solvent system for simultaneous quantification of gallic acid and quercetin was achieved with ethyl acetate: formic acid (13.5:9:0.6 v/v/v/v) mobile phase that gave well-resolved spots at Rf 0.24 and 0.52 for gallic acid and quercetin, respectively (Table 4.21). Well-resolved spots for, gallic acid and quercetin reference compounds in all the five plant samples were visualized at 254 nm and 366 nm without any post-derivatization treatment.

Table 4.21: Method validation for Gallic acid and Quercetin quantification

Parameters	**Gallic acid**	**Quercitin**
Linearity range	0.5-2.0 µg	0.5-2.0 µg
Correlation coefficient	99.4%	99.0%
Regression equation	area=16032+10655 gallic acid (ug/spot)	area=40741+4002quere citin conc. (ug/spot)
Calculated SD Value		
a. Limit of detection (LOD) (ng) [3×SD/S]	30	40
b. Limit of quantification (LOQ) (ng) 6[10×SD/S]	90	120
Rf	0.24	0.52
Precision	0.4	0.52
Intraday RSD (%), n=5	0.45	0.53
Interday RSD (%), n=5	0.47	0.55
Recovery (%) Mean Recovery (%)	100.3	99.92

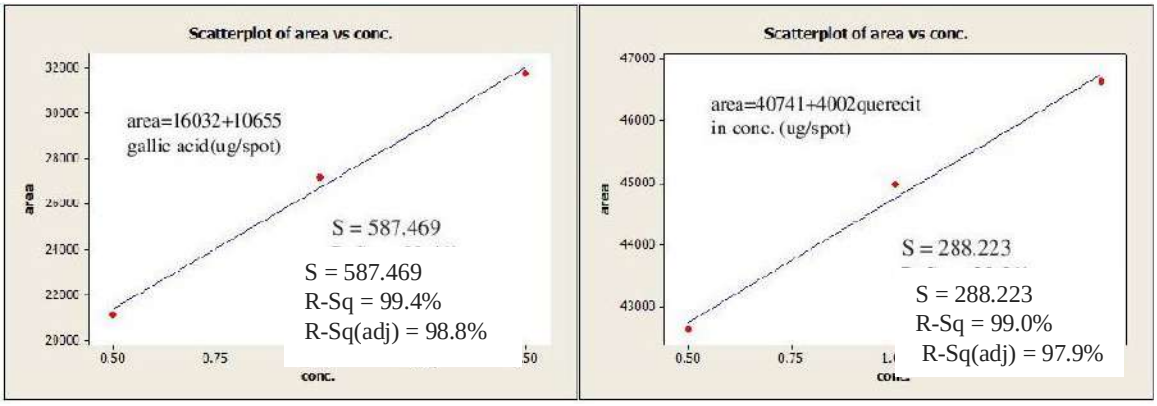


Figure 4.21: The linearity graph of the standard Gallic acid and Quercetin

HPTLC-Densitogram patterns obtained for all the five plant samples and standard compounds depicted that the peak corresponding to, Rf 0.24 and Rf 0.52 were superimposable in all the test samples (Fig. 4.21(a-c)). The spectrum characteristics corresponding to this peak were also found to match exactly, indicating the compound corresponding to Rf of the standard and the test samples to be identical. Linearity of the calibration curve was achieved between 0.5-2.0 µg for quercetin whereas 0.5-2.5 µg range showed good linearity for quercetin (Figure 4.22(a-f)). The phytochemical screening of *A. catechu*, *A. bracteosa*, *B. ciliata*, *U. dioica*, and *Z. armatum* was based on Gallic acid and Querecitin. HPTLC was used for the quantitative estimation of Gallic acid and Quercetin in all five plant samples. Gallic acid and quercetin from the extracts of all five samples were confirmed by matching their single spot at Rf = 0.24 and 0.52 values with the peaks of standards (Fig. 4.23(a-c)).

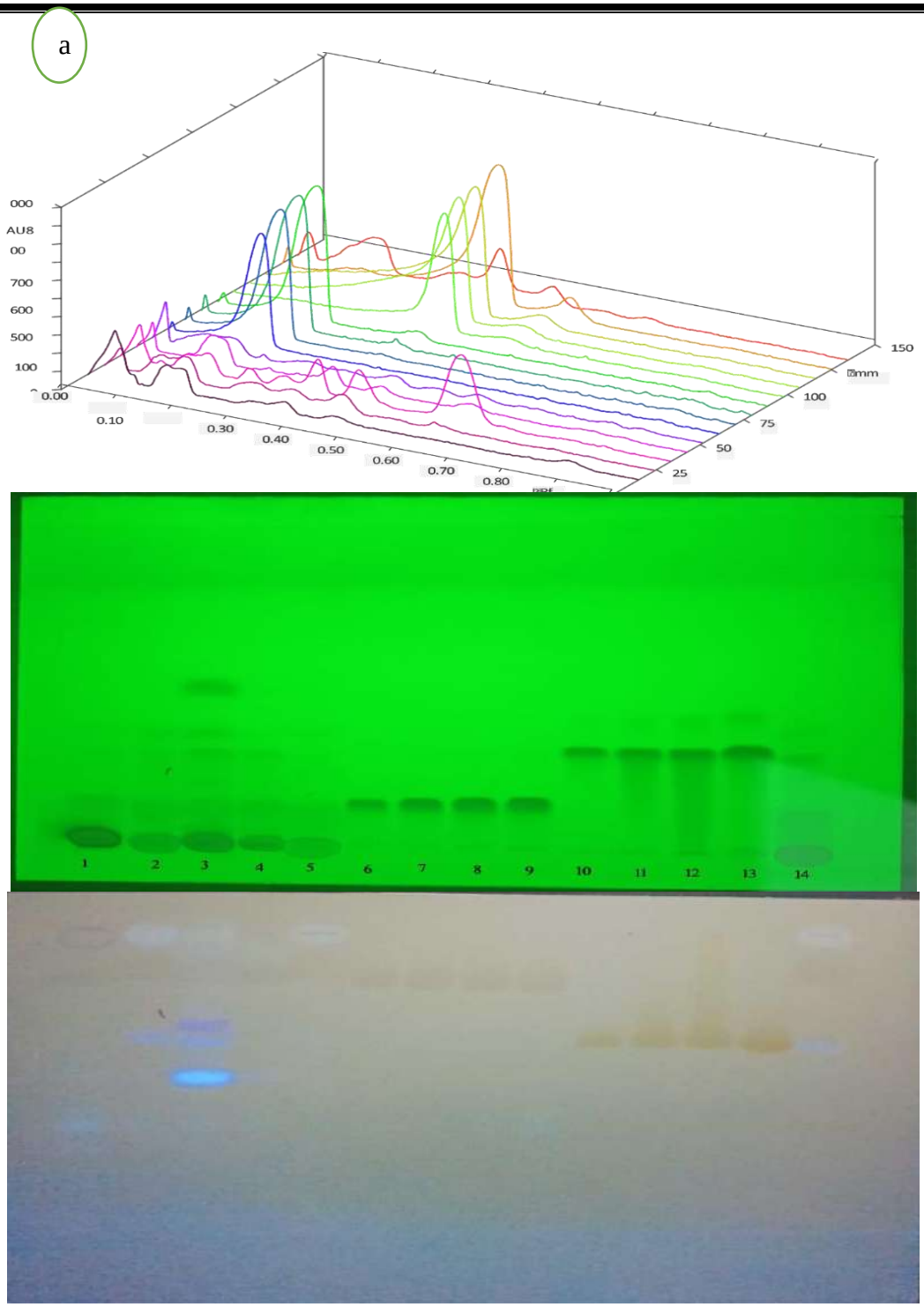


Figure 4.21(a-c): 3-D Chromatogram (a) HPTLC Fingerprinting of simultaneous quantification of gallic acid, quercetin standards along with *Acacia catechu*, *Ajuga bracteosa*, *Bergenia ciliata*, *Urtica dioca* and *Zanthoxylum armatum* sample.

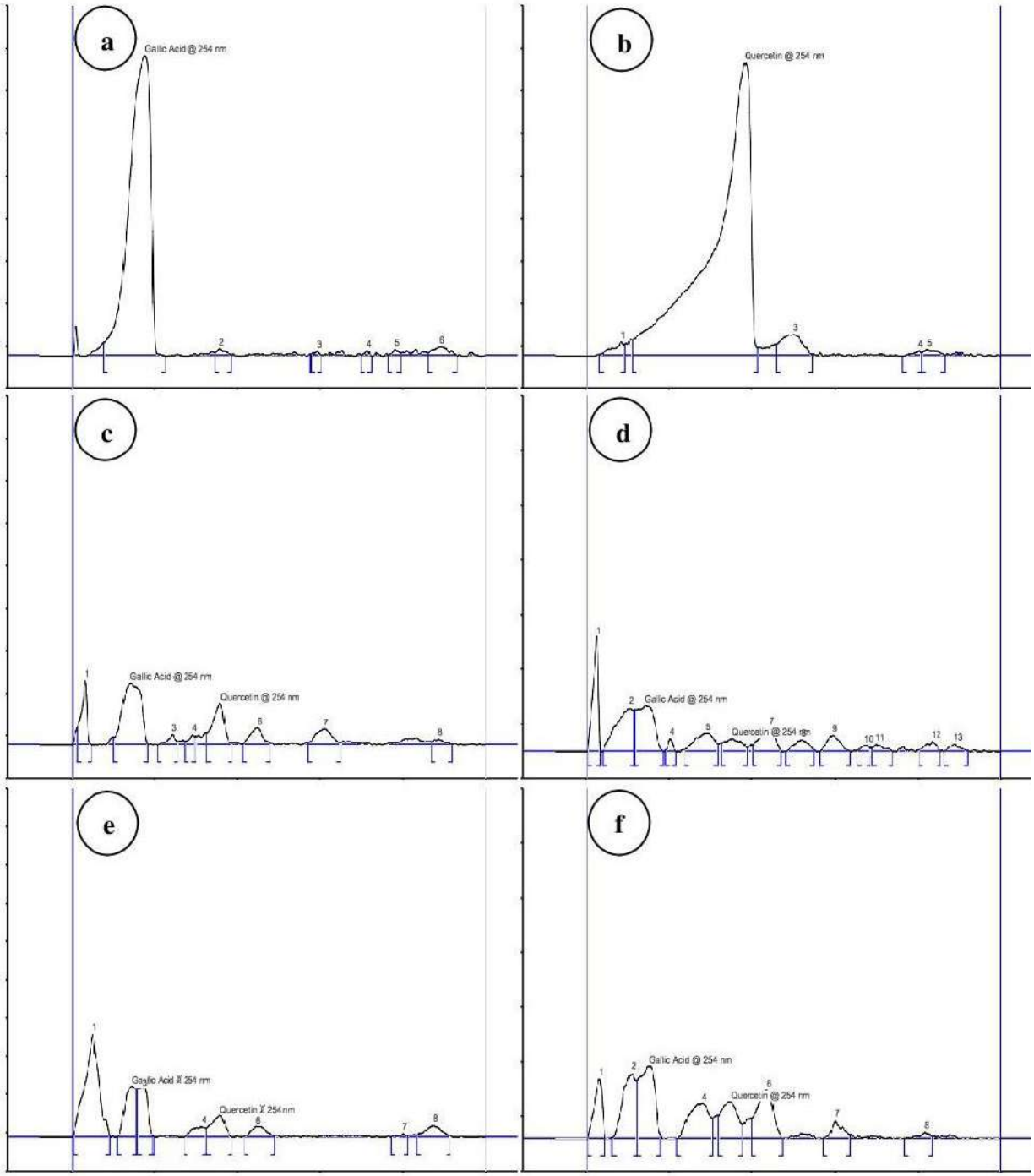


Figure 4.22(a-f): Simultaneous Densitometric-HPTLC Method Development: (a-b) Densitometric graph showing isolation of standard Gallic acid and Quercetin, (c-f) Densitograms of Gallic acid and Quercetin standards along with *Acacia catechu, Ajuga bracteosa, Bergenia ciliata, Urtica dioca.* Densitograms obtained from *Acacia catechu, Ajuga bracteosa, Bergenia ciliata,Urtica dioca* samples containing marker compounds at 254 nm.

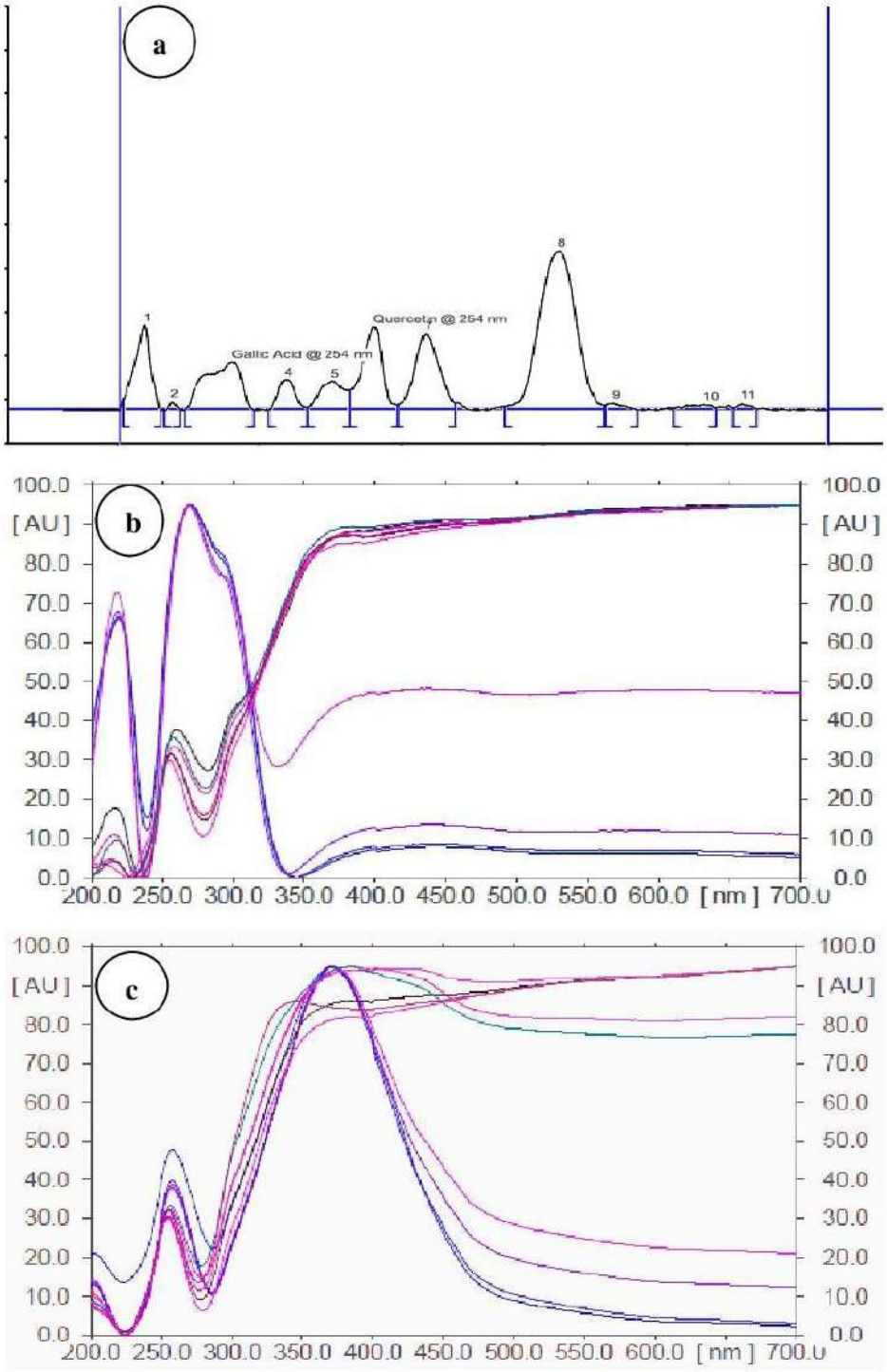


Figure 4.23(a-c): (a) Densitogram obtained from *Zanthoxylum armatum* sample containing marker compounds at 254 nm (b-c) Overlay spectra of Gallic acid and Quercetin with *Acacia catechu, Ajuga bracteosa, Bergenia ciliata, Urtica dioca* and *Zanthoxylum armatum* samples at 254 nm.

The quantity of Gallic acid and Querecitin in all the plant samples was evaluated by applying the linear regression equation and the content was displayed in Table 4.22. Polyphenolics i.e. Gallic acid and Querecitin were present in all five plant samples.

Table 4.22: Quantification of Gallic acid and Quercetin in *A. catechu* heartwood, *A. bracteosa* leaves, *B.* rhizome, *U. dioica* leaves, and *Z. armatum* fruits.

Plant	Part used	%age conc. of Gallic acid	%age conc. of Quercitin
Acacia catechu	Heartwood	0.018	0.00463
Ajuga. bracteosa	Leaves	0.010	0.00170
Bergenia. ciliata	Rhizome	0.011	0.00315
Urtica dioica	Leaves	0.014	0.00452
Zanthoxylum armatum	Fruits	0.016	0.00895

4.1.13 Threat status of plants reported:

Out of the 63 antidiabetic species reported, *Aconitum heterophyllum, Bergenia ciliata, Picrorhiza kurroa, Saussurea costus,* and *Swertia chairata* are the species facing threats in the wild (Goraya and Ved, 2017; Barik *et al.*, 2018; IUCN, 2020; Gowthami *et al.*, 2021). The surge in commercial demand, climate change, habitat fragmentation, over-exploitation, and the emergence of invasive and extraterrestrial species have caused the dwindling of these medicinal plants.

- **Our experience in the field suggests for incorporation of the following strategies:**

1. An integrated approach incorporating both conventional and emerging technologies should be the current path.
2. Community-based methods are critical to the conservation of medicinal plants in the Himalayan region. A participatory approach involving locals and gatherers can help in the revival of these plants in the wild.
3. One of such local Sh. Rajat Sharma has been successful in the cultivation of two critically endangered species i.e. *Aconitum heterophyllum* and *Saussurea costus.* He as also cultivated *Picrorhiza kurrooa* is quite passionate for the revival of these plants in natural habitat and in turn is earning revenue (Plate 15(a-f)).

4. To aware nomadic collectors and locals for cultivation and even in natural habitats can help to reverse population status of these highly traded species.

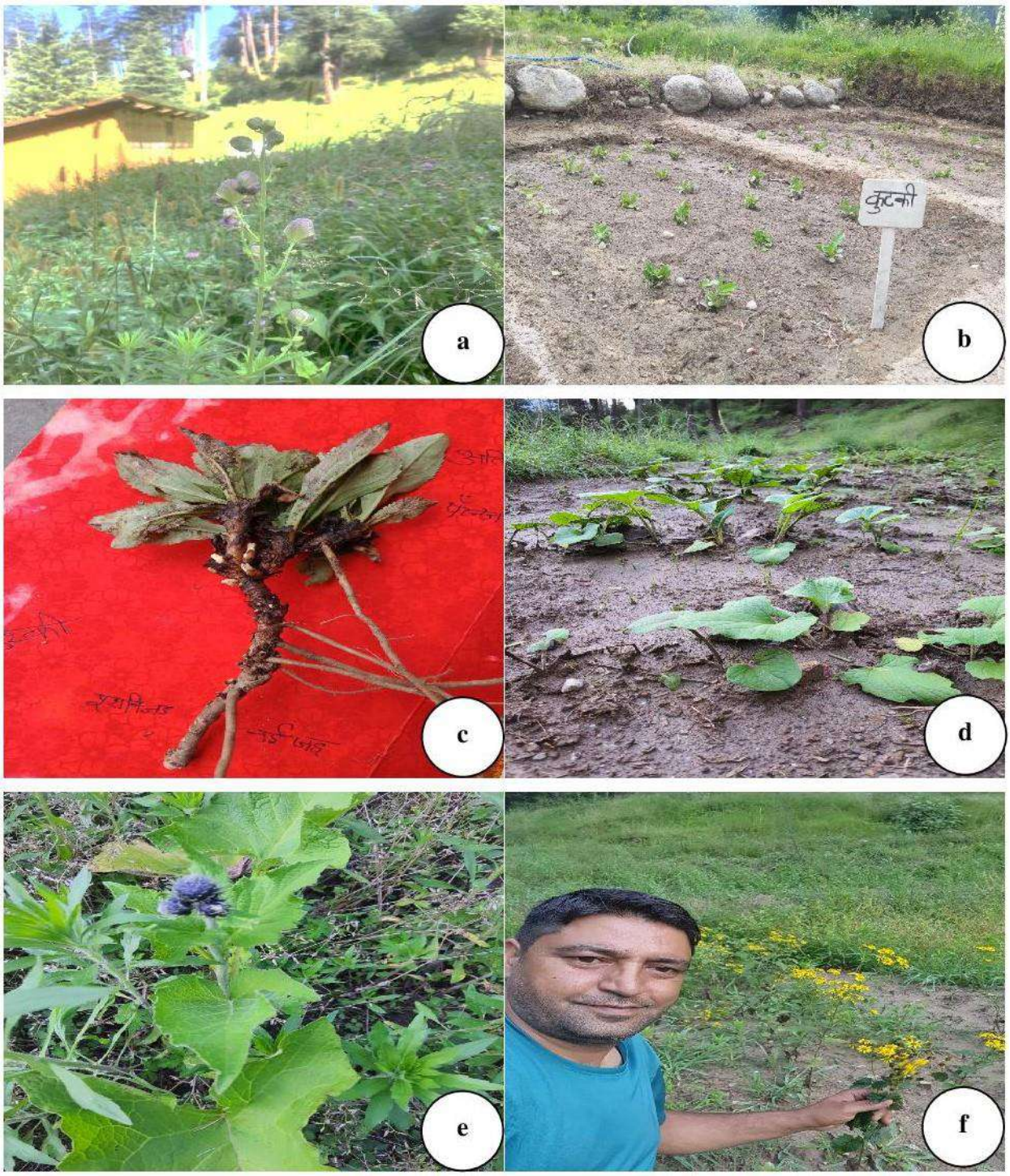


Plate 15(a-f): Cultivation of (a) *Aconitum heteropyllum,* (b) *Picrorhiza kurroa,* and (c) *Picrorhiza kurroa,* (d) *Saussurea lappa* after harvesting and (e) in cultivation, and (f) Mr Rajat Sharma, a progressive farmer involved in cultivation of *Aconitum heterophyllum,*

Picrorhiza kurroa and *Saussurea lappa* in natural habitats in Bani range of North-west Himalayas.

4.2 Discussion

4.2.1 Important Ethnobotanic Insights Regarding T2DM by informants:

As stated by the participants, the onset of this metabolic disease is accompanied by a low emotional status. Anxiety, fear, irritability, and undefined preoccupations are common experiences. Various symptoms experienced by the patients during the initial phase of the ailment have a physiological background. Insulin resistance typically develops before the hyperglycaemic period, and the amount of circulating insulin is not able to cope with raised blood glucose levels. Thereafter, characteristic diabetic symptoms such as increased hunger, thirst, and urination develop. The patients clearly remembered this one-of-a-kind experience. For instance, hormones antagonistic to insulin action (adrenaline and glucagon) are released in response to a sudden emotional disturbance (e.g., anxiety, fear). The glucose levels in the blood have already surged and available insulin fails to maintain glucose levels; resultantly the individual feels low and depressed, which the participants characterized as the onset of the ailment. Few people reported developing hyperglycemia during the pandemic lockdown, which might be due to a sudden increase in levels of stress. Consultation with allopathic doctors and diagnostic laboratory testing are used to confirm T2DM but informants typically use metabolic indications such as fatigue, sudden loss of weight, and polyuria, particularly at night hours. Metabolic symptoms are primarily used by informants in the present study to diagnose diabetes mellitus which is common across communities despite diverse cultures, ethnicities, and religious beliefs. The traditional healers in India (Dixit and Tiwari, 2020), Bangladesh (Rahmatullah *et al.*, 2013), Nigeria (Abo *et al.*, 2008), Iran (Bahmani *et al.*, 2014), and Thailand (Andrade *et al.*, 2020) used similar practice. According to the interviewees, the key factors of T2DM progression were family history and obesity. Obesity, along with lifestyle and hypertension, has been deciphered as a paramount factor by Kharroubi and Darwish (2015) whereas another ethnobotanical study by Broholm *et al.* (2019) attributed genetics, weight, and a sedentary lifestyle of the patient as driving factors for developing T2DM.

Folklore links flavor and taste to define the potency of plants for a particular disease. In the present study, 80% of species were found to be bitter, 11% possessed pungency along with degree of astringency, and the rest were nutty to acidic. Taste-based method of selection of hypoglycemic

plants through bitterness is also practiced in Thailand (Andrade *et al.,* 2020). Ethnic people link the degree of bitterness to the increased potential of lowering hyperglycemia (Neamsuvan *et al.,* 2015). Patients reported feeling lighter (perhaps due to a hypoglycemic episode), less cloudy vision, and less weariness after receiving the medication. Most of them reported alleviation from physiological symptoms such as decreased urine and push, as well as increased energy levels.

Most informants had a good knowledge of plant species occurring in the wild and their precise location. THPs and tribal have complete knowledge of phenological phases as well as the location and timing of harvest, particularly for temperate high-altitude species, whilst natives typically obtain these plants from local markets or "Pansari" shops. Pansaria are specialty stores that exclusively sell herbal plants and items.

Traditional medicinal systems across cultures pay precise attention to how to manage diet to keep glucose levels within range (Bouzabata, 2018; Parasher *et al*.,2023). THPs have precise and customized knowledge about the diet a diabetic should follow. They stress staying on low carbohydrate and low-fat diet. Complex carbohydrate sources like *Bajra, Jowar,* and *Chari* were generally recommended. They were the preferred carbohydrate source instead of wheat and rice. Eating in smaller amounts lowers stress on the liver and it was one of the *mantras* they suggest, which is a way to lower calorie burden. Adding metals like silver, magnesium, copper, and iron was also suggested as they ameliorate pancreatic function. Natives especially in remote hilly terrains attributed white sugar and packed foods to sporadically increase diabetes. Jaggery was considered to be a safer option than sugar.

4.2.2 Knowledge and characteristics of anti-diabetic plants

The present ethnobotanical survey recorded sixty-three plant species used to manage hyperglycemia. These numbers were greater in comparison to the earlier reported range of 14 to 54 anti-hyperglycemic species in all the ethnobotanical studies carried out in India for anti-diabetic flora(Tarafdar *et al.*,2014; Daimari *et al.* 2019; Kumar *et al.,* 2019; Mishra *et al.,* 2019; Sarna, 2020; Gupta *et al.,* 2021) and in different parts of globe(Erasto *et al.,* 2005; Yaseen *et al.,* 2015; Fakhry and Migahid, 2016; Barkaoui *et al.,* 2017; Mrabti *et al.,* 2021; Belmouhoub *et al.,* 2022). The abundance of anti-diabetic plants in this region can be attributed to their medical effectiveness in treating diabetes, the sharing of knowledge across different cultures, and the district's diverse vegetation, which includes 22 different types of forests. The anti-diabetic species were mostly

from Fabaceae, Rutaceae, Asteraceae, Lamiaceae, Apocynaceae, Poaceae, and Ranunculaceae. These families have also been documented as the most significant in various earlier ethnopharmacological surveys (Shinkafi *et al.,* 2015; Dixit and Tiwari, 2020;; Mrabti *et al.*, 2021). The dominance of a particular family in folkloric medicine is the reflection of local flora. However, there was no published documentation of plants against T2DM available for the Kathua region for comparative assessment. Members of the Fabaceae family are known to contain anthocyanins, phenolic acids, flavonols, and proanthocyanidins (Kan *et al.,* 2018; Mechchate *et al.,* 2020). These compounds show strong anti-inflammatory and antioxidant potential which renders them the basis for their further exploration of bioactivities in stress-mediated ailments like diabetes mellitus (de Lima *et al.,* 2019; Gomes *et al.,* 2019; Moreno-Valdespino *et al.,* 2020). high levels of sesquiterpene lactones and hydroxycinnamic acid esters are found in members of Asteraceae (Idres *et al.,* 2023) which have confirmed antioxidant capacity (Olayinka *et al.,* 2017), anti-inflammatory (Hwang *et al.,* 2014; Liu *et al.,* 2017) and insulin-sensitizing molecules (Schlernitzauer *et al.,* 2013). Similarly, species of the family Lamiaceae contain compounds like hydroxycinnamic acids, forskolin,marrubiin, and triterpenes like oleanolic and ursolic acids that have also been proven to possess prominent anti-diabetic properties (Etsassala *et al.,* 2021).

Herbs were the dominant life forms in the present study. A similar trend has been witnessed in many ethnobotanical studies conducted globally for documentation of traditional plant species used for T2DM (Yaseen *et al.,* 2015; Gupta *et al.,* 2021; Mrabti *et al.*, 2021). Leaves were recorded as the most preferred plant parts for formulations and direct consumption as well. This is contrary to the observations of Daimari *et al.* (2019), Mishra *et al.* (2019), and Dixit and Tiwari (2020) wherein trees were cited as major life forms. Barkaoui *et al.* (2017) recorded shrubs as the predominant life form in Morocco. They also have higher therapeutic efficacy and more diverse phytochemicals (Rao *et al.,* 2015; Hua *et al.,* 2020). The prevalence of herbaceous plants in ethnomedicinal flora could be attributed to their ease of availability and collection as compared to trees and shrubs.

The higher usage of leaves is plausibly due to their fast regeneration capacity, more production of secondary metabolites, and more availability throughout the year (Rao *et al.,* 2015; Parasher *et al.*,2023).

4.2.3 Mode of Consumption

The decoction and powdered form were the most preferred mode of usage of plants. This is in coherence with many ethnobotanical studies on anti-diabetic plants (Neamsuvan *et al.,* 2015; Mrabti *et al.,* 2021). However, in a study by Yaseen *et al.* (2015) in Pakistan, decoction and juice were recorded as the primary ways of consuming traditional plant medicine. The usage of decoction is closely related to more use of herbs and leaves in traditional medicine preparations. Since, they can be gathered fresh or shade-dried and stored in jars, and liquids are easy to consume. Besides, the decoctions contain a high amount of bioactive molecules (Yaseen *et al.,* 2015; Hu *et al.,* 2020).

4.2.4 The most important anti-diabetic plants

The most used hypoglycaemic species in the survey were *Berberis lyceum, Syzygium cumini, Trigonella- foenum-graceum, Momordica charantia, Tinospora cordifolia, Zanthoxylum armatum, Emblica officinalis, Catharanthus roseus* and *Utrica dioca. Berberis lyceum* with 81 use reports and a UV value of 0.24 was the most used anti-diabetic plant in study area. *Berberis* spp. has traditionally been used for the management of diabetes across world ;in countries like Iran, China, and Pakistan (Hamayun *et al.,* 2006; Sood *et al.,* 2013; Madiseh *et al.,* 2014; Rana *et al.,* 2019). The plant is an ample source of diverse bioactive moieties, comprising alkaloids, flavonoids, anthocyanins,and polyphenols (Srivastava *et al.,* 2015; Belwal *et al.,* 2020; Nazir *et al.,* 2021) concomitant with numerous vitamins and minerals. The most active metabolite occurring in *Berberis* species is berberine, belonging to the class of benzylisoquinoline alkaloids. Studies have shown its synergistic effect on diabetes and its complications through *in vitro* and *in vivo* studies (Srivastava *et al.,* 2010; Bukhari *et al.,* 2022; Aslam, 2017; Wang *et al.,* 2018).

In traditional and folk medicine, formulations used to manage diabetes, all parts of *Syzygium cumini,* particularly the seeds, have been in use for their therapeutic effects. Flavonoids are quite abundant in the seeds and are responsible for free radical scavenging as well as protecting antioxidant enzymes (Ravi *et al.,* 2004). Alkaloids like jambosine and jambolin are known to inhibit the conversion of starch to glucose (Craveiro *et al.,* 1983). Furthermore, kaempferol and gallic acid in *Sygium cumini* seeds possess high alpha-glucosidase activity (Rashid *et al.,* 2022).

Trigonella foenum-graecum, an age-old spice and flavouring agent *is* frequently used in Ayurvedic formulations (Sharma *et al.,* 1996). Its seeds are prescribed for diverse illnesses like diabetes, gut

issues, raised triglycerides, and inflammation in traditional medicine (Sharma *et al.,* 1990). *Trigonella foenum-graecum* is rich in dietary fibers and has a long history of usage as a hypoglycemic agent in Egypt, India, northern Africa, and southern Europe (WHO,2013). Coumarins, *4- hydroxyisoleucine (4-HI), galactomannan,* saponins, *trigonelline,* and lipids are responsible for the hypoglycemic and hypocholesterolemic effects of Fenugreek seeds in T2DM patients (Madar *et al.,* 1988; Basch *et al.,* 2003).

Momordica charantia has stayed a propitious anti-diabetic plant across cultures (Leung *et al.,* 2009). It occupies a pivotal place in the traditional medicine system of countries like China, India, Mauritius, Turkey, Pakistan, and Africa (Palamthodi and Lele, 2014;), Mootoosamy and Mahomoodally, 2014; Yaseen *et al.,* 2015; Yaldiz *et al.,* 2015; Peter *et al.,* 2019; Gupta *et al.,* 2021). Its fruits contain alkaloids, saponins, glycosides, phenolics, and resins (Liu *et al.,* 2021). Saponins like Momordicine II and 3-hydroxy cucurbit a-5, 24-dien-19- al-7, 23- di-O-β-glucopyranoside isolated from *Momordica chairanta* exhibited insulin-releasing activity in MIN6 β-cells at conc. of 10 and 25 μg/mL (Keller *et al.,* 2011; Liu *et al.,* 2021 Vicine, polypeptide-p, and charantin are the most potent antidiabetic compounds found in bitter melon (Joseph and Jini, 2013).

Acacia catechu is employed in folk medicine and *Ayurveda* for managing T2DM along with gastrointestinal disorders and oral ulceration (Khare,2012). The extract of dried heartwood is used for ameliorating pain and blood sugar levels in many Asian cultures (Kumari *et al.,* 2021). The extract of *A. catechu* wood contains phenolics such as catechin, delphinidin, and epicatechin, which possess good inhibition of α-amylase and α-glucosidase (Zhu *et al.,* 2021).

Aegle marmelos's leaves and bark extracts are claimed to have hypoglycemic properties, as per ancient Ayurveda texts (Kamanth, 2002). Flavonoids like Quercetin and rutin are the two most active molecules found in *A. marmelos* and have been reported to possess anti-hyperglycaemic action. Other compounds like ellagic acid, ferulic acid, and eugenol do improve insulin secretion (Mohan *et al.,* 2019).

4.2.5 Consensus for anti-diabetic plants

Very high Fic values lying from 0.75 (THPs) to 0.92 (local ethnic people) were recorded for three categories of informants. Previous ethnobotanical studies conducted on the medicinal flora of JKUT by Bhatia *et al.* (2014), and Rao *et al.* (2015) have also observed a similar trend of very

high values of F_{ic} for diabetes for various regions. Locals exhibited a strong inclination to share anti-hyperglycemic species amongst the community. They recommend different formulations to each other. Nearly, the majority of the patients incorporate plants in their diabetic management as suggested by an acquaintance or family member. Plant species are collected from the wild, cultivated in home spaces, herbal sellers, or other known sources who cultivate or possess knowledge of the species, such as friends or family members. Among the three groups, THPs divulged the least amount of information sharing. The plausible reason can be the widespread idea that knowledge disclosure could lessen the potency of the medicine, as well as trade secrets linked with them and their profession.

4.2.6 Disease consensus Index (DCI):

The plants showing high DCI in the present study have been reported ethnobotanically in other studies globally as well as in India. Kumar *et al.* (2019) reported *A. cepa*, *A. sativum*, *Ocimum sanctum*, and *Curcuma longa* usage by the Jaunsar tribe of Chakrata, Uttarakhand for T2DM. *Allium sativum*, *Mangifera indica*, and *Syzygium cumini* have been traditionally used in Latin American societies of Brazil and Mexico (Trojan-Rodrigues *et al.,* 2012). In the north-east Himalayas also, studies have reported significant usage of these species for T2D management (Tarafdar *et al.,* 2012; Hazarika *et al.,* 2020). In a similar study, in Sursagar, Rajasthan, India, Goyal (2015) reported DCI for *Momordica charantia* (0.71) and *Syzygium cumini* (0.62) which is equal to our reported values. Andrade-Cetto in a similar study reported a DCI of 0.07 for *Momordica charantia.* The said species are common and people have good knowledge of their botany. They have been very well documented by scientific studies as well. S-methyl cysteine sulfoxide(I), S-allyl cysteine sulfoxide, Allicin, Alliin (2), and allyl sulfide are hypoglycaemic molecules in *Allium cepa* and *Allium sativum*. S-methyl cysteine sulfoxide (200 mg/kg) when administered orally to alloxan-induced diabetic mice improved metabolic parameters (Zhai *et al.,* 2018).

Curcumin is the most potent identified bioactive in *Curcuma longa* and it is found to improve the islet cell viability and derail ROS in islet cells. Curcumin enhances the number of pancreatic islets and curbs t-cell-mediated loss in pancreatic islets. It is indicated by an increased HOMA-β and decreased C-peptide as documented by Chuengsamarn *et al.* (2012); which improves basal insulin secretion in human islets.

Mangiferin (1,3,6,7-tetrahydroxyxanthone-C2-β-D- glucoside) is the most promising polyphenol having hypoglycemic potential (Mistry *et al.,* 2023). Leaf extract showed significant inhibition of alpha-amylase activity up to (51.4 % ± 2.7) at a conc. of 200 µg/ml. Besides, improving glucose adsorption capacity (2.7 ± 0.19) mM glucose/g extract concomitant with an upsurge in glucose uptake in LO-2 liver cells (143 ± 9.3) % (Ngo *et al.,* 2019). The effectiveness of *Psidium guajava* leaves and fruits in hyperglycemia management has been validated by many studies. Administration of 10mg/kg b.w. of fruits of *Psidium guajava* showed antihyperglycemic activity in diabetic mice (Tella *et al.,* 2022). A positive effect on the regulation of insulin signaling was deciphered upon a dosage of 200 mg/kg ethanolic extract given to STZ-induced diabetic mice (Jayachandran *et al.,* 2020). Yang *et al.,* 2020 demonstrated that leaf extract of guava leaves decreased fasting sugar levels and improved insulin resistance in diabetic mice. Flavonoids extracted from *P.guava* reduce insulin resistance (Beidokhti *et al.,* 2020). Polysaccharides from guava have been shown to have excellent alpha-glucosiadse inhibition with EC_{50} of 2.27 µg/mL and 0.18 mg/ml inferring that their activities were 1379 and 17 times more than the positive control (Zhang *et al.,* 2016). Bioactives like gallic acid, chlorogenic acid, quercetin, rutin, syringic acid, kaempferol, apigenin, cinnamic methyl gallate, and epicatechin contribute to antidiabetic effects of guava leaves (Ugbogu, 2022).

4.2.7 Pharmacological and Toxicological Studies

Many of the documented plants have been examined for their pharmacological activities. However, few antidiabetic validation studies have been carried out for *Artemisia scoparia*, *Pilea scripta*, *Rhabdosia rugosa*, *Saussurea lappa,* and *Skimmia anquetilia*. *Pilea scripta*, *Rhabdosia rugosa,* and *Skimmia anquetilia* can be explored for their traditional hyperglycemic claims.

Literature survey reveals that most of these hypoglycemic plants are quite safe for consumption whereas *Acacia nilotica*, *Cassia absus*, *Catharanthus roseus*, *Gymnema sylvestre*, *Holarrhena pubescens*, *Momordica charantia*, *Nigella sativa*, *Phyllanthus niruri* are mildly toxic (Temburna *et al.,* 2014; Singh *et al.,* 2016; Ahmad *et al.* 2017; Manzo *et al.,* 2019; Zahara *et al.,* 2020; Raji *et al.* 2021; Kumar *et al.* 2022). Species like *Aconitum heterophyllum*, *Bergenia ciliata, Bryophyllum pinnatum, Calotropis procera,* and *Datura innoxia* are toxic (Nyirimigabo *et al.,* 2014; Ahmad *et al.,* 2018; Yemitan *et al.,* 2020; Wadhwani *et al.* 2021; Baig *et al.,* 2021). *Cassia*

absus and *Picrorhiza kurroa* (Ahmad *et al.* 2017; Almeleebia *et al.,* 2022) are reported to be abortifacient plants and hence, not prescribed to pregnant women patients.

Ayurveda does outline specific detoxification methods for every toxic medicinal plant species before it can be consumed. *Aconitum heterophyllum* is highly toxic and is generally detoxified *Shodhana*. During *Shodhana* or detoxification/purification, toxic plants are treated with either cow urine or cow milk (Jaiswal *et al.,* 2013). The said methods have proven effective in detoxifying *Aconitum heterophyllum* (Jaiswal *et al.,* 2013). Few studies have evidenced that *Bergenia ciliata* and *Bryophyllum pinnatum* might be toxic, but in the present study, informants and patients have never reported any toxicity related to these species. *Calotropis procera* is placed under the *Upavisha* (less toxic) class in Ayurveda and its *Shodhana* is not prescribed. If any toxicity symptom like vomiting, stomachache, and diarrhea occurs, the patient is given honey, *ghee*, or cow milk mixed with coarse sugar for relief. The present study reports the use of leaves of *Datura innoxia* which are non-toxic, however, the seeds of said species are toxic and are purified by treating cow urine/milk before consumption.

4.2.8 A comparison with other similar ethnomedicinal field studies on anti-diabetic plants

The present ethnobotanical study was exclusively first on ethnomedicinal flora documenting traditionally used or known anti-diabetic plants in JKUT. Sixty-three plants were reported. The critical assessment of the earlier ethnobotanical field studies (Kumar and Bhagat 2012; Bhushan and Kumar 2013; Manhas *et al.* 2015; Rao *et al.* 2015; Gupta 2016; Sharma *et al.* 2017; Bhushan and Khajuria 2018; Singh *et al.* 2020; Kumar *et al.* 2021) carried out in Kathua district so far has demonstrated only 17 anti-hyperglycaemic species. A comprehensive assessment of all the earlier ethnomedicinal studies conducted in the erstwhile state of Jammu & Kashmir (Tali *et al.,* 2019) has documented a total of 29 anti-diabetic species. In a similar study conducted in the adjoining state of Himachal Pradesh, 23 anti-diabetic species were recorded (Gupta *et al.,* 2021). The comprehensive review of all these ethnobotanical studies reveals that 46 species are a new record for JKUT, and 36 plant species for the Western Himalayas. The literature survey for the ethnobotanical studies on antidiabetic flora carried out worldwide shows that *Pilea scripta*, *Rhabdosia rugosa*, and *Skimmia anquetilia* are added for the first time to the anti-diabetic flora of the world.

4.2.9 Phytochemical analysis of the few most preferred anti-diabetic species

Preference Ranking was used to assess the most effective plants of the study area and *Ajuga bracteosa*, *Urtica dioica*, *Acacia catechu, Bergenia ciliata*, and *Zanthoxylum armatum* were selected for further phytochemical investigations on its basis. Preference ranking has been used in several ethnobotanical studies to determine the degree of effectiveness of the species against a particular disease or multiple diseases. The index rests on the paradigm that elder informants possess more corpus of traditional knowledge (Martin, 2010; Tekley *et al.,* 2013; Kidane *et al.,* 2018; Tefera and Kim, 2019; Hu *et al.,* 2020).

4.2.9.1 Total Phenolic Content (TPC)

The TPC in ethanol extracts ranged from 56.36 ± 2.8 to 134.19 ± 6.70 mg GAE/g. *Acacia catechu* and *Bergenia ciliata* had the greatest phenolic contents of while the smallest TPC was recorded in *Zanthoxylum armatum, Ajuga bracteosa, and Utrica dioca*. Total phenolic concentration is affected by the extraction procedure and solvents used to dissolve endogenous compounds in plants (Siddhuraju *et al.,* 2007). Phenolics possess antioxidant action due to their redox characteristics. The hydroxyl groups in plant extracts facilitate free radical scavenging. Phenolics are more soluble in polar organic solvents due to a hydroxyl group present, therefore, ethanol was selected as the extracting solvent (Wang & Weller, 2006). Sulaiman *et al.* (2012) reported a TPC of 78.12 ± 2.35 mg in *Acacia catechu* using hydro-alcoholic extraction. Barkatullah *et al.* (2012) reported a TPC value of 21.68 ± 1.28 mg/g in ethanolic extracts of *Zanthoxylum armatum* fruits which are low then present study, similar results were for the bark (16.48 ± 3.24 mg/g). Ali *et al.* (2018) found the total phenolic content of 337.26 ± 4.24 mg/g in methanolic extract the aerial part extracts of *Ajuga bracteosa*. The total amount of phenolic compounds in *Utrica dioca* roots of 150 ± 3.87 mg/g by Taraseiviene *et al.* (2023). TPC in *Bergenia ciliata* crude extract are higher as compared to an earlier study where it was highest in ethyl acetate fraction (80.96 ± 4.29mg/g) (Zafar *et al.,* 2019). The values of phenolic content in this current study varied slightly compared to those in the literature. This may be due to the presence of different amounts of sugars, carotenoids or ascorbic acid, or the duration, geographical variation, or methods of extraction, which may alter the amount of phenolics (Uddin *et al.,* 2012; Burri *et al.,* 2017).

4.2.9.2 Total Flavonoid Content (TFC)

The *Zanthoxylum armatum* fruit extract was having the smallest amount of flavonoids, while the *Acacia catechu* had the highest flavonoid content. Flavonoids are secondary bio actives with antioxidant activity, the potential of which relies on the number and position of free OH groups (Panche *et al.,* 2016). In a survey of past literature reports it was found that Parkhe *et al.* (2018) found the TFC of 2.84 mg/100gm in the *Acacia catechu* dried roots hydroalcoholic extract. Phuyal *et al.* (2020) determined the TFC of the ethanolic extracts of *Zanthoxylum armatum* fruit was 22.8 mg/g and that of bark was 18.33 ± 3.58 mg/g. TFC in *Ajuga bracteosa* are comparatively higher than a past report wherein the maximum flavonoids (7.50 ± 2.56 mg/g) were displayed by *Ajuga bracteosa* leaves aqueous extract followed by roots extract (5.80 ± 4.25 mg/g) reported by Guglani *et al.* (2020). In another study by Kayani *et al.* (2016) methanolic extracts showed high TFC. In folklore medicine, aqueous extracts are used, and methanol is also polar, which supports the reason of efficacy of aqueous solvents. Similarly, Fattahi *et al.* (2014) found the TFC was 133.91 ± 6.34 mg in *Urtica dioca* aqueous extract of TFC in *Bergenia ciliata* were also high as compared to a previous study by Zafar *et al.* (2019) TFC were higher in crude extract (88.40 ± 3.18 mg/g) followed by n-butanol fraction (60.10 ± 2.46 mg/g) in rhizomes of the *Bergenia ciliata.*

4.2.9.3 DPPH assay

The antioxidant activity of the ethanolic leaf extracts of the selected species was evaluated by the DPPH assay method. The DPPH method is generally used to evaluate the antioxidant activity in medicinal plants, and it is a convenient method to measure the scavenging potential of free radicals (Laxa *et al.,* 2019). The absorbance of the DPPH radical at wavelength 517 nm decreases as it is scavenged. DPPH free radical scavenging assay is widely used assays as it is advantageous compared to other laboratory-generated free radicals and is accurate. *Ajuga bracteosa* leaves showed antioxidant activity as high as standard Ascorbic acid. The high flavonoids and phenol content levels of *Acacia catechu, Zanthoxylum armatum, Ajuga bracteosa, Utrica dioca,* and *Bergenia ciliata* plants correspond to their high antioxidant levels.

Many complex diseases are treated and prevented with antioxidant-based drug formulations. Plants are a rich source of natural antioxidants and contain diverse antioxidative secondary metabolites with therapeutic potential. Polyphenols are the most common antioxidant compounds found in plant matter. Their antioxidant activity springs from their redox properties, which make them

useful as reducing agents, hydrogen donors, singlet oxygen quenchers, and metal chelators (Kim *et al.,* 2011). Flavonoids, phenolic acids, stilbenes, tannins, coumarins, and lignans are common phenolic compounds found in medicinal plant tissues attributing them with antioxidant activity (Kahkonen *et al.,* 1999).

DPPH has the advantage of being unaffected by specific side reactions caused by various additives, such as metal ion chelation and enzyme inhibition, which distinguishes it from laboratory-generated free radicals like the hydroxyl radical and superoxide anion can be affected by side reactions. Antioxidant molecules react with DPPH, causing the free radical to be scavenged by hydrogen donation. When an antioxidant is present in the medium, the color of a freshly prepared DPPH solution changes from deep purple to yellow (Kasote *et al.,* 2015).

Guleria *et al.* (2011) reported the ethyl acetate fraction of heartwood of *A. catechu* has the highest antioxidant DPPH radicals (4.76 ± 0.14 µg/mL). Mukhijal *et al.* (2014) analyzed the ethanolic bark extract for in vitro antioxidant potential via DPPH, nitric oxide radical scavenging activity, and reducing power assay; petroleum ether and ethyl acetate extract has shown maximum antioxidant activity with IC50 values of 85.16 ± 1.05 and 99.25 ± 2.53 in DPPH assay and 72.39 ± 1.53 and 94.81 ± 2.56 in Nitric oxide radical scavenging assay. The antioxidant activity of different plant parts of *Ajuga bracteosa* was done by Guglani *et al.* (2020) against various in-vitro antioxidant assays. The aqueous extract of leaves exhibited significantly ($P<0.05$) highest antioxidant activity in DPPH, and potassium ferricyanide reducing power assay, with IC50 values of 0.2707 ± 0.0008, 0.4409 ± 0.0020, and EC50 values 0.3413 ± 0.0030 mg/mL, respectively, followed by the other parts of the plant. The leaves extract recorded the highest total phenolics, flavonoids, and tannin contents as compared to roots and flowers.

Kukric *et al.* (2012) determined the antioxidant activity of *Utrica dioca* by using DPPH and ABTS methods, with IC50 values, were 31.38 and 23.55 µg/mL, respectively. These results showed the weak and moderate antioxidant capacity of stinging nettle. Rajkumar *et al.* (2010) reported EC50 of 36.24 µg/mL by DPHH assay in *Bergenia ciliata* rhizomes. Zafar *et al.* (2019) reported in *Bergenia ciliata* rhizome, an inhibition of 87.50±0.70% in DPHH assay at 1000ul of crude extracts.

4.2.9.4 Alpha-amylase Assay

Antidiabetic activities of *Acacia catechu, Zanthoxylum armatum, Ajuga bracteosa, Utrica dioca, and Bergenia ciliata* have been reported in several parts. Aryal *et al.* (2021) determined the *α*-amylase inhibition of the *Acacia catechu* extracts. Among the tested fractions, ethyl acetate and water fraction showed the most potent activity with an IC_{50} value ranging within 9–114.9 *μ*g/mL against the *α*-glucosidase enzyme as compared to acarbose ($IC_{50} = 344.23 \pm 1.03$ *μ*g/mL) and results obtained for ACH in the present study also confirm same. Paiva *et al.* (2019) reported α-amylase activity (53.5%) in the methanolic extract of *Zanthoxylum armatum* and α-glucosidase inhibition of 99.4% in the stem of *Zanthoxylum armatum* of The IC50 values of the extracts in the case of α-amylase was 25.9 and 61.5 μg/mL, while in α-glucosidase IC50 values were between 21.6 and 26.5 μg/ml. The results indicate that the extracts are potentially useful for the treatment of diabetes. Zahra *et al.* (2017) evaluated alpha-amylase inhibition in hexane extract of *Ajuga bracteosa* (44.70 ± 0.30% α-amylase inhibition at 200 μg/mL conc. Nickavar and Yousefian (2010) reported alpha-amylase inhibition from *Urtica dioica* leaves at an IC50 of 1.89 mg /ml.60% inhibition at 2 mg/mL of *Utrica dioca* aqueous extract was reported by Rahimzadeh *et al.* (2014), *Utrica dioca* extracts showed inhibition of α-amylase in conc. and time-dependent way. In the present study, it is lower, and thus UDL can be used for inhibitor development to control post-meal blood glucose hike. Furthermore, Sapkota *et al.* (2022) suggested ethyl acetate extract of *Bergenia ciliata* showed significant inhibitory activity against α-amylase with IC50 values of 38.50 ± 1.32 μg/mL. Numerous factors like degree of ripeness, processing, and storage, influence plant polyphenol concentration, which may account for heterogeneity in plant IC50 values (Aryal *et al.*, 2021). The IC50 value of the control acarbose was 6.1 g/mL is lower than that of plant extracts, and is not surprising as plant extracts are combinations of multiple chemicals in comparison to single molecule Acarbose.

4.2.9.5 Alpha glucosidase assay

Ajuga bracteosa leaves have been assessed for the first time for alpha-glucosidase inhibition to the best of our knowledge. Earlier, chloroform and n-hexane extracts of roots of *A. bracteosa* showed alpha-glucosidase inhibition with IC50 values of 299.2 μg/mL and 131.7 μg/mL, respectively (Hafeez *et al.*, 2017). The α-glucosidase and α-amylase inhibitory activity of *Acacia catechu* ethanolic seed extract (53.77 ± 0.86 %) was confirmed at a concentration of 500 μg/mL. IC50

value of α-glucosidase activity 187.80 ± 4.15 µ g/mL (Lakshmi *et al.,* 2015). The fruits of *Zanthoxylum armatum* showed maximum α-glucosidase inhibition (96.61 ± 2.13 and 93.58 ± 2.31% respectively (Alam *et al.,* 2018).

Utrica dioica leaves showed 69.922% ± 0.014 and 71.93 ± 0.0136 inhibition at 500 ug/mL which was higher than an earlier study by Rahimzadeh *et al.* (2014) wherein 60% inhibition was seen with 2 mg/mL. *Bergenia ciliata* is one of the traditional remedies used for diabetes since prehistoric times. In an earlier study by isolated the active compounds from Pakhanbhed. Extraction and fractionation of the extract led to the isolation of two active compounds, (−)-3-O-galloylepicatechin and (−)-3-O-gallocatechin.

The IC50 value for sucrose, maltase, and α-amylase was 560, 334, and 739 µM, respectively for [(−)-3-O-galloylepicatechin] and 297, 150 and 401 µM, respectively for [(−)-3-O-galloylcatechin] (Bhandari *et al.,* 2008). Synthetic α-glucosidase inhibitors are used widely but may cause severe gastrointestinal disturbances; hence the use of natural products has raised to overcome the side effects caused by synthetic drugs.

4.2.9.6 Correlation Analysis

Correlation measures statistically the relationship between different variables concomitant with changes in one variable associated with changes in the other, either in the same direction (positive correlation) or in the opposite direction (negative correlation) (Schober *et al.,* 2018). In the present study, strong positive correlations were observed between TPC with *α*-amylase and *α*-glucosidase inhibition. However, TFC and *α*-glucosidase inhibition correlate with *α*-amylase inhibition. TFC exhibited a significant positive correlation with alpha-amylase and glucosidase. The *α*-glucosidase inhibition and antioxidant activity depicted a significant linear correlation, implying that good antioxidant status results in better inhibition.

Increased oxidative stress causes insulin resistance or impaired insulin secretion leading to late diabetic complications. Antioxidants inhibit lipid peroxidation and depress advanced glycation and, thus help in the management of T2DM (Sapkota *et al.,* 2022). The positive correlation between TPC, TFC, *alpha-amylase* inhibition, and *alpha-glucosidase* inhibition is also consistent with a previous study by Shen *et al., (*2019) in fruits of *Abelmoschus esculentus*. A positive correlation between TPC, TFC, and carbohydrate hydrolyzing enzyme inhibition was recorded

indicating that TPC and TFC are contributors to the inhibition of alpha-amylase and glucosidase enzymes.

Aryal *et al.* (2021) reported the very weak correlation of TPC, and TFC with antioxidant activity, thereby implying that blood glucose is being lowered by inhibition of carbohydrate hydrolyzing enzymes.

4.2.9.7 LC-MS-ESI-QTOF Analysis

In Acacia catechu heartwood molecules like Catechin, epicatechin, quercetin, gallic acid, and kaempferol are present which have exhibited antidiabetic potential in vivo and in vitro studies. Quercetin possesses 15-25 times greater inhibition of alpha-glucosidase than acarbose (Li *et al.*, 2020). It acts by inhibiting the GLUT2 transporter and enhancing the expression of GLUT4 (Cahyana and Adiyanti, 2021). Catechin ameliorated diabetic neuropathy upon administration at a rate of 50 mg/kg b.w in STZ diabetic rats(Adepalli and Suryavanshi,2020). Gallic acid enhances glucose absorption by 19.2% in insulin-resistant mouse hepatocytes. (Kahkeshan *et al.*, 2019). At a dosage of 10-38 mg/kg for 4 weeks, increased expression of insulin genes, and insulin substrate receptor 1 was observed in diabetic mice(Huang *et al.*, 2016).

Phytochemicals like Ajugin A, Ajugin D, Ajugin E, Beta-Sitosterol, Stigmasterol, Bracteatin, Dihydroclerodin, and Clerodinin D in *Ajuga bracteosa* were present. Ward *et al.* (20117) demonstrated that Stigmasterol protects beta cells from glucolipotoxicity, and depresses free radical generation in human islets and INS 1 cells. Administration of beta-sitosterol and stigmasterol at a dose of 100 and 200 mg/kg b.w. for 04 weeks reduced blood sugar levels and restored serum insulin levels (Ramu *et al.*, 2016). Neo-clerodane terpenoids reduced fasting glucose levels and improved insulin resistance in diabetic mice (Fan *et al.*, 2021). Withanolides like Ajugin A, Ajugin D, and Ajugin E are also potent antidiabetic molecules contributing to strong antioxidant potential and alpha-glucosidase inhibition.

In *Bergenia ciliata* rhizome, the presence of molecules like Limonene, Beta-Sitosterol, Afzelechin, Arbutin, Bergenin, Camphor, Catechin, Gallic Acid, Galloylcatechin, Glucoside, and Leucocianidol phytochemicals (Wagle *et al.*, 2016; Singh *et al.*, 2021; Ghosh *et al.*, 2021). β-sitosterol normalized glucose and lipid profile 20mg/kg b.w.for 20 days in diabetic mice and the docking score was good with glucosidase enzyme (Ponnulakshmi *et al.*, 2019). Catechin and

epigalloylepicatechin exhibit good inhibition against carbohydrate metabolizing enzymes. Various studies support the role of bergenin in ameliorating diabetic retinopathy, neuropathy, and nephropathy (Ambika, S., & Saravanan, R. 2016, Yang *et al.,* 2016; Quan *et al.,* 2023).

3,4-Divanillyltetrahydrofuran, Afzelin, Dehydrodiconiferyl alcohol, Ethyl cholate, Gossypetin, Isolariciresinol, Isovitexin, Neoolivil, Nicotiflorin, Olivi, Pentadecanoic acid, and Secoisolariciresinol are few potent bioactives in *Utrica dioica* (Singh *et al.*2013; Zang *et al.,* 2014; Bourgeois *et al.,* 2016; Franciskovic *et al.,* 2017; Jeszka 2022). Secoisolariciresinol forms a stable complex with diabetic targets DPP-4, alpha-amylase and beta-glucosidase at a binding energy of -7.04732084 kcal/mol, -3.82946181 kcal/mol, and -4.16077089 kcal/mol respectively (Salim *et al.,* 2020). 3,4-Divanillyltetrahydrofuran reverses hypogonadism in diabetic mice (Yang *et al.,* 20022). Vitexin shown to improve insulin signaling by upregulating insulin IRS-1. In vivo and in vitro studies have demonstrated that vitexin increases levels of antioxidant enzyme glutathione reductase and superoxide dismutase, decreases apoptosis in islet tissue, improved islet cell regeneration, and reduces fasting blood glucose(Wang *et al.,* 2017; Nurdiana *et al.,* 2017).

In *Zanthoxylum armatum* fruits, Tambuletin, berberine, magnoflorine, nitidine, tambetarine, xanthyletin, and zanthoxyletin were few bio-actives having therapeutic potential (Bhat *et al.,* 2018; Zhuo *et al.,* 2021; Sahu *et al.,* 2021; Kalyankumarju 2022; Hu *et al.,* 2023). Magnoflorine increases insulin levels in RINm5F cells (Patel *et al.,* 2011), and inhibits the Aldose reductase enzyme(Jung *et al.,* 2008). Alpha hydroxyl sanshool, an important chemical in the Zanthoxylum genus exerts an increase in glucose uptake by cells and enhances hepatic glycogen synthesis (Zhang *et al.,* 2022)

4.2.9.8 Simultaneous estimation of polyphenolic compounds (Gallic acid and Quercetin) by HPTLC:

Few studies have done quantification of polyphenolics in these five plants. Kumar *et al.* (2019) reported Gallic acid in the range of 0.006-0.020% and Quercetin lying in the range of 0.031 to 0.084% from bark fractions of *Acacia catechu* along with 8 other polyphenols. Roy *et al.,* 2012 quantified Quercetin in ethanolic bark extract, and the content was 0.070% w/w, in ethanolic root extract, quercetin was reported to be 2.11% w/w.In *Ajuga bracteosa,* Zahra *et al.* (2017) reported quantification of polyphenols with Quercetin content (0.065% w/w) and Gallic acid (0.089% w/w). Tessema *et al.* (2023) quantified Gallic acid to the tune of 11.25±0.1 mg/100 g and Quercetin 1.56±0.5 mg/100g. In *Bergenia ciliata,* there are several studies of simultaneous quantification of phenolics and flavonoids (Dhalwal *et al.,* 2008; Bhandari *et al.,* 2008; Dharmedar *et al.,* 2011;

Pandey *et al.,* 2017). Dhaliwal *et al.* (2008) quantified Gallic acid in methanolic rhizome extract and the content was 0.024±0.011%. Dharmender *et al.* (2011) reported a content of 0.88±0.01 from methanolic rhizome extract by HPTLC. Studies by Shrivastava (2014) in *Bergenia ciliata* rhizomes from Uttarakhand reported Gallic acid (0.027±0.2%). In two other studies, the same authors reported content of 0.415±0.2 % and 0.024±0.2% in methanolic extracts of rhizomes (Shrivastava *et al.,* 2014a; Shrivastava *et al.,* 2015). Our findings are per earlier reports regarding Gallic acid content in *Bergenia ciliata* rhizome. In *Urtica dioica* leaves, Pinnelli *et al.* (2008) quantified Quercetin content to be 0.057 ±0.051 mg/g of dry weight through HPLC-DAD. Franciskovic *et al.* (2017) reported Quercetin in *Urtica dioica* leaves (0.01536±0.004%). In another study by Orcic (2013), quercetin content worked out was 0.0124%. Trineeva and Slivkin (2019) reported a content of 0.002 to 0.00025 % Gallic acid from *Urtica dioica* leaves. Rolta *et al.* (2020) quantified quercetin (159.3197 ug/mg) by HPTLC in *U.dioica* leaves. Alam and Saqib (2015) detected Gallic acid qualitatively via HPTLC at 260 nm. Sabir *et al.* (2017) reported Gallic acid (0.91%) and Quercetin (1.68%) from pericarps of *Zanthoxylum armatum*. Agnihotri *et al.* (2023) estimated Gallic acid (3.23 mg/g of dry weight) along with five other phenolics in root extracts by HPLC-DAD.

The variation in content concerning other studies conducted plausibly because of geographical location, age of the plant, and metabolic status of the plant (Nikolova and Ivancheva, 2005; Monschein *et al.,* 2009). In recent times, HPTLC fingerprinting has emerged as a vital and efficient tool for the identification of the bioactive principle of medicinal plants. The HPTLC method developed and validated for the simultaneous estimation of Gallic acid and Quercetin in crude extracts of these plants happens to be simple, sensitive yet precise, and can be suitably used for the quantification of Polyphenolics in plant extracts. Results obtained in our study imply that the choice of plants by folklore for diabetes does have a relevant scientific basis. Polyphenolics have been evidenced in several studies to ameliorate diabetic complications besides improving beta cell function and insulin resistance. Quercetin is reported to promote beta cell proliferation and insulin secretion (Peng *et al.,* 2017), regulate AMPK which in turn enhances GLUT-4 expression and translocation, regulate inflammatory pathways nuclear factor kappa B (NF-κB) and various interleukins (Iskender *et al.,* 2017). Gallic acid also upregulates PPARγ and AMPK expression thereby improving glucose metabolism (Bak *et al.,* 2013; Variya *et al.,* 2020) and depresses ER stress and apoptosis of beta cells; decline in interleukin levels and NFKβ thus, suppressing

inflammation, a major contributor to insulin resistance (Obafemi *et al.*, 2021). Quantification of these polyphenolics in all five plants thus yields a basis for the traditional usage of them for controlling blood glucose levels.

4.2.9.9 Suggestive strategy to revive the population of plants Facing the threat

Though all these species are being given protection by legislation and are notified for JKUT as endangered by Govt of India, Gazette Notification 2018 and there is a ban on their trading still traditional gatherers especially tribals eludes govt. norms and agencies. They result in unsustainable harvesting in October-November before coming down to the plains. Involving tribals and locals in cultivation will be a sustainable and feasible option.

1. Technical interventions to address bottlenecks that species face in the wild are also required.
2. Self-help groups and women folk can be encouraged to adopt the cultivation of these plants in their respective areas.
3. Implementation of rotational harvesting by govt. can also help.
4. A greater margin of benefits at the local level will aid in the promotion of sustainable harvesting. Thus, there is a need to improve and aware locals the pre- and post-harvesting techniques which is the most integral stage involved in the trading of these high-altitude species.

The nomadic and local gatherers were well-versed with plants and their customary harvesting methods. They used to gather and store some of the most important medicinal herbs for their daily needs or disease treatment. Conventional medicinal practitioners were well-versed in conventional ethics, norms, and practices. Their collection techniques were based on religious practices and beliefs. Because seasonal variation was so essential in the collection of various plant parts, collectors, particularly traditional healers, had designated specific areas for collection based on plant phenology. They used to collect different plant parts according to the lunar calendar. In general, young leaves were collected in the spring, flowers and mature leaves in the summer, and fruits, seeds, and rhizomes in the fall. Traditionally, the harvesting of plants in demand was subject to the various phenophases of desired species; however, collectors today rarely adhere to traditional norms and begin harvesting prematurely, which hinders the growth and yield of the produce (Sharma and Kala, 2016). Previously, collectors had a reasonable understanding of the taxonomic identity of plants to be collected and the portion of those plants required for the intended

use. As it was necessary for the treatment, they used to collect only the most exceptional materials. However, as time has passed, the number of such traditional collectors has diminished. Also, the number of traditional healers has declined as a result of a decline in young people's interest in practicing traditional medical systems. To maximize efficacy, Vaidya and other traditional healers collect plants at specified time.

Survival of plants depends upon the type of part commercially important. Entire plant extraction and roots has a negative impact on the survival of the species, whereas the removal of leaves, fruits and seeds is regarded as less destructive. *Aconitum heterophyllum, Bergenia ciliata, Picrorhiza kurroa, Saussurea costus,* and *Swertia chairata* which are facing threat, roots/rhizome is medicinally important. Unsustainable harvesting has been observed in these species wherein to obtain root, the whole plant is uprooted, often accompanied by no flowering and seed set. Traditionally, *Aconitum heterophyllum, Bergenia ciliata, Picrorhiza kurroa, Saussurea costus, and Swertia chairata* were harvested with a gap of 2-3 years but in recent years with zero gap leading to highly reduced numbers. This has led to a drastic fall in population as well as regeneration. Unsustainable harvesting, early harvesting, and diminished regeneration have accelerated the decline in medicinal plant availability.

Conclusions

The present study was carried out in the Kathua district with informants from the local Doras, the *Gujjar* tribe, and Traditional Health Practitioners (THPs). Sixty-three anti-diabetic species were documented. The ethnopharmacological studies are lacking for *Artemisia scoparia, Saussura costus,* and *Bergenia ciliata,* whereas *Pilea scripta, Rhabdosia rugosa,* and *Skimmia anquetilia* are a new addition to the anti-diabetic flora of the world. All these species may be studied further for their pharmacological validation, and phytochemical analysis to find some novel drugs in the future. Quantification of polyphenolics in a few species and good alpha-amylase and glucosidase inhibition validate the corpus of traditional knowledge that the local Dogra community, THPs, and tribals possess. Documentation of this Traditional Knowledge will serve for its conservation.

CHAPTER 5

SUMMARY

5. Summary

Plant use for healing is perhaps as old as humankind as testified by fossil records aging 60,000 years ago from the Middle Palaeolithic Age. The traditional system of medicine is not only looked for alleviation of ailments but also as a repository of total well-being. It is easily accessible, low cost, and safer because of long-term use by local ethnic communities.

Diabetes mellitus prevalence has increased exponentially in recent years. The disease affects more than 65.1 million Indians, expected to go up to 80 million by 2025, thereby making it the diabetic capital of the world. About one million Indians per year die because of diabetic complications. This calls for holistic management of the disease to reduce complications and mortality.

Due to the presence of the Himalayas, Northern India houses an immense diversity of medicinal plants, out of 8644 reported species, 1748 are medicinal plants, thus prospects of discovering new leads from the traditionally available knowledge of plants is immense The ethnobotanical information reveals about 800 plants may have antidiabetic potential and near about 30% of them have been pharmacologically screened. Ethnobotanical investigations inventorize the information on the cultural interaction of local folks with plants. Therefore, traditional local communities worldwide have a great deal of knowledge about native plants on which they intimately depend.

The Jammu & Kashmir State (32^{o} 17′ and 36^{o} 58′ N Lat., 72^{o} 35′ and 80^{o} 30′ E Long.) is located mostly in the Himalayan Mountains and Shiwaliks, this region of India has a diverse biogeography and a high diversity of vegetation especially in terms of medicinal plant wealth. Many medicinal plant species having industrial potential are growing wild in this region. A large number of people belonging to various ethnic groups are still practicing their traditional health care systems. The traditional treatment systems adopted by these ethnic communities are being used generation-wise without any scientific validation. The present study documented traditional knowledge of plants used by the local population to alleviate diabetic suffering.

The present study was carried out in District Kathua, Jammu and Kashmir, India. Regular ethnobotanical field surveys were carried out from April 2019 to November 2022 at different locations in the district. Field surveys along with discussions and interviews through semi-structured questionnaire were used to gather information about traditionally used hypoglycaemic species of the area. A pre-informed consent was taken before the interview. A total of 310

informants comprising 14 Traditional Health Practitioners (THPs), 93 tribals belonging to the Gujjar tribe, and 203 local Dogra community participated in the survey. All the species reported were authenticated for botanical names and herbarium specimens were deposited in the Herbarium of the University of Jammu.

Informants reported sixty-three species from 58 genera and 34 families. A significant variation was observed between knowledge of plants among three groups of informants. THPs knew a greater number of plants as compared to tribal and locals. The dominating family of the antidiabetic flora of Kathua was Fabaceae wit 5 genera and 6 spp. Herbs (47.6%) were the major life forms recorded and Leaves were the most preferred part used plausibly owing to ease of harvest and seat of synthesis of many secondary bio actives.

Factor informant consensus (F_{ic}) was highest for locals (0.92) followed by tribals (0.90) and least by THPs. Thus, locals depict a strong inclination of knowledge sharing as compared to tribals and THPs.

The Disease Consensus Index (DCI) was used to indicate the most significant plants of the district. High DCI was observed for plants as *Allium sativum* (1.25), *Allium cepa* (1.04), *Psidium guajava* (0.84), *Ocimum sanctum* (0.76), *Momordica charantia* (0.75). The said values of DCI for respective plants have been in coherence with few earlier studies.

Calculation of Use value (UV) indicated that *Berberis lyceum, Syzygium cumini, Trigonella foenum-graceum, Momordica charantia, Tinospora cordifolia, Zanthoxylum armatum, Emblica officinalis, Catharanthus roseus* and *Urtica dioica* were the most used plants with 81 use reports and UV of 0.24.

Preference ranking index was lastly used to assess species most important preferred species assigned by key 34 informants. *Ajuga bracteosa* (3.84), *Urtica dioica* (3.75), *Acacia catechu* (3.65), *Bergenia ciliata* (3.59), *Zanthoxylum armatum* (3.59), *Momordica charantia* (3.53), *Tinospora cordifolia* (3.47), *Emblica officinalis* (3.44), and *Coccinia indica (*3.26) are the ten most preferred plants recommended by informants.

Ajuga bracteosa, *Urtica dioica*, *Acacia catechu*, *Bergenia ciliata* and *Zanthoxylum armatum* were subjected to phytochemical analysis. All the five plants had good amount of phenolics and flavonoid content. Highest phenolic content was recorded in ethanolic extract of *Bergenia ciliata*

rhizome (127.24 ± 0.66 mg GAE/g). TFC was highest in Acacia catechu heartwood (256.13± 0.59). DPHH assay recorded highest antioxidant activity (98.50±0.34%) comparable to standard Ascorbic acid (99.356 ± 0.27%).

In vitro antidiabetic potential of these plants was assessed by α-amylase and α-glucosidase inhibition assay. Aqueous extract of *Acacia catechu* heartwood showed highest alpha amylase inhibition (84.42± 0.51%) followed by methanolic extract of *Zanthoxylum armatum* Fruits (75.80 ± 0.11 %), and minimum by exhibited by *aqueous Bergenia ciliata Rhizome* (52.16 ± 0.01%**)** followed by methanolic ZAF (358.94 ± 4.25 µg/mL). IC50 value of aqueous *Acacia catechu* heartwood extract *(*125.40±0.04 ug/ml) was lower than acarbose (175.3944±0.0285 ug/ml). Maximum alpha glucosidase inhibition was exhibited by Ajuga bracteosa leaves in both aqueous (85.72 ± 0.14%) and methanolic (81.55± 0.33 %). IC50 value was 128.89±0.044 ug/ml and was lower than standard Acarbose (162.39±0.0285 ug/ml). Other extracts also showed good inhibition of both alpha amylase and glucosidase enzyme. Inhibition of these key carbohydrate digesting enzymes is one of the strategies to manage postprandial hike in blood glucose levels. It also validates the usage of these plants traditionally by ethnic people in the T2DM management.

Untargeted metabolomics of these plants was done by using LC -ESI-QTOF-MS led to isolation of 23 compounds in *Acacia catechu* heartwood,17 in *Ajuga bracteosa* leaves ,9 in *Bergenia ciliata* rhizome, 14 in *Urtica dioica* leaves and *Zanthoxylum armatum* fruits each.

A precise, simple and validated method was developed for simultaneous quantification polyphenolic compounds i.e. Gallic acid and Quercetin. The concentration of Gallic acid in *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata* rhizome, *Urtica dioica* leaves and *Zanthoxylum armatum* fruits was 0.01849%, 0.01034 %, 0.011%, 0.01414 % and 0.01551% w/w respectively. Similarly, quercetin estimated *Acacia catechu* heartwood, *Ajuga bracteosa* leaves, *Bergenia ciliata* rhizome, *Urtica dioica* leaves and *Zanthoxylum armatum* fruits was 0.00463%, 0.0017%, 0.00315%, 0.00452% and 0.00895% w/w.

So far population status of documented species was concerned, out of 63 documented plants was concerned, *Aconitum heterophyllum, Bergenia ciliata, Picrorhiza kurroa, Saussurea lappa, Swertia chairata* are the species facing threat in wild. Encouraging local farmers and volunteers to cultivate these species can help in their revival. One of such local Sh. Rajat Sharma has been

successful in the cultivation of two critically endangered species i.e. *Aconitum heterophyllum* and *Saussurea lappa.* Awaring nomadic collectors and locals for cultivation and even in natural habitats can help to reverse the population status of these highly traded species.

The present study reported 46 spp. for first time from JKUT, and 36 spp. for the Western Himalayas. *Pilea scripta*, *Rhabdosia rugosa*, and *Skimmia anquetilia* are new additions to the hypolycemic flora of the world. This piece of work has recorded a bit of Traditional Knowledge corpus that local ethnic and traditional communities possess. Validation of this folklore usage of documented species brings to light these plants for further pharmacological exploration by other researchers.

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ANNEXURES

Annexure-I

PUBLICATIONS:

1. Published Paper titled," Traditionally used anti-diabetic plants in Kathua district of Union of Jammu and Kasmir, India" in Journal of Ethnopharmacology. 2023 Sep 7;319(Pt 1):117087. doi: 10.1016/j.jep.2023.117087.
2. Published Paper titled,pu"Potent Anti-diabetic Activity of Traditional Medicinal Plants from Jammu & Kasmir: A review in Plant Cell Biotechnology and Molecular Biology.22(33 & 34):606-616;2021.
3. Manuscript titled," Habenaria species and its ethnomedicinal importance: An overview "published in Tropical Journal of Natural Product Research (Scopus indexed)2021;5(11):1905-1912.

CONFERENCES:

1. Presented poster on the topic" Traditional Knowledge of Antidiabetic Plants amongst Tribals and Traditional Health Practitioners in Kathua District, UT of Jammu and Kasmir", in the 5th International Conference on Advances in Agriculture Technology and Allied Sciences (ICAATAS2022) on June4-5,2022 held at MS Swaminathan School of Agriculture Technology, Centurion University, Gajapati, Odisha (0nline mode)

2. Presented paper titled" Antidiabetic, antioxidant and PLC Analysis of Polyphenolic compounds from five traditionally used plants from Kathua district of UT Of Jammu and Kashmir" in Second International Conference on Plant Physiology and Biotechnology held from20-21 April 2023 organized by the School of Biosciences & Bioengineering.
3. Presented paper titled" Ethnobotanical survey of Antidiabetic Flora of Kathua District, UT of Jammu and Kashmir", in the 3rd International Conference of Pharmacy (ICP-2022) on the theme of "Practice, Promotion& Publication of Innovation: A way of Transforming Health" on 09 & 10TH Of November,2022 organized by School of Pharmaceutical Sciences in collaboration with Indian Pharmaceutical Association at Lovely Professional University, Punjab.
4. Presented paper titled" In-vitro assessment of the antidiabetic potential of three traditionally used plants in Kathua Distt. Of UT Of Jammu & Kashmir" in International

Conference on Science for Survival: To explore the unexplored dimensions " organized at GCW, Udhampur, JK on 10-11 February 2023.

5. Presented paper titled" Traditional knowledge of antidiabetic plants amongst tribals, traditional practitioners and locals in Kathua Distt. Of UT Of Jammu & Kashmir" in 02 day International Conference on the theme Ethnobotany: Present and Future Perspectives by Deptt. Of Botany at Govt. Degree College, Billawar, JK on 25-26 November,2022.
6. Presented paper on the topic" Ethnobotanical survey of Antidiabetic plants used amongst tribals, traditional practitioners and locals in Kathua District, UT of Jammu and Kashmir", in National Conference on Emerging Trends in Genetic Engineering and Molecular Biology on 28-29 of September 2022, organized by Centre of Molecular Biology, Central University, Jammu in collaboration with J & K Science, Technology and Innovation Council, Deptt. Of Science and Technology.

7. Presented poster on the topic" Ethnomedicinal uses of orchid genus Habenaria, in the International Conference on Advances in Agriculture Technology and Allied Sciences (ICRTC2021) on 28-30 September 2021 organized by Akal University, Bathinda Punjab in collaboration with Indian Chemical Society, Kolkata.
8. Attended UGC Sponsored Short Term Course on Plagiarism and Ethical issues in Research work conducted from 03-03-2020 to 09-03-2020 organized by HRDC, Guru Nanak Dev University, Amritsar.

Annexure-II

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Traditionally used anti-diabetic plants in Kathua district of Union Territory of Jammu and Kashmir, India

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ARTICLE INFO

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1. Introduction

Diabetes mellitus (DM) is multifactorial metabolic disarray with complex etiologies that have both chronic and acute consequences (American Diabetes Association, 2019). It continues to be a major global health challenge with high morbidity, mortality, and economic burden (Andrade et al., 2020). As per International Diabetes Federation Diabetes Atlas (10th Edition, 2021) global diabetics in the age group of 20–79 years old in 2021 were 10.5% (537 million), 643 million by 2030 and expected to be 783 million by 2045 (12.2%). Economic burden will surge to 1054 billion US$ by the end of 2045 (Sun et al., 2022). Besides, 541 million adults have impaired glucose tolerance, making them highly vulnerable to diabetes. Epidemiology data show that the number of diabetes in India has significantly increased. Now 77 million, with a projected increase to 124.9 million by 2045, as well as 39.4 million people who do not yet have their diabetes diagnosed. Recent estimates project Diabetes as the 7th leading cause of mortality globally causing 1.55 million excess deaths (Rehman et al., 2020).

DM is mainly characterized by chronic high blood sugar owing to inappropriate action of insulin because insulin resistance, deficit or both. Disturbance in glucose homeostasis leads to persistent hyperglycemia interrupting carbohydrate, lipid and protein metabolism (Khan et al., 2014). It causes failure, dysfunction, and long-term damage to nerves, kidneys, eyes, blood vessels, and heart. These co-morbidities result in premature deaths (Salsali and Nathan, 2006; Padhi et al., 2020). The severity of the impairment is associated with the duration of diabetes and the state of hyperglycemia. Hyperglycemia is coupled with formation Advanced glycation products and Reactive oxygen species inside cells. This metabolic interruption promotes inflammation leading to numerous micro and macro-vascular complications (Gerber and Rutter, 2017). The risk for diabetes is increased with the factors like older age, smoking, physical inactivity, unhealthy diet, obesity, overweight, gestational diabetes, family history, and ethnicity (Kharroubi and Darwish, 2015; Broholm et al., 2019).

Type 1 diabetes accounts for 5–10% of diabetics is autoimmune in nature; T-cell mediated loss of pancreatic β-cells whereby exogenous insulin intake is mandatory (Salsali and Nathan, 2006; Kharroubi and Darwish, 2015). It is majorly observed in adolescents and children (Lukmanji, 2003). Type 2 diabetes mellitus (T2DM) accounts for more than 90% of diabetics resulting from the inability of the body to effectively utilize the produced insulin or its deficit (Spellman, 2010). The resistance to insulin is the consequence of the non-responsiveness of the insulin target organs: liver, adipose tissue, and skeletal muscles (Tripathy and Chavez, 2010). Oxidative stress coupled with inflammation spurs signaling pathways like c-Jun Amino Terminal Kinase and IkappaB kinase nuclear kappa B (NF-KB) pathways resulting in blockage of insulin action (Padhi et al., 2020; Naqvi et al., 2023).

Oral diabetic medications generally used include biguanides, thiazolidinediones, sulfonylureas, Dipeptidyl Peptidase-4 inhibitors, Sodium-Glucose Transport Protein 2 inhibitors, α-glucosidase inhibitors, and non-sulfonylurea secretagogues (DeFronzo, 1999; DeFronzo et al., 2019). Episodic hypoglycemia, increased lipid reserves, and digestive problems are the results of achieving a euglycemic index solely with

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POTENT ANTI-DIABETIC ACTIVITY OF TRADITIONAL MEDICINAL PLANTS FROM JAMMU AND KASHMIR: A REVIEW

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Review Article

ABSTRACT

Diabetes is a serious human ailment which afflicts various walks of life and raises concerns of health care industry in recent time. Instead of the availability of multiple treatment regimes for managing diabetes, the complications associated with it are still costly to be managed by available drugs. Natural products have been established by extensive research efforts for their anti-diabetic properties and emerge as potential sources for discovering new drugs. The preference is given for developing herbal formulations due to low cost and lesser side effects. There is still a great demand for developing new drugs of plant origin with anti-diabetic activities, due to the lack of scientific validation for majority of plant derived potential anti-diabetic agents. India is a vast reserve and a home of many medicinal plants with proven antidiabetic properties. In India, the state of Jammu and Kashmir due to wide range of elevations and diverse biogeography produce high diversity of vegetation especially in terms of medicinal plant wealth. Medicinal plants like *Berberis lyceum, Aegle marmelos, Artemisia sp, Allium sp, Tinospora cordifolia, Trigonella foenum,* etc. are the cultivars of Jammu and Karshmir with proven antidiabetic properties. In this review article, we reviewed the published studies describing the medicinal plants from Jammu and Kashmir for improving diabetes and associated complications. The detailed action mechanisms of phyto-active constituents of these medicinal plants are also described. However, the scientific validation of plant origin anti-diabetic drugs is required through in vitro and in vivo studies for their commercial exploitation.

Keywords: Medicinal plants; diabetes; herbal drugs; natural products; Jammu and Kashmir; India.

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Review Article

Habenaria Species and Its Ethnomedicinal Importance: An overview

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ABSTRACT

Orchidaceae family to which the orchids belong is the second largest flowering plant family having around 850 genera. The members of this family includes mainly terrestrial orchid which are used for various beneficial effects in traditional medicine. Although detailed pharmacological studies on medicinal orchids are not available, however, reports have suggested that medicinal orchids possess wide usage by the local community for treating various ailments. *Habenaria Willd.* is an important genus in this family that largely contains terrestrial plants. Most of the reports for the medicinal usage of Habenaria species are from two large Asian countries India and China and they are generally used for treating kidney disorders, sexual dysfunction, spermatorrhoea, menstrual disorders, haematuria, hernia, tinnitus, nervousness and backache. In Ayurveda also the different species of Habenaria are used for revitalization or as aphrodisiac and are given a common name "Riddhi". This review article aims to introduce different species of Habenaria genus which are known for their medicinal value and thus can be considered for more effective propagation and conservation actions.

Keywords: Orchids; Habenaria; Traditional medicine; "Riddhi"; Medicinal plants.

Introduction

Orchidaceae is the most evolved and the largest flowering plants family which is comprised of around 750-850 genera and contains 25,000 to 35,000 species.[1,2] The members of this family exist throughout the world except hot deserts and icy cold Antarctica. However the greatest diversity of these plants occurs in sub-tropical and tropical regions. The exquisite beauty of the complex flowers undoubtedly makes orchids ornamental elite. Orchids are also becoming an object of business worth million dollars nowadays. A rise in the rate of 10–20% of world floriculture trade was observed with increasing popularity of orchids as both potted floriculture crop as well as cut flowers.[3] Many orchids are also emerging to possess medicinal importance in addition to their ornamental value however their role is often overlooked as herbal medicine. Orchids have historically been used for their medicinal properties and possess various therapeutic applications as apparent from the published literature, but the information is although scanty and usually corresponds to a particular community or region.

An important genus in this family is *Habenaria Willd.* which largely contains terrestrial plants.[4] This genus is the largest among the subfamily Orchidoideae and currently known to contain around 835 species throughout the world (WCSP 2018). The pantropical distribution of Habenaria was observed with almost equal number of species found in continents of Asia, Africa and America.[5] There is only one comprehensive taxonomic study of this genus attempted by Kraenzlin (1901)[6] because of its wide distribution and large size where 347 species were recognized.

However, many taxonomic problems are present in defining this genus which further warrants the need for conducting critical studies particularly to identify the relationship amongst its species and its generic delimitation. A large number of Habenaria species (170 species are found in Brazil.[5,7]

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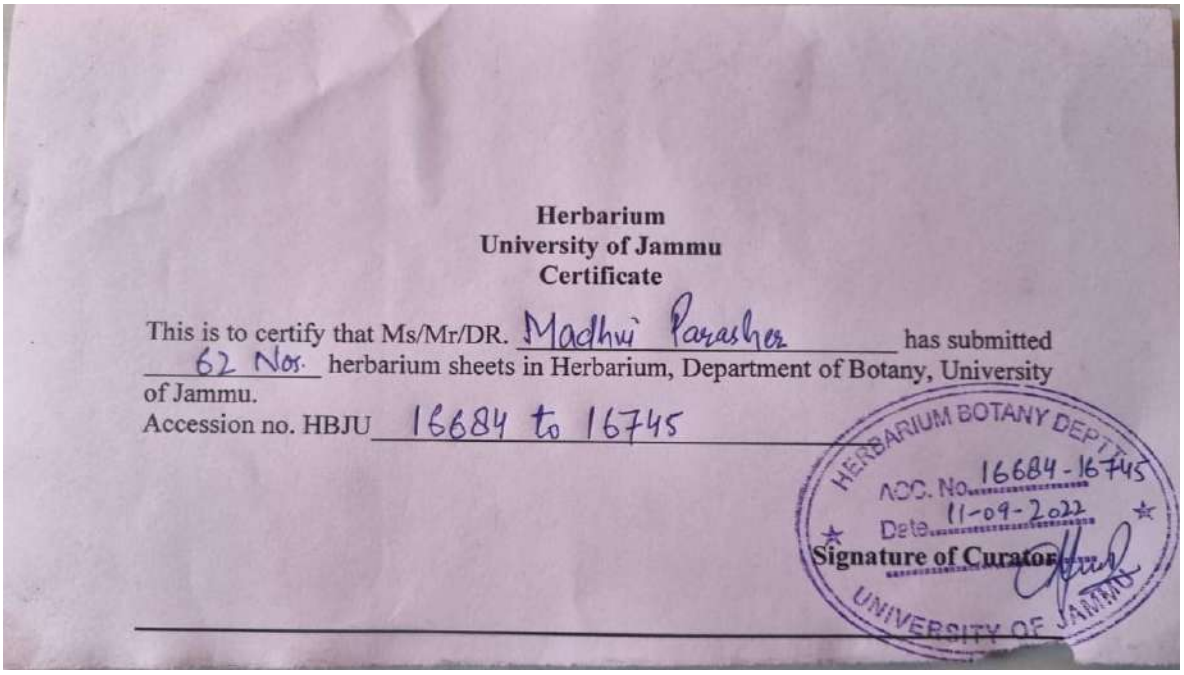
The genus also shows wide distribution throughout India with known 60–90 species which include 35–40 endemic species. They are mainly enriched in Western Ghats, with 50 species including 25–30 endemic ones.[8]

The Habenaria plants appear short with a subterranean tuber and whorl of leaves. They have terminal inflorescence containing multiple flowers distinguished by large, conspicuous, multilobed and flat lip. Monochromatic flowers generally appear white or green however they are brilliant pink, orange or yellow in some species. Distinct dry and wet seasons are required for the growth of Habenaria. The dormant phase is required for proper flowering or just survival. It needs a dormant phase to flower properly, or even just to survive.[9,10] The derivation of generic name is from Latin habena (strap, whip, veins, bridle) describing the presence of lip fringe of thread shapein some species. The petal shape and the lip form are the basis of classification of this genus member. In this review article we described some important Habenaria species and their medicinal values.

Overview

Around 54 Habenaria species have been identified in India and China together of which around 13 were found to have importance in Indian and Chinese medicinal systems.[11-13] Although the medicinal usage of orchids belonging to this genus in these two large Asian countries is not overlapping but there are certain exceptions like *H. arietina* (syn. *H. intermedia*) with known health improving effects in both the countries. *H. arietina* is used in both countries as a tonic in for treating people with weak intelligence quotient (IQ). The practitioners of Unnani and Siddha medicinal systems in India use Habenaria species as component of tonics used for treating consciousness lapses and uses as blood purifiers .[14] Chinese sources report several Habenaria species for common usage like replenishing "kidney yin", treating sexual dysfunction, spermatorrhoea, menstrual disorders, haematuria, hernia, tinnitus, nervousness and backache as shown in Figure 1.[12,13]

H. dentata is used by Taiwanese and Thai herbalists for treating infected wounds.[15,16] The genus Habenaria is among the few orchids which were mentioned in herbal texts of ancient India and were given Sanskrit names "Riddhi and Vriddhi".[16,17] Habenaria species are considered in India to be tonics of Vriddhi and Siddhi used as a blood



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Poster Presentation Title: ETHNOMEDICINAL USES OF ORCHID GENUS HABENARIA

Dr. Bubun Banerjee	Dr. Sandeep Kumar	Dr. Sawarn Singh	Prof. Chitranjan Sinha
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