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Exploring Folklore Ecuadorian Medicinal Plants and Their Bioactive Components Focusing on Antidiabetic Potential: An Overview

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Abstract: Diabetes mellitus (DM) is a metabolic disorder characterized by the deficiency of insulin production and is one of the concerning health problems worldwide, especially in developing countries. Considering the systemic toxicity associated with current antidiabetic medications and their limited efficacy, there is an urgent need to discover new plant-based natural antidiabetics. Since time immemorial, medicinal plants have played an important role in the management of health disorders. In recent years, herbal medicine has experienced exponential growth in popularity worldwide, owing to its natural origin and fewer side effects, appealing to both developing and developed nations. Ecuador has a rich cultural history in ethnobotany that plays a crucial role in their people's lives. Several Ecuadorian medicinal plants have hypoglycemic or anti-hyperglycemic properties that are rich with bioactive phytochemicals. These medicinal plants were extensively used in traditional medicine preparation in Ecuador for many decades to treat diabetes because of their cost-effectiveness, available traditional knowledge, and low toxicity. Many Ecuadorian medicinal plants are reported to have antidiabetic properties that reduce blood sugar levels, and oxidative stress, regulate intestinal function, improve insulin resistance, inhibit α-amylase and α-glucosidase, lower gluconeogenic enzymes, stimulate glucose uptake mechanisms, and play an important role in glucose and lipid metabolism, yet there is a substantial lack of integrated approach between the existing ethnomedicinal practice and pharmacological research. Therefore, this review aims to discuss and explore the traditional medicinal plants used in Ecuador for treating DM and their bioactive phytochemicals, which are mainly responsible for their anti-diabetic properties.

Keywords: antidiabetic; anti-hyperglycaemic; bio-active compound; hypoglycaemic; medicinal plant

1. Introduction

Diabetes mellitus (DM) represents a major public health challenge triggered by rising obesity rates and characterized by high comorbidity, reduced quality of life, and premature mortality, as well as major economic and societal expenses [1]. Long-term diabetes can cause a variety of complications, including microvascular complications like nephropathy, neuropathy, and retinopathy, as well as macrovascular complications like atherosclerosis, heart attack, and peripheral blood vessel disease [2,3]. The pervasiveness of diabetes has increased at the national, regional, and global levels [4].

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Additionally, the International Diabetes Federation (IDF) anticipates that 578 million individuals are expected to have DM by 2030, escalating to 629 million by 2045, with a global prevalence of 9.9% [5]. Besides, the average prevalence of diabetes in South and Central America reached 9.4% in adults, impacting around 32 million people. Ecuador additionally ranked among the 20 countries with the highest prevalence of DM (5.5%) during that period [6]. Following the IDF 2021 study, 4.7% of Ecuadorians aged 20-79 had diabetes [7]. Diabetes was ranked as the second largest cause of mortality in Ecuador in 2021, after COVID-19 [8]. Diabetes-related expenditures per person are estimated at approximately 2,280 USD annually [7]. Dismantled health systems and high out-of-pocket health costs pose an enormous financial burden on individuals for effective disease management [9]. Diabetes is an intricate condition that renders individuals susceptible to various repercussions such as cardiovascular disease, chronic kidney disease (CKD), cancer, TB, influenza, and COVID-19, therefore, necessitating multiple therapeutic approaches [10,11]. Diabetes therapy includes insulin and oral antidiabetic medications such as sulfonylurea, biguanides, α-glucosidase inhibitors, and glinides. Nonetheless, in nations with limited resources, these medications are expensive and challenging to obtain [12]. These treatments have their own set of limitations, ranging from the emergence of resistance and undesirable side effects to a lack of sensitivity in vast sectors of the patient population. These treatments are associated with adverse reactions; for example, thiazolidinediones prompt liver toxicity; sulphonylureas could exacerbate heart disease, reduce blood glucose levels below the normal range, and increase body weight gain; and bloating, flatulence, diarrhea, and abdominal discomfort and pain are the most frequently reported issues with glucosidase inhibitors [13,14]. The shortcomings of currently existing oral antidiabetic medications, particularly in terms of efficacy and safety, combined with the disease's growth as a global epidemic, have prompted a coordinated effort to discover drugs that may more effectively treat diabetes [15]. Furthermore, with a growing prevalence of DM in rural communities around the world, as well as the detrimental effects of synthetic medicine, there is an imperative need for the development of indigenous, inexpensive botanical sources for anti-diabetic crude or purified drugs [16,17].

During the last few decades, several medicinal plants like *Allium sativa* L., *Trigonella Graecum Foenum, Silybum marianus, Citrullus colocynthis, Zingiber officinale*, etc., have been useful in treating diabetes and are used empirically as anti-diabetic and anti-hyperlipidemic remedies [18–22]. Ecuadorian herbs like *Foeniculum vulgare, Cajanus cajan, Urtica dioica, Verbena litoralis*, etc., used in traditional medicine were found to exhibit anti-diabetic and anti-hypoglycemic activities [23–27]. Furthermore, the amalgamation of bioactive components present in the above-mentioned plants is not only responsible for combating diabetes but also for antimicrobial, anti-inflammatory, antioxidant, and anti-fungal activities [28,29]. For example, bioactive compounds like tau-cadinol, α-cadinol, spathulenol, caryophyllene oxide, trans-anethole, fenchone, estragole, limonene, α-phellandrene, etc., imparted the antidiabetic property to the Ecuadorian herbs and has provided positive results during clinical trials [28–31].

Several Ecuadorian ethnic groups rely extensively on medicinal plants to safeguard their medical condition [32]. The clinical expertise of traditional healer practitioners has been meticulously maintained over thousands of years [23]. Therefore, herbal drugs have gained legitimacy throughout the years because of the apparent efficacy and safety of plants [33]. As a result, many doctors, particularly those in government intercultural health districts, now practice a combination of contemporary and conventional medicines. Several ethnopharmacological research have been carried out in Ecuador. Despite being a multi-cultural country, reviews of ethnopharmacological studies, particularly for the treatment of diabetes, are scarce. This review provides a systematic analysis of recent phytochemical and antidiabetic studies conducted on Ecuadorian medicinal plants, with particular emphasis on the potential relationships between traditional applications and pharmaceutical properties, as well as the therapeutic potential of natural remedies. Plant species could consist of both native and introduced species. Thus, we incorporated pharmacological evidence (preclinical and clinical trials), phytochemical concerns, and toxicological assessments. The results of our reviews are expected to highlight gaps within existing research and provide critical direction for future frameworks aimed at developing cost-effective and novel phytomedicines that combat DM.

2. Materials and methods

The methodology of this review was based on the scientific information gathered mainly from available online scientific publications in English and Spanish language to obtain the most recent data. Databases like Scopus, ScienceDirect, ResearchGate, SciELO, PubMed, and Web of Science were searched based on keywords such as traditional medicine of Ecuador, medicinal plants with antidiabetic activity, ethnopharmacological activities, plants used for the treatment of diabetes, ethnobotanical surveys of Ecuador, and phytochemical composition of medicinal plants. We also used a published book to gather knowledge about Ecuadorian plants used in their traditional medicine [34].

The selection of plant species from Ecuador with antidiabetic potentials was conducted based on available scientific evidence such as in vitro activities, in vivo studies, phytochemical analysis, clinical trials, and toxicological evidence published in scientific journals. Scientific names, families, and synonymous names of all selected plant species and all the taxonomic data used in this review were according to the International Plant Names Index (https://www.ipni.org/), Plants of the World Online (https://powo.science.kew.org/), and WFO Plant List (https://wfoplantlist.org/). All plants were sorted alphabetically according to botanical family and summarized in a final table.

3. Diabetic Burden and Its Impact on the Health and Economy of Ecuador

DM is the most chronic endocrine dysfunction and is often linked to hyperglycemic conditions and insulin deficiency, insulin resistance, or both [35,36]. Furthermore, it is currently among the top 10 major causes of mortality and disability worldwide, being dubbed as the epidemic of the 21st century [37]. Long-term DM may culminate in several complications like peripheral blood vessel disease, atherosclerosis, heart attacks, neuropathy, nephropathy, and retinopathy [2,38,39]. Approximately 422 million individuals in developing countries suffer from diabetes, with the majority residing in low and middle income nations, and is solely accountable for more than 1.5 million deaths annually [40], and is expected to reach 700 million by 2045 [41]. It is also predicted that the prevalence rate of diabetes in Latin America and the Caribbean will rise to 11.3% [42]. According to IDF 2021 study, 4.7% of Ecuadorians have diabetes [7] and around 63% of the Ecuadorian population will be subjected to DM cases in the future [43]. Diabetes was Ecuador's second most common cause of death in 2021 after COVID-19 [8]. Ecuador has 40% poverty rate with fragmented health systems and high out-of-pocket health costs leading to financial burdens on individuals [7,9]. The cost of treating diabetes is USD 3747.44 per person, which represents 73% of the minimum annual income of an Ecuadorian employee [44]. Contemporary treatment for diabetes focuses on suppressing and controlling blood glucose levels through lifestyle changes, diet, and weight control. Antidiabetic medications, such as insulin injections and oral hypoglycemic drugs, are responsible for the side effects like hypoglycemia, lactic acid intoxication, and gastrointestinal upset. Efforts are being made to find suitable antidiabetic and antioxidant therapies to address these side effects. Also, antidiabetic drugs are scarce and expensive in Ecuador which causes a huge financial burden during the post-treatment phase of diabetes. Due to the high prevalence and long-term complications of DM such as obesity, edema, and cardiovascular threats [45], there is an utmost need for developing new oral hypoglycemic agents from herbal and medicinal plants. Previous studies by Chikhi et al. (2014) [46] confirmed high anti-diabetic activities in *Atriplex halimus*. During the last few decades, medicinal plants like *Allium sativum, Eugenia jambolana, Momordica charantia, Ocimum sanctum, Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Trigonella foenum graecum,* and *Withania somnifera* with proven antidiabetic properties were used for developing natural, safe, and cost-effective herbal anti-diabetic drugs [47], and were supplemented with a plethora of bioactive compounds such as alkaloids, glycosides, terpenes, flavonoids, etc., [48]. However, Ecuadorian herbs like *Schinus molle, Opuntia soehrensii, Lepidium meyenii, Cyclanthera pedate, Smilax officinalis, Uncaria tomentosa*, etc., used in traditional medicine are reported to possess anti-diabetic, anti-oxidant, anti-inflammatory, and anti-hypoglycemic activities [27]. Thereupon, more such Ecuadorian plant species should be explored focusing on the anti-diabetic properties to develop cost-effective and safe anti-diabetic herbal remedies which can be of great economic importance for the pharmaceutical industries in Ecuador.

4. Medicinal Plants with Anti-Diabetic Potential Used in Traditional Medicine of Ecuador

Based on the literature survey 27 plant species belonging to 23 botanical families were identified, of which 15 are native to Ecuador and the rest 12 were introduced from other locations, and are used in the traditional medicine of Ecuador to treat hyperglycaemia. The highest representation of species comes from families Asteraceae, Apiaceae, Costaceae, and Leguminosae, with two representatives each, followed by 19 families each containing one species. Figure 1 describes the botanical family distribution of 27 plant species. However, Asteraceae is the most encountered ethnobotanical family that represents the highest number of species in South America [49,50].

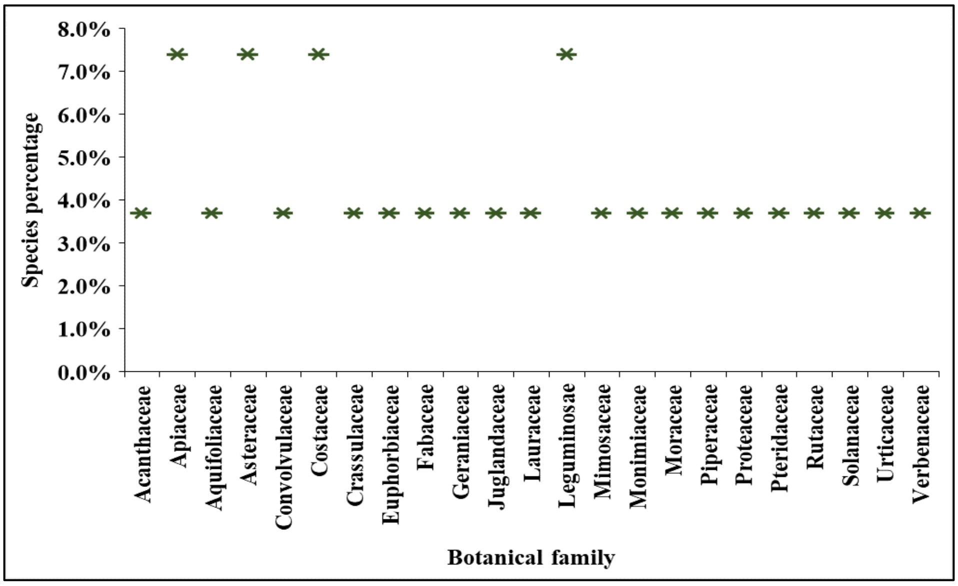

Figure 1. Family representation of 27 Ecuadorian medicinal plants used for the treatment of diabetes.

Adiantum poiretii, a perennial rhizomatous geophyte belonging to Pteridaceae family, thrives mainly in the wet tropical biome. Its native range extends to tropical & subtropical America, Nigeria, Ethiopia, S. Africa, Arabian Peninsula, Indian Ocean, India, and Sri Lanka. It serves a vital role in the traditional medicine of Ecuador because of its medicinal and environmental benefits [23,51]. The methanol extract from *A. poiretii* was found to possess antidiabetic properties, revealing moderate inhibition activity against α-glucosidase, an enzyme responsible for reducing post-meal blood sugar spikes, with calculated IC_{50} values of 46.3 µg/mL. However, no significant activity on α-amylase was observed in the study [26].

Another plant species *Artocarpus altilis*, commonly referred to as breadfruit and classified under the Moraceae family, is recognized for its richness in carbohydrates and diverse beneficial properties including antibacterial, antitubercular, antiviral, antifungal, antiplatelet, anti-arthritis, and antidiabetic activities. Ethanolic extract of these plant leaves exhibited significant α-glucosidase inhibitory activity [52].

Baccharis genistelloides is often identified as an herb or shrub within the Asteraceae family, that is one of the native South American plants widely used in traditional medicine, often prepared through infusion, which is attributed to its anti-inflammatory properties [53]. A study by Jaramillo Fierro & Ojeda Riascos (2018) [26] revealed that *B. genistelloides* showed significant inhibitory activity against α-glucosidase enzymes, with an IC_{50} value of 154.6 µg/mL. This suggests the capability of *B. genistelloides* to modulate glucose metabolism and beckons further exploration within therapeutic contexts.

Cajanus cajan, also known as Fréjol de palo, is a perennial shrub in the Fabaceae family, native to Asia and widely used as a pulse in the region. Their extracts are globally employed for treating various ailments including diabetes, dysentery, hepatitis, and measles. Notably, the leaves of Cajanus cajan are abundant in flavonoids and stilbenes, which are responsible for the beneficial effects on human health [54]. The antidiabetic activity of *Cajanus cajan* was tested on alloxan-induced diabetic Swiss albino mice. The result revealed that orally administered doses of plant extract showed higher potential for reduction of blood glucose levels with a maximum reduction of 54.51% of blood glucose level and an IC_{50} value of 17.44 µg/mL was obtained [54].

Costus comosus, often known as red tower ginger is a perennial plant originating from Ecuador, belonging to the Costaceae family. Beyond its aesthetic appeal, this rhizomatous plant has a longstanding history of medicinal applications. Traditionally, its leaves and rhizomes were utilized to address a variety of ailments such as fever, rash, asthma, bronchitis, intestinal worms, diabetes, and liver diseases. The study of antidiabetic properties of *C. comosus* was based on their inhibition abilities on α-glucosidase and α-amylase enzymes. A study by Jaramillo Fierro & Ojeda Riascos (2018) [26] elucidated that the extract of *C. comosus* showed inhibitory activity only on α-glucosidase with an IC_{50} value of 57.9 µg/ml.

Croton wagneri, commonly known as moshquera blanca or moshquera, is a shrub belonging to the Euphorbiaceae family and endemic to the Andean region of Ecuador, where it thrives abundantly. This shrub is documented in at least seven populations ranging from the Carchi province in the north to the Azuay province in the south [55]. Incorporation of this plant into food preparations is a promising approach for locals to enhance nutritional value. A study by Jaramillo Fierro & Ojeda Riascos (2018) [26] revealed that *C. wagneri* has a lower inhibitory effect on α-amylase ($IC_{50} > 1000$) and α-glucosidase with an IC_{50} value of 162.4 ± 1.34 µg/mL.

Foeniculum vulgare, commonly known as fennel, stands as a widely recognized perennial herbaceous plant extensively employed in global herbal medicine and culinary practices. Belonging to the Apiaceae family, fennel has a rich history in ethnobotanical applications, addressing diverse health concerns such as gastrointestinal issues, hormonal disorders, and reproductive and respiratory diseases. Fennel provides flexible culinary choices in Ecuador, whether consumed raw, cooked, or baked [56]. The antihyperglycemic effect of aqueous extract of *F. vulgare* was demonstrated in a study on streptozotocin-induced diabetic (STZ) rats resulting in reduced blood glucose levels after 6 h from administration and without any loss of body weight. Furthermore, it improved oral glucose tolerance in diabetic rats [57].

Glycyrrhiza glabra, a member of the Leguminosae family, holds a prominent position in the ancient medical traditions of Ayurveda, serving as both a medicinal herb and a flavouring agent. Commonly referred to as licorice, liquorice, or sweet wood, *G. glabra* is predominantly found in Mediterranean regions and specific areas of Asia [58]. This plant species has a traditional value in Ecuador, used for various purposes in food and traditional medicine preparation [59]. The effect of glycyrrhizin, extracted from *G. glabra* root, was studied on streptozotocin-induced diabetic rats. The results showed an improvement in modulating blood glucose levels and confirmed the ability to lower blood insulin levels [25].

Ilex guayusa, commonly referred to as Guayusa, is an underexplored holly species belonging to the only extant genus of the family Aquifoliaceae, thriving in the upper Amazon basin across Colombia, Ecuador, and Peru. Guayusa holds cultural significance as societies in this region traditionally brew an infusion from its leaves for consumption [60,125]. A study by Jaramillo Fierro & Ojeda Riascos (2018) [26] revealed that *I. guayusa* showed moderate inhibitory activity with an IC_{50} value of 176.5 µg/ml for α-glucosidase inhibition, but its high antioxidant potential contributes to the treatment of diabetes due to its ability to counteract oxidative stress, a factor in the complications of diabetes.

Ipomoea carnea, commonly known as Morning Glory and a member of the Convolvulaceae family, is a shrub that holds a prominent place in Ecuadorian folk medicine for its historical use in managing diabetes and demonstrating muscle relaxant properties. Notably, it is well-known for its substantial antioxidant properties, boasting high levels of phenolic compounds, flavonoids, and tannins, underscoring its potential therapeutic values [61]. Research on *I. carnea* leaf extracts explored their phenolic, flavonoid, and tannin content alongside their potential in treating diabetes in Wistar rats. After three weeks of oral administration, both aqueous and alcoholic extracts showed a decrease in blood glucose levels with the alcoholic extract demonstrating superior efficacy. Furthermore, a reduction in body weight was observed [61].

Justicia colorata, locally known as Insulina, is a shrub indigenous to Ecuador and Peru, belonging to the Acanthaceae family. This plant is commonly consumed in Ecuador through the infusion method. The antidiabetic effect of *J. colorata* was confirmed in a study in Ecuador focusing on in vitro hypoglycemic and antioxidant activities. The results showed α-glucosidase inhibition activity with an IC_{50} value of 622.1 μg/mL [26].

Chamomile (*Matricaria chamomilla*), a prized medicinal herb native to Europe and belonging to the Asteraceae family, is renowned as the "star among medicinal species." Chamomile is widely known for its broad popularity and extensive use in the folk and traditional medicine of Ecuador [62,63]. The antidiabetic activity of *M. chamomilla* ethanolic extract of the aerial part was studied in streptozotocin-induced diabetic rats. This study revealed that the administration of varying doses of *M. chamomilla* led to a notable decrease in postprandial hyperglycemia, oxidative stress, and enhancement of the antioxidant system [64].

Neonelsonia acuminata, native to Mexico, Venezuela, and Peru, is a perennial herb within the Apiaceae family. This plant grows primarily in the subalpine or subarctic biome. Its root is employed in the traditional medicine of Ecuador and is often consumed in its raw form [23]. The inhibitory effects of *N. acuminata* on α-glucosidase and α-amylase were analysed in this study. The results showed activity only on α-glucosidase with IC_{50} values of 198.7 μg/mL, introducing an inhibitory capacity similar to established drugs used in diabetes treatment. Additionally, *N. acuminata* displayed remarkable free radical scavenging activity (DPPH), indicating its prospective role as an alternative enzyme inhibitor and antioxidant in the management of DM [26].

Oreocallis grandiflora, a species native to Ecuador within the Proteaceae family, is commonly known as cucharillo, cucharilla, gañal, and algil. Traditionally, its leaves and flowers were harvested during the blooming phase, and are orally administered for the treatment of liver disease, vaginal bleeding, and inflammation of the ovaries and uterus. Additionally, it is employed as a remedy for digestive issues, diuretic effects, and hypoglycemic conditions [65]. A study performed by Jaramillo Fierro & Ojeda Riascos (2018) [26] revealed an impressive ability to slow down both α-amylase and α-glucosidase enzymes, with an IC_{50} value of 161.5 ± 1.30 μg/mL for α-amylase and an incredibly low IC_{50} value of 2.8 ± 0.40 μg/mL for α-glucosidase inhibition. These values signify its strong capability in inhibiting these enzymes, especially α-glucosidase, crucial for regulating blood sugar after meals. Moreover, its notable antioxidant activity suggests it could be valuable in combating oxidative stress, a significant factor in diabetes-related complications.

Pelargonium graveolens, a kind of herb within the Geraniaceae family, is recognized for its aromatic properties. Its global cultivation primarily focuses on the extraction of essential oils employed mainly in the perfume industry due to its highly desirable scent [66]. In Ecuador, this plant species is commonly used in traditional medicine. The essential oil from *P. graveolens* was evaluated using an α-glucosidase inhibition assay. Findings showed a promising efficiency of *P. graveolens* essential oil in inhibiting α-glucosidase enzyme with an IC_{50} value of 93.72±4.76 μg/mL similar to the IC_{50} value of acarbose that was 80.4±2.17 μg/mL. Therefore, its efficiency in reducing post-meal blood sugar spikes can be an effective remedy for diabetes [67].

Avocado (*Persea americana*), native to Mexico and belonging to the Lauraceae family, has surged in popularity as a "superfood" for its unique nutritional profile and health benefits. Besides culinary uses, it is traditionally used in Ecuador for medicinal purposes including blood pressure and blood sugar management, antiviral properties, and cardiovascular health. A study by Abd Elkader et al. (2022) [68] exhibited that ethanolic extracts of avocado fruit exhibited higher α-amylase inhibition activity. Another study by Ojo et al. (2022) [24] exhibited maximal α-glucosidase inhibitory activity of 56.41% in alloxan-induced diabetic male Wistar rats injected with aqueous extract of *P. americana* seeds and also 21.42% of α-amylase inhibitory activity.

Physalis peruviana, also called golden berry or Cape gooseberry, is a tropical herb from the Solanaceae family. The plant extract of this species has a history in folk medicine, used for treating diabetes, hepatitis, malaria, dermatitis, asthma, and rheumatism [69]. The aqueous extract from dried

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leaf powder of *P. peruviana* showed a notable decrease in blood sugar levels in guinea pigs at a dose of 100 mg/kg. However, higher doses caused intoxication [70].

Piper crassinervium, known as Guabiduca in Ecuador, is a shrub in the Piperaceae family found throughout South America. It has a rich value in traditional medicine in Ecuador for its valuable essential oil that makes it commercially viable [71]. A study by Jaramillo Fierro & Ojeda Riascos (2018) [26] confirmed that extract from *P. crassinervium* effectively brings down glucose absorption and suppresses postprandial hyperglycemia. The results revealed the ability to inhibit α-glucosidase enzyme which helps to break down complex sugars into simple forms.

Ruta graveolens, commonly known as Rue, is a subshrub from the Rutaceae family, originally from the Mediterranean but now grown worldwide. It has been integral to European pharmacopeia since ancient times. Extracts and essential oils from Rue are utilized in drug development due to their diverse pharmacological benefits, including antibacterial, analgesic, anti-inflammatory, antidiabetic, and insecticidal properties. Traditionally, it has been used in Ecuador for pain relief, eye problems, rheumatism, and dermatitis [72]. Antidiabetic properties of *R. graveolens* were studied using α-glucosidase and α-amylase inhibition assay. Findings revealed that methanolic extract showed higher inhibitory activity of α-glucosidase and α-amylase with an IC_{50} value of 281 and 215 μg/mL, respectively, which showed better activity than the reference drug acarbose [73].

Siparuna eggersii, a shrub belonging to the Monimiaceae family, is endemic to the Loja province in Ecuador, locally known as "Monte del oso." It has a high ethnic value in equatorial regions but this species is currently facing the threat of extinction [74]. The inhibitory activity of *S. eggersii* on α-glucosidase and α-amylase was investigated in a study that demonstrated notable inhibitory activity against α-glucosidase enzymes, revealing an IC_{50} value of 28.3 μg/mL. This finding suggests a compelling potential of *S. eggersii* portable for diabetes treatment [26].

Urtica dioica L., commonly known as nettle, is a perennial flowering plant originating from Europe, temperate Asia, and western North Africa, with widespread cultivation across the globe [75]. As a member of the Urticaceae family, nettle is recognized for its valuable bioactive compounds, including formic acid and abundant flavonoids, making it an important subject in phytotherapy. Numerous studies highlighted its therapeutic potential for treating prostatic hyperplasia, rheumatoid arthritis, allergies, anemia, internal bleeding, kidney stones, burns, and infectious diseases, supported by studies showcasing its anti-proliferative and antimicrobial activities [76]. Antihyperglycemic activity of the aqueous extract of *U. dioica* was demonstrated in a study by Bnouham et al. (2003) [77] on male Wistar rats and Swiss mice of both sexes. The results indicated a decrease in glycaemia by approximately 33% compared to the control, during the first hour after glucose insertion. Furthermore, the reduction of intestinal glucose absorption was observed in this study.

Verbena litoralis, a South American herb in the Verbenaceae family, is historically used in traditional medicine for diarrhea, fever, gastrointestinal issues, and sexually transmitted diseases. This plant attracted more attention for its nerve growth factor-potentiating activity [78]. A study by Jaramillo Fierro & Ojeda Riascos (2018) [26] elucidated the inhibitory activity of the key enzyme α-glucosidase, that responsible for breaking down sugars. The results exhibited that *V. litoralis* extract showed inhibitory activity on α-glucosidase with IC_{50} values 337.9 μg/mL. However, the extract was found ineffective in α-amylase inhibition.

Out of 27 Ecuadorian plant species 22 of them have rational reports supporting antidiabetic properties that were pharmacologically elucidated. However, no existing pharmacological studies have provided evidence supporting the antidiabetic activity of *Bryophyllum gastonis-bonnieri*, *Costus villosissimus*, *Juglans neotropica*, *Pithecellobium excelsum*, and *Myroxylon peruiferum*. Yet, these plants are found to be used in Ecuadorian traditional medicine to treat diabetes [34,59,79,80]. Table 1 summarizes the list of medicinal plants with antidiabetic potential used in the traditional medicine of Ecuador. A map representing the distribution of these 27 medicinal plants with antidiabetic properties is shown in Figure 2.

Table 1. Ecuadorian medicinal plants used in traditional medicine to treat diabetes.

Family	Scientific name	Local name (Vernacular name)	Plant part used	Traditional preparations	Pharmacological activity as antidiabetic	References
Acanthaceae	*Justicia colorata* (Nees) Wassh.	Insulina	Leaf, stem	Infusion	α-glucosidase inhibitory activity, antioxidant activity	[26]
Apiaceae	*Foeniculum vulgare* Mill.	Hinojo, *eneldo*	Whole plant	Infusion	Reduction of blood glucose level in streptozotocin-induced diabetic rats	[56,57,124]
	Neonelsonia acuminata (Benth.) J.M.Coult. & Rose ex Drude	Zanahoria blanca	Root	Eaten raw	α-glucosidase inhibitory activity, antioxidant activity	[23,26]
Aquifoliaceae	*Ilex guayusa* Loes.	Guayusa	Leaf	Infusion	α-glucosidase inhibitory activity, antioxidant activity	[26,125]
Asteraceae	*Baccharis genistelloides* (Lam.) Pers.	Tres filos	Aerial part	Aqueous infusion	Reduction in blood sugar levels observed in diabetic mice	[26,51,126]
	Matricaria chamomilla L.	Chamomile	Whole plant	Infusion	Decrease in postprandial hyperglycaemia in streptozotocin-induced diabetic rats, antioxidant activity	[63,64]
Convolvulaceae	*Ipomoea carnea* Jacq.	Borrachera, matacabra	Aerial part	Infusion	Decrease in blood glucose levels in streptozotocin-induced diabetic Wistar rats	[34,61]
Costaceae	*Costus comosus* Roscoe	Caña	Stem	Decoction	α-glucosidase inhibitory activity	[26,51]
	Costus villosissimus Jacq.	Caña agria	Leaf, stem	Infusion	Not known	[80]
Crassulaceae	*Bryophyllum gastonis-bonnieri* (Raym.-Hamet & H.Perrier) Lauz.-March.	Dulcamara	Leaf	Juice, crushed	Not known	[59,79]
Euphorbiaceae	*Croton wagneri* Müll.Arg.	Moshquera	Leaf	Aqueous infusion	α-amylase and α-glucosidase inhibitory activity	[34,61]
Fabaceae	Cajanus cajan (L.) Millsp.	Fréjol de palo	Bark	Infusion	Reduction in blood glucose levels in alloxan-induced diabetic Swiss albino mice, high antioxidant activity	[34,54]
Geraniaceae	*Pelargonium graveolens* L'Hér.	Esencia de rosa	Flower, leaf, stem	Infusion	α-glucosidase inhibitory activity	[23,67]
Juglandaceae	*Juglans neotropica* Diels	Nogal, tocte	Leaf	Infusion	Not known	[34]
Lauraceae	*Persea americana* Mill.	Aguacate	Leaf, fruit, seed	Aqueous infusion, decoction	α-amylase and α-glucosidase inhibitory activity in alloxan-induced diabetic male Wistar rats	[24,51,127]
Leguminosae	*Glycyrrhiza glabra* L.	Zaragoza	Leaf, stem	Infusion	Improvement in modulating blood glucose levels and lowered blood insulin levels in streptozotocin-induced diabetic rats	[25,59]

	Myroxylon peruiferum L.f.	Bálsamo, chaquino	Bark	Infusion	Not known	[34]
Mimosaceae	*Pithecellobium excelsum* (Kunth) Mart.	Chaquiro	Bark	Infusion	Not known	[34]
Monimiaceae	*Siparuna eggersii* Hieron.	Monte del oso	Leaf	Crushed, infusion	α-glucosidase inhibitory activity	[26,51]
Moraceae	*Artocarpus altilis* (Parkinson) Fosberg	Fruto del pan	Leaf	Aqueous infusion	α-glucosidase inhibitory activity	[26,51,52]
Piperaceae	*Piper crassinervium* Kunth	Guabiduca	Stem, leaf	Decoction	α-glucosidase inhibitory activity	[26,51]
Proteaceae	*Oreocallis grandiflora* R.Br.	Cucharillo	Leaf, bark, flower	Aqueous infusion	α-amylase and high α-glucosidase inhibitory activity, antioxidant activity	[23,26,51]
Pteridaceae	*Adiantum poiretii* Wikstr.	Culantrillo	Aerial part	Aqueous infusion	α-glucosidase inhibitory activity	[23,26,51]
Rutaceae	*Ruta graveolens* L.	Ruda	Stem, leaf	Infusion	α-amylase and α-glucosidase inhibitory activity	[73]
Solanaceae	Physalis peruviana L.	Uvilla, uchuva, uvilla lanuda	Fruit	Juice	Decrease in blood sugar levels tested in guinea pigs	[23,69,70]
Urticaceae	*Urtica dioica* L.	Ortiga	Whole plant	Infusion, fresh	Decrease in blood glucose levels tested in male Wistar rats and Swiss mice, reduction of intestinal glucose absorption	[77,128]
Verbenaceae	*Verbena litoralis Kunth*	Verbena	Whole plant	Cooked, infusion	α-glucosidase inhibitory activity	[26,124]

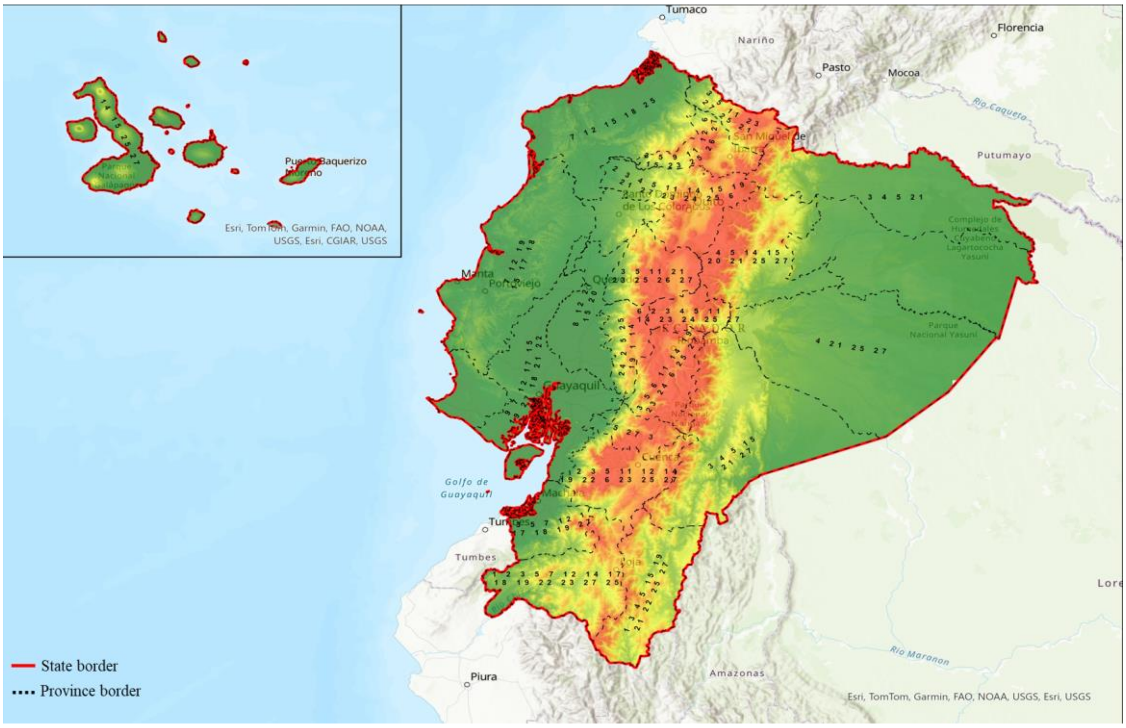

Figure 2. A simplified map showing the distribution of 27 medicinal plants with antidiabetic properties in Ecuador. 1-*Justicia colorata* (Nees) Wassh, 2-*Foeniculum vulgare* Mill., 3-*Neonelsonia acuminata* (Benth.) J.M.Coult. & Rose ex Drude, 4-*Ilex guayusa* Loes., 5-*Baccharis genistelloides* (Lam.) Pers., 6-*Matricaria chamomilla* L., 7-*Ipomoea carnea* Jacq., 8-*Costus comosus* Roscoe, 9-*Costus villosissimus*

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Jacq., 10-*Bryophyllum gastonis-bonnieri* (Raym.-Hamet & H.Perrier) Lauz.-March., 11-*Croton wagneri* Müll.Arg., 12-*Cajanus cajan* (L.) Millsp., 13-*Pelargonium graveolens* L'Hér., 14-*Juglans neotropica* Diels, 15-*Persea americana* Mill., 16-*Glycyrrhiza glabra* L., 17-*Myroxylon peruiferum* L.f., 18-*Pithecellobium excelsum* (Kunth) Mart., 19-*Siparuna eggersii* Hieron., 20-*Artocarpus altilis* (Parkinson) Fosberg, 21-*Piper crassinervium* Kunth, 22-*Oreocallis grandiflora* R.Br., 23-*Adiantum poiretii* Wikstr., 24-*Ruta graveolens* L., 25-*Physalis peruviana* L., 26-*Urtica dioica* L., 27-*Verbena litoralis* Kunth.

5. Active Compounds of Ecuadorian Medicinal Plants and Their Anti-Diabetic Properties

Due to the systemic toxic exposure and limited efficacy of current antidiabetic medication, new plant-based natural antidiabetic drugs are in utmost need to be discovered. To circumvent these hurdles plant-based medication approach can be adopted as a sustainable alternative antidiabetic agent. The phytochemicals are mainly responsible for the biological activity of the plant extracts [81]. Phytochemicals found in plant extracts are the major contributors with various anti-inflammatory, antioxidant, and antidiabetic properties, which are effective, economical, and low in toxicity [82]. The activity of phytochemicals-based drugs not only increases the antidiabetic activity but also acts as an enhanced anti-inflammatory and antioxidant agent that can dramatically improve the targeting of the interaction site while minimizing systemic exposure and associated toxicity. Medicinal plants are the key source of producing a variety of phytochemicals such as alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannin which have immense antidiabetic effects employed through various mechanisms such as regulation of glucose and lipid metabolism, insulin secretion, stimulating β cells, NF-kB signaling pathway, inhibition of gluconeogenic enzymes, and reactive oxygen species (ROS) protective action [29].

Ecuadorian medicinal plants have a plethora of active phytochemicals that have in-vitro and in-vivo evidence in support of anti-diabetic properties. Flavonoids are the major bioactive compounds found in most of the Ecuadorian medicinal plants that possess antidiabetic properties. Due to their hydroxyl groups and aromatic rings, they serve as natural antioxidants [29]. Flavonoids such as cirsimaritin, cirsiliol, hispidulin, genkwanin, and apigenin are the major bioactive compounds found in *Baccharis genistelloides* [53]. A study by Alqudah et al. (2023) [83] showed the importance of cirsimaritin in type-2 diabetes. They observed reduced levels of serum glucose and a reduction in the increased serum insulin level in diabetic rats. Another study by Escandón-Rivera et al. (2019) [84] showed hypoglycemic effect of *Bromelia karatas* on STZ-NA-induced diabetic rats and the chemical composition analysis revealed, cirsiliol as one of the major compounds responsible for this activity. Another flavone hispidulin confirmed the stimulation of glucagon-like peptide-1 and suppressed hepatic glucose production in STZ-NA-induced diabetic rats [85]. Genkwanin is also a potent antioxidant that is responsible for α-amylase inhibitory activity [86]. A study by Ihim et al. (2023) [87] reported that apigenin facilitates glucose-stimulated insulin secretion and prevents endoplasmic reticulum (ER) stress-mediated β-cell apoptosis in the pancreas. Other flavones such as pinostrobin, genistein, quercetin-3-O-hexose, myricetin 3-O-β-glucuronide, isorhamnetin hexuronide, quercetin 3-O-rutinoside, quercetin 3-O-β-glucuronide, isorhamnetin hexoside, isorhamnetin 3-O-rutinoside are the major bioactive compounds that have antidiabetic properties found in *Cajanus cajan* [88], *Ilex guayusa* [89], *Oreocallis grandiflora* [90], *Pelargonium graveolens* [91], *Verbena litoralis* [92].

Similarly, plant-derived phenols are bioactive compounds that possess immense antidiabetic activity through various mechanisms such as AMPK pathway activation, α glucosidase or α amylase inhibition, glucose regulation, insulin sensitivity improvement, and PPAR activation [93]. Chlorogenic acid, caffeic acid, coumaric acid, ellagic acid, ferulic acid, and vanillic acid are the natural phenols found in many Ecuadorian plants such as *Ilex guayusa* [89], *Pelargonium graveolens* [91], *Persea americana* [31,94], *Verbena litoralis* [92], and *Artocarpus altilis* [95]. The antidiabetic activity of chlorogenic acid is attributed to an increase in the glucose uptake in L6 muscular cells and a rise in insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans [96]. Another natural phenol coumaric acid showed antidiabetic activities by lowering the blood glucose level, and gluconeogenic enzymes and increasing the activities of hexokinase, glucose-6 phosphatase dehydrogenase, and GSH via increasing the level of insulin [97]. A study by Narasimhan et al. (2015)

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[98] exhibited that ferulic acid improves insulin sensitivity and hepatic glycogenesis, also inhibits gluconeogenesis, and maintains insulin signaling to maintain normal glucose homeostasis. Similarly, caffeic acid was reported to reduce hepatic glucose output and enhance adipocyte glucose uptake, insulin secretion, and antioxidant capacity [99]. Singh et al. (2022) [100] found reduced hyperglycemia and GSH, and increased liver enzymes in diabetic rats as protective effects of vanillic acid.

Another class of important bioactive group terpenoids are the major compounds found in many natural products and several terpenoids have been reported as antidiabetic agents. Some of them are under various stages of pre-clinical and clinical evaluation to develop them as antidiabetic agents. These compounds mainly act as enzyme inhibitors responsible for the development of insulin resistance, normalizing plasma glucose and insulin levels, and play an important role in glucose metabolism by inhibiting several pathways involved in diabetes and associated complications [101]. Numerous research reported that bioactive terpenoids are associated with anti-diabetic properties. Betulinic acid, camphene, myrcene, fenchone, limonene, α-phellandrene, carvone, spathulenol, caryophyllene oxide, germacrene D, α-pinene, β-caryophyllene, α-humulene, catechin, phytol, carvacrol, hexahydrofarnesyl acetone, (E)-β-ionone are found in various Ecuadorian medicinal plants, for instance, *Cajanus cajan* [88], *Costus comosus* [102], *Croton wagneri* [55], *Foeniculum vulgare* [103], *Glycyrrhiza glabra* [104], *Ipomoea carnea* [30], *Myroxylon peruiferum* [105], *Persea americana* [31,94], *Physalis peruviana* [106], *Matricaria chamomilla* [107], *Piper crassinervium* [108], *Siparuna eggersii* [74], *Urtica dioica* [109] which are used traditionally for their anti-diabetic properties.

Fatty acids represent significant bioactive compounds capable of serving as potent antidiabetic agents by reducing blood cholesterol levels, stabilizing lipid and protein metabolism, enhancing the liver's detoxification function, and stimulating immune-protective mechanisms. Additionally, they increase the elasticity of blood vessel walls, decrease permeability, enhance microcirculation, and inhibit the oxidation of cell membrane lipids [110]. n-Hexadecanoic acid is a plant-based fatty acid mainly found in several Ecuadorian plants such as *Artocarpus altilis* [95], *Costus comosus* [102], and *Glycyrrhiza glabra* [104]. It is a potent antioxidant agent and can inhibit α-amylase and α-glucosidase activity that are responsible for glucose production in the body [111]. Another natural fatty acid dodecanoic acid also acts as a natural antidiabetic agent found in *Glycyrrhiza glabra* [104]. It was found that dodecanoic acid (lauric acid) decreases fasting blood glucose levels and induces β-cell regeneration in high-fat diet/streptozotocin-induced type 2 diabetic male Wistar rats [112].

2-Heptadecenal is an aldehyde found in *Artocarpus altilis* [95] which acts as a natural inhibitor of α-amylase and α-glucosidase enzyme. A study by Natta et al. (2023) [113] reported anti-glycaemic properties of *Artocarpus heterophyllus* where they found 2-heptadecenal as the major compound responsible for this activity. Anethole is another phenylpropanoid found in *Urtica dioica* [109] and *Foeniculum vulgare* [103]. This active compound is reported to suppress diabetic nephropathy in streptozotocin-induced diabetic rats by decreasing blood glucose levels and downregulating angiotensin II receptor (AT1R) and TGF-β1 expression [114]. The phenylpropene namely estragole (methyl chavicol) acts as an enzyme inhibitor against α-amylase, lipase, and tyrosinase and serves as a potent antioxidant agent that can improve diabetes [115,116]. This bioactive compound is also found in *Foeniculum vulgare* [103]. n-Hexacosane is a natural alkane that improves blood glucose levels, glucose tolerance, glycated hemoglobin, and liver glycogen [117] found in *Physalis peruviana* [106]. The polysaccharide holocellulose and organic polymer lignin are found in *Juglans neotropica* [118]. Holocellulose mainly acts as an activator for glucokinase in reducing blood sugar [119] and lignin acts as a natural antioxidant and can increase the inhibitory effect on α-amylase [120]. Another natural polycyclic aromatic hydrocarbon naphthalene found in *Urtica dioica* [109] can act as a potential anti-hyperglycemic agent by inhibiting the α-glucosidase enzyme [121].

In conclusion, we found that Ecuadorian medicinal plants are rich in phytochemicals that can be a potential antidiabetic agent. Table 2 summarizes the list of active compounds with antidiabetic properties found as major compounds in the Ecuadorian medicinal plants that are mainly used as traditional medicine against diabetes.

Table 2. Active phytochemicals of Ecuadorian medicinal plants and their antidiabetic properties.

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Scientific name	Active compounds with antidiabetic properties	Bioactive chemical group	Antidiabetic properties	Reference
Adiantum poiretii	No proper evidence found	-	-	-
Artocarpus altilis	n-Hexadecanoic acid	Fatty acid	α-amylase and α-glucosidase inhibitory activity and antioxidant activity	[111]
	Ellagic acid	Phenol	α-amylase inhibitory activity and antioxidant activity, stimulate insulin secretion and decrease glucose intolerance	[129]
	2-Heptadecenal	Aldehyde	α-amylase and α-glucosidase inhibitory activity	[113]
Baccharis genistelloides	Cirsimaritin	Flavonoid	Reduces elevated level of serum glucose in diabetic rats and abrogated the increase in serum insulin	[83]
	Cirsiliol	Flavonoid	Hypoglycaemic effect	[84]
	Hispidulin	Flavonoid	Stimulates glucagon-like peptide-1 and suppresses hepatic glucose production	[85]
	Genkwanin	Flavonoid	α-amylase inhibitory activity and antioxidant activity	[86]
	Apigenin	Flavonoid	Facilitates glucose-stimulated insulin secretion and prevents ER stress-mediated β-cell apoptosis in the pancreas	[87]
Bryophyllum gastonis-bonnieri	Flavonoids	Flavonoid	α-amylase and α-glucosidase inhibitory activity, improves insulin resistance, antioxidant activity, inhibitors of Glucose Cotransporter	[130]
Cajanus cajan	Betulinic acid	Terpenoid	Reduces blood glucose, α-amylase and improves insulin sensitivity as well as pancreas histopathology	[131]
	Pinostrobin	Flavonoid	Reduces the blood sugar level of diabetic mice	[132]
	Genistein	Flavonoid	Inhibits hepatic glucose production, increases β-cell proliferation, reduces β-cell apoptosis, and shows antioxidant activity	[133]

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Costus comosus	Camphene	Monoterpene	Reduces fasting blood sugar and blood insulin levels.	[134]
	n-Hexadecanoic acid	Fatty acid	α-amylase and α-glucosidase inhibitory and antioxidant activities	[111]
Costus villosissimus	Not known		Not known	
Croton wagneri	Myrcene	Monoterpene	α-amylase and α-glucosidase inhibitory activities	[135]
Foeniculum vulgare	Trans-anethole	Phenylpropanoid	Suppresses diabetic nephropathy in rats by decreasing blood glucose levels and downregulating AT1R and TGF-β1 expression	[114]
	Fenchone	Monoterpenoid	Protects against the increased blood glucose level and decreased level of antioxidant enzyme activities in alloxan-induced diabetic rats	[136]
	Estragole	Phenylpropene	α-amylase and lipase inhibitory activity, antioxidant activity	[115]
	Methyl chavicol	Phenylpropene	α-amylase and tyrosinase inhibitory activity, antioxidant activity	[116]
	Limonene	Monoterpene	Inhibits protein glycation, stimulates the uptake of glucose and breakdown of fats, upregulates glucose transporter 1 (GLUT1) expression, and suppresses α-amylase and α-glucosidase	[140]
	α-Phellandrene	Monoterpene	Increases glucose uptake, enhances glycerol-3-phosphate activity and triglyceride accumulation, and regulates adipositic function	[137]
Glycyrrhiza glabra	n-Hexadecanoic acid	Fatty acid	α-amylase and α-glucosidase inhibitory activities and antioxidant activity	[111]
	Dodecanoic acid	Fatty acid	Decreases fasting blood glucose level and induces	[112]

			β-cell regeneration in diabetic rat	
	Carvone	Terpenoid	Improves glycoprotein components and controls glucose metabolism	[147]
Ilex guayusa	Chlorogenic acid	Phenol	Increases glucose uptake in L6 muscular cells and raises insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans.	[96]
	Quercetin-3-O-hexose	Flavonoid	Inhibits the activity of glucose transporter, enhances glucose uptake, reduces hepatic glucose production, protects against pancreatic islet beta-cell, α-glucosidase inhibition	[130]
Ipomoea carnea	Spathulenol	Sesquiterpenoid	Strong antioxidant, α-amylase, and α-glucosidase inhibitory activities	[138]
	Caryophyllene oxide	Sesquiterpene	α-amylase and α-glucosidase inhibitory activities and antioxidant activity	[139]
Juglans neotropica	Holocellulose	Polysaccharide	Acts as an activator for glucokinase in reducing blood sugar	[119]
	Lignin	Organic polymer	Improves inhibitory effect on α-amylase activity, antioxidant activity	[120]
Justicia colorata	No proper evidence found	-	-	-
Matricaria chamomilla	Germacrene D	Sesquiterpene	Strong inhibitor of α-glucosidase	[140]
Myroxylon peruiferum	Germacrene D	Sesquiterpene	Strong inhibitor of α-glucosidase	[140]
	α-Pinene	Terpene	Inhibition of α-amylase	[141]
	Spathulenol	Sesquiterpenoid	Strong antioxidant, α-amylase, and α-glucosidase inhibitory activities	[138]
	Caryophyllene oxide	Sesquiterpene	α-amylase and α-glucosidase inhibitory activity and antioxidant activity	[139]
	Limonene	Monoterpene	Inhibits protein glycation, stimulates the uptake of glucose and breakdown of fats,	[142]

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			upregulates glucose transporter 1 (GLUT1) expression, and suppresses α-amylase and α-glucosidase	
Neonelsonia acuminata	No proper evidence found	-	-	-
Oreocallis grandiflora	Myricetin 3-O-β-glucuronide	Flavonoid	Stimulates 2-deoxy-glucose uptake in C2C12 myocytes	[143]
	Isorhamnetin hexuronide	Flavonoid	Decreases glucose level, and oxidative stress, modulates lipid metabolism and adipocytic activity	[144]
	Quercetin 3-O-rutinoside	Flavonoid	Regulates whole-body glucose homeostasis, reduction of intestinal glucose absorption, insulin secretion, and insulin-sensitizing actions, as well as enhances glucose utilization in peripheral tissues	[145]
	Quercetin 3-O-β-glucuronide	Flavonoid	Stimulates 2-deoxy-glucose uptake in C2C12 myocytes	[143]
	Isorhamnetin hexoside	Flavonoid	Decreases glucose level and oxidative stress modulates lipid metabolism and adipocytic activity	[145]
	Isorhamnetin 3-O-rutinoside	Flavonoid	Decreases glucose levels and oxidative stress, modulates lipid metabolism and adipocytic activity	[145]
Pelargonium graveolens	Chlorogenic acid	Phenol	Increases glucose uptake in L6 muscular cells and raises insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans.	[96]
	Quercetin-3-O-hexose	Flavonoid	Inhibits the activity of glucose transporter, enhances glucose uptake, reduces hepatic glucose production, Protects against pancreatic islet beta-cell, α-glucosidase inhibition	[130]

	β-Caryophyllene	Sesquiterpene	Exhibits selective agonism on cannabinoid receptor type 2 (CB2R), which plays a role in glucose and lipid metabolism, antioxidant, anti-inflammatory activities	[146]
	Caryophyllene oxide	Sesquiterpene	α-amylase and α-glucosidase inhibitory activities, and antioxidant activity	[139]
	α-Humulene	Sesquiterpene	Prevents oxidative stress through the reduction mechanism of 8-hydroxy-2-deoksiguanosin in the pancreatic β-cells	[147]
	Catechin	Sesquiterpenoid	Reduces blood sugar source, regulates intestinal function, improves insulin resistance, and has antioxidant and anti-inflammatory activities	[148]
Persea americana	Caffeic acid	Phenol	Reduction of hepatic glucose output and en hances adipocyte glucose uptake, insulin secretion, and antioxidant capacity	[99]
	Chlorogenic acid	Phenol	Increases glucose uptake in L6 muscular cells and raises insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans.	[96]
	Coumaric acid	Phenol	Lowers the blood glucose level, and gluconeogenic enzymes and increases the activities of hexokinase, glucose-6 phosphatase dehydrogenase, and GSH via increasing levels of insulin.	[97]
	Ferulic acid	Phenol	Improves insulin sensitivity and hepatic glycogenesis also inhibits gluconeogenesis and maintains insulin signalling to maintain	[98]

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			normal glucose homeostasis.	
Physalis peruviana	Phytol	Diterpenoid	Stimulates insulin resistance by activation of nuclear receptors and heterodimerization of RXR with PPARγ	[149]
	n-Hexacosane	Alkane	Improves blood glucose, glucose tolerance, glycated hemoglobin, and liver glycogen	[117]
Piper crassinervium	Germacrene D	Sesquiterpene	Strong inhibitor of α-glucosidase	[140]
	β-Caryophyllene	Sesquiterpene	Exhibits selective agonism on cannabinoid receptor type 2 (CB2R), which plays a role in glucose and lipid metabolism, antioxidant, and anti-inflammatory activities.	[146]
	Spathulenol	Sesquiterpenoid	Strong antioxidant, α-amylase, and α-glucosidase inhibitory activities	[138]
Pithecellobium excelsum	No proper evidence found	-	-	-
Ruta graveolens	No proper evidence found	-	-	-
Siparuna eggersii	Germacrene D	Sesquiterpene	Strong inhibitor of α-glucosidase	[140]
	Caryophyllene oxide	Sesquiterpene	α-amylase and α-glucosidase inhibitory activities and antioxidant activity	[139]
Urtica dioica	Carvacrol	Monoterpenoid	Improves diabetes-related enzymes, insulin resistance, insulin sensitivity, glucose uptake, and anti-oxidant, and anti-inflammatory activities.	[150]
	Carvone	Monoterpenoid	Improves glycoprotein components and controls glucose metabolism	[151]
	Naphthalene	Polycyclic aromatic hydrocarbon	α-glucosidase inhibitory activity	[121]
	(E)-Anethole	Phenylpropanoid	Suppresses diabetic nephropathy in rats by decreasing blood glucose levels and	[114]

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			downregulating AT1R and TGF-β1 expression.	
	Hexahydrofarnesyl acetone	Sesquiterpene	α-glucosidase inhibition activity	[152]
	(E)-β-Ionone	Sesquiterpenoid	α-amylase and α-glucosidase inhibitory activities and antioxidant activity	[153]
	Phytol	Diterpene	Stimulates insulin resistance by activation of nuclear receptors and heterodimerization of RXR with PPARγ	[149]
Verbena litoralis	Chlorogenic acid	Phenol	Increases glucose uptake in L6 muscular cells and raises insulin secretion from the INS-1E insulin-secreting cell line and rat islets of langerhans.	[96]
	Caffeic acid	Phenol	Reduction of hepatic glucose output and enhanced adipocyte glucose uptake, insulin secretion, and antioxidant capacity	[99]
	Apigenin	Flavonoid	Facilitates glucose-stimulated insulin secretion and prevents ER stress-mediated β-cell apoptosis in the pancreas	[87]
	p-Coumaric acid	Phenol	Lowers the blood glucose level and gluconeogenic enzymes, and increases the activities of hexokinase, glucose-6 phosphatase dehydrogenase, and GSH via increasing the level of insulin.	[97]
	Vanillic acid	Phenol	Reduced hyperglycemia and GSH, increased liver enzymes found in diabetic rats, anti-inflammatory activity	[100]
	Ferulic acid	Phenol	Improves insulin sensitivity and hepatic glycogenesis also inhibits gluconeogenesis and maintains insulin signalling to maintain normal glucose homeostasis.	[98]

6. Conclusion and Future Perspectives

DM is a metabolic disease characterized by persistent hyperglycemia that can be brought on by several factors, including lifestyle choices and genetics [122]. Over 422 million individuals in developing countries suffer from diabetes [123]. Diabetes-related expenditures per person are anticipated to be about 2,280 USD per year in Ecuador with 40% poverty rate, fragmented health systems, and high out-of-pocket health costs, which can put a substantial financial strain on Ecuadorians with diabetes for effective treatment [7,9]. To circumvent this, there is an utmost need to switch to herbal plant-based drugs that are natural, safe, non-GMO, cost-effective, and above all, the 27 above-mentioned herbs are a fundamental part of the health systems of several Ecuadorian ethnic groups [51]. Immense anti-diabetic properties were found in several Ecuadorian plant species which are ethanopharmacologically established such as *I. guayusa, A. poiretii, and A. altilis with α*-glucosidase and α-amylase inhibitory activities that are key enzymes for carbohydrate metabolism. Similarly, *A. altilis, F. vulgare*, and *I. carnea* were found to exhibit high anti-diabetic potential during the clinical trials conducted in animals. The contemporaneous occurrence of an extensive range of phytochemicals such as alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannin, etc., are the main active compounds present in Ecuadorian medicinal plants that responsible for high antidiabetic properties is often a hallmark of the practice of phytotherapy. However, the bioactive compounds directly associated with the anti-diabetic activity of some plants are still unexplored. Apart from these, plants like *B. gastonis-bonnieri, C. villosissimus, J. neotropica, P. excelsum,* and *M. peruiferum* that are used as a part of folklore medication for treating diabetes, are deprived of pharmacological studies to elucidate their anti-diabetic activity.

Comprehending the application of Ecuadorian herbs in the treatment of diabetes poses numerous obstacles. Several Ecuadorian plant species used as traditional medication against diabetes, lack rational elucidation of phytochemical constituent and cytotoxicity analysis, pharmacological activities, and clinical trials. In the case of *J. colorata* and *A. poiretii* where the preclinical experimental reports supported anti-diabetic activity, identification and purification of bioactive components, pharmacodynamics, pharmacokinetics, bioavailability, and bioactivity should be conducted to understand the metabolism of the bioactive compounds. Standardized formulation should be introduced to reduce the production batch heterogeneity caused due to geographical and environmental factors. Since the pharmacological studies on *P. graveolens, C. comosus, and O. grandiflora* showed an optimistic outlook, more robust clinical studies using rats and humans and investigation of standardized extracts, are required to analyze the efficacy from both the traditional use and potential use perspectives. Also, the determination of the long-term side effects of natural herbal product formulations individually and in combination with synthetic drugs is required. Furthermore, large-population human clinical evaluations before diabetic patients can rely solely on plant-based therapies for controlling diabetes with no side effects.

In this review, we elucidated 27 traditionally used Ecuadorian medicinal plants that can be used as potential anti-diabetic drugs, that can add great economic value to the pharmaceutical and food industries in Ecuador and other developing countries. However, further studies would confirm their practical application in the above-mentioned industries.

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