REVIEW ARTICLE

Traditional Herbal Medicines for Diabetes Used in Europe and Asia: Remedies From Croatia and Sri Lanka

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ABSTRACT

Diabetes is a global pandemic where alternative means of combating the disease have been the focus of research in recent years. Herbal remedies for diabetes have proven to be a valuable alternative therapy given the fact that many of the existing synthetic drugs are incapable of curbing the disease progression. This review article serves as an appraisal of highlighting the variety and diversity of herbal remedies that are present around the world by looking at only 2 countries—Croatia and Sri Lanka—located in Europe and Asia, respectively. The following herbs were selected for review: from Croatia: (1) *Cichorium intybus*, (2) *Olea europaea*, (3) *Taraxacum campylodes*, (4) *Urtica dioica*, and (5) *Vaccinium myrtillus*; and from Sri Lanka: (1) *Acacia catechu*, (2) *Allium sativum*, (3) *Aloe vera*, (4) *Cinnamomum zeylanicum*, (5) *Gymnema sylvestre*, and (6) *Zingiber officinale*. The botanical origins, bioactive compounds, evidence-based studies on antidiabetic properties, as well as uses and applications of these herbs in various ailments, are included herein. A plethora of scientific evidence on the antidiabetic potency of these herbs exists to date, through which it is apparent that they could be promoted as alternative therapies for diabetes. (*Altern Ther Health Med.* 2019;25(3):40-52.)

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INTRODUCTION

Diabetes mellitus has become a global pandemic leading to a multitude of microvascular and macrovascular complications, often resulting in a high rate of mortality.[1] Although many kinds of antidiabetic medicines have been developed, almost all of them are chemical or biochemical agents conceived under laboratory conditions. These medicines carry significant side effects and a complete recovery from this disease condition has not been reported to date as well.[2,3] High rates of mortality have been witnessed in patients with diabetes who are incessantly administered with chemically synthesized drugs.[2,3] Given these shortcomings, herbal antidiabetic remedies have received much attention due to their relative safety, cost effectiveness, and reduced toxicity when administered at recommended dosages.[4] Nearly 25% of the world's population relies on traditional medicinal systems for different aspects of primary health care.[4,5] Given these positive aspects of herbal remedies, the purpose of this review is to appraise herbs from Croatia and Sri Lanka, which are traditionally used as antidiabetic medicines. These 2 countries were selected because their traditional medicinal systems are lesser known around the world, despite being

Table 1. Family, Latin, and Common Names of Antidiabetic Plants From Croatia and Sri Lanka[a]

Traditional Medicinal System	Latin Name	Family	Common Name	Distribution	Part of Plant Used for Antidiabetic Treatments
Croatia	*C intybus*	Asteraceae	Common chicory (English), Vodopija (Croatian)	Europe, North Africa, and Western Asia	Herb, root, and folium
Croatia	*O europaea*	Oleaceae	Olive tree leaf (English), List masline (Croatian)	Mediterranean region, Africa, Southwest Asia, and the Himalayas	Folium
Croatia	*T campylodes*	Asteraceae	Common dandelion (English), Maslacak (Croatian)	Eurasia	Herb and folium
Croatia	*U dioica*	Urticaceae	Stinging nettle (English), Kopriya (Croatian)	Asia, America, and Europe	Entire herb
Croatia	*V myrtillus*	Ericaceae	Bilberry (English), Borovnica (Croatian)	Europe, Asia, and North America	Entire herb
Sri Lanka	*A catechu*	Leguminosae	Cutch tree (English), Catechu tree (English), Heartwood tree (English), Katu Andara (Sri Lankan)	India, Myanmar, Nepal, Pakistan, and Thailand	Entire herb
Sri Lanka	*A sativum*	Alliaceae	Garlic (English), Bijeli luk (Croatian), Češnjak (Croatian), Sudu lunu (Sri Lankan)	Central Asia, Europe	Bulb
Sri Lanka	*A vera*	Aloaceae	Aloe (English), Komarika (Sri Lankan), Anigini (India), Ghiguvara (India), Ghikumar (India)	North Africa, deserted regions in Saudi Arabia, India, and Sri Lanka	Folium
Sri Lanka	*C zeylanicum*	Lauracaeae	Cinnamon (English), Kurundu (Sri Lankan)	Sri Lanka	Bark
Sri Lanka	*G sylvestre*	Asclepiadaceae	Masbadda (Sri Lankan), Muwa Kiri Wal (Sri Lankan)	Sri Lanka	Folium
Sri Lanka	*Z officinale*	Zingiberaceae	Ginger (English), Inguru (Sri Lankan)	India	Rhizome

[a]Names include their regional distribution and parts of the plants used as adjuvant therapy to treat diabetes.

well established and used by locals. The following herbs were selected for review: from Croatia: (1) *Cichorium intybus* L, (2) *Olea europaea* L, (3) *Taraxacum campylodes* G. E. Haglund, (4) *Urtica dioica* L, and (5) *Vaccinium myrtillus* L, and from Sri Lanka: (1) *Acacia catechu* Willd, (2) *Allium sativum* L, (3) *Aloe vera*, (4) *Cinnamomum zeylanicum* Blume, (5) *Gymnema sylvestre*, and (6) *Zingiber officinale* Roscoe. Details on the botanical origins, bioactive compounds, in vivo and in vitro studies on antidiabetic properties, as well as uses and applications of the herbs in various other ailments, are provided herein.

SEARCH STRATEGY AND SELECTION CRITERIA

The typical methodology used for systematic reviews was modified for this paper due to the unavailability of proper and resourceful databases containing in vitro and in vivo evidence on the antidiabetic efficacy of the selected herbs. Searches were conducted in a 2-stage process. The main focus of the first stage was herbals thematically related to the topic of the review, such as the traditional usage of herbs. For the Croatian herbs, hardcover books that were considered for the review process included all books published in Croatia and surrounding countries (former Republic of Yugoslavia) in the last 50 years; the oldest book included in the review is *Lijecenje Biljem*.[6] As for the Sri Lankan herbs, the same strategy was used, although the unavailability of books published in English posed a significant barrier. Most of the books were published in Sinhala, which is one of the primary native languages of Sri Lanka. Nevertheless, to avoid translational errors, books that were published only in English were chosen with occasional referencing of Sinhala books for verification purposes. The oldest book that was cited in this review for the Sri Lankan herbs was by Jayaweera.[7] Altogether, these selected books were used to create the list of antidiabetic herbs from the 2 respective regions, and the selection of plants, was done on the basis of the highest number of citations. In other words, plants that were mentioned by a majority of authors were selected for the next stage of the review process.

The second stage of the review process included detailed analyses of scientific databases containing journal papers, such as HRČAK (Croatian database), PubMed, Cochrane, MEDLINE Plus, ScienceDirect, Web of Science, and GoogleScholar. The following key words were used as the search terms: *ayurveda*, *garlic*, *Allium sativum*, *common chicory*, *C intybus*, *olive tree*, *Olea europea*, dandelion, *Taraxacum campylodes*, stinging nettle, *Urtica dioica*, bilberry, *Vaccinium myrtillus*, *Aloe vera,* ginger, *Zingiber officinale*, heartwood tree, *Acacia catechu*, cinnamon, *Cinnamomum zeylanicum*, *Gymnema sylvestre*, *Croatia*, *Yugoslavia*, *Sri Lanka*, *herbs*, *herbal remedies*, *traditional medicine*, and *diabetes*. Important, one plant—*Allium sativum*—was the only plant used in both countries and because it is not native to Croatia, it was decided that it will be described as belonging to Sri Lanka. The last search was conducted on February 17, 2017. Some review articles were also included because they provide comprehensive information, which are beyond the scope of this manuscript. The material available in all the references were organized into the following 3 sections per antidiabetic herb: (1) botanical origin; (2) bioactive compounds, in vivo and in vitro studies on antidiabetic properties; and (3) other uses and applications. Table 1 provides a summary of details of the herbs, whereas Table 2 provides an overview of the other medicinal uses and applications of the selected herbs.

Table 2. Overview of Medicinal Uses and Applications of the Herbs

Traditional Medicinal System	Latin Name	Diseases and Disorders for Which the Herbs Are Used as Treatments
Croatia	*C intybus*	Digestive disorders,[6,9,47,97] loss of appetite,[6] liver,[47,97] spleen,[47,9] kidney stones,[47,97] thick bile and jaundice,[47,97] malaria[6]
	O europea	Parasitic disorders (giardia, intestinal worms, etc), gastric ulcers caused by *H pylori*, *C jejuni*, *S aureus*, and MRSA,[98] cancer,[99] hypertension,[100] atherosclerosis,[100] boosting immune function,[99] anti-inflammatory,[99] antioxidant,[99,101] antimicrobial,[99,101] neurological disorders[99]
	T campylodes	Gallbladder disorders, digestive complaints,[102] arthritic and rheumatic diseases,[30,103] breast and uterus cancers,[30,103] acute gastrointestinal inflammation,[30] indigestion, obesity-related complications[30,102]
	U dioica	Gout,[6,36,104,105] kidney disease,[6,36,104,105] urinary tract infections,[6,36,104,105] prostate diseases,[6,36,104,105] allergies,[6,36,104,105] bleeding,[6,36,104,10] hypertension,[6,36,104,105], hyperplasia[35,106] high blood pressure,[107] hypolipidemic and liver and renal damage,[108] antimicrobial,[109,110], antiulcer,[109,110] analgesic effects [109,110], antibacterial,[109,110] anti-inflammatory,[111] antirheumatic[111]
	V myrtillus	diarrhea,[48,112,11] scurvy,[48,112, 113] mouth and throat inflammations,[48,112,113] vision disorders, bladder infections[6,47,97]
Sri Lanka	*A catechu*	Chest ailments,[7] chronic diarrhea,[5,7], dysentery [5,7]
	A sativum	Asthma,[7,114,115] coughs,[7, 114,115] breathing difficulties[7,114,115] lung disorders,[7,114,115] rheumatism[7, 114, 115], indigestion[7,114,115]
	A vera	Hair-fall,[7] baldness,[7] constipation,[7,67,116] dyspepsia,[7,67,116] cough, asthma, nervous disease,[7,67,116] granular enlargement of the spleen,[7,67,116] burns,[116] scalds[116]
	C zeylanicum	Dyspepsia,[76,114] flatulence,[76,114] diarrhea,[76] dysentery,[76,114] vomiting,[76,114] bronchitis,[76,114] cramps of the stomach,[76,114] toothaches,[76,114] paralysis of the tongue,[76,114] cancer,[76,114] infections[73]
	G sylvestre	Asthma,[81,114] vision impairments,[81,114] inflammations,[81] snake bite[7]
	Z officinale	Loss of appetite,[60] vomiting, nausea,[60] cough,[60] common cold,[60] allergic reactions,[60] acute and chronic bronchitis,[60] respiratory troubles,[60] headaches,[60] toothaches,[60] swollen gums,[60] antimicrobial effects,[117] larvicidal activity,[118,11] anticancer activity[120,121]

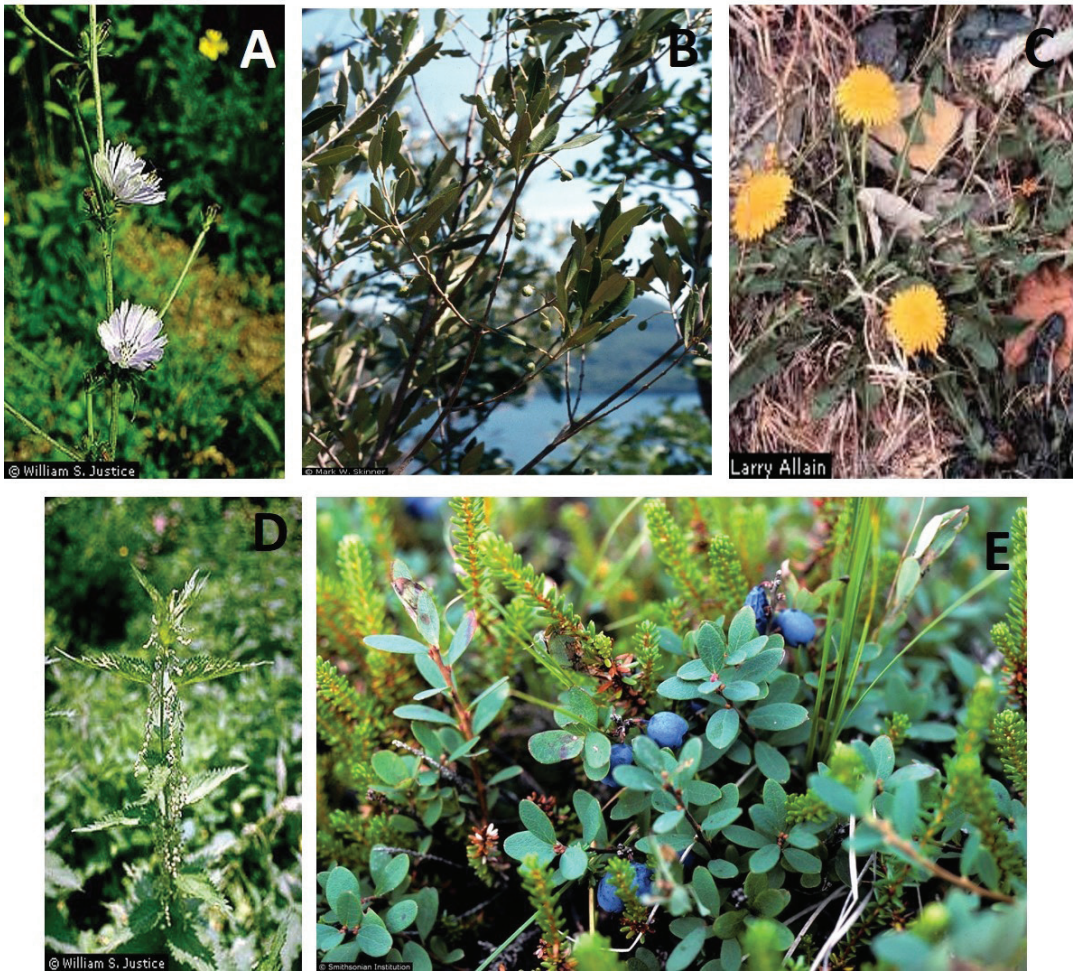
CROATIAN ANTIDIABETIC HERBS

Cichorium intybus (Asteraceae)

Botanical Origins. *C intybus* (Table 1) is a bushy perennial approximately 30 to 150 cm in height. It has numerous lateral branches which spread at an angle from the central stem.[8-10] The plant is somewhat stiff and angular and it has a strong, deep taproot.[10,11] When broken, the plant exudes a white sap.[10] The lower leaves of the plant are large and spread out, whereas the upper leaves are smaller and less divided with bases clasping the stems.8,10 It has blue flowers (or white or pink on rare occasions) (Figure 1A), which can be seen open on a sunny day, typically from June to September.[8,10] It can grow on any type of soil and is often considered a weed.[8,10] The roots can be roasted and used as a substitute for coffee.[11]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. In a survey consisting of 17 Croatian herbalists, *C intybus* ranked fourth in a list of herbal remedies recommended for the improvement of glycemic control.[12] The whole plant, especially its root, is rich in different chemical compounds (more than 100), of which inulin is the most abundant constituent present in the root.[9] For inulin alone, the European Food Safety Agency (EFSA) possesses substantiated health claims related to its fructo-oligosaccharides and its effect on the reduction of postprandial glycemic response. The pharmacological studies on *C intybus* mostly investigate the testing of aqueous and/or alcoholic extracts. The most quoted study on the antidiabetic effect was done on the ethanolic extract by Pushparaj et al.[13] Male Sprague Dawley rats were treated with streptozotocin to induce diabetes, and they were given a dose of 125 mg/kg body weight of the ethanol extract of *C intybus* which significantly attenuated the serum glucose levels in the oral glucose tolerance test. The same amount given orally for 14 days reduced serum glucose by 20%, triglycerides (TG) by 91% and total cholesterol (TC) by 16% with no changes in insulin secretion, while hepatic glucose-6-phosphatase (G6Pase) activity was markedly reduced.[13] The antidiabetic effect of the aqueous seed extract of *C intybus* has also been investigated by Pushparaj et al.[14] Early-stage and late-stage diabetes were differently induced in male Wistar albino rats by streptozotocin-niacinamide and streptozotocin alone. The 4-week treatment with *C intybus* extract prevented weight loss in both early-stage and late-stage diabetic rats, with normalization of alanine aminotransferase, TG, TC, and glycosylated hemoglobin.[14] A resistance to excessive increase in fasting blood sugar was also observed through an oral glucose tolerance test.[14] In early-stage diabetic rats, the *C intybus* treatment led to the increase in insulin levels pointing toward the insulin-sensitizing action of chicory, which was not observed in late-stage diabetic rats (probably due to inability to produce insulin).[14] In addition, a study on *C intybus* leaf powder administered to diabetic Wistar rats, had led to a decrease in blood glucose levels to near normal values.[15] *C intybus* administration had also decreased the malondialdehyde (MDA) levels and increased glutathione content according to the study by Ahmad and others.[15] Anticholinesterase activity was restored to near normal, whereas lipopolysaccharides in the brain had decreased and catalase activity had increased in this study. Samarghandian et al[16] investigated protective effects of *C intybus* extract against oxidative damage in diabetic rats. In this study, the streptozotocin-induced diabetic, male Sprague–Dawley rats were divided into control (C), diabetic (D), D + *C intybus*-treated (125 mg/kg/day) groups; they were treated for 4 weeks with the ethanolic extract of *C intybus* while body

Figure 1. Pictures of the Croatian Antidiabetic Herbs: (A) *C intybus*, (B) *Olea europaea*, (C), *T campylodes*, (D) *U dioica*, (E) *V myrtillus.* Note: Permissions have been obtained from the respective owners.



weight and blood glucose were measured weekly.[16] At the end of the 4-week period, the diabetic rats resulted in a significant reduction in blood glucose, TG, TC, low-density lipoprotein (LDL) cholesterol levels, and a significant elevation in high density lipoprotein (HDL) cholesterol levels.[16] In the treated diabetic group, there was a significant increase in glutathione, superoxide dismutase (SOD), glutathione-*s*-transferase (GST), and catalase with a decline in MDA levels compared with the nontreated diabetic group.[16] Furthermore, Tousch et al[17] had described caffeic acid and chlorogenic acid from *C intybus* as potential antidiabetic agents. Both these compounds had increased glucose uptake in muscle cells and were also able to stimulate insulin secretion from an insulin-secreting cell line and islets of Langerhans.[17] According to Tousch et al,[17] chicoric acid was also identified as a new potential antidiabetic agent exhibiting both insulin-sensitizing and insulin-secreting properties.

Olea europaea (Oleaceae)

Botanical Origins. *Olea europaea* (Table 1) is a tree characterized by whole, oblong, or elliptical coriaceous leaves, which are generally lanceolate and grow bilaterally at the same level on the stem. They are grey-green in color in the upper part of the leaf and silvery on the lower part of the blade (Figure 1B) with flowers in axillary position, of a whitish color and relatively small; the fruit is a succulent drupe of varying dimensions.[18]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. The primary antidiabetic mechanism of action of *O europaea* includes the stimulation of insulin release, thereby increasing the peripheral uptake of glucose. It also acts as an α-glucosidase inhibitor, thus reducing the absorption of carbohydrates in the gut.[19] The main bioactive ingredient in *O europaea* leaf was reported to be oleuropeoside, which can constitute up to 6% to 9% of dry matter and tannis.[19] Along with oleuropein, there is also oleanolic acid responsible for the antidiabetic effects of *O europaea* leaves.[20] Other bioactive components found in *O europaea* leaves as reported by Sedef and Karakaya[21] and Eddouks et al[22] include secoiridoids, flavonoids, and triterpenes, whereas Ghanbari et al[23] and Abaza et al[24] have reported the existence of hydroxytyrosol, tyrosol, tocopherol, elenolic acid derivatives, caffeic acid, p-coumaric acid, and vanillic acid as well as the following flavonoids: luteolin, diosmetin, rutin,

luteolin-7-glucoside, apigenin-7-glucoside, and diosmetin-7-glucoside. Cells treated with *O europaea* leaf extract and oleuropein had partly improved necrotic and apoptotic cell death, while inhibiting reactive oxygen species (ROS).[25] The study by Al-Azzawie and Alhamdani[26] proved the effects of oleuropein as an antihyperglycemic and antioxidant agent in alloxan-induced diabetic rats. In this study, it was observed that the blood glucose levels along with most of the antioxidants were restored to nearly normal values.[26] The effect of the extract was also observed to be more potent than the reference drug, glibenclamidem.[26] More interesting, in the same study, besides lowering the serum glucose, TC, urea, uric acid, TG, and creatinine, the extracts had also increased the serum insulin levels in the diabetic rats.[26] In a randomized, double-blinded, placebo-controlled, crossover trial on middle-aged overweight men, the effect of *O europaea* polyphenols was examined on glucose homeostasis.[27] The results concluded that *O europaea* leaf extract supplementation resulted in a 15% improvement in insulin sensitivity compared with the placebo group.[27] In the study by Ebrahimpoor and others,[28] the antidiabetic effects of the alcohol extract of *O europaea* leaves was examined in diabetic rats. Dosages of 0.10, 0.25, and 0.50 g/kg were administered for 14 days where the treatment had significantly decreased the serum glucose, TC, TG, urea, uric acid, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, while increasing the serum insulin level.[28]

Taraxacum campylodes (Asteraceae)

Botanical Origins. *Taraxacum campylodes* is a perennial herb that grows 5 to 51 cm in height from a branched stem base with a thick, deep taproot (Table 1).[10,29] Leaves are basal, 5 to 40.25 cm in length, 1.25 to 10 cm broad, and pinnately lobed with hollow midribs and winged stalks (Figure 1C). Flower heads rise from the basal leaves on hollow stalks and are composed of yellow ray florets. They are 2.5 to 5 cm in diameter and surrounded by 2 rows of involucre bracts. The whole plant contains a white, milky juice.[30]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. *T campylodes* contains a wide number of pharmacologically active compounds, from flavonoids such as luteolin, apigenin, and isoquercitrin (a quercetin-like compound), as well as caffeic and chlorogenic acid, as well as terpenoids, triterpenes, and sesquiterpenes.[30] The hypoglycemic effects of *T campylodes* is hypothesized to extend from α-glucosidase activity or its effect on lipid metabolism via lipid peroxidation, although both mechanisms may be possible.[31] It is possible that *T campylodes*'s effect is related to the stimulation of pancreatic β-cell release of insulin, which further leads to insulin resistance and contribute to β-cell burnout in patients with diabetes.[30] This insulin secretagogue activity could be observed for *T campylodes* ethanolic and aqueous extracts at a concentration of 40 μg/mL.[30] Goksu et al[31] reported a case of a woman diagnosed with severe hypoglycaemia, which resolved after consumption of *T campylodes* as a salad. On the other hand, Petlevski et al[32] observed a significant decrease in glucose and fructosamine levels after administration of an herbal concoction containing 9.7% *Taraxaci radix* (*T campylodes* and lyophilized 60% ethanol extract) to alloxan-induced nonobese diabetic (NOD) mice at a concentration of 20 mg/kg body weight. Petlveski et al32 also used the same dosage during a 7-day treatment to test the effect on the catalytic concentrations of GSTs and MDA in the liver of diabetic NOD mice. They reported a significant increase in the catalytic concentration of GSTs and a nonsignificant decrease in MDA concentration, which was confirmed by others as well.[30]

Urtica dioica (Urticaceae)

Botanical Origins. *Urtica dioica* (Table 1) is a perennial plant with an annual growth of up to 0.6-m tall shrub, which bears opposite, cordate, deeply serrate, pointed leaves.[33] Flowering and fruiting time is from June to October. Flowers are monoecious (individual flowers are either male or female, but both sexes can be found on the same plant) and are pollinated by wind.[33] The stem and leaves of the plant are covered with stinging trichomes (Figure 1D). The fluid present in the trichomes contains histamine, 5-hydroxytryptamine, acetylcholine, a small amount of formic acid, and leukotrienes that enter the skin and causes blistering.[33] The plant prefers to grow on loose soil with organic matter rich in nitrogen and high phosphate levels for rapid growth.[33]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. The proposed antidiabetic mechanism of action of *U dioica* includes an increase in insulin secretion, and inhibition of excessive hepatic glucose production.[19] According to Dar et al,[34] the bioactive compounds include antihistamines, hydroxycinnamic acid derivatives, and flavonoids. Nahata and Dixit[35] have identified β-sitosterol and related compounds, daucosterol, and campesterol. Mahady et al[36] have identified oxalic acid, linoleic, ursolic acid, 14-octacosanol, oleanolic acid, scopoletin, neo-olivil, lecithin, *U dioica* agglutinin, and polysaccharides. An in vivo study by Farzami et al[37] showed that 30 minutes after intraperitoneal injections of the active component of *U dioica* extract, a significant rise in serum insulin was recorded, accompanied by a drop in glucose level of blood sera in normal and streptozotocin diabetic rats. Farzami et al[37] suggested that the blood lowering effect of the extract was due to the enhancement of insulin secretion by Langerhance islets. The results of Bnouham et al[38] indicated that *U dioica* extract has a significant antihyperglycemic effect in an oral glucose tolerance test (OGTT) model, where it was suggested that the observed effect may in part be a result of a reduced intestinal glucose absorption. In the randomized, double-blind, placebo-controlled clinical trial by Kianbakht et al,[39] encapsulated *U dioica* extract was given to patients with type 2 diabetes mellitus for 3 months, and the final outcome included a significant reduction of fasting blood glucose levels, 2-hour postprandial glucose, and HbA_{1c} when compared with a placebo. The anti-inflammatory

potential of the herb was observed in patients with type 2 diabetes in a study by Namazi et al.[40] They conducted a randomized double-blind control trial, where 8 weeks of using hydroalcoholic extract of *U dioica* had resulted in a significant decrease in interleukin 6 (IL-6) and high sensitive CRP (hs-CRP).[40] In addition, it was shown that *U dioica* could reduce/decrease obesity-induced insulin resistance, which was found in mice skeletal muscle by enhancing levels of Akt phosphorylation,[41] and through regulating glucose transporter type 4 (GLUT4) translocation.[42] In addition, the antioxidant potential was shown when an aqueous-methanol extract of *U dioica* was given to streptozocin-induced type 1 diabetic rats, by reducing glutathione content and decreased lipid peroxidation levels of erythrocyte, plasma, retina, and lens tissues.[43] Also possible pancreatic tissue repair mechanisms have been proposed for dried *U dioica* leaf alcoholic and aqueous extracts.[44]

Vaccinium myrtillus (Ericaceae)

Botanical Origins. *Vaccinium myrtillus* (Table 1) is a perennial deciduous shrub (up to 50 cm).[10,44,45] This plant has sharp-edged green branches, green elongated leaves on short stems, and dark blue berries (Figure 1E).[44] It flowers in May and June with 5-mm long pale green to reddish flowers, while ripened fruits appear in July and August.[45] It occurs in the wild on/heathlands and acidic soils.[45] *V myrtillus* is a relative of the blueberry, and its fruit is commonly used to make pies and jams.[45]

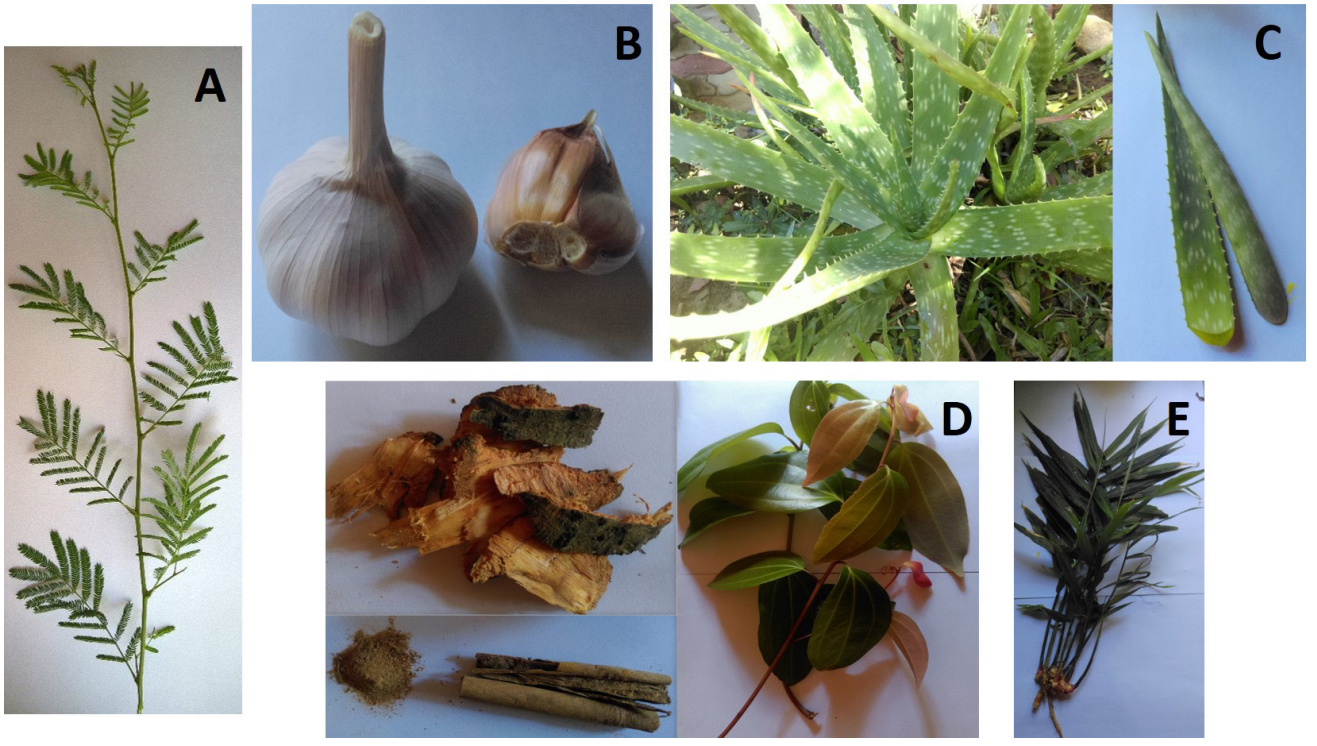
Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. In a survey consisting of 17 Croatian herbalists, *V myrtillus* leaf ranked third in a list of herbal remedies recommended for the improvement of glycemic control.[12] A similar survey in Italy was performed on 685 herbalists and *V myrtillus* was ranked fourth herein.[46] From *V myrtillus*, the following pharmacologically active compounds have been isolated: flavonoids (anthocyanins), berries), vitamins (berries), sugars (berries), pectins (berries), quercetin (leaves), catechins (leaves), tannins (leaves), arbutin (leaves), mirtilin and neomirtilin (leaves), iridoids (leaves), organic acids (leaves).[47] *Vaccinium myrtillus* leaf has been used for lowering blood glucose for centuries; however, pharmacological models have not clearly proven this property where it is sometimes attributed to the chemical compound called neomirtilin.[48] There is little or no data about antidiabetic effects of *V myrtillus* on humans. However, some in vitro and animal studies give evidence that *V myrtillus* could have a role in treating or preventing type 2 diabetes.[48] Tsuda et al[49] have investigated the gene expression profile of isolated rat adipocytes treated with anthocyanins. In this study, they have initiated the upregulation of hormone sensitive lipase and enhancement of the lipolytic activity with the treatment of adipocytes.[49] These results indicate a role for anthocyanins in preventing the metabolic syndrome.[49] In addition, Jayaprakasam et al[50] found that anthocyanins stimulate insulin secretion from cultured rodent pancreatic β-cells, with cyanidins and delphinidins being the most effective. Güder et al[51] investigated antiamylase, antiglucosidase, and antioxidant activities of methanol (ME), ethanol (EE), acetone (AE), and water (WE) extracts of bilberry fruit. Compared with the standards, ME, WE and EE showed strong total antioxidant activities with IC_{50} (μg/mL) values of 24.46 ± 0.34, 25.24 ± 0.78, and 27.48 ± 0.60, respectively. At the same time, ME (IC50 61.38 ± 1.40 μg/mL) and EE (IC_{50} 65.52 ± 1.19 μg/mL) demonstrated very effective inhibitory activity against α-amylase and moderate inhibitory activity against α-glucosidase.[51] All extracts also showed a higher reducing power and metal chelating activity as well as superoxide anion, DPPH radical, and H_2O_2 scavenging activities.[51] Cignarella et al[52] conducted an animal study with a water-alcohol extract of *V myrtillus* leaves given to streptozotocin-induced diabetic rats (3 g/kg/day for 4 d), where a significant decrease (26%) in rats' plasma glucose was observed. In addition, Petlevski et al[32] found significant decreases in serum glucose and fructosamine in alloxan-induced diabetic mice after administration of a dosage of 20 mg/kg of *V myrtillus* for 7 days. Takikawa et al[53] reported that *V myrtillus* extract (mainly fruit) added to the diet of type 2 diabetic mice lowered serum glucose and improved insulin sensitivity in diabetic mice. This happened through activation of AMP-activated protein kinase in white adipose tissue, skeletal muscles, and liver, which was accompanied with upregulation of GLUT4 (in white adipose tissue and in skeletal muscles) and suppression of glucose production in the liver.[53] Moreover, Asgary et al[54] investigated the effects of *V myrtillus* in alloxan-induced diabetic rats. *V myrtillus* powder and glibenclamide were administered for 4 weeks following alloxan injection, and *V myrtillus* supplementation resulted in a significant reduction of glucose compared to the control as well as glibenclamide treatment.[54] The *V myrtillus*–treated group had elevated insulin, but it had also reduced TC, LDL, and very low density lipoprotein cholesterol (VLDL) and TG levels, with no significant changes in CRP.[54] Histological examinations revealed a significant elevation of the islet size in *V myrtillus* and glibenclamide-treated groups.[54] Ferreira and et al[55] studied the effects of decoctions of *V myrtillus* leaves on Goto-Kakizaki (GK) rats, as well as the possible toxic effects of *V myrtillus* over mitochondrial respiratory activity indexes. Results from the study by Ferreira et al[55] showed that *V myrtillus* leaf decoctions presented significant benefits on glycemic control. Moreover, GK rats treated during 4 weeks with *V myrtillus* decoction presented an improvement of mitochondrial respiratory parameters evaluated (respiratory control ratio and FCCP stimulated respiration), which could be explained with mitochondrial biogenesis improvement initiated by quercetins present in *V myrtillus* leaves.[55]

SRI LANKAN ANTIDIABETIC HERBS

Acacia catechu (Leguminosae)

Botanical Origins. *Acacia catechu* is a 15-m tall, medium-sized or small-sized, thorny tree (Table 1).[56] The bark of the tree is greyish-brown and peels off in long strips.[56]

Figure 2. Pictures of the Sri Lankan Antidiabetic Herbs: (A) *A catechu*; (B) *A sativum* bulblets; (C) *A vera* Plant in Its Natural Habitat and Its Leaves; (D) *C zeylanicum* fresh bark, dried powder, dried bark sticks and leaves; (E) *Z officinale* Whole Plant With Its Rhizome



As shown in Figure 2A, the leaves are pinnate and compound, while the leaflets are attached along rachis.[56] Flowers are white to pale yellow in color with axillary spikes of 10 to 15 cm in length.[56] Fruits are strap-shaped pods, shiny brown in color, and contain ovoid-shape 3 to 10 seeds per pod.[56]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. Catechin (Figure 3) is found in the heartwood of *A catechu*, which is known to possess antidiabetic properties.[7] The gum yielding from the tree consists of L-arabinose, D-rhamnose, L-glycuronic acid, and D-galactose.[7] Several research findings focused on the antidiabetic activity of ethanol and aqueous extracts of the *A catechu*.[56,57] Jarald et al[56] in particular, had conducted an in vivo study to find out the performance of the antihyperglycemic activity of plant extracts using solvents such as petroleum ether, acetone, aqueous, or ethanol of the *A catechu* bark. Glucose induced models were used for the study of the hypoglycemic activity of the various solvent extracts, where the water-insoluble fraction of the ethanolic extract had showed a maximum activity on hypoglycemic activity.[56] Studies revealed that alkaloids and flavonoids were found in the ethanolic extract and water-insoluble fraction of the ethanolic extract.[5] Further, antidiabetic activity was shown in these extracts was due to the presence of alkaloids and flavonoids that were not found in other solvent extractions.[5] Pulok et al[58] concluded that the fractions of the extracts of the plant also showed decreases of other complications associated with diabetes in in vitro models used for the study. Better antidiabetic activities could be served by inclusion of this identified effective fractions of this plant rather than the existing formulations with a crude aqueous extract.[58]

Allium sativum (Alliaceae)

Botanical Origins. *Allium sativum* is generally known as garlic (Table 1). It is widely used for flavoring dishes as well as medicinal purposes. Leaves of *A sativum* are long, flat and narrow.[30] As shown in Figure 2B, the bulb is the edible part of garlic and consists of bulblets, grouped together between membranous scales and covered within a whitish skin, which holds the bulblets as in a sac. Whitish flowers rise from the center of the bulb. Flowers bloom only sparingly, often supplanted by purplish red solid bulbils crowded to form a globular head.[30,59] *A sativum* is easily grown in sandy soil with different pH levels and can be cultivated all year round.[59]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. The strong odor of *A sativum* is due to sulphur-containing compounds such as *S*-allylcysteine, which is also responsible for most of its medicinal effects.[60] In addition, antibiotic, anticoagulant, antioxidant, hypotensive, hypocholesterolaemic, and hypoglycemic-like compounds have been identified in *A sativum*.[61,62] Jayaweera[7] verified the presence of antidiabetic compounds such as volatile oil, allisin, alliin, inulin, allyl disulphide, myrosinase, and choline, which are mostly found in the bulb of *A sativum* (Figure 4). Thomson et al[62] has investigated the effectiveness of an aqueous extract of raw *A sativum* on controlling the hypoglycemic activity along with other complications that arise with diabetes using STZ-induced diabetic rats. Study

Figure 3. Chemical Structure of Catechin, Which Is Found Abundantly in *A catechu*

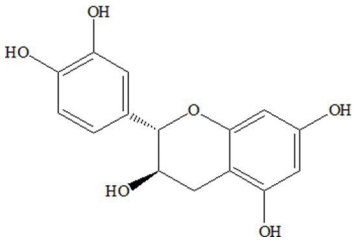


Figure 4. Bioactive Antidiabetic Compounds Present in *A sativum*

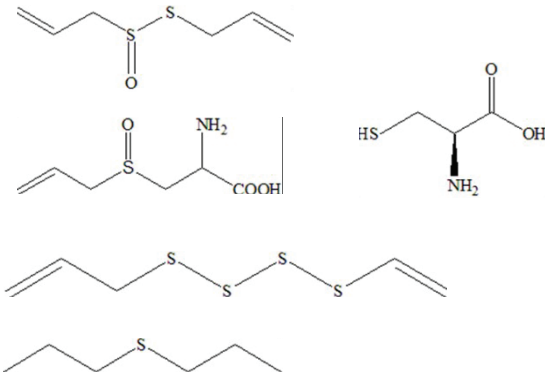
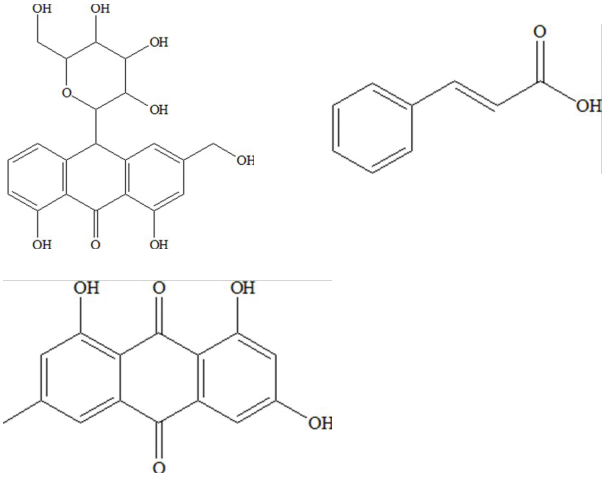


Figure 5. Chemical Structures of Antidiabetic Bioactive Compounds Present in the *A vera* Plant



models were treated daily with 500 mg/kg of raw *A sativum* extraction for period of 7 weeks.[62] The results from the study reinforces that raw *A sativum* has significant hypoglycemic effects along with hypocholesterolaemic and hypolipidemic effects.[62] The mechanism of hypoglycemic activity of *A sativum* was discussed by many research findings. Allicin in *A sativum* has been shown to enhance the serum insulin by effectively combining with compounds such as cysteine, which would spare insulin from thiol-group reactions, which are a common cause of insulin inactivation.[61,63,64] S-allyl cysteine sulfoxide's antioxidant activity has a beneficial effect on diabetes. *A sativum* oil or diallyl sulphide in *A sativum* acts as an antidiabetic agent, resulting in increased serum insulin levels.[65] The antidiabetic effects of *A sativum* extract was compared with a glibenclamide by Eidi et al[61] using streptozotocin-induced diabetic rats. According to the study, 14 days after oral administration of *A sativum* extract (0.5 g/kg) showed a significant decrease in serum glucose and the hypoglycemic effect was high in the extract than the antidiabetic drug. Modak et al[59] states that hypoglycemic activity of *A sativum* was due to increased hepatic metabolism, increased insulin release from pancreatic β-cells, or an insulin-sparing effect. An in vivo study was conducted using sucrose fed rabbits by Ashraf et al.[66] These models were orally fed with aqueous homogenate garlic for 2 months and results has shown a significant increase in hepatic glycogen and free amino acids content leading to decrease fasting blood glucose.[66] Mostafa et al[64] compared the blood glucose level lowering effect of *A sativum* with a glimepiride using streptozotocin-induced diabetic rats. *A sativum* extract was orally given at a dose of 1 g/kg body weight for 14 days. The study clearly revealed a significant hypoglycemic effect of *A sativum* compared with glimepiride. Another study was conducted by Ashraf et al[66] to evaluate the potential antihyperglycemic activity of *A sativum* using patients with type 2 diabetes. *A sativum* tablets of 300 mg were administered thrice daily, with metformin 500 mg twice daily for 24 weeks, and this was compared with another group that was given placebo + metformin 500 mg twice daily. The study concluded that the combined *A sativum* tablet with the typical antidiabetic remedy showed significant reduction in fasting blood glucose in diabetic patients.

Aloe vera (Aloaceae)

Botanical Origins. *Aloe vera* is a drought-resistant and succulent plant with a very short, cylindrical, thick, simple, woody stem, while the roots are fibrous and fleshy (Table 1).[67] As shown in Figure 2C, the leaves are lance-shaped. Figure 2C also shows the entire *A vera* plant, generally containing a stiff grey to bright green color, oozing a clear gel in a central mucilaginous pulp. Flowers can be seen in the dry season but the fruit is typically rare.[7]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. *A vera* leaves have been identified to contain barbaloin, cinnamic acid, and emodin (Figure 5).[7] Patel et al[5] and Sreenivasan et al[68] evaluated the effect of *A vera* leaf pulp extract and an *A vera* leaf gel extract on diabetic rats. Both studies identified that the pulp extract displayed a hypoglycemic effect, especially in type 2 diabetic rats. In a few other studies, single and repeated doses of the bitter principle extract of *A vera* showed hypoglycemic effect in diabetic rats, which was through stimulation of synthesis or release of insulin from pancreatic beta cells.[58,67,69] In the investigation by Sreenivasan et al,[68] a drop in the blood sugar level was observed in patients with diabetes through oral administration of *A vera* juice at least 2 weeks, twice per day. Further, the ability of lowering the blood glucose level was

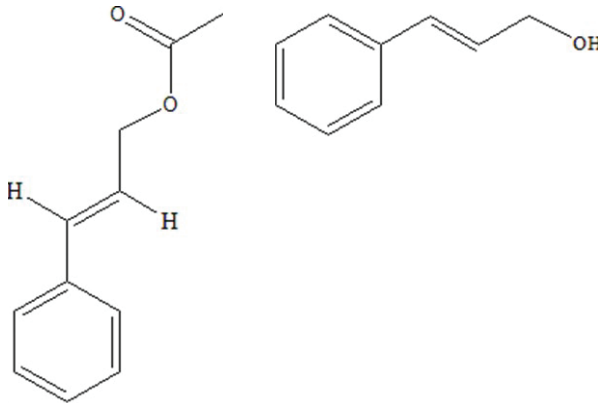
studied in detail by Sreenivasan et al[68] using 5 patients with diabetes and Swiss albino mice. In the study on Swiss albino mice with diabetes, serum glucose level had been decreased with the ingestion of *A vera* daily for 4 to 14 weeks.[68] Oral use of *A vera* gel decreases fasting blood glucose level among patients with type 2 diabetes.[70] The study by Tanaka et al[71] revealed that the phytosterols that are derived from *A vera* gel have a long-term blood glucose level control effect and authors stated that this would be useful for the long-term treatment of type 2 diabetes. Also, no adverse side effect symptoms were observed from pathological findings.[71]

Cinnamomum zeylanicum (Lauracaeae)

Botanical Origins. *Cinnamomum zeylanicum* (Table 1) is an aromatic plant species that is moderate in size and grows up to 9 to 10 m in length.[72] The bark of the tree is rather thick and reddish in color and used for medicinal purposes (Figure 2D). Young leaves used as a typical trick of tropical trees to make themselves look unappealing to predatory insects by assuming a limp, reddish appearance, as if wilting.[7] Once they mature, they perk up and darken to a deep green color. The leaves of *C zeylanicum* are oval shaped and shiny in color than the surface below. The typical *C zeylanicum* aroma is found in the bark as well as the leaves. Flowers bloom in February, which are pale yellow in color. Fruits are bluish and the seeds exist without an endosperm. Edible parts are harvested in the rainy season.

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. Different parts of the *C zeylanicum* tree contains different chemical constituents. The chief constituent is an essential oil that contains cinnamyl acetate, cinnamyl alcohol, and other volatile substances (Figure 6).[7] The essential oil also contains sugar, mannite, starch, mucilage, and tannicacid.[7] Oil from the leaves contains eugenol, which is useful in perfume and flavoring industries.[7] The roots contain camphor, eucalyptol, and safrol.[7] Polyunsaturated fats are found in seeds.7 Many studies have evaluated the positive effects of *C zeylanicum* on glycemic control. Mang et al[73] has done a trial on the effectiveness of *C zeylanicum* aqueous extract and cinnamon powder on hypoglycemia, using patients with type 2 diabetes, and was compared with an antidiabetic drug placebo capsule. *C zeylanicum* extract had given a higher reduction in fasting plasma glucose levels than the placebo-treated patients.[73] In the same study, *C zeylanicum* demonstrated a potential for reducing postprandial intestinal glucose absorption by inhibiting pancreatic α-amylase and α-glucosidase, stimulating cellular glucose uptake by membrane translocation of GLUT4, stimulating glucose metabolism and glycogen synthesis, inhibiting gluconeogenesis, and stimulating insulin release and potentiating insulin receptor activity. Toxic effects were not identified in cinnamon on using against diabetes.[74] Potentiality of antidiabetic properties in the ethanolic extract of *C zeylanicum* leaves were studied by Tailang et al[75]; the study was carried out using alloxan-induced diabetic rats. A significant reduction was observed in fasting blood glucose levels in trial models. The study by Shen et al[76] found that with a use of pancreatic islet cell line, *C zeylanicum* extract was able to act as a stimulator for insulin secretion from the cells. Further, they revealed that *C zeylanicum* prevented diabetes by enhancing the catabolism of glucose through upregulation of the uncoupling protein-1 in brown adipose tissue (BAT) and in the meantime, translocation of GLUT4 to the plasma membrane in both BAT and muscle was achieved. *C zeylanicum* is well known for its pharmacological properties in the treatment of type 2 diabetes, on the basis of preclinical and clinical data.[77,78,79] The ability of *C zeylanicum* to reduce blood glucose as well as its antioxidant property has been verified in a few studies using diabetic rat models.[65,78] The flower and bark can both be used medicinally, although the bark is more commonly used.[77] Consuming regular *C zeylanicum* tea than regular tea has shown an increased antioxidant level, increased thiols, and decreased lipid peroxidation.[7]

Figure 6. Bioactive Antidiabetic Compounds Present in *C zeylanicum*



Gymnema sylvestre (Asclepiadaceae)

Botanical Origins. *Gymnema sylvestre* is a branched plant and a woody climber (Table 1). The leaves of the plant are simple, broad and ovate.[7] Flowers are small and rather long with hairy pedicles grouped in them, which typically bloom from November to February.[7]

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. Aqueous leaf extracts of *G sylvestre* was orally ingested once per day for 30 days to alloxon-induced rats to investigate the antidiabetic activity by Mall et al.[78] The study observed a decrease in fasting blood glucose levels; this was hypothesized due to the increased activity of enzymes responsible for utilization of glucose by insulin-dependent pathway or regenerate β-cells in the pancreas.[78,80,81] Also, the study demonstrated a decrease in total cholesterol and serum triglycerides with hypoglycemic activity.[78] Another study determined the effect of antihyperglycemia of the leaf and callus extracts of *G sylvestre* on diabetic rats through an intraperitoneal route,[82] thereby observing the exhibition of antidiabetic activity of rat modules. Chemicals found in the extracts were capable of

Figure 7. Gymnemic Acid, Which Is Abundantly Found in *G sylvestre* as an Antidiabetic Compound

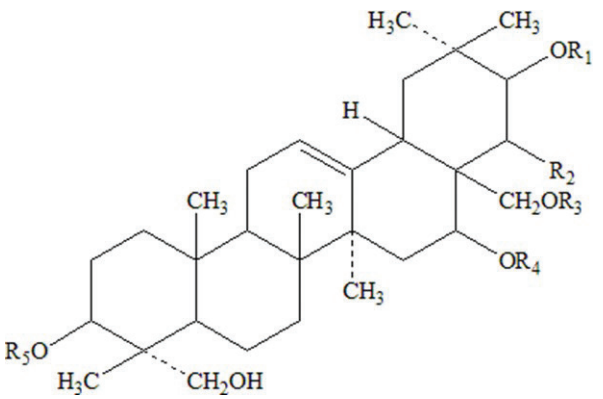
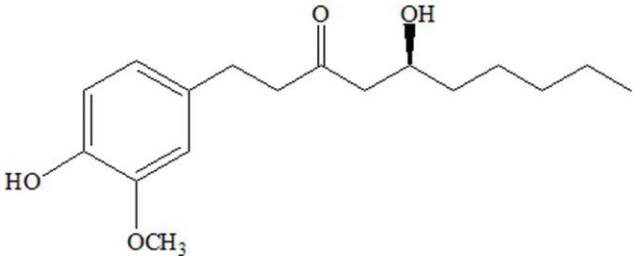


Figure 8. Chemical Structure of [6]-gingerol, the Most Potent Antidiabetic Bioactive Compound in *Z officinale*



fully restoring pancreatic β-cells function and thus curing type 1 diabetes.[82] Triterpene saponines were found in *G sylvestre* leaves.[81,83] Gymnemic acids, which are found in *G sylvestre* leaves, have antidiabetic, antisweetener and anti-inflammatory activities.[81,83] Figure 7 shows the chemical structure of gymnemic acid. This acid is known to delay the glucose absorption in the blood.[81,83] Leaf extracts of *G sylvestre* is found to cause hypoglycemia in laboratory animals as well as have found to use as a medicinal herb, which help to treat adult onset of diabetes.[81,83] In patients with diabetes, once the leaf extraction is administrated, the bioactive compounds start to stimulate the pancreas and thereby increase the secretion of insulin, and it promotes regeneration of islet cells and it increases utilization of glucose by insulin-dependent pathways.[81,83] In the in vivo study by Aralelimath and Bhise,[84] it was revealed that oral administration of active *G sylvestre* extract for 40 days leads to hypoglycemia and, hence, this could be used as a drug for treating patients with diabetes.[84] People in the early stages of diabetes could be treated with *G sylvestre* to delay or prevent full-blown clinical diabetes because of its ability to regenerate β-cells.[84] Daisy et al[85] also state through their in vivo study that the active compounds in *G sylvestre*, such as dihydroxy gymnemic triacetate, possesses hypoglycemia activity in long-term treatment and this could be used as a potential antidiabetic drug. The antihyperglycemic activity of *G sylvestre* leaf extracts was also proven by an in vivo study by El Shafey et al.[82] Results from the study has shown a 20% decrease in plasma glucose levels in treated diabetic models.

***Zingiber officinale* (Zingiberaceae)**

Botanical Origins. *Zingiber officinale* is a well-known aromatic spice because of its aesthetic appeal and adaptability to grow in humid, shaded habitats in the tropics.[86] The rhizome of *Z officinale* is thick and branched. The center is pale yellow and has a brown corky outer layer. The spicy lemon scent is caused by a mixture of volatile compounds such as shogaols, zingerone, and gingerols. The leaves of the plant are green in color and are approximately 1.2 m long, annually arising from the buds on the rhizome as shown in Figure 2E. The leaf bases are wrapped tightly with one another. *Z officinale* produces clusters of white and pink flower buds which bloom into pale yellow color flowers.

Bioactive Compounds, In Vivo and In Vitro Studies on Antidiabetic Properties. Jafri et al[87] conducted an in vivo study to evaluate the hypoglycemic effect of aqueous extract of *Z officinale*. A 500 mg/kg body weight dose was given to alloxan-induced diabetic rats and the change of plasma glucose levels were investigated.[87] According to this study, a significant decrease was identified in the *Z officinale* extract-treated diabetic rats after 21 days of oral ingestion.[87] Iranloye et al[88] had identified reduced MDA levels along with reduced blood glucose levels in alloxan-induced diabetic male rats. The study concludes that dietary *Z officinale* has a hypoglycemic effect by enhancing insulin synthesis and has a high antioxidant activity. The 6-gingerol, tannins, flavonoids, polyphenolic compounds and triterpenoids were some of the active compounds found in *Z officinale*.[89] Hypoglycemic potentiality of *Z officinale* was reported in streptozotocin-induced diabetic rats, treated with the aqueous extract of *Z officinale* for a 7-week period. Fresh *Z officinale* juice also carries an antihyperglycemic effect. Ethanol extract of *Z officinale* (10 mg/kg body weight) controls type 1 diabetes while decreasing serum cholesterol, serum triglyceride, and blood pressure.[90] Antiglycating potential and inhibition of the polyol pathway in *Z officinale* has been shown to prevent diabetic cataract in rats.[91] *Z officinale* as a dietary source can be used as a prevention or delay of diabetic complications.[91] The most abundant antihyperglycemic agent is [6]-gingerol (Figure 8). A higher concentration of [6]-gingerol in *Z officinale* extract produce marked reduction in fructose-induced hyperglycemia.[92] A 51% decrease in serum glucose was observed in a study with administration of ethanol extract ginger to normal rabbits.[93] Raw ginger has been demonstrated to possess the ability to reverse diabetic proteinuria in diabetic rats.[94,95] The activity of hepatic G6Pase enzyme was shown to be inhibited by *Z officinale*, thereby causing a reduction of blood glucose levels.[96] A study in Iran by Mozaffari-Khosravi et al[96] reveals that patients with type 2 diabetes leads to lowering fasting blood sugar and HbA_{1C} and also variation in fasting insulin, insulin resistance, increase of sensitivity to insulin, and quantitative insulin sensitivity check index by daily consumption of 3 g of ginger powder supplement in a capsule for 8 weeks.

CONCLUSIONS

This review discussed 11 herbs that have been used for antidiabetic purposes in Croatia and Sri Lanka. Despite their localized usage in these 2 countries, it is evident that their availability around the rest of the world makes them easily accessible and cost-effective means of complementary and alternative therapies for diabetes. In addition, the usage of all these herbs for a variety of other ailments and therapeutic uses makes them versatile—a characteristic mostly extending due to their possession of various categories of bioactive compounds of proven therapeutic effects. Bioactive compounds responsible for antidiabetic activity vary widely. However, the general public is familiar with all these plants but for a different types of applications. For example, *A sativum* is the best known for its antimicrobial activity and has been used as spice in both countries, *O europea* is the most famous for its fruits and "liquid-gold" (ie, olive oil), while *Z officinale* is a very famous spice that has received a lot of attention in the West. One of the most interesting plants discussed is *C intybus* due to its compound inulin. Inulin has been recognized by food industry and found its application in a wide variety of food products, including drinks and dairy products. Still, inulin is rarely discussed as a potent antidiabetic component but rather as a potent modulator of bowel movement. Many of these plants have been forgotten and only sparsely used. However, as emphasized throughout this study, the highest value of all discussed plants is their combined effect, namely on other risks which correlate with diabetes onset (ie, lipid profile and anti-inflammatory effects). Current antidiabetic medications do not have the ability to induce such complex activity on several levels and, thus, many medicines have to be administered to contain all the complications. For diabetes, recognition and timely treatment of risk factors for diabetes's microvascular and macrovascular complications is crucial for life expectancy and the overall quality of life improvement. Thus, it is hoped that through this review, these herbal material will be given due attention to promote them among the diabetic population as well as those around the world who seek the containment of overall health and wellness.

AUTHOR DISCLOSURE STATEMENT

The authors do not have any conflicts of interest to share, financial or otherwise.

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