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Review

Mechanisms of action of Sri Lankan herbal medicines used in the treatment of diabetes: A review

Dona Nirmani Ann Wijewickrama Samarakoon [a,*], Deepthi Inoka Uluwaduge [b], Malitha Aravinda Siriwardhene [b]

[a] Department of Biomedical Science, Faculty of Health Sciences, KIU, Koswatta, Battaramulla 10120, Sri Lanka
[b] Department of Allied Health Sciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Soratha Mawatha, Nugegoda 10250, Sri Lanka

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ABSTRACT

Natural plant-based remedies for diabetes mellitus have been proven to be safe and effective alternatives to Western medications, and details about more than 400 plants are available in the literature. Sri Lanka is a tropical country which is blessed with many natural plant products that can be utilized for the treatment of diabetes. But the knowledge of these plant-derived remedies, especially their doses, mechanism of action and toxicity has not been extensively researched. Therefore, this review focuses on documenting the plant-based remedies that the Sri Lankan Aurvedic physicians use and the extent of research that has been carried out on each of these plant-based remedies.

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Contents

1. Introduction

Sri Lanka is a tropical country with abundant evergreen forests and herbaceous plants, many of which have been used in Sri Lanka's rich history of natural plant-based remedies.

* Corresponding author.
E-mail address: nirmani@kiu.ac.lk (D.N.A.W. Samarakoon).

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Though there are many common diseases in the world, the study of diabetes mellitus carries a high level of importance. The global prevalence of diabetes has increased drastically in the past few years [1]. The prevalence of diabetes is growing most rapidly in low- and middle-income countries [2]. In Sri Lanka, diabetes is more common in the urban sector (8%, compared to 5% in the rural sector) and among populations living in the richest households (9% for the highest wealth quintile) [3]. Diabetes affects various organ systems, therefore individuals with diabetes have a greater risk of developing serious health complications, such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy and atherosclerosis [4]. Natural products with complex chemical mixtures can be used to treat these complications of diabetes.

The development of novel antidiabetic drugs and therapeutic agents from herbal materials holds great importance. Although there are several allopathic antidiabetic drugs available, they have complications and unpleasant side effects in patients [5]. Therefore, globally there is a great demand for exploring and investigating herbal medicines for the treatment of diabetes. In Sri Lanka, approximately 60%–70% of the rural population relies on indigenous medicinal systems for their main source of primary health care [5]. Sri Lanka has a great history of herbal remedies within the practices of Ayurveda, Unani, Siddha and other traditional therapies used for the treatment of diabetes mellitus.

The present review relies on documentation of common herbs used in Ayurvedic medical system of Sri Lanka, with special emphasis on their mechanism of action.

2. Blood glucose-reducing mechanisms of therapeutics

Antihyperglycaemic and hypoglycemic therapeutics (herbal or synthetic) have the ability to modify blood glucose levels by the following mechanisms: insulinomimetic activity, anti-absorptive activity, α-glucosidase inhibitory activity, α-amylase inhibitory activity and antioxidant activity.

2.1. Insulin-secreting activity

There are a large number of natural products with proven insulin-secreting activity [6]. These therapeutics stimulate the activity of pancreatic β cells by increasing the insulin secretion. Some of them are insulin mimetic and enhance the peripheral utilization of glucose, increasing the synthesis of hepatic glycogen and decreasing glycogenolysis [7].

These mechanisms are mediated by different chemical compounds in plants. These compounds include roseoside, epigallocatechin gallate, β-pyrazol-1-alanine, cinchonain-Ib, leucocyandin 3-O-β-D-galactosyl cellobioside, leucopelargonidin-3-O-α-L rhamnoside, glycyrrhetinic acid, dehydrotrametenolic acid, strictinin, isostrictinin, pedunculagin, epicatechin, christinin-A, momordicine I and momordicine II [7,8]. These compounds play a major role in improving insulin sensitivity in tissues and have been reported to be beneficial in reducing postprandial hyperglycemia [9].

In allopathic medicine, sulfonylureas are the drugs in use with insulin-secreting properties that induce glucose-independent insulin release from β cells of pancreas [10].

2.2. Anti-absorptive activity

Glucose is absorbed to the enterocytes via Na^+/glucose cotransporter (SGLT). Glucagon-like peptide and glucose-dependent insulinotropic polypeptide act as activators of SGLT, while cholecystokinin and leptin act as inhibitors of SGLT [11].

Anti-absorptive agents act by reducing absorption of glucose from the gastrointestinal tract by blocking the Na^+/SGLT1 [12]. Some anti-absorptive compounds block the Na^+/K^+ ATPase pump in intestinal cells and therefore prevent glucose absorption [13].

In vitro SGLT1 activity can be investigated by using brush-border membrane vesicles prepared from mouse small intestine, and by measuring the uptake of glucose by those cells [14].

These drugs should be administered before eating which will significantly reduce the glucose-induced hyperglycemic effect, thus reducing the postprandial glucose levels in the blood [15].

2.3. α-Glucosidase inhibitory activity

These are the compounds with the ability of reversible inhibition of enterocyte membrane-bound α-glucosidases, thereby retarding the breakdown of disaccharides to glucose and subsequently delaying the absorption of simple sugars. Therefore α-glucosidase inhibitors that reduce postprandial hyperglycemia have shown beneficial effects in diabetes [9]. In Western medicine acarbose is one of the well-known α-glycosidase inhibitors [16,17]; even though they are found to be effective as therapeutics, they exhibit several side effects such as bloating, diarrhea, abdominal discomfort and flatulence [18].

Though carbohydrates consist of complex structures, they can get rapidly absorbed in the intestine due to the presence of the α-glucosidase enzyme that breaks disaccharides into absorbable monosaccharides. α-Glucosidase inhibitors can inhibit this digestion process and reduce the postprandial glucose levels in the blood [19]. The α-glucosidase enzyme catalyzes the final step of carbohydrate digestion. Therefore, α-glucosidase inhibitors can stop the production of d-glucose from dietary carbohydrates and delay the glucose absorption [20].

It has been shown that plants containing flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, stilbenoids (polyphenol), triterpenes, acids (including chlorogenic acid, betulinic acid, syringic acid, vanillic acid, bartogenic acid, oleanolic acid, dehydrotrametenolic acid, corosolic acid, ellagic acid, ursolic acid and gallic acid), phytosterol, myoinositol and other phenolic compounds can exert this effect [20,21].

2.4. α-Amylase inhibitory activity

α-Amylases catalyze the hydrolysis of internal α-(1,4)-glycoside linkages in starch and other related polysaccharides [22]. Therefore inhibition of salivary and pancreatic amylase prevents carbohydrates from break down, thus reducing their absorption [23]. Although both α-amylase and α-glucosidase inhibitors have somewhat similar mechanisms in exerting their action, α-amylase inhibitors are considered to be better, as they do not lead to accumulation of maltose which can lead to many side effects such as flatulence, diarrhea and abdominal pain [24].

There are different methods to investigate the α-amylase inhibitory activity, such as measurement of fecal sugar and extraction of the enzyme to measure its available concentration using a substrate or gelatinizing starch [25]. In Western medicine, acarbose is used as an α-glucosidase inhibitor, but no drug has been synthesized to inhibit α-amylase activity [26]. Chemical compounds isolated from plants with proven α-amylase inhibitory activity are flavonoids, catechins, tannins and phenolic compounds [24,27].

2.5. Antioxidant activity

Antioxidants act either directly or indirectly through various mechanisms to prevent oxidant-induced cell damages. They can reduce the generation of reactive oxygen species (ROS), scavenge ROS, or interfere with ROS-induced alterations. Modulating mitochondrial activity is an important option for controlling ROS production [28]. Increased ROS and increased oxidative stress have been observed in diabetes mellitus, leading to many complications; therefore in diabetes management it is beneficial to have substances that combat these ROS to prevent complications [29]. Therefore, plant substances with antioxidant activity are potentially useful in controlling diabetes.

3. Literature survey on antidiabetic plants

Data on traditional plants used for the treatment of diabetes were gathered by interviewing 20 practitioners of traditional medicine who practiced as Ayurvedic physicians (Sarwanga Roga; 6 males and 14 female; aged 40–75 years) in Yakkala, Western Province, Sri Lanka. This area is well known for Ayurveda and traditional medicine-based treatments.

Based on the information provided by these practitioners, an extensive literature survey was conducted to research the mechanisms of action for the antidiabetes herbal therapies they recommended; this survey included scholarly articles published in Google Scholar and PubMed. Keywords used were antidiabetic, mechanism of action, active compound, plants, etc. No time limitation was added; only articles written in English were included.

4. Mechanisms of antidiabetic plants

According to interviews, 46 different plants were used by the Ayurvedic physicians to treat diabetes mellitus, although they were not aware of the scientific studies involving the plants that they are used. However, the literature survey showed that most of the plants had been proven to have antidiabetic therapeutic effects and mechanisms of action had also been documented. Therefore to preserve and to acknowledge the traditional knowledge among Sri Lankan Ayurvedic physicians it is of utmost importance to document such details. Only 17 plants were used in the present survey study, as most of physicians included these plants in whole or parts for antidiabetic preparations.

The plants for which antidiabetic mechanisms of action have been proven are shown in Table 1. Pictures of the 17 plants are shown in Fig. 1. The structures of some of the active compounds are shown in Fig. 2.

5. Discussion

Natural plant-based remedies have been proven to be safe and effective alternatives for the treatment of diabetes mellitus and the antidiabetes literature includes studies of more than 400 medicinal plants [66]. Although they are extensively used in developing tropical countries like Sri Lanka, the scientific research on dose, mechanism of action and activity has not been completed for most of these plants. It is important to identify these under-studied plants and investigate their toxicity and activity and to rationalize the usage of these natural substances.

The South Asia has the highest abundance of antidiabetic plants, including 36% of those documented [67]. Therefore, there is a remarkable demand for these plant products as antidiabetic agents in the zone of the world.

The evidence suggests that most of the plants under review had more than one mechanism of antidiabetic activity. Those plants included *Costus speciosus*, *Averrhoa bilimbi*, *Camellia sinensis*, *Nigella sativa*, *Artocarpus heterophyllus*, *Averrhoa carambola*, *Alternanthera sessilis*, *Andrographis paniculata*, *Annona squamosa*, *Azadirachta indica* and *Ipomoea batatas*. Therefore, it can be concluded that the antidiabetic activity of those plants is mediated by summation of all possible mechanisms. This indicates the importance of administering the proper dose of the particular plant in order to minimize the risk of hypoglycemia.

Table 1
Selected antidiabetic plants used in Sri Lanka for the treatment of diabetes.

No.	Plant	Family	Plant morphology	Part used	Method of preparation and administration	Mechanism of antidiabetic effect	Active compound	References
1	*Costus specisous*	Zingiberaceae	Rhizomatous herbs. Stems branched or unbranched, stout, up to 1 m tall, leafy	Leaves	Fresh leaves eaten as salad	*In vitro* antioxidant effect	Costunolide and eremanthin	[30–33]
2	*Averrhoa bilimbi*	Oxalidaceae	The tree is cauliflorous with 18–68 flowers in panicles that form on the trunk and other branches reaching up to 15 m in height. Bilimbi leaves are alternate, pinnate, measuring approximately 30–60 cm in length. Each leaf contains 11–37 leaflets	Fruit Leaves	Decoction Fresh fruit Fresh leaves are pounded and juice is consumed	*In vivo* insulin-secretory activity α-Glucosidase inhibitory activity Antioxidant	Not found	[30,34,35]
3	*Camellia sinensis*	Theaceae	Evergreen trees or shrubs that are usually trimmed to below 2 m when cultivated for its leaves. Leaves: 5–9 in a branch, 2–3 cm broad; flowers: yellowish white, 2.5–4 cm in diameter, with 7–8 petals	Tender leaves	Prepared in the form of "tea"	Inhibit intestinal glucose absorption; α-glucosidase and α-amylase inhibitory activity; marked antioxidant activity	Not found	[30,36,37]
4	*Nigella sativa*	Ranunculaceae	An annual flowering plant which grows up to 20–30 cm. Leaves are linear and finely divided	Seed	Raw seeds are eaten	Accelerate pancreatic β-cell proliferation; antioxidant activity, and antiabsorptive activity	Thymoquinone	[38–41]
5	*Artocarpus heterophyllus*	Moraceae	Grows as an evergreen tree that has a relatively short trunk with a dense treetop. It easily reaches heights of 10–20 m and trunk diameters of 30 to 80 cm. The leaves are alternate and spirally arranged	Matured fresh leaves	*Decoction	α-Glucosidase inhibitory effect; α-amylase inhibitory effect; 1,1-diphenyl-2-picrylhydrazyl-free radical scavenging activity	Cycloheterophyllin, artonin A and artonin B	[30,42–45]
6	*Moringa oleifera*	Moringaceae	A fast-growing, deciduous tree, that can reach a height of 10–12 m (32–40 feet) and trunk diameter of 45 cm. The tree has an open crown of drooping, fragile branches and the leaves build up feathery foliage of tripinnate leaves	Leaves	Raw leaves are eaten as a salad	Strong antioxidant	Quercetin-3-O-glucoside and quercetin-3-O-(6′-malonyl-glucoside)	[46,47]

(*continued on next page*)

Table 1 (*continued*)

No.	Plant	Family	Plant morphology	Part used	Method of preparation and administration	Mechanism of antidiabetic effect	Active compound	References
7	*Allium sativum*	Amaryllidaceae	Abulbous plant, growing up to 1 m (3.3 feet) in height	Bulb	Bulb is cooked and eaten with other food as a curry. Bulbs boiled in water and drink twice a day	Antihyperglycemic	Volatile oil, allin and allicin	[48,49]
8	*Averrhoa carambola*	Oxalidaceae	A small, slow-growing evergreen tree with a short trunk. The compound leaves are soft, medium-green; they are spirally arranged around the branches in an alternate fashion	Fruit	Fruit is eaten as whole	α-Amylase inhibitory effect; antioxidant effect	Apigenin-6-C-β-fucopyranoside and apigenin-6-C-(2-O-α-L-rhamnopyranosyl)-β-L-fucopyranoside	[50–52]
9	*Aegle marmelos*	Rutaceae	Small to medium-sized tree, up to 13 m tall with slender drooping branches and rather shabby crown. The leaf is trifoliate, alternate, with each leaflet of (5–14) cm × (2–6) cm in size, ovate with tapering or pointed tip and rounded base, untoothed or with shallow rounded teeth	Leaves and root bark	Leaves are crushed and the juice is consumed *Decoction	Antioxidant	Not found	[30,53] [54]
10	*Alternanthera sessilis*	Amaranthaceae	Annual or usually perennial herbs, to about 30 cm tall in wetter places; stems about 0.1–1 m long, rooting at the nodes; stem and branches green or purplish, with a narrow line of whitish hairs down each side of the stem and tuft of white hairs in the branch and leaf axils	Entire plant	Fresh plant is crushed with water and juice is given to drink	α-Glucosidase inhibitory effect; antioxidant effect	α-Spinasterol and stigmasterol	[30,55,56]
11	*Allium cepa*	Amaryllidaceae	A perennial herb usually grown as an annual, 15–50 cm high, with red subterranean bulbs, 1.5–2.5 cm in diameter. Leaves: 3–5 to a bulb, hollow, 20–30 cm long, 0.4–0.8 cm broad, terete	Bulb	Fresh bulb or juice of the fresh bulb is consumed	α-Amylase inhibitory effect	S-methyl cysteine sulfoxide	[30,57,58]
12	*Andrographis paniculata*	Acanthaceae	Stem up to 75 cm height. Leaves: ovate-elliptic to elliptic-lanceolate tapering to base, weakly lineolate with cystoliths, glabrous	Entire plant	*Decoction	α-Glucosidase and α-amylase inhibitory activity; insulinomimic activity	Not found	[30,59,60]
13	*Annona squamosa*	Annonaceae	Tree: 5–10 m tall Leaf blade: 10–20 cm long, 2–5 cm wide, lanceolate, acute or obtuse and shortly decurrent at base, gradually long-acuminate at apex, pubescent on both sides	Leaves	*Decoction	Insulinomimic activity; antioxidant activity	Quercetin-3-O-glucoside	[30,61,62]
14	*Azadirachta indica*	Meliaceae	A tall tree with spreading branches, stem and young parts glabrous. Leaves: opposite, pinnately compound, estipulate, crowded; rachis: 15–22.5 cm long	Leaves	Leaves are crushed and the juice is consumed	α-Glucosidase and α-amylase inhibitory activity	Meliacinolin	[63]
15	*Centella asiatica*	Apiaceae	Prostrate stems: 10 cm–1 m long. Leaves: 1–6, clustered on a short shoot at each node, orbicular to reniform in outline, 0.5 to 2 cm long, 1–3 cm broad, margins entire, crenate or dentate	Entire plant	Fresh plant is pounded and the juice is consumed	Antioxidant activity	Several phenolic constituents	[29]
16	*Hibiscus rosa-sinesis*	Malvaceae	Shrubs to 2 m tall, with hairy branchlets; hairs recurved. Stipules: filiform, about 4 mm, caducous; petiole: 1–2 cm, hairy; leaf blade: (6–12) cm × (2.5–6) cm, surfaces nearly glabrous or stellate pilose, with 3 basal veins, broadly cuneate to nearly rounded base, and crenate-serrate margin	Flower	Fresh flower is added to boiling water and kept till it becomes cool consumed as a drink	Antioxidant activity	Not found	[64]
17	*Ipomoea batatas*	Convolvulaceae	Vines; the stem is usually somewhat succulent but sometimes slender and herbaceous; perennial, glabrous or pubescent. Leaves: variable from cordate to ovate, 5–10 cm long, glabrous or pubescent	Leaves	Fresh leaves are pounded and the extract is consumed	Antioxidant activity; insulinomimic activity	Caffeoyldaucic acid and caffeoylquinic acid derivatives; anthocyanins	[65]

*Preparation of the decoction: 60 g of dried crude plant material or 120 g of fresh plant material is boiled in 1920 mL of water until the volume reduces to 240 mL. This preparation is referred to as the decoction which is administered twice daily.

Fig. 1. Selected plants used in Sri Lanka for the treatment of diabetes. The numbers of the images correspond to the sequence of numbers in Table 1.

Most of the active compounds in the above plant materials have been individually analyzed for their antidiabetic mechanism of action.

According to Eliza et al. [33], eramanthin extracted from *C. specisous* acts primarily by stimulating insulin release from pancreatic β cells. The effect has been proven on streptozotocin (STZ)-induced diabetic rats and further they showed that the compound does not have any effect on the insulin level in a healthy control group.

Artonins A and B extracted from *A. heterophyllus* have shown promising 2,2-diphenyl-1-picrylhydrazyl free radical scavenging activity, indicating the antioxidant effects of the extracts. Even though there was evidence of the inhibition of α-glucosidase and α-amylase by the dried crude leaf extract of *A. heterophyllus*, no evidence was found supporting the antidiabetic effect of the purified phytochemicals [45].

Quercetin-3-O-glucoside extracted from *Moringa oleifera* and *A. squamos* demonstrated antioxidant potential when tested with the hypoxanthine–xanthine oxidase assay, confirming its potential antidiabetic effect [46]. Further it has also been able to reduce blood-glucose levels in alloxan-induced diabetic rats [62].

The compounds isolated from *A. carambola* have shown antioxidant activity, but at the same time had toxic effects when tested against *Artemia salina* [51].

Meliacinolin extracted from *A. indica* acts as an antihyperglycemic agent in STZ nicotinamide-induced diabetes mice by reducing the severity of oxidative stress and of hyperglycemia induced by STZ, through the improvement of hyperlipidemia, insulin resistance and antioxidant defense system [63]. No evidence was found for the mechanism of action *in vitro*.

Anthosyanin extracted from *I. batatas* also showed 1,1-diphenyl-2-picrylhydrazyl-free radical scavenging activity, providing evidence of the antioxidant properties of the plant [65].

Major advantages of using plant products for the treatment of diabetes include low cost, abundance and the ability to target more than one mechanism of action with a single therapy. Commonly used food additives with potent hypoglycemic activity can be used in combination therapy with Western medicine for better glycemic control. Furthermore these natural compounds can be used as alternative therapy for patients who do not respond to currently available treatment.

However, major drawbacks include that the herbal medicines are complex mixtures of bioactive entities, with varying degrees of therapeutic effects and that the relative concentrations of chemical constituents of the plant material may vary with season of collection, region of cultivation, growing condition and many more other external and environmental factors. Difficulty in identifying the drug interactions, unknown undesirable side effect, lack of proper standardization of treatment and that synergies in use may lead to toxicity are other significant limitations to incorporating herbal medicines into the Western medical system.

Considering all these factors, ongoing research into these plant materials should focus on clinical trial approaches. The drug inter-

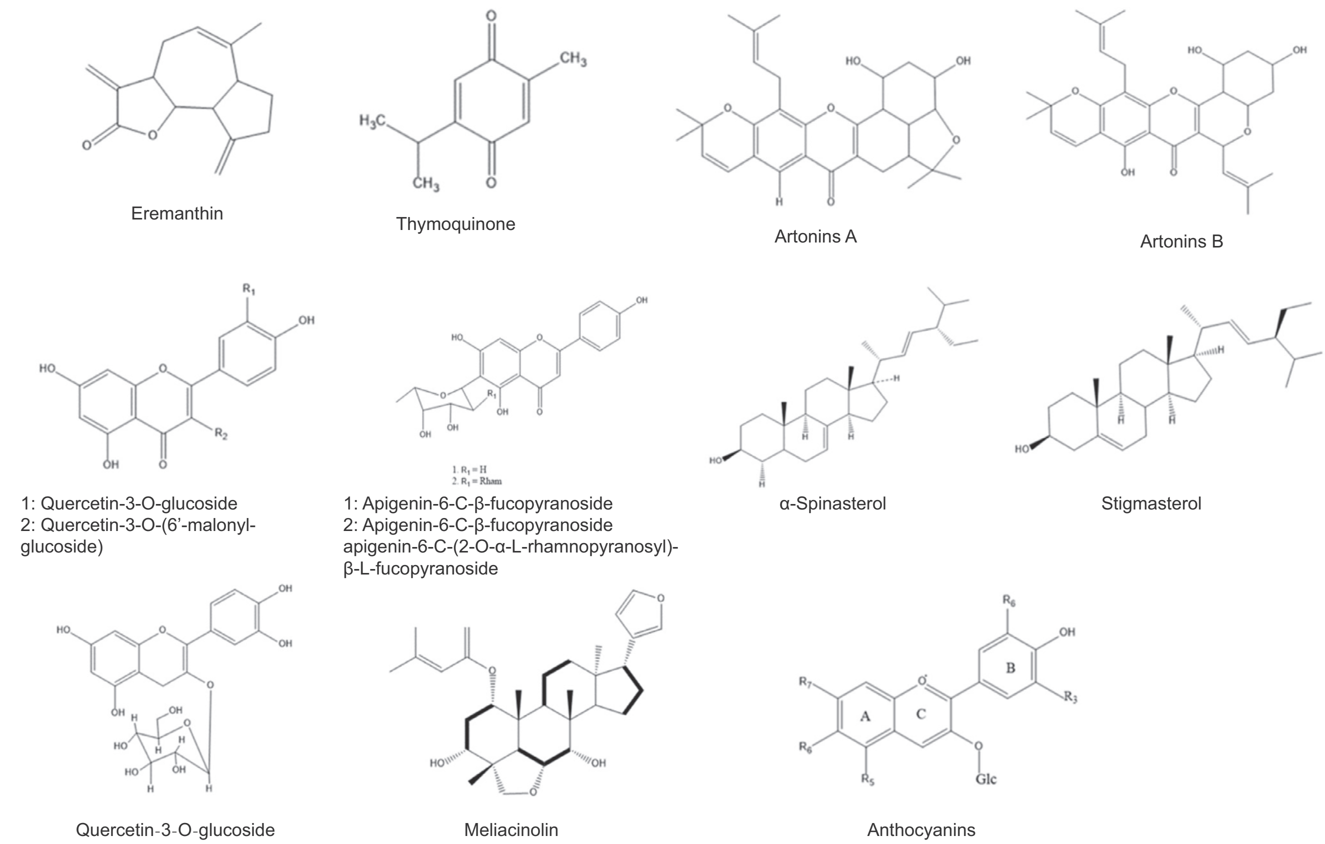

Fig. 2. Isolated chemical compounds with antidiabetic activity.

action with the conventional medications has to be assessed for possible pharmacokinetic and pharmacodynamic changes in those medications in synergistic use.

6. Conclusion

Even though some plants have been isolated as effective for treating diabetes mellitus, their mechanism of action and active phytochemicals have not been well researched, in general. This highlights a current need for researchers to explore the hidden treasures in such plants in order to promote their safe therapeutic use in the treatment of the devastating disease, diabetes mellitus.

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Conflict of interests

The authors declare that there is no conflict of interest regarding publication of this paper.

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