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A review on selected herbal plants as alternative anti-diabetes drugs: chemical compositions, mechanisms of action, and clinical study

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ABSTRACT

Herbal utilization, as an antidiabetes agent, is an interesting topic to find acceptable herbal drugs to decrease blood glucose levels. The aim of this review is to evaluate the potency of selected herbal medicines to reduce blood glucose levels and to identify the chemical compounds responsible for reducing glucose. The mechanisms of action of different herbal medicines used might be also different. The reduction of blood glucose levels by *Aloe vera, Andrographis paniculata, and Trigonella foenum-graecum* through minimum 3 mechanisms of action, such as increased GLP-1 secretion and inhibited amylase, glucosidase, and SGLT 2. While *Andrographis paniculata* has more than 4 mechanisms of action, such as increasing GLP secretion, activating PPAR γ-receptor, and also inhibiting amylase, glucosidase, and SGLT 2 but it did not inhibit DPP 4 in diabetic patients.

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Introduction

Herbal use is an interesting part of the last decade due to many synthetic drugs and raised side effects for long-time use, especially antidiabetes drugs. Several synthetic drug types such as biguanide, sulfonylurea, thiazolidinediones, a-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1), and dopamine-2 agonists, dipeptidyl peptidase 4 (DPP-4), and sodium-glucose cotransporter-2 (SGLT 2) inhibitors have been existed in the Market [1]. However, they will cause side effects including cancer, hepatitis, allergy, etc. for long consumption [2]. As a consequence, because natural medicine is less toxic than synthetic drugs, many people are turning toward it for disease treatment. We used to say, "**Let food be your medicine, and medicine be your food**" [3]. We now understand that natural sources of disease treatment will provide numerous benefits because they are safer to consume.

China is one of the countries that has developed natural drug development, namely traditional china medicine (TCM). Many herbals have been approved in China for antidiabetes such as *Panax ginseng, Momodica charantia, Lagenaria siceraria, and Psidium guajava* [4]. Currently, China has produced more than 30 TCM products known as Yuquan Wan, Xiaokeling Pian, Tangniaoling Pian, etc. [5]. These products contain two or more herbals where they produce synergism activity. Therefore, TCM products significantly affect to reduce diabetes as much as 1.2 folds western drugs

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[6]. The big problem is no standard for diabetes patients to consume TCM [7]. Based on this issue, a review of selected herbals is critical because it will explain everything before we can combine them to create TCM-like products.

Hopefully, the herbs will support or replace the synthetic diabetes drugs that have been recommended. As a result, this review will investigate several potential herbals for diabetic treatment, including active compound types, potency, mechanism of action, and toxicity. These herbal plants have been widely used for diabetic treatment all over the world. The goal of this review is to assess selected herbal plants as future candidates for antidiabetic drug-like TCM.

Phytochemical of selected herbal candidates as an antidiabetic agent

The herbal plants contain several active compounds that are greatly affecting their biological activity including alternative antidiabetic drugs. Secondary metabolites should be reported as a drug discovery from the herb and can be developed in the next research through the synthesis pathway. For example, the synthesis of vitexin derivates becomes new compounds such as vitexin-4'-O-β-glucoside and vitexin-5-O-β-glucoside where both new compounds have better solubility than vitexin [8]. Vitexin is a natural compound that can be isolated from herbal plants including *Anredera cordifolia* [13]. Moreover, the studies related to isolation, purification, and identification of the putative active compounds are important parts of discovering new drugs or lead compound sources that can be expanded in future research [9]. Besides, the active compounds play a significant role and are able to explain their mechanism compared with crude herbal extract because it contains more complex active compounds. Therefore, the mechanism of action that happened will be explained easier based on the pure compound obtained. Figure 1 depicts several metabolite groups that are reported as anti-diabetes agents.

This review showed that the herbal medicines mentioned are potential antidiabetic drugs based on *in-vitro* and *in-vivo* evaluations. Several biological pathways of the selected herbal medicine have been mentioned in Table 1. Some herbal medicines will increase insulin secretion to control blood glucose levels while other herbal medicines inhibit α-glucosidase, DPP IV, etc. These mechanisms of action were significantly affected by the chemical compounds of the herbals. Chemical compounds such as flavonoids and their derivatives are responsible for diabetes treatment via various mechanisms of action [10]. As a result, the metabolite groups depicted in Figure 1 can be used to treat diabetes via a variety of mechanisms of action.

Table 1 demonstrates that each herbal contains dominant chemical groups as secondary metabolites that are responsible for biological activities such as diabetes. However, antidiabetic agents from selected herbals are not only limited to flavonoids and their derivatives. Even, flavonoid derivatives including rutin are less effective due to only inhibiting 52% of α-glucosidase at 250 μg/ml [27, 28]. A lot of active compounds from these herbals affect significantly reducing blood glucose levels that are grouped into triterpenoid groups, phytosterol groups, phenolic groups, and alkaloid groups as shown in Figure 1. However, each putative active compound will lead to the mechanism of action occurring, especially as inhibitory agents of α-amylase, α-glucosidase, PTP 1B, SGLT 2, and also modulatory agents of GLP 1 and insulin secretion.

Novel triterpenoids have been studied and found to have a variety of mechanisms of action, including plasma glucose, plasma insulin/C-peptide, serum lipid markers, sugar metabolism enzymes, glucose oxidation, and insulin signaling molecules [29]. Despite this, phenolic groups have been linked to diabetes prevention in cell, animal, and clinical studies [30]. Based on this review, we can deduce that differences in the active compounds or metabolite group types of the herbs will result in different mechanisms of action.

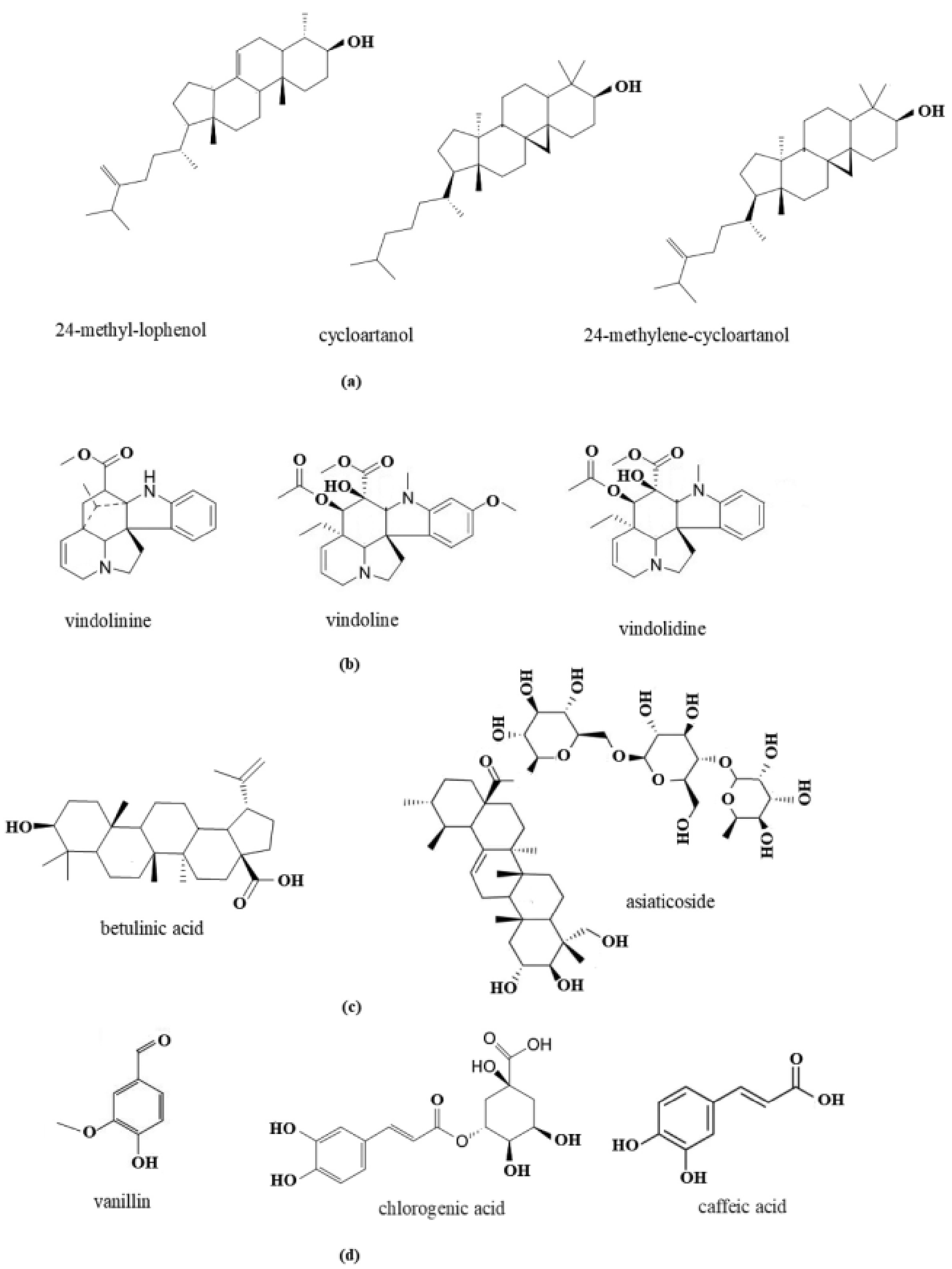

Figure 1. The putative metabolites have been reported as antidiabetes agents from selected herbal plants: a) phytosterol groups; b) alkaloid groups; c) triterpenoid groups; and d) phenolic groups.

Their mechanism of action of selected herbal as antidiabetes

Furthermore, this review explained 11 herbal plants which contain the complex active compounds that lead to their mechanism of action. Several mechanisms of action related to treating diabetes are to improve insulin sensitivity, stimulate insulin secretion, protect pancreatic islets, and even inhibit the intake of intestinal carbohydrates [5]. Generally, anti-diabetic drugs will control blood glucose levels in two ways including action and metabolism. The liver converts

Table 1. The putative active compound types from herbal plants play a significant role in treating diabetes.

Herbal plant sources	The putative active compounds				References
	Chemical compound names	Approaches Techniques used	Testing Evaluation	Biological Activities	
Aloe vera	five phytosterol : Lophenol, 24-methyl-lophenol, 24-ethyl -lophenol, cycloartanol, and 24-methylene-cycloartanol	The isolated active compounds	In-vivo using mice	They can decrease blood glucose levels at long-term effects with decreased levels is approximately 64%, 28%, 47%, 51%, and 55% of control levels, respectively	[11]
Andrographis paniculata	Andrographolide	Isolated active compounds	In-vivo using rats	It decreased blood glucose levels and improved pancreatic organs (islet and beta cells)	[12]
Anredera cordifolia	8-Glucosylapigenin (vitexin)	Molecular docking (in silico)	The isolated compound and glibenclamide interact against the CYP3A4 receptor	The combination of vitexin with glibenclamide can increase binding energy stability up to -4.4 (kcal/ mol). Thus, the addition vitexin increases its potency as anti-diabetes	[13]
		Isolated active compound	In-vitro (α-glucosidase inhibitory activity)	This isolate has IC50 of 20.23 μg/mL	[14]
Catharanthus roseus	4 alkaloids: vindoline, vindolidine, vindolicine and vindolinine	Isolated active compound	In-vitro (increase glucose uptake in β-TC6 and C2C12 skeletal muscle cells and inhibition activity of PTP-1B	Vindolicine is the best alkaloid reported can increase glucose uptake at a dose of 12.5 μg/mL and has IC50 of PTP-1B is 11.6 μg/mL	[15]
Centella asiatica	betulinic acid, centellasapogenol, and methyl brahmate	Molecular docking (in silico)	They inhibited Sodium-glucose co-transporter 2 (SGLT-2)	Strong binding energy and structural stability	[16]
	Asiaticoside	An Isolated active compound	In vivo using albino mice	It can reduce blood glucose levels at a dose of 5.6 mg/ kg BW mice	[17]
Clitoria ternatea	triterpenoids, flavonol glycosides, anthocyanins, and steroids	Phytochemical screening	In vivo using albino mice	it significantly decreases the serum glucose contents of rat	[18]
Cosmos caudatus	Rutin, quercetin 3-O-glucoside, quercetin 3-O-xyloside, quercetin 3-O-arabinofuranoside and quercetin 3-O-rhamnoside	Metabolomic approaches	In vitro (α-glucosidase inhibitory activity)	IC50 of etanolic leaf extract: 12.6–40.9 μg/mL	[19]

(*Continued*)

Table 1. (Continued).

Herbal plant sources	The putative active compounds: Chemical compound names	Approaches Techniques used	Testing Evaluation	Biological Activities	References
Moringa oleifera	anthraquinone, 2-phenylchromenylium (Anthocyanins), and hemlock tannin	In silico Approaches	active binding of active compounds from *Moringa oleifera* with mutated protein of diabetes mellitus	They can interact strongly with targeted protein of diabetes mellitus	[20]
	Quinic acid, Caffeic acid, Chlorogenic acid, Gallic acid, Coumaroylquinic acid, Astragalin, Kaempferol-3-O-rutinoside, Vitexin, Rutin, Quercetin-acetyl-glucoside, Quercetin-malonyl-glucoside, Isoquercetin, Kaempferol acetyl glycoside, and Quercetin	In silico Approaches	Binding Interaction of active compounds with human pancreatic α-amylase	It has minimum docking scores and its binding affinity is high	[10]
	4-hydroxyphenylacetonitrite, fluoropyrazine, methyl-4-hydroxybenzoate, and vanillin	The Isolated compound	In-silico approaches, In Vitro using insulin secretion stimulators, and In vivo using mice and Wistar rats.	They can stimulate insulin secretion (in-vitro), and reduce blood glucose levels in diabetic rats (in vivo). Even, in silico approaches also showed hydrogen interaction with active site residue.	[21]
	Agnucastoside C	The Isolated compound	In vivo using female mice	It can change the serum thyroid hormones, insulin, glucose, different lipids; hepatic lipid peroxidation, and enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase of female mice	[22]
Orthosiphon stamineus	Sinensetin, salvigenin, tetramethylscutellarein, 3,7,4′-tri -O-methylkaempferol, and orthosiphol A	The Isolated compounds	In vitro (α-glucosidase inhibitory activity)	tetramethylscutellarein (3) and d 3,7,4′-tri-O-methyl kaempferol α-glucosidase with IC50 values of 6.34 and 0.75 mM, respectively. While orthosiphol A (5) selectively inhibited intestinal maltase with an IC50 value of 6.54 mM.	[23]
Psidium guajava	lanost-7-en-3β-ol-26-oic acid, anost-7-en-3β, 12β-diol-26-oic acid, lanost-7- en-3β, 12β, 29-triol-26-oic acid, and lanost-7-en-3β-ol-26-oic acid-3β-D-glucopyranoside	The isolated compounds	In-vivo using rats	They significantly decrease blood glucose levels	[24]
	Dihydro-3,3,′4,′5,7 – pentahydroxyflavone glycoside and apigenin 7-O-glucoside	The isolated compounds	In vitro (α-glucosidase inhibitory activity)	-	[25]
Trigonella foenum-graecum	N-linoleoyl-2- amino –butyrolactone (N55)	an isolated compound	In vitro (as a modulatory GLP 1 activity)	It enhances GLP-1 signaling	[26]

PTP-1B: protein tyrosine phosphatase-1B
GLP 1: Glucagon-like Peptide-1

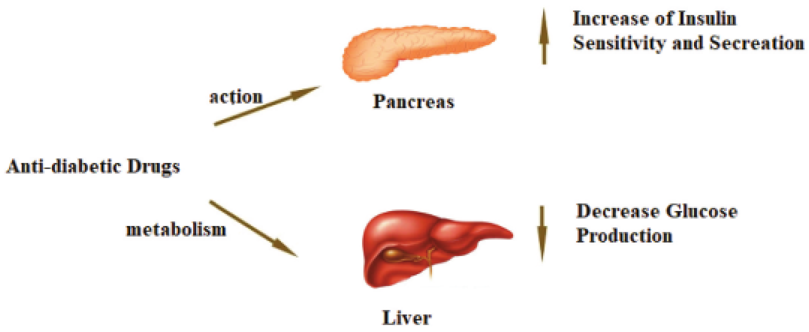

Figure 2. General pathways of mechanism of actions of anti-diabetic drugs.

glycogen to glucose, so that it is an essential organ for regulating the uptake and release of glucose. While the pancreas increases insulin production from ß-cells while decreasing glucagon production from α-cells for controlling blood glucose levels. The illustration of both pathways is given in Figure 2.

Therefore, the mechanism of action of herbal medicine may be more than one mechanism of action (Figure 3). The mechanism of action of the herbal plants sustains the development of herbal use for diabetes medications. However, the combination of herbal use may be improving its potency due to synergistic action may happen [31, 32]. Therefore, the information on the mechanism of actions of herbal plants is an important part to support medication fruitfulness. Reference [32] Zang et al. said that the development of traditional Chinese medicine (TCM) is greatly related to biological activities, including the Jun-Chen-Zuo-Shi formula that can be interpreted based on its biological activities. Furthermore, to ensure the effectiveness of the herbal combination, it can be tested by in-vivo tests and clinical trials on humans.

Figure 3 demonstrates how various herb's mechanisms of action can work together to provide broad effects. These occur as a consequence of the fact that particular various types of potent compounds found in herbs assist in lowering blood sugar levels. Therefore, taking plants instead of synthetic medications may be more advantageous because the chemical compounds in herbs have synergistic effects. The challenging aspect is finding out which substances are responsible as well as where inactive compounds are found. Therefore, herbs can be consumed in larger amounts than synthetic drugs, and implementing their use is difficult to fully understand.

The herbs that prevent the enzymes α-amylase and α-glucosidase from breaking down carbohydrates or oligosaccharides can reduce the quantities of glucose that flow into the bloodstream. Besides, DPP4 inhibitors can avoid GLP-1 from becoming deactivated as well as promote insulin sensitivity and production. A further benefit of SGLT 2 inhibitors is that they prevent glucose readsorption, which could raise blood sugar levels. Even so, increased insulin sensitizers caused by activated PPAR γ-receptors will decrease the amount of glucose produced by the liver. In order to assess these herbs' effectiveness in regulating blood glucose levels, it is crucial to understand how they work metabolically.

Figure 3 shows that all herbal plants act as α-glucosidase and α-amylase inhibitory agents. Herbal plants also have more than two mechanisms of action in reducing blood glucose levels, such as *Aloe vera*, *Andrographis paniculata*, and *Trigonella foenum-graecum*. *Aloe vera* extract will increase insulin secretion, which can control blood glucose levels [33]. Reference [11] Tanaka et al. isolated successfully five phytosterols from this herbal that are potentially reducing blood glucose levels. Furthermore, *Andrographis paniculata* is a herbal candidate for anti-diabetes. This herbal has been reported that it can reduce blood glucose levels through four mechanisms of action (Figure 3). Tarigan et al., [34] said that *Andrographis paniculata* has increased GLP-1 levels but does not inhibit DPP 4 in diabetic patients. One of the potent active compounds of A. *paniculata* as antidiabetes is Andrographolide [12].

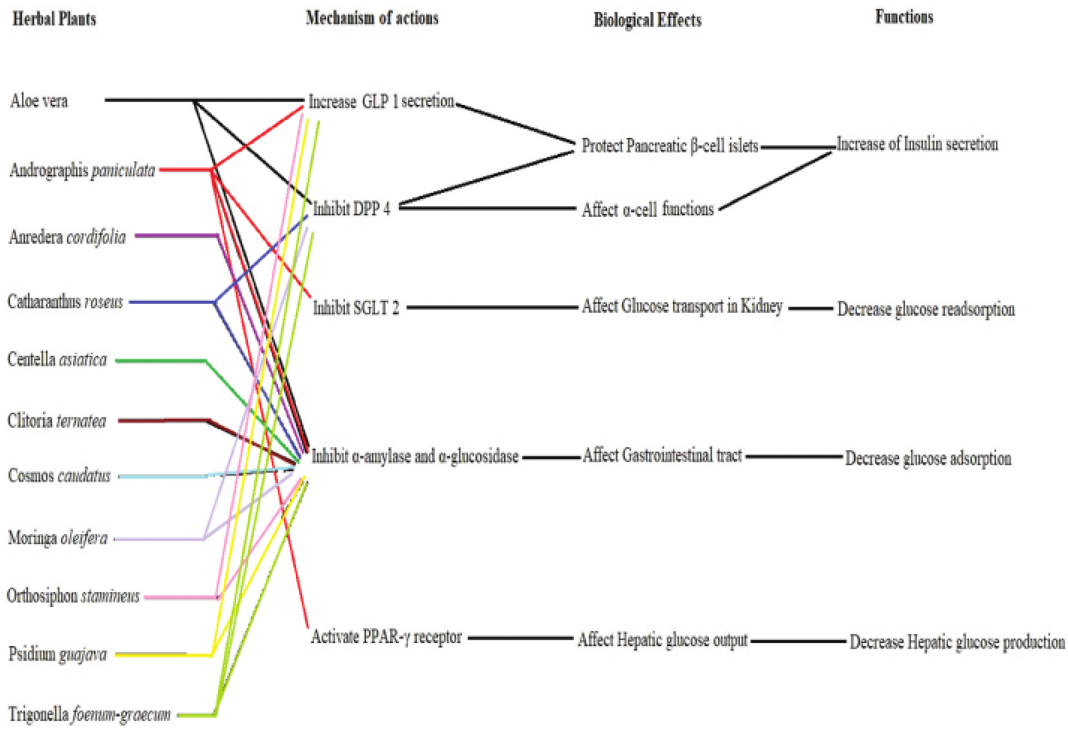

Figure 3. Mechanism of actions from herbal plants in reducing blood glucose levels using in-vitro-based evaluation.

In this review, the last herbal, which contains more than 2 mechanisms of action in reducing blood glucose levels, is *Trigonella foenum-graecum*. One of the isolated active compounds is N-linoleoyl-2-amino – butyrolactone (N55) which can improve GLP-1 excretion [26]. This result was also supported by the clinical studies that *Trigonella foenum-graecum* seed is able to reduce glucose levels in diabetes patients. Any 10 clinical studies explained the beneficial effect of *Trigonella foenum-graecum* seed in diabetes patients [35]. Even, the consumption of *Trigonella foenum-graecum* powder as much of as 25 g can improve lipid metabolism with no adverse effect [36].

Several herbal plants have two mechanisms of action are *Catharanthus roseus*, Moringa *oleifera*, *Orthosiphon stamineus*, and *Psidium guajava*. *Catharanthus roseus* contains several alkaloids that play a significant role in reducing blood glucose levels. Reference [15] Tiong et al. have successfully isolated 4 alkaloids from *Catharanthus roseus* such as vindoline, vindolidine, vindolicine and vindolinine (Table 1). These alkaloids act as antidiabetes agents. Furthermore, several active compounds of Moringa *oleifera* that have a significant effect on diabetes management are coumaroylquinic acid, astragalin, kaempferol-3-O-rutinoside, vitexin, rutin, quercetin-acetyl-glucoside, quercetin-malonyl-glucoside, isoquercetin, kaempferol acetyl glycoside, and quercetin where they have the smaller binding energy of Human pancreatic alpha-amylase than acarbose [21]. This result was supported by the clinical study of the use of *Moringa oleifera* tea as glycemic control for diabetes patients.

For *O. stamineus*, it contains active compounds that interact with peptides including GLP-1 and ghrelin levels will stimulate insulin secretion, which contributes to decreasing blood glucose levels [37]. They can even reduce glucose-6-phosphatase activity and increase glucose-6-phosphate dehydrogenase activity and raise glycogen levels [38]. Reference [39] Ngo and Chua reported that rosmarinic acid is one of the active compounds from O. *stamineus* in controlling diabetes. Another herbal plant is *Psidium guajava*. It has been evaluated by clinical trials in China. Its potency as an alternative drug's antidiabetes due to flavonoid derivatives as the putative active compounds reduce blood glucose levels. Besides, this herbal plant also contains lanost-7-en-3β-ol-26-oic acid, anost-7-en-

3β, 12β-diol-26-oic acid, lanost-7- en-3β, 12β, 29-triol-26-oic acid, and lanost-7-en-3β-ol-26-oic acid-3β-D-glucopyranoside as lanosterol-type triterpenoids groups [24].

This review also reported several herbal plants which were predicted to only prevent diabetes through the inhibition of α-amylase and α-glucosidase activities. They are A. *cardifolia*, C. *caudatus*, C. *asiatica*, and C. *ternatea* (Figure 3). These herbal plants may inhibit blood glucose content through other mechanisms, but in-depth research has not been carried out yet. Therefore, we support that further research can be done in the future so that it can ensure other mechanisms of action in lowering the blood sugar of these herbal plants. However, they have great potential in lowering the blood glucose level of diabetic patients.

Clinical study of the selected herbal plants as an antidiabetic agent

Previous explanations have elaborated that selected herbal plants contributed to reducing blood glucose levels. The selected herbal plants reduced blood glucose levels through one or more mechanisms of action based on in-vitro evaluations. This result depicts that each herbal is responsible to treat diabetes through different mechanisms of action. Previous studies have shown that selected herbals are good candidates as alternative antidiabetes drugs based on *in-vitro* and *in-vivo* evaluations.

Furthermore, the clinical study of the selected herbal medicines can be conducted to ensure their safety, efficacy, and efficiency. However, in-vitro and in-vivo testings are the screening evaluation to choose the potent extracts which will be tested further, in particular clinical study. The clinical studies reported that each of herbal medicines are also decreasing blood glucose levels throughout the different mechanisms of action as in vitro evaluation explained before.

According to the literature review, only *Catharanthus roseus* has not yet been used in clinical studies. Other medicinal plants have been tested on humans to ensure their efficacy. According to Table 2, some herbal remedies have a significant chance of becoming herbal anti-diabetes drugs. The amount of each plant used varies greatly depending on the chemical compounds that are present. This review indicates that between 15 and 100 individuals contributed to these investigations. Unfortunately, this level of evidence remains at 7, with only the use of *Trigonella foenum-graecum* in capsule and extract forms reaching level 2. As a consequence, more clinical studies to ensure the potency of these herbs should be conducted in the

Table 2. The Reported Clinical Study of the Selected Herbal as antidiabetic agents.

		Clinical Studies				
Herbal plants	Herb form	Participants	Study Evidence levels	Parameters	Effects and Doses	References
Aloe vera	*Aloe vera* juice 80%	50 participants (age: 35–60)	Level 7	Blood sugar levels	It can reduce blood glucose levels at least 2 weeks after treatment (twice/day)	[40]
Andrographis paniculata	*Andrographis paniculata* extract	73 participants (age: 18–60)	Level 7	GLP-1, DPP-4 enzyme, Fasting Plasma Insulin, Insulin concentrations measured	It will affect these parameters at a dose of 550 mg extract for 14 days (twice/day)	[41]
Centella asiatica	*Centella asiatica*	43 participants (age: 18–55)	Level 7	HbA1c level, TSS	The reductions of TSS from baseline using 240 mg per day for 1 year and not affect to HbA1c level	[42]
Clitoria ternatea	*Clitoria ternatea* water extract	15 participants (age: 20–40)	Level 7	Plasma glucose, insulin, and uric acid	It significantly decreased plasma glucose at a dose of 1 g or 2 g for 30–60 min after consumption	[43]

(*Continued*)

Table 2. (Continued).

Herbal plants	Herb form	Clinical Studies: Participants	Study Evidence levels	Parameters	Effects and Doses	References
Cosmos caudatus	Fresh leaves	100 participants (age: 30–65)	Level 7	HbA1C, fasting glucose, insulin	the consumption of 15 g of fresh leaves reduced blood glucose levels for 8 weeks	[44]
Moringa oleifera	*Moringa oleifera* tea	103 participants (age: 18–65)	Level 7	blood glucose level	It will be evaluated the change in blood glucose levels at a dose of 4 grams of *Moringa oleifera* tea (twice/day) for 4 weeks	NCT04314258
Orthosiphon stamineus	*Orthosiphon stamineus* extract (NuvastaticTM 1000 mg)	100 participants (age: 18–65)	Level 7	Retinal Thickness	It will be observed thickness of DR patients who consume Nuvastatic products three times per day for 12 months	NCT04552600
Psidium guajava	*Psidium guajava* (PG) leaf extract and capsule of PG fruit	50 participants (mean age: 59)	Level 7	Blood glucose levels	A dose of 500 mg PG leaf extract is less effective compared with metformin, but a capsule of PG (same dose) fruit reduced blood glucose levels in 5 weeks	[45]
Trigonella foenum-graecum	*Trigonella foenum-graecum* extract and capsule form	100 participants (age: 22–55), meta-analysis	Level 2	HbA1c levels, Fasting blood glucose	The consumption of its seed extract in the dose range of 5–25 g and recommended at least 5 g per day in capsule form	[35]

*TSS: total symptom score
DPP-4: dipeptidyl peptidase-4
HbA1C: hemoglobin A1c
DR: Diabetic Retinopathy

future. Therefore, it is a preliminary investigation before an adequate number of participants is collected. Furthermore, Phase 2, Phase 3, as well as Phase 4 clinical studies can be conducted on these herbs as the forthcoming phase of the study. According to Sharwan et al., [46]reported that In-vitro, preclinical, and clinical research, among other methods, are necessary for officially approved herbs. Thus, the herbs used as diabetes antidiabetics in the most recent study were described in this review.

Future recommendation

Selected herbal medicines have been speculated as alternative anti-diabetes drugs. The evaluation of nine plants as herbal medicines has been conducted by clinical trial testing (Table 2). It is a great opportunity for herbal development in the future, especially nutraceutical products. Nutraceuticals are good role in controlling human body health due to they contain high nutrients and pharmaceutical functions. The herbal medicines that have been evaluated through clinical trials increase their potency including safety, efficacy, and efficiency.

We could deduce through this review that the nine herbal remedies mentioned above have lowered diabetes based on a number of factors, including blood glucose levels, HbA1C, TSS, and so forth. However, further investigation is required before using these herbs as diabetes medications. To confirm the effectiveness of these herbs as well as herbal diabetes drugs, additionally, phase 2, phase 3, and phase 4 clinical trials on their use should be carried out. As a direct outcome of this evaluation, future efforts to produce nutraceutical goods will be supported.

Conclusion

The review revealed that the selected herbal medicines had significant potential as potential anti-diabetes drug alternatives. Furthermore, each of these herbs has an original mechanism of action for lowering blood sugar. This is owing to the fundamental fact that each herb's power to work is strongly impacted by the presence of different active compounds. Several plants will decrease blood glucose levels following 4, 3, 2 or 1 mechanism of actions. *Aloe vera*, *Andrographis paniculata*, and *Trigonella foenum-graecum* have a minimum of 3 mechanisms of action such as increased GLP 1 secretion and inhibition amylase, glucosidase, and SGLT 2. While *Andrographis paniculata* has more than 4 mechanisms of action such as increasing GLP secretion, activating PPAR ɣ-receptor, and also inhibit amylase, glucosidase, and SGLT 2 but it did not inhibit DPP 4 in diabetic patients. There is a substantial chance that a lot of mechanisms of action occur, which will boost the impact of herbal medicines in lowering blood sugar.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Author contributions

MA: conceptualization, Data processing, writing-original draft preparation, editing, revising the manuscript and funding acquisition; IJ: supervision; AK: supervision; QUA: supervision; NUR: supervision and revising the manuscript, YDA: supervision, all authors approved the final version of the manuscript.

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