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Phytotherapy for diabetes mellitus; A review of Middle Eastern and North African folk medicinal plants

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ABSTRACT

Diabetes mellitus (DM) is considered as one of the most common metabolic disorders affecting huge number of people worldwide. Despite the availability of large numbers of drugs in the market to treat the disease, there is still a need for new sources to deal with the problem and avoid side effects. In the pursuit of discovering safer and more effective anti-diabetic drugs, herbal and folk medicine drugs from regions all over the world have captured researchers' interest. Middle Eastern and North African medicinal plants contain a variety of pharmacologically active components that have shown to possess promising anti-diabetic potential. However, few data have been reported about medicinal plants from these regions in comparison to plants from other regions. Anti-diabetic medicinal plants from the MENA (the Middle East and North Africa) region, their role in controlling DM, and suggested mechanisms for the anti-diabetic activity of some medicinal plants are discussed in this review. Many of these plants have not been fully investigated and characterized, yet they have great potential for further development as anti-diabetic drugs.

Implication for health policy/practice/research/medical education:
This review provides up to date information on anti-diabetic medicinal plants from the Middle East and North Africa regions, many of which have not been fully investigated. This review will create a wide interest in these plants as potentially safe and effective anti-diabetic drugs for humans use in future.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder affecting people worldwide. According to the World Health Organization, there are currently 220 million people with type 2 DM, with expectations to increase to more than 365 million by 2030. The highest increase in disease incidence is currently in undeveloped countries in Africa and Asia and herbal medicines are mostly investigated and used for this problem in these regions (1-4).

Type 1 diabetes is insulin-dependent, while type 2 or non-insulin dependent DM is treated with oral anti-diabetic medications (4,5). Drugs used to treat type 2 diabetes are not without limitations (6); for example, Metformin and Glucagon-like peptide-1 agonists are associated with gastrointestinal distress (6). Sulfonylureas usually cause hypoglycemia and weight gain, while Pioglitazone may increase the possibility of developing bladder cancer and other disorders, such as edema, heart failure, weight gain, and distal bone fractures in postmenopausal women (6), in addition to the high cost of these medications. Therefore, patients seek other methods of treatment.

In low- and middle-income countries, patients rely on folk medicine as a cheaper alternative to modern pharmaceuticals. Phytomedicines or plant-based remedies are used worldwide to treat diabetes and other diseases. Many locally grown herbs have shown significant anti-diabetic effects in many countries (7,8). Their main advantages are the low cost and lower levels of adverse effects and their ability to control blood glucose levels. Therefore, delaying the development of diabetic complications. Many of these herbs enhance insulin release, boost glucose uptake by muscle or adipose tissues,

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and reduce glucose absorption from the intestine and glucose yielding from the liver (7,8).

Historically, plant extracts were prepared and used either orally, topically, or by vapor inhalation for managing diseases (7,8). The Ancient Egyptians were the first to investigate the medicinal uses of castor oil, wine, opium, mints, and beer (7). In recent years, there has been an increasing interest in investigating the anti-diabetic effects of many medicinal plants, due to their wealth of biologically active material. This review aims to highlight the anti-diabetic effects of traditional plants cultivated in the Middle East and North Africa (MENA) region that has been recently used in research.

Methods

A comprehensive search using terms; Diabetes, phytotherapy, herbal medicine, folk medicine, in vivo, in vitro, and clinical trials yielded close to 20000 results spanning the period 1990 to 2020. The majority of the data available used plant extracts either in vitro or in vivo, with a minimal number (<1%) of clinical trials using plant-based therapy present in the literature. We selected mainly plants cultivated in the MENA as the primary focus for our review.

Phytoconstituents and their mechanisms of action

Plant extracts exert their function due to the presence of a wide range of phytoconstituents or chemical compounds, each with a specific mechanism in reducing blood glucose or restoring it to normal levels (9). These compounds range from alkaloids, carbohydrates, anthranoids, flavonoids, saponins, amino acids, peptidoglycans, polyphenols, glycosides to vitamins, minerals, and inorganic compounds. Each constituent works on a specific metabolic pathway (9).

Among the most common phytoconstituents in plants are alkaloids, which are nitrogen-containing chemical compounds with a wide range of therapeutic potential. Many alkaloids exert their hypoglycemic activity as a result of having alpha-glucosidase (GLA) inhibiting activity (10). GLA catalyzes the cleavage of glucose from disaccharides and oligosaccharides. This inhibition will delay the absorption time of glucose by slowing the breakdown of starch in the small intestine so that glucose can slowly enter the bloodstream. Another alkaloid, allyl propyl disulfide from *Allium sativum* exerts its hypoglycemic effect through affecting glycogen synthesis (11). Mostly, this happens as a result of inhibiting lactate dehydrogenase enzyme. The enzyme catalyzes the conversion of pyruvate into lactate. Carbohydrates like pectin, pectin fibers, mucilaginous fibers and guar gum from *Trigonella foenum graecum*, as well as glucomannan, caryophyllene, cellulose, and mannose from *Aloe vera,* affect insulin secretion, absorption, and digestion of carbohydrates (12). Anthranoid compounds such as chrysophanic acid and cinnamic acid from *Aloe vera* possibly enhance insulin secretion and synthesis. C-glycosides from *Trigonella foenum graecum* lower glucose levels by targeting carbohydrate metabolism and glucose transport (13).

Flavonoids are present in a wide range of plants and are considered poly-hydroxy polyphenolic compounds (14). Flavonoids such as apigenin, quercitrin, quercetin, rutin, 7-O-glucoside, and naringenin from *Camellia sinensis* aid the restoration of pancreatic β-cells and enhance the secretion of insulin (14). Epigallocatechin gallate, epigallocatechin, epicatechin, catechin and quercetin from *Camellia sinensis* and *Punica granatum* have free radical scavenging and insulinemic activity (14,15). Also, citrus bioflavonoids like hesperidin and naringin from *Camellia sinensis* target glycolysis, glycogen synthesis, and gluconeogenesis. Some peptidoglycans like Fenugreekine from *Trigonella foenum graecum* and glucosamines from *Aloe vera* are involved in glucose transport, carbohydrate digestion, and absorption (16). Sotolon and trigonelline extracted from *Trigonella foenum graecum* restore β cells of the pancreas and enhance insulin secretion (16). Curcumin, turmerone, zingiberene, and germacrone from *Curcuma longa* also improve the metabolism of glucose.

Vitamins like A and E present in a range of plants might help in controlling glucose concentration (17). Minerals such as zinc from many plants like, for example, *Aloe vera* improves insulin sensitivity when present in high serum levels (18). Amino acids and carboxylic acid derivatives are among the phytoconstituents of medicinal value in diabetes. For example, leucine, isoleucine, and alanine from *Aloe vera* stimulate insulin secretion. Also, ferulic acid extracted from *Curcuma longa* boosts free radical scavenging activity and the secretion of insulin (19).

MENA region anti-diabetic medicinal plants

A map of the plants cultivated in the MENA region is shown in Figure 1. A distinction between the geographic locations is shown on the map. Below we summarize the most common anti-diabetic medicinal plants cultivated and used in the region together with the most recent reported data on *in vitro* and *in vivo* experimental models of DM in Table 1 (Middle East) and Table 2 (North Africa). Clinical studies of Middle Eastern and North African anti-diabetic medicinal plants are shown in Table 3.

Limitations of using anti-diabetic Middle Eastern and North African plants

Despite the presence of previous research about many medicinal plants from both regions supporting their anti-diabetic effectiveness, some limitations might prevent the proper exploitation of these plants. Lack of standardization might be on the top of the main challenges that hinder the progress of utilizing the regions' medicinal plants. Variations in doses, anti-diabetic parameters, and

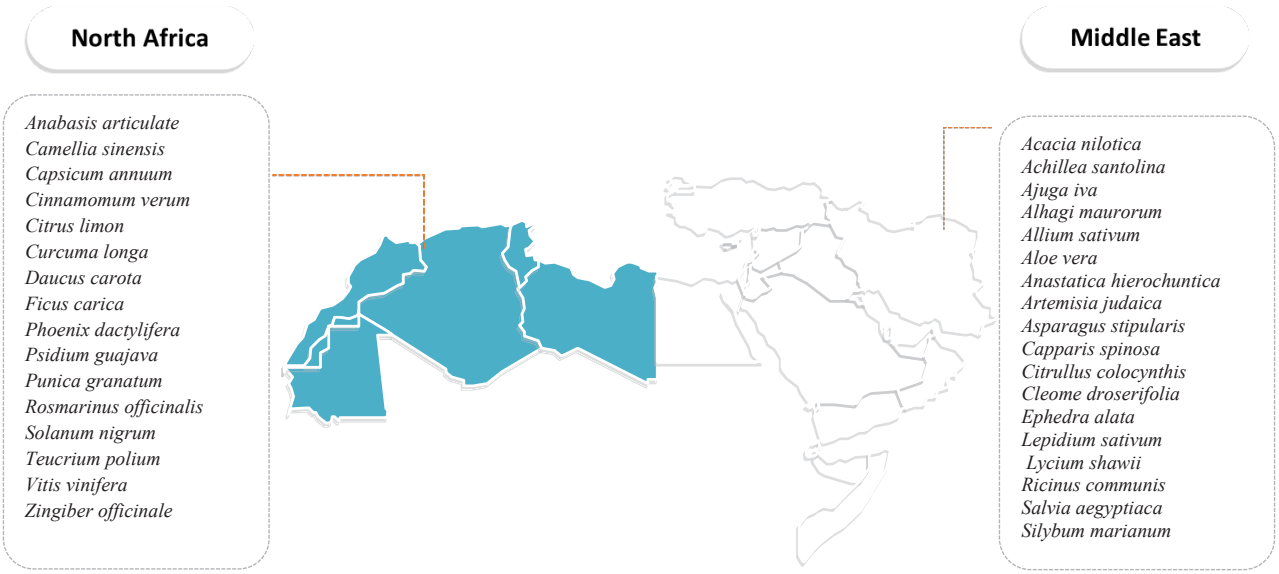

Figure 1. Map showing MENA region anti-diabetic medicinal plants.

duration of therapy make it challenging to determine the medicinal plant with the best reported anti-diabetic effect (20). Moreover, previous reports demonstrated that lack of data exchange among traditional herbal practitioners and between practitioners and researches might represent a threat in utilizing these plants (7). Another challenge facing the utilization of anti-diabetic plants is the continuous destruction of the plants' natural habitat as a result of climate as well as environmental changes leaving many endangered species facing the possibility of extinction in the coming few years (7).

Discussion and future perspectives

Plant-derived products in the global market are provided mainly from either Chinese, Indian, and Western plants. In comparison to plants from other regions, like China or India, medicinal plants from the MENA region have never been adequately investigated, explored, evaluated, or exploited. Extensive research is needed to fill the gap in information concerning safety, toxicity, contamination, possible interaction with other synthetic drugs, and proper dosage (8,20,21). Chinese traditional medicine is successfully promoted via a science-based approach. The great effort and financial support that has been put by China was evident by 3563 extracts, 64 715 compositions, and 130 kinds of Chinese herbs-derived drugs under development. Other countries and or regions could adopt this successful approach in utilizing and promoting traditional medicine to take advantage of their herbal heritage.

This review provides a summary of the anti-diabetic role of some typical Middle Eastern and North African medicinal plants through previous experiments done *in vitro, in vivo,* and clinical trials. From the collected data, medicinal plants from both regions not only hold a remarkable hypoglycemic potential but also help to delay the development and progression of complications through their antioxidant, hepatoprotective, renal-protective, and anti-hyperlipidemic effects.

Most *In vitro* studies investigated the effects of plants on the enzymes; Alpha-amylase (ALA) and GLA. The inhibition of ALA activity, together with GLA, is considered to be a successful strategy for the management of diabetes. Both ALA, which breaks down long-chain carbohydrates and GLA, which catalyzes glucose cleavage from disaccharide, is effective in delaying glucose absorption (22). In our review, *in vitro* GLA and ALA inhibition were consistent with exhibiting hypoglycemic effects *in vivo* in almost all plants included. However, plants like *A. santolina* and *T. polium*, did not inhibit GLA and ALA *in vitro,* although showing an anti-diabetic effect *in vivo*. It can be suggested that they exert their hypoglycemic effect by mechanisms other than lowering these enzymes. Time and money-saving computational chemistry tools like molecular modeling and molecular docking allow for the prediction of molecule's inhibition actions of enzymes. For example, molecules from *Rosemary* and *Salvia* can inhibit the dipeptidyl peptidase 4 (DDP4) enzyme, which is involved in the treatment of type 2 DM (23).

Animal studies in this review investigated an array of parameters to address the anti-diabetic potential of medicinal plants. Improving these parameters is essential to demonstrate efficacy. Together with fasting blood glucose (FBG) and serum insulin levels, liver parameters like alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (γGT) were used to estimate hepatocyte injury. It is suggested that hyperglycemia promotes the accumulation

Table 1. Summary of in vitro, in vivo animal studies showing the anti-diabetic effect of plants cultivated in the Middle East region

Plant name	Model used	Extract and plant part	Treatment	Outcome	Reference
Acacia *(Vachellia) nilotica* L. (Babul, or gum Arabic tree)	*In vivo* STZ- diabetic rats	Aqueous and methanolic extracts of the leaves	300 mg/kg/d PO for 3 weeks	Decrease (↓) FBG, platelet aggregation, TG Increase (↑) serum insulin	(26, 27)
	In vivo (Alloxan-diabetic mice)	Aqueous extract of the stem bark	50, 100, 200, 300 mg/kg/d (either PO or IP) for 1 month	↓ FBG, ALT, AST, ALA and ALP ↑ CRTN, BIL and GTP IP route more effective (>) than PO route.	(28-31)
	In vitro	Methanolic extract of the seeds	-	↓ AIA, GLA, FRAP ↓ ß-carotene degradation, DPPH radical scavenging activity	
Achillea santolina L.	*In vitro*	Aqueous extract of the aerial parts	-	No effect (X): ALA and GLA	(32)
	In vivo		125, 250 and 500 mg/kg PO for 130 min.	↓ overall glycemic excursion	
	In vivo (STZ- diabetic rats)	Aqueous extract of the leaves	150 and 250 mg/kg/d PO as single dose and for 30 days	↓ FBG	(33)
Ajuga iva L.	*In vivo* (Alloxan-diabetic rats)	Aqueous extract of the leaves	10, 20 mg/kg PO for 15 days	↓ FBG, BUN, CRTN, TG, and TC ↑ Serum insulin, SOD, GPx, CAT, PR	(34)
		Aqueous extract of the aerial parts	100, 200, and 300 mg/kg PO for 15 days	↓ FBG, TG, and TC	(35)
Alhagi maurorum Medik (Camel thorn plant)	*In vivo* (STZ- diabetic rats)	Aqueous and ethanolic extract of the aerial parts	300 mg/kg PO for 4 weeks	↓ FBG, TG, TC, LDL-C, VLDL-C, ALT, AST, BIL, MDA, GR ↑ SOD, GPx, GST X Serum insulin	(36)
Allium sativum L. (Garlic)	*In vivo* (STZ- diabetic rats)	Ethanolic extract of the bulb	0.1, 0.25 and 0.5 g/kg/d PO for 14 days	↓ FBG, TC, TG, Urea, Uric acid, CRTN, ALT, and AST ↑ Serum insulin	(37)
		Aged garlic extract	100, 300 and 600 mg/kg/d IP for 8 weeks	↓ FBG, TG, TC, Uric acid, glycosylated-Hb, and MDA ↑ CAT, SOD	(38)
Aloe vera L. (Brum. f.)	*In vivo* (STZ- diabetic rats)	Aqueous extract of the leaves	300 mg/kg/d PO for 3 weeks	↓ FBG ↑ Serum insulin Improve pancreatic β-cell function	(39)
Anastatica hierochuntica L. (Kaff Maryam)	*In vivo* (Alloxan-diabetic rabbits	Methanolic extract of the whole plant	100 mg/kg/d PO for 4 weeks	↓ FBG, TG, TC, LDL-C, VLDL-C, ALT, AST, and ALP ↑ SOD and GPx	(40)
Artemisia Judaica L. (Wormwood or sagebrush)	*In vivo* (Alloxan-diabetic rats	Aqueous and ethanolic extracts of the aerial parts	Aqueous extract 250 & 500 mg/kg/d PO. Ethanolic extract 500 and 1000 mg/kg/d PO, for 2 months	↓ FBG and TG X TC	(41)
Asparagus stipularis L. *(*Forssk*)* (Asparagus)	*In vivo* (High-fructose diet)	Aqueous extract of the dry shoot	100 mg/kg/d, PO for 4 weeks.	↓ FBG, AST, ALT, ALP, BIL, TC, and TG ↑ HDL-C	(42)
Capparis spinosa L. (Caper bush)	*In vivo* (STZ-induced diabetic rats)	Aqueous extract of the fruit	20 mg/kg/d, PO for 15 days	↓ FBG	(43)

Table 1. Continued

Plant name	Model used	Extract and plant part	Treatment	Outcome	Reference
Citrullus Colocynthis L. (Schrad) (Bitter Apple)	*In vivo* (STZ-induced diabetic rats)	Petroleum ether extract of the fruit	300 and 500 mg/kg/d PO for 14 days	↓ FBG ↓ TBARS	(44-48)
	In vivo (Alloxan-diabetic rats	Aqueous extract of the leaves	250 & 500 mg/kg/d PO for 60 days	↓ FBG, Gly-Hb, G6P, and FBPase ↑ Liver hexokinase	
Cleome droserifolia L. (Spider flower)	*In vivo* (Alloxan-diabetic rats	Methanolic extract of the stem and the leaves	310 mg/kg/d PO for 30 days	↓ FBG, TG, TC, LDL-C, AST, and ALT, Urea, and CRTN ↑ Serum insulin and HLDL-C	(49, 50)
Ephedra alata Decne	*In vivo* (Alloxan-diabetic rats	Aqueous extract of the aerial parts	100, 200, and 300 mg/kg/d PO for 28 days	↓ FBG, TG, TC, LDL-C, amylase, lipase, MDA and PC ↑ HLDL-C, SOD, CAT, and GPx	(51)
Lepidium Sativum L. (Garden Cress)	*In vivo* (STZ- diabetic rats)	Aqueous extract of the seeds	20 mg/kg/d PO as acute (single dose) and chronic treatment (for 15 days)	↓ FBG in acute and chronic treatment X Serum insulin	(52)
Lycium shawii Roem. & Schult. (Desert thorn)	*In vivo* (STZ- diabetic rats)	Ethanolic extract (80%) of the aerial parts	500 mg/kg/d PO and IP	↓ FBG	(53, 54)
Salvia aegyptiaca L. (Egyptian sage)	*In vivo* (STZ- diabetic rats)	Methanolic and hydroethanolic extracts of the whole plant	500, 1000, 1500, and 2000 mg/kg/d PO for 14 days	↓ FBG, TG, TC, LDL-C, VLDL-C, AST, ALT, ALP ↑ HLDL-C Improve the appearance of pancreatic islets histologically	(55)
	Computational (molecular docking)	-	-	↓ Dipeptidyl peptidase 4 (DPP-4) enzyme	(23)
Silybum marianum (L.) *Gaertn.* (Milk thistle)	*In vivo* (STZ- diabetic rats)	Aqueous extract of the aerial parts	20 mg/kg/d PO for 15 days	↓ FBG X Serum insulin	(56)

Abbreviations: 2, 2-Diphenyl-1-picrylhydrazyl (DPPH), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Alpha-amylase (ALA), Alpha-glucosidase (GLA), Blood urea Nitrogen (BUN), and Creatinine (CRTN), total Bilirubin (BIL), Dipeptidyl peptidase 4 (DPP-4), Fasting blood glucose (FBG), Ferric reducing/antioxidant power (FRAP), Glutamyl transpeptidase (GTP), Glutathione (GSH), Glutathione peroxidase (GPx), Glutathione reductase (GR), Glutathione-S-transferase (GST), intraperitoneal (IP), Low-density lipoprotein-cholesterol (LDL-C), Malondialdehyde (MDA), oral (PO), Streptozocin (STZ), Super oxide dismutase (SOD), Total protein (PR), Triglycerides (TG), Total Cholesterol (TC), Thiobarbituric acid reactive substances (TBARS), Very low-density lipoprotein-cholesterol (VLDL-C).
↓: decrease, ↑: increase, X: no effect, >: more effective.

Table 2. Summary of *in vitro*, *in vivo* animal studies showing the anti-diabetic effect of plants that are cultivated in the North African region

Plant Name	Model used	Plant part & extract preparation	Treatment	Outcome	References
Anabasis articulata (Forssk.)	*In vivo,* STZ-induced diabetic rats	Ethanolic and petroleum ether extract of the aerial parts	400 mg/kg/d PO for 1 month	Decrease (↓) FBG, cortisol, and TNF-α Increase (↑) Serum insulin and α- fetoprotein	(57)
Camellia sinensis (L.) *Kuntze* (tea shrub)	*In vivo* (STZ-induced diabetic rats)	Ethanolic extract of the leaves	100, 200 mg/Kg PO for 4 weeks	↓ FBG, serum and hepatic MDA; ↑ TAC	(58)
Capsicum annuum L. (Peppers)	*In vitro*	Aqueous extract of the leaves	-	↓ ALA and GLA	(59)
	In vivo (STZ-induced diabetic rats)		100, 200 and 300 mg/kg PO	↓ FBG	
	In vivo (STZ-induced diabetic rats)	Ethanolic extract of the fruit	300 mg/kg/d PO for 4 weeks	↓ FBG, ALT, ALP, Urea, CRTN and CKMB and HOMA-IR ↑ Serum insulin and ↑ HOMA-β	(60)
Cinnamomum Verum J.Presl (Cinnamon)	*In vivo* (Alloxan-induced diabetic rat models)	Aqueous extract of the bark	200, 400, 600 and 1200 mg/kg/d PO for 1 month	↓ FBG	(61)
Citrus limon (L.) Osbeck (Lemon)	*In vivo* (Alloxan-induced diabetic rat models)	Hexane extract of the peel	10 mg/kg/d PO for 4 days	↓ FBG; ↑ Serum insulin	(62)
	In vitro	Essential oil of the peel obtained by hydrodistillation	-	↓ ALA and GLA	(63)
	In vivo (Alloxan-induced diabetic rat models)	Aqueous extract of the peel	100,200,300 mg/kg/d PO for 14 days	↓ FBG	(64)
Curcuma longa L. (Turmeric)	*In vivo* (STZ- induced diabetic rats)	Methanolic extract of the rhizomes	100 mg/kg twice weekly, 250 mg/kg twice weekly, 500 mg/kg/d PO	↓ FBG, CRTN ↑ Serum uric acid. Low dose improved ALT, AST, High dose and PO: ↑ ALT & AST. Islet cell and renal tissue protection. Limited protection of Liver tissue.	(65, 66)
	In vitro	Methanolic extract of the rhizomes (Comparing the effects of the 3 Curcuminoids (BDMC, Curcumin and DMC)	-	↓GLA (BDMC > Curcumin > DMC)	(67)
Daucus carota L. (Wild carrot)	*In vivo* (STZ- induced diabetic rats)	Methanolic extract of the seeds	100, 200 and 300 mg/kg/d PO for 6 days	↓ FBG; Serum insulin	(68)
Ficus carica L. (Fig)	*In vivo* (STZ-induced diabetic rats)	Aqueous extract of the stem bark	500 mg/kg/d PO for 21 days	↓ FBG, TG, and TC, LDL-C, and VLDL-C ↑ Serum insulin and HDL-C	(69)
	In vivo (High glucose diet induced-diabetic rats)	Aqueous extract of the leaf, peel, and pulp	50 and 100 mg/kg/d for 56 days	↓ FBG; ↑ Serum insulin	(70)
Phoenix dactylifera L. (Date)	*In vivo* (Alloxan-induced diabetic mice)	Aqueous and Ethanolic extracts of the leaves	20 mg/kg/d PO for 28 days	↓ FBG	(71)
Psidium guajava L. (Guava)	*In vivo* (High fat diet-induced diabetic mice)	Ethanolic extract of guava leaves	5 mg/kg daily by oral gavage for 7 weeks	↓ FBG, TG, TC, LDL: HDL ratio and HOMA-IR X LDL-C and weight gain ↑ Endothelial functions	(72)
Punica granatum L. (Pomegranate)	*In vivo* (Alloxan-induced diabetic rats)	No extract (crude husk powder was used)	1000 mg/kg/d PO for 10 days	↓ FBG, Hb content and HDL-C ↓ TG, TC, LDL-C, VLDL-C, and Gly-Hb	(73)
	In vivo (STZ-induced diabetic rats)	Aqueous and ethanolic extracts of the flower	200 and 400 mg/kg/d PO for 1 month	↓ FBG, TG, TC, LDL-C, VLDL-C, Gly-Hb, TBARS and G6P ↑ SOD, GPx and CAT	(74)

Table 2. Continued

Plant Name	Model used	Plant part & extract preparation	Treatment	Outcome	References
Rosmarinus officinalis (Salvia rosmarinus Spenn.*)* (Rosemary)	*In vivo* (STZ-induced diabetic rats)	Aqueous extract of the leaves	200 mg/kg/d PO for 21 days	↓ FBG, TG, and TC ↑ TAC, amylase, and TP	(75)
	Computational (molecular docking)	-	-	↓ DPP-4 enzyme	(23)
Solanum nigrum L. (Black nightshade)	*In vivo* Normal albino rats	Ethanolic extract of the whole plant except the roots	250 mg/kg/d PO for 1 week	↓ FBG	(76)
	In vivo (Alloxan-diabetic rats)	Silymarin (50 g/mg) solution	40 mg/kg/d P.O for 6 weeks	↓ FBG, Gly-Hb, and LPO Improve the appearance of pancreatic islets histologically	(76)
	In vivo (Alloxan-diabetic guinea pigs	Aqueous extract of the leaves	200 mg/kg/d PO for 28 days	↓ FBG	(77)
Teucrium polium L. (Golden germander)	*In vivo* (STZ-induced diabetic rats)	Aqueous extract of the aerial parts	500 mg/kg/d PO for 6 weeks	↓ FBG; ↑ Serum insulin	(78)
	In vitro	Aqueous extract of the aerial parts	-	X ALA and GLA	(32)
	In vivo (Starch-induced diabetic rats)		125, 250, and 500 mg/kg PO for 130 min.	X Overall glycemic excursions ↓ FBG 45min post starch administration	
	In vivo (Normoglycemic rats	Aqueous extract of the aerial parts	100 mg/kg/d for 210 min	↓ FBG at different 30, 60, 90 120, 180, and 210 min.	(25)
Vitis vinifera L. (Grape vine)	*In vivo* (STZ-induced diabetic rats)	Aqueous extract of the leaves	250, 500 mg/kg PO for 14 days	↓ FBG, body weight, and MDA ↑ GSH	(79)
	In vivo (Alloxan-induced diabetic rats)	Aqueous extract of grape skin	200 mg/kg/d PO for 19 days	↓ FBG and insulin resistance, antioxidant effect ↑ insulin-signaling cascade	(80)
	In vitro	Gallic acid, catechin, epicatechin, coumaric acid, ferulic acid, caffeic acid, syringic acid, kaempferol, quercetin, rutin, and *trans*-resveratrol were purchased	-	↓ Glycogen phosphorylase (Quercetin was most effective)	(81)
Zingiber officinale Roscoe (ginger)	*In vitro*	Ethyl acetate extract of the root	-	↓ ALA and GLA	(82)
	In vivo (Alloxan-induced diabetic rats)	Aqueous extract of the root	500 mg/kg/d PO for 6 weeks	↓ FBG	(83)
	In vitro	Ethyl acetate extract of the rhizomes	-	↓ LDL oxidation; ↑ Glucose uptake	(84)

Abbreviations; 2, 2-Diphenyl-1-picrylhydrazyl (DPPH), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Alpha-amylase (ALA), Alpha-glucosidase (GLA), Blood urea Nitrogen (BUN), and Creatinine (CRTN), total Bilirubin (BIL), decrease (↓), Dipeptidyl peptidase 4 (DPP-4), Fasting blood glucose (FBG), Ferric reducing/antioxidant power (FRAP), Glutamyl transpeptidase (GTP), Glutathione (GSH), Glutathione peroxidase (GPx), Glutathione reductase (GR), Glutathione-S-transferase (GST), Increase (↑), intraperitoneal (IP), Low-density lipoprotein-cholesterol (LDL-C), Malondialdehyde (MDA), more effective (>), No effect (X), oral (PO), Streptozocin (STZ), Super oxide dismutase (SOD), Total protein (PR), Triglycerides (TG), Total Cholesterol (TC), Thiobarbituric acid reactive substances (TBARS), Very low-density lipoprotein-cholesterol (VLDL-C), homeostatic model assessment of insulin resistance (HOMA-IR)
↓: decrease, ↑: increase, X: no effect.

Table 3. Summary of clinical trials showing the anti-diabetic potential of plants cultivated in the Middle East and North Africa regions

Plant name	Model used	Number of patients	Preparation	Treatment	Outcome	Reference
Allium sativum L. (Garlic)	Type 2 diabetic patients	210	Fruit extract tablets	300, 600, 900, 1200, and 1500 mg PO per day for 24 days	↓ FBG, and Gly-Hb	(85)
Aloe vera L. *(Brum. f.)*	Hyperlipidemic type 2 diabetic patients	30	Aloe vera gel capsules	300 mg PO twice /day for 8 weeks	↓ FBG, TC, LDL-C, and Gly-Hb	(86)
	Obese prediabetic and early non-treated diabetic patients	132		294 mg twice/ day PO per day for 8 weeks	↓ FBG, serum insulin, body weight, and body fat mass	(87)
	Pre-diabetic patients	72		300 and 500 mg PO twice/day for 8 weeks	↓ FBG, TC, LDL-C, and Gly-Hb ↑ HDL-C	(88)
Capparis spinosa Linnaeus (Caper bush)	Type 2 diabetic patients	54	Fruit extract capsules	400 mg caper fruit extract thrice/day for 2 months	↓ FBG and TG X TC, LDL, HDL, ALT, AST CRTN, ALP and BUN	(89)
Cinnamomum verum J.Presl (Cinnamon)	Type 2 diabetic patients	140	Cinnamon bark capsules	500 mg capsules twice/day for 3 months	↓ FBG, BMI, TG, TC, LDL-C, Gly-Hb, and HOMA- IR (insulin resistance) ↑ HDL-C	(90)
Curcuma longa L. (Turmeric)	Healthy subjects	14	Curcuma longa rhizome capsules	6000 mg divided into 15 capsules once	X FBS and glycemic index ↑ Serum insulin	(91)
Punica Granatum L. (Pomegranate)	Type 2 diabetic patients	85	Pomegranate juice	1.5 mL/kg/d for 3 h	↓ FBG and HOMA-IR (insulin resistance) ↑ HOMA-β (β-cell function)	(92)
Silybum marianum (L.) Gaertn.(Milk thistle)	Type 2 diabetic patients	51	Seed extract tablets	1-200 mg 3 times per day for 4 months	↓ FBG, TG, TC, LDL, ALT, AST, and Gly-Hb	(93)
	Type 2 diabetic patients	40		140 mg thrice/day for 45 days	↓ FBG, TG, TC, HDL/LDL, HOMA-IR (insulin resistance)	(94)
Zingiber officinale Roscoe (ginger)	Type 2 diabetic patients	64	Ginger rhizome powder	3-2 g/kg/d for 2 months	↓ Serum insulin, TG, and LDL-C.	(95)

Abbreviations; 2, 2-Diphenyl-1-picrylhydrazyl (DPPH), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Alpha-amylase (ALA), Alpha-glucosidase (GLA), Blood urea Nitrogen (BUN), and Creatinine (CRTN), total Bilirubin (BIL), decrease (↓), Dipeptidyl peptidase 4 (DPP-4), Fasting blood glucose (FBG), Ferric reducing/antioxidant power (FRAP), Glutamyl transpeptidase (GTP), Glutathione (GSH), Glutathione peroxidase (GPx), Glutathione reductase (GR), Glutathione-S-transferase (GST), Increase (↑), intraperitoneal (IP), Low-density lipoprotein-cholesterol (LDL-C), Malondialdehyde (MDA), more effective (>), No effect (X), oral (PO), Streptozocin (STZ), Super oxide dismutase (SOD), Total protein (PR), Triglycerides (TG), Total Cholesterol (TC), Thiobarbituric acid reactive substances (TBARS), Very low-density lipoprotein-cholesterol (VLDL-C).
↓: decrease, ↑: increase, X: no effect

of reactive oxygen species, accelerates cell damage, and contributes to the development and worsening of diabetic complications. Blood urea, creatinine (CRTN), and uric acid levels are indications of the kidney damage associated with hyperglycemia-caused oxidative stress. Among the investigated parameters is homeostatic model assessment of insulin resistance (HOMA-IR), which is used for the assessment of insulin resistance (24). It is suggested that hyperglycemia leads to insulin resistance in peripheral tissues as a result of the impairment of insulin secretion and sensitivity (24). Antioxidant parameters like super oxide dismutase (SOD) and glutathione peroxidase (GPx) were used to assess the antioxidant potential. Interestingly, anti-diabetic plants may contribute to protection against developing DM, as shown in some clinical trials. For example, *A. vera* delayed the onset of the disease in pre-diabetic patients (Table 3).

In conclusion, more investigations are needed to utilize medicinal plants from these regions as a source of future drugs that contribute to managing the disease more efficiently than current medications. For example, *T. polium,* which is grown in the Mediterranean region, showed potent glucose-lowering activity similar to insulin in one study. However, the exact hypoglycemic agents and their mechanisms of action are yet to be identified (25). That is why more research should be directed towards understanding the mechanisms responsible for the anti-diabetic activity of many plants. Finding ways to circumvent the limitations of utilizing medicinal plants is essential. A database of medicinal plants in both regions showing critical data such as usage parameters, safety, toxicity, contamination, and drug interactions might help face limitations. Pharmaceutical companies, together with government authorities, should help to provide more research and start initiatives to spread awareness among traditional practitioners and to protect endangered medicinal plant species from extinction, which will eventually pave the way for using the regions' medicinal plants commercially.

Authors' contribution

SA, MB, NE contributed in designing the study, performed data collection and manuscript preparation. AA supervised and edited the manuscript. Final version of the manuscript was confirmed by all authors. SA, MB, NE contributed equally

Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

No ethical approval was required for this review article

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