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

Sara S. Abou Zekry1, Marwa T. Badawy1, Nada M. Ezzelarab1, Ahmed Abdellatif1,2*

1Biotechnology Program, School of Sciences and Engineering, the American University in Cairo, 11835, Egypt
2Department of Biology, School of Sciences and Engineering, the American University in Cairo, 11835, Egypt

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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,
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 glycoprotein 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 glucosamin, 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). Soetelon 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
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, 64715 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 (DPD4) 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...
| 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 ↓ β-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 (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/d PO for 15 days         | ↑ Serum insulin, SOD, GPx, GST X Serum insulin | ↓ FBG, TG, and TC                                                       | (35)      |
| **Alhagi maurorum Medik** (Camel thorn plant)           | In vivo (STZ- diabetic rats)   | Aqueous and ethanolic extracts 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, 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                    | ↑ Serum insulin                               | ↓ 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                                                                  | (39)      |
|                                                        |                               |                                                             |                                               | ↑ Serum insulin improve pancreatic β-cell function                    |           |
| **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, 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 HDL-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, amyrase, lipase, MDA and PC ↑ HDL-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) | Ethanol 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 ↑ HDL-C Improve the appearance of pancreatic islets histologically | (55) |
| | Computational (molecular docking) | - | - | ↓ Dipeptidyl peptidase 4 (DPP-4) enzyme | (23) |
| Silibum 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-amyrase (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 dismutate (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 (Forsk.)        | *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                                     | (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 annum L. (Peppers)         | *In vitro*                                      | Aqueous extract of the leaves                                          | -                                            | ↓ ALA and GLA                                                            | (59)       |
| 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, CR TN                                             | (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                                   | (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                               | (72)       |
|                                    | *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                                             | (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                                     | (74)       |
| Punica granatum L. (Pomegranate)    | *In vivo (Alloxan-induced diabetic rats)*        | Aqueous and ethanolic extracts of the flower                           | 1000 mg/kg/d PO for 10 days                  | ↓ FBG, Hb content and HDL-C                                             | (73)       |
### 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) |
|  | Computations (molecular docking) | - | - | ↓ DPP-4 enzyme | (23) |
|  | *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 PO for 6 weeks | ↓ FBG, Gly-Hb, and LPO Improve the appearance of pancreatic islets histologically | (76) |
| *Solanum nigrum* L. (Black nightshade) | *In vivo* (Alloxan-diabetic guinea pigs) | Aqueous extract of the leaves | 200 mg/kg/d PO for 28 days | ↓ FBG | (77) |
|  | *In vivo* (STZ-induced diabetic rats) | Ethanolic extract of the whole plant except the roots | 250 mg/kg/d PO for 1 week | ↓ FBG | (76) |
| *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) | Aqueous extract of the aerial parts | 125, 250, and 500 mg/kg PO for 130 min. | ↓ Overall glycemic excursions ↑ FBG 45min post starch administration | (25) |
| *Vitis vinifera* L. (Grape vine) | *In vivo* (STZ-induced diabetic rats) | Aqueous extract of the aerial parts | 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 (TP), 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)      |
| Capparis spinosa Linnaeus   | Obese prediabetic and early non-treated diabetic patients | 132               | Fruit extract capsules | 294 mg twice/day PO per day for 8 weeks                                    | ↓ FBG, serum insulin, body weight, and body fat mass                    | (87)      |
| Cinnamomum verum J. Presl   | Pre-diabetic patients                            | 72                 | Fruit extract capsules | 300 and 500 mg PO twice/day for 8 weeks                                    | ↓ FBG, TC, LDL-C, and Gly-Hb                                              | (88)      |
| 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)      |
| Zingiber officinal Roscoe    | Type 2 diabetic patients                        | 40                 | Seed extract tablets   | 140 mg thrice/day for 45 days                                             | ↓ FBG, TG, TC, HDL/LDL, HOMA-IR (insulin resistance)                     | (94)      |

Abbreviations: 2, 2-Diphenyl-1-picrylhydrazyl (DPPH), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Alpha-amylose (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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