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Review Article

Antidiabetic Effects of Artemisia Species: A Systematic Review

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Abstract

Background: Over the last century, human life style and food habits have drastically changed which lead to various chronic diseases. Diabetes mellitus is one such disease which is causing serious problems to human health. Allopathic drugs are not much effective in handling the disease and its complications. Hence focus has been turned towards the traditional system of medicine. Medicinal plants play an important role in the management of diabetes mellitus. **Methods:** Experimental studies conducted on species of Artemisia on diabetic animal models and human published since the year 2000 until April, 2017 were reviewed. Each article was critically appraised by two independent reviewers for their methodological quality using the JBIMAStARI tool. **Result:** A total of 14 studies were included in this review and the blood glucose data obtained from these critically reviewed studies clearly showed that both the aqueous and alcoholic extracts of species of Artemisia produced significant hypoglycemic effects in alloxan, Streptozotocin and high fat diet induced diabetic animals and diabetic humans with different mechanisms of action as compared to standard antidiabetic medications. **Discussion and Conclusion:** The antidiabetic effect of single or multiple doses of aqueous and alcoholic extracts of Artemisia species was due to the active compounds of these plants and they all are effective in lessening the blood glucose level in all of those experimental studies. Despite the presence of known antidiabetic medicines in the pharmaceutical market, therapeutic remedies from these medicinal plants have been utilized with success to treat this disorder and its complications with a relatively less side effects.

Keywords: *Artemisia, diabetes mellitus, review*

Introduction

Diabetes mellitus (DM) is a complex and a fast growing medical problem throughout the globe, in both developed and developing countries. World health organization (WHO) defines diabetes as a multifaceted group of disorders that impairs the metabolism of carbohydrates, fat and protein; caused by lack of insulin secretion and/or reduced sensitivity of the tissue to insulin.[1]

The metabolic dysregulation associated with DM causes secondary pathophysiological changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on health care systems.[2] Diabetes mellitus is a global health crisis, which has been persistently affecting humanity, irrespective of the socioeconomic profile and geographic location of the population.[3,4] Despite advances in understanding and management of this metabolic disorder, the rate of morbidity and mortality due to this disorder is increasing every year. Globally, an estimated 415 million adults were living with DM in 2015 and this figure is expected to increase to 642 million by the year 2040.[5]

World Health Organization (WHO) estimates report that densely populated Asian countries such as India and China's expenditure is going to be more than US$1 trillion annually for treating this disease and its complications due to huge increase of diabetic cases by 2030.[6]

Current therapeutic measures to treat this disorder include use of insulin and other agents such as amylin analogues, alpha glycosidase inhibitors, sulphonylureas, and biguanides. These drugs also have certain adverse effects such as causing hypoglycemia at higher doses, liver problems, lactic acidosis and diarrhea.[7] Apart from these available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes. Traditional herbal medicines are used throughout the world. Herbal drugs are prescribed widely because of their effectiveness, lesser side effects and relatively lower cost.[8]

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Management of DM with medicinal plants along with dietary restrictions has caught the attention of most researchers. Even today, natural sources form the basis for a large number of modern drugs and one or more active ingredients from them is to be found in 25% of all prescriptions.[9] There is a dire need for other strategies to complement the current modern pharmacotherapy of DM. Herbal drugs comprise a significant amount of conventional medicine and literature reveals anti-diabetic activity exhibited by more than 400 plant species.[10]

Plants are very common in use in our daily either as nutrients or as sources of food and are being consumed by patients as well as healthy people.[11] Easy availability, raw consumption, lesser side effects and low cost makes the herbal preparations desirable among available therapies.[12]

In Western and African folk medicine, several species of the genus Artemisia are used for their claimed healing properties and for the cure of specific ailments. Among those, more than 400 species have been reported to show antidiabetic activity, some species of the genus Artemisia are widely used in traditional medicine as medicinal plants to treat patients with DM.[13] This review is aimed to identify, critically appraise and provide summarized evidence of experimental studies that justify the traditional claim of Artemisia species for treatment of DM.

Methods

The objective of this review is to systematically identify, appraise and synthesize the best available evidence on the effectiveness of species of Artemisia for DM. The review includes studies conducted on different species of Artemisia and their antidiabetic effects on diabetic animals and humans published since the year 2000. A three staged search strategy was used to identify all relevant published literature in English language. Databases searched were PubMed, CINAHl, PopLine, LILACS, MedNar, and MEDLINE. Secondary search was carried out using Google Scholar and Elsevier's Scirus, to identify articles that are not indexed well in traditional bibliographic databases. The search strategy used or modified for the various databases and search engines was with initial keywords/search terms: ["Antidiabetic Agents" OR "Hypoglycemics" OR "Hypoglycemic Effects" OR "Hypoglycemic Effect" OR "Hypoglycemic Drugs" OR "Antihyperglycemics" OR "Antihyperglycemic Agents" OR "Antidiabetics" OR "Antidiabetic Drugs"] AND ["Artemisia"]. Studies done on animals and humans using alloxan, Streptozotocin and high fat diet as diabetic inducing agents, articles with clear objectives and methodologies; articles published up to April 2017; and articles published in English language were included in this review. All papers selected for inclusion in the review were subjected to a rigorous, independent appraisal by two reviewers prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute.[14]

Result

A total of 156 relevant papers were identified in the literature search from databases, majority of these were duplicates, and hence 61 papers were left after removing duplication. All of them were retrieved for preliminary evaluation. Following review of titles and abstracts against the review objectives and inclusion criteria, 25 articles were excluded. The entire texts of the remaining 36 studies were retrieved for detailed evaluation, after which, 19 of them were excluded. The remaining 17 studies were assessed for methodological quality using the JBI-MAStARI critical appraisal tool and, subsequently, 14 studies were included in the review while 3 studies were deemed to be of insufficient methodological quality and did not meet inclusion criteria and were excluded from the review [Figure 1]. Table 1 shows characteristics of articles included in this review.

This review included studies conducted on nine species of Artemisia (*A. herba-alba, A. judaica, A. afra, A. amygdalina, A. dracunculus, A. ludoviciana*, *A. absinthium, A. nilagirica* and *A. sphaerocephala*). Only one study was done on humans; the remaining used experimental animal models. In those studies, investigators treated diabetic animals and humans with plant extracts for a duration ranging from 7 to 60 days. Except for two studies,[15,16] all included standard antidiabetic medications as reference to compare the effect of extract with those drugs. Glibenclamide was the most commonly used reference drug. Nine studies employed multiple dosage regimens to assess dose dependent hypoglycaemic effect of extracts while five studies used single dosage regimen of extracts throughout the study period [Table 2].

Among studies that reported phytochemicals identified from the extract, flavonoids were the most common secondary metabolites followed by alkaloids and glycosides. Two studies used polysaccharides extracted from *A. sphaerocephala* seeds.

Discussion

Even in the era of highly advanced bio medicine, herbal medicines are area of focus for researchers around the world to complement modern drugs and as sources for development of novel drugs. The mechanism of most of the herbs used has not been scientifically determined. Many traditional plants and their derived bioactive compounds are used for treatments of diabetes through various mechanisms of actions[28] and, there has been increased scientific interest in medicinal plants research that has been reported to be used traditionally to manage diabetes. This is due to increase efficacy of new plant derived drugs, growing interest in natural products, and the presence of serious side effects, high cost and poor availability of modern antidiabetic drugs for many rural populations particularly in developing countries.[29]

Table 1: Summary of characteristics of studies included in the review

Author	Year	Species of *Artemisia*	Part(s) extracted	Type of extract	Experimental model	Effect on BG level
Awad *et al*.[15]	2012	*herba-alba*	Aerial part	Alcoholic	Alloxan-induced Diabetic rats	Plant extract significantly reduces BG level
Tastekin *et al*.[17]	2006	*herba-alba*	Above ground part	Aqueous	Alloxan-induced Diabetic rats	The extract is found to be anti-diabetic comparable with standard drug
Iriadam *et al*.[16]	2006	*herba-alba*	Aerial part	Aqueous	STZ induced diabetic rabbits	The extract produced a significant hypoglycemic effect in normal and diabetic rabbits
Nofal *et al*.[18]	2009	*judaica*	Aerial part	Both aqueous and alcoholic	Alloxan-induced Diabetic rats	Produced significant decrease in BG level compared to the diabetic control group, and had no significant difference compared to glibenclamide group
Afolayan and Sunmonu *et al*.[19]	2011	*afra*	Leaves and stems	Aqueous	STZ induced Diabetic rats	The extract significantly restored normal glucose and insulin levels in the diabetic rats to near normal
Ghazanfar *et al*.[7]	2014	*amygdalina*	whole plant	Alcoholic	STZ induced Diabetic rats	The extracts showed an increased dose-dependent significant anti-hyperglycemic effect
Daradka and Abas[20]	2014	*absinthium*	Whole part	Alcoholic	Alloxan-induced Diabetic rats	A. absinthium ethanol extract exhibited a time-dependent significant hypoglycemic activity when compared with diabetic control group of rats
Pal *et al*.[21]	2015	*nilagirica*	Leaf and flowering tops	Alcoholic	STZ induced Diabetic rats	The difference between the experimental and control rats in lowering the fasting plasma glucose levels were Statistically significant in diabetic rats
Zhang *et al*.[22]	2006	*sphaerocephala*	Seeds polysaccharide	Aqueous	Alloxan-induced Diabetic rats	Doses dependent anti-hyperglycemic activity was observed with A. sphaerocephala polysaccharide diabetic rats
Xing *et al*.[23]	2009	*sphaerocephala*	Seeds gum	Aqueous	STZ induced Diabetic rats	Compared to diabetic control, rats in the A. sphaerocephala gum group had significantly lower fasting BG, and had significantly higher liver glucokinase activity and liver glycogen level
Ribnicky *et al*.[24]	2006	*dracunculus L*	Seeds	Alcoholic	STZ induced and genetically diabetic mice	Reduced BG level by 20% in STZ induced and 24% in genetic mice as compared with controls, but no significant reduction in BG of nondiabetic mice

Contd...

Table 1: Contd...

Author	Year	Species of Artemisia	Part(s) extracted	Type of extract	Experimental model	Effect on BG level
Anaya-Eugenio *et al*.[25]	2014	*ludoviciana*	Aerial parts	Alcoholic	STZ induced male mice	Oral administration of the extract to normal mice significantly decreased the BG level in a single dose. In STZ-induced mice the significant hypoglycemic effect was observed at the three different doses
Issa and Hussen Bule[26]	2015	*afra*	Aerial part	Alcoholic and aqueous	Alloxan induced diabetic Swiss albino mice	The BG level was significantly decreased by 24% in groups that received aqueous extract of A. afra
Li *et al*.[9]	2015	*absinthium*	Leaf	Aqueous	Diabetic human	Use of A. absinthium capsules for 30 days significantly reduced the serum glucose level of diabetic individuals as compared to the baseline value of this groups by 32%

BG: Blood glucose, STZ: Streptozotocin, *A. absinthium*: *Artemisia absinthium*, *A. sphaerocephala*: *Artemisia sphaerocephala*, *A. afra*: *Artemisia afra*

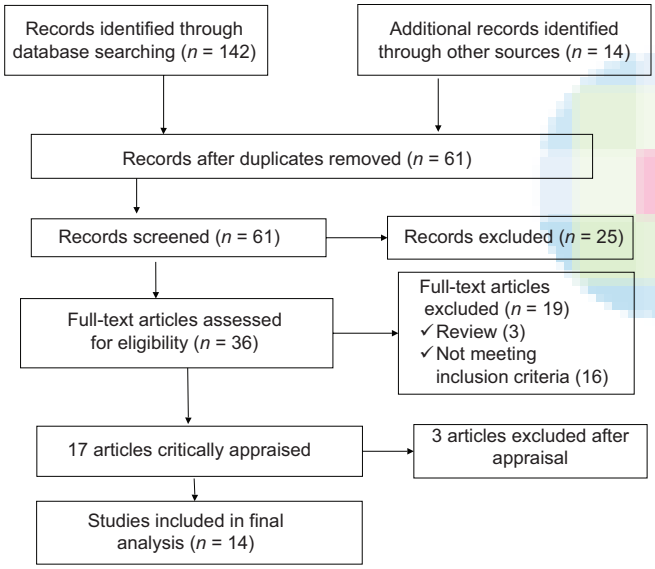

Figure 1: Flow chart for selection process of articles

The finding of this review is consistent with results of studies conducted on the species of Artemisia across many regions with different experimental animals and humans.[28-30] The blood glucose data obtained from these critically reviewed studies clearly indicate that both the aqueous and alcoholic extracts of species of Artemisia produced significant hypoglycemic effects in alloxan, Streptozotocin and high fat diet induced diabetic animals with different mechanisms of action. Their Hypoglycemic effect was comparable with that of the usual hypoglycemic drugs repaglinide, insulin, metformin and glibenclamide.[7,15,19,20] However, as can be seen from the study of some of those species of Artemisia, such as *Artemisia herba-alba* have a greater potency in decreasing the serum glucose level and animals treated with this plant showed only mild visible undesirable clinical symptoms whereas the synthetic oral hypoglycemic agents can produce serious side effects.[15]

The significant anti-hyperglycemic activity of ethanolic and aqueous extraction of *A. absinthium* may be due to the presence of active components such as α-and ß-thujones, thujyl alcohol, azulenes, bisabolene, cadinene, sabinene, pinene, and phellandrene.[31] Whereas, the antidiabetic effects of the plants *Artemisia afra, Artemisia judaica* and *Artemisia amygdalana* may be due to the presence of active compounds such as flavonoids and saponins[18,26,32] and also the active ingredients such as tannins, flavonoids, terpenes, steroids and alkaloids in *Artemisia niagirica* and *Artemisia sphaerocephala* and the substance apigenin in the *Artemisia herba-alba* probably make them have a nature of decreasing the serum glucose level.[21,23,33]

The exact molecular mechanisms of action of most of these components to reduce blood glucose is not clearly known. But, it is hypothesized that the reduction in blood glucose level may be due to the presence of thujone, a major component of these medicinal herbs, which had an effect in insulin-sensitizing action. Thujone can increase free insulin-stimulated glucose transporter by activation of adenosine monophosphate-activated protein kinase.[20] A reported data about the hypoglycemic activities of flavonoids, tannins and apigenin proved that they increase insulin secretion and have insulinomimetic effect.[34] The main function of flavonoids are antioxidant activity.[35] Supplementation of antioxidants may be a protective factor against free radical induced beta cell damage, thus preventing and ameliorating diabetes mellitus.

Table 2: Detailed description of study characteristics included in the review

Author	BG cut off for diabetes	Study duration (days)	Dose of extract	Phytochemicals identified	Reference drug
Awad *et al*.[15]	FBS >170 mg/dL	60	390 mg/kg/day	Glycosides, coumarins, alkaloids, flavonoids, phenolics, terpenes	None
Tastekin *et al*.[17]	Not specified	10	390 mg/kg/day	Not reported	Repaglinide Insulin
Nofal *et al*.[18]	FBS >200 mg/dL	30	0.25 and 0.5 g/kg for aqueous, 0.5 and 1 g/kg for alcoholic extract	Flavonoids, saponins Terpenes, tannins	Glibenclamide
Afolayan and Sunmonu[19]	FBS >250 mg/dL	14	50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	Not reported	Glibenclamide
Ghazanfar *et al*.[7]	FBS >200 mg/dL	14	50 mg/kg/day 100 mg/kg/day 250 mg/kg/day 500 mg/kg/day	Alkaloids, phenolics, Glycosides, tannins Flavonoids, terpenes Steroids	Glibenclamide
Daradka and Abas[20]	FBS >250 mg/dL	10	200 mg/kg/day 500 mg/kg/day 1000 mg/kg/day	Not reported	Glibenclamide
Pal *et al*.[21]	FBS >200 mg/dL	28	200 mg/kg/day 400 mg/kg/day	Flavonoids, steroids Terpenoids, saponins Tannins, essential oils Alkaloids	Glibenclamide
Zhang *et al*.[22]	RBS >11.0 mmol/L	28	50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	Polysaccharide fraction was used	Glibenclamide
Xing *et al*.[23]	RBS >11.1 mmol/L	60	0.3%, 0.9% and 2.7% of daily food	Gum extracted from the seed	Metformin
Ribnicky *et al*.[27]	Not specified	7	500 mg/kg/day	Flavonoids, sesquiterpene lactones and coumarin derivatives	Metformin, troglitazone, insulin
Anaya-Eugenio *et al*.[25]	Not specified	14	100 mg/kg for Normal mice 31.6, 100, and 316 mg/kg are for STZ induced mice	Isolation of eupatilin, jaceosidin, arglanin, salvinine, and 3, 5-dicaffeoylquinic acid	Glibenclamide
Iriadam *et al*.[16]	FBS >250 mg/ml	7	85 mg/kg	Not reported	None
Issa and Hussen Bule[26]	FBG >250 mg/dL	14	500, 750, and 1000 mg/kg of the extract for both aqueous and methanolic extracts	Chromophores, saponins, phosphosteroid and withanoids, flavonoids, tannins, and anthraquinone	Glibenclamide
Li *et al*.[9]	FBS >211 mg/dL	30	1 g/day	Not reported	None

BG: Blood glucose, FBS: Fasting blood sugar, FBG: Fasting BG, RBS: Random blood sugar, STZ: Streptozotocin

Moreover, the safety and efficacy of these plants were assessed through the administration of both the aqueous and ethanolic extracts of these species which attenuated the elevated activities of all investigated enzymes in diabetic animals comparable to the control. This may be an indication of the relatively nontoxic nature and protective action of the extracts in the primary organs of the body which are commonly affected by toxic insults.[11,32,36-39]

Conclusion and Recommendation

In this systematic review, we can conclude that the antidiabetic effect of single or multiple doses of aqueous and ethanolic extracts of Artemsia species were due to the active compounds of these plants and they all are effective in decreasing the blood glucose level in all of those experimental studies. Despite the presence of known antidiabetic medicines in the pharmaceutical market, therapeutic remedies from these medicinal plants have been used with success to treat this disorder and its ramifications with relatively lesser side effects. According to WHO recommendation, antihyperglycemic agents of natural plant origin used in traditional medicine are important. Therefore it may be better to consider these species in assessing of their general toxic profile and formulation of antidiabetic drugs.

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Conflicts of interest

There are no conflicts of interest.

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