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Indigenous Drugs in Ischemic Heart Disease in Patients with Diabetes

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Abstract

Background: India is currently facing the silent epidemic of ischemic heart disease, type 2 diabetes mellitus (T2DM), hypertension, and stroke. Both diabetes and ischemic heart disease appear in Indian people a decade earlier compared to whites. The recent evidence that certain medicinal plants possess hypoglycemic, lipid-lowering, and immunomodulating properties on account of their rich flavonoid and/or other glucose-lowering active constituents merits scientific scrutiny in this regard.
Objectives: The present communication aims to give a brief review of those plants that could be useful in T2DM associated with hypertension, ischemic heart disease, and/or dyslipidemia.
Methods: *Aegle marmelos* (bael), *Allium sativum* (garlic), *Curcuma domestica* (turmeric), *Eugenia jambolana* (jamun), *Murraya koenigii* (curry leaves), *Trigonella foenum graecum* (fenugreek), and *Terminalia arjuna* (arjun) have been found to be useful in diabetes associated with ischemic heart disease. Their active biomolecules have been identified. They have also been demonstrated to be safe in long-term use.
Conclusions: Further clinical research regarding their potency and efficacy vis-à-vis oral hypoglycemics needs to done.

Introduction

India is currently facing the silent epidemic of ischemic heart disease (IHD), type 2 diabetes mellitus (T2DM), hypertension, and stroke. It is estimated that India presently has 29.8 million coronary heart disease, 19.3 million diabetic, and 118 million hypertensive patients.[1–4] It is also known that both IHD and T2DM appeared in Indian people a decade earlier compared to whites.[2,3,5] Incidentally, diabetes was first described and its herbal remedy mentioned by Sushruta in 600 BC.[6]

Both T2DM and IHD are basically vascular diseases characterized by endothelial dysfunction.[7,8] It is therefore logical to look for a remedy that will correct the endothelial dysfunction in the entire vascular system. The recent evidence that certain medicinal plants possess hypoglycemic, lipid-lowering, and immunomodulating properties on account of their rich flavonoid and/or other glucose-lowering active constituents merits scientific scrutiny in this regard.[9,10] The present communication aims to give a brief review of those plants that could be useful in T2DM associated with hypertension, IHD, and/or dyslipidemia. Notable plants that have been shown to be useful in diabetes and associated cardiovascular conditions are (1) *Aegle marmelos* (bael), (2) *Allium cepa* (onion), (3) *Allium sativum* (garlic), (4) *Azadirachta indica* (neem), (5) *Curcuma domestica* (turmeric), (6) *Eugenia jambolana* (jamun), (7) *Ficus bengalensis* (banyan), (8) *Gymnema sylvestre* (gudmar), (9) *Glycyrrhiza glabra* (licorice), (10) *Momordica charantia* (karela), (11) *Murraya koeingii* (curry leaves), (12) *Ocimum sanctum* (tulsi), (13) *Phyllanthus amarus* (gooseberry), (14) *Pterocarpus marsupium* (vijaysar), (15) *Punica granatum* (pomegranate), (16) *Swertia chirayita* (chiretta), (17) *Trigonella foenum graecum* (fenugreek), (18) *Terminalia arjuna* (arjun), (19) *Tinosporia* (guduchi), and (20) *Zingiber officinale* (ginger) (Table 1).

Certain plants and spices containing flavonoids have been used for thousand of years in ancient system of medicine. Plant flavonoids protect against lipid peroxidation in arterial cells and lipoproteins and thus attenuate development of atherosclerosis.[11] Of the many actions of flavonoids, their anti-oxidant and antiproliferative activities stand out. Moreover, their inhibitory action on inflammatory cells makes them a useful therapeutic tool in attenuating the process of atherosclerosis.

In addition, medicinal plants rich in flavonoids restore lipid homeostasis, control hyperglycemia, possess immunomodulating properties, modify coagulation pathways, and have antimitotic properties. As the metabolic syndrome

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Table 1. Useful Medicinal Plants in Ischemic Heart Disease and Diabetes

S.no.	Name of the plant	Vernacular name	Flavonoids/active constituents	Clinical indications
1.	*Aegle marmelos*	Bael	Scopoletin, aegeline-2	Diabetes mellitus, dyslipidemia
2.	*Allium cepa*	Onion	*S*-methyl cysteine sulphoxide	Dyslipidemia, hypoglycemic
3.	*Allium sativum*	Garlic	S-allyl cysteine sulphoxide, allicin	Dyslipidemia, hypoglycemic
4.	*Azadirachta indica*	Neem	β-Sitotosterol, kaempferol quercetin, myricetin, nimbidin	Immunomodulation
5.	*Curcuma domestica*	Turmeric	Curcumin	Anti-inflammatory, hypolipidemic
6.	*Eugenia jambolana*	Jamun	Triterpenic acid, oleanolic acid, crategelica acid	Hypoglycemic
7.	*Ficus bengalensis*	Banyan	Leucocyanidin, pelorgonidin, leucodelphindin	Hypoglycemic
8.	*Gymnema sylvestre*	Gudmar	Gymnemica acid(+), quercitol, lupeol	Hypoglycemic
9.	*Glycyrrhiza glabra*	Licorice	Hydrophobic flavonoids	Immunomodulation
10	*Momordica charantia*	Karela	Charantin	Hypoglycemic
11.	*Murraya koenigii*	Meethi, curry leaves	Alkaloids, Koenigicine, Koenimbine, phytosterolins	Hypolipidemic, hypoglycemic
12.	*Ocimum sanctum*	Tulsi, holy basil	Luteolin, apigenin, orientin, molludistin	Immunomodulation, hypolipidemic, hypoglycemic
13.	*Phyllanthus amarus*	Amla, goose berry	Gallic acid, ellagic acid, emblicanin A, B and E	Hypolipidemic, hypoglycemic, antioxidant
14.	*Pterocarpus marsupium*	Vijaysar	(-) epicatechin, marsupin, pterosupin, pterostilbene	Hypoglycemic
15.	*Punica granatum*	Pomegranate	Pelorgonidin, glycosides, sitosterol, gallic acid, ellagic acid	Hypolipidemic, hypoglycemic
16.	*Swertia chirayita*	Chiretta	Mangeferin, amarogentin, amaroswerin, sweroside, swertiamarin	Hypoglycemic
17.	*Trigonella foenum graecum*	Methi, fenugreek	Trigonelline	Hypolipidemic, hypoglycemic
18.	*Terminalia arjuna*	Arjun	Arjunetin, arjunolone, arjunone, bicalein, gallic acid, ethyl gallate, luteolin, quercetin, kempferol, pelorgonidin	Hypolipidemic, anti-ischemic, anti-inflammatory
19.	*Tinosporia cordifolia*	Guduchi	Arabinogalactan polysacchride, tinosporiaside, cardioside, columbin, 20-β hydroxyecdysone	Hypoglycemic
20.	*Zingiber officinale*	Ginger	Oleoresin -6-gingerol (1-4-hydroxy-3-methoxyphenyl-5 hydroxy-3 decanone), 8- gingerol, 10-gingerol, 6 shogaol	Hypoglycemic

is characterized by endothelial dysfunction, dyslipidemia, dysglycemia, immunological aberrations, and coagulation abnormalities, it would only be appropriate to test using them in people suffering from metabolic syndrome. One of the essential components of such drug therapy should be the implementation of other lifestyle measures like cessation of smoking/tobacco, exercise regimen, and healthy diet as advocated in ancient system of medicine and duly recommended by the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III) and European Atherosclerosis Society guidelines.

As (1) *A. marmelos,* (2) *A. cepa,* (3) *A. sativum,* (4) *E. jambolana,* (5) *M. charantia,* (6) *O. sanctum,* (7) *P. amarus,* (8) *T. foenum graecum,* and (9) *T. arjuna,* are the most commonly used among those listed above, a brief discussion on the following nine plants is being done for their putative usefulness in T2DM complicated by IHD.

1. *A. marmelos* (bael): It is a subtropical tree and is cultivated throughout India. Leaves, fruits, stem, and roots of *A. marmelos* have been found to be useful in dyslipidemia, hyperglycemia, and hypertension. In a study by Kesari et al., aqueous seed extract of *A. marmelos* was reported to lower total cholesterol by 25.49%, triglycerides by 45.77%, and low density lipoprotein (LDL) 53.97% with enhancement of high density lipoprotein (HDL) by 33.43%.[12]

In another study by Upadhaya et al., aqueous extract of *A. marmelos* leaves was used to evaluate the hypoglycemic and antioxidant effect on male albino diabetic rats. At the end of 4 weeks, there was a decrease in blood glucose, increase in erythrocyte glutathione, and a decrease in malondialdehyde in male albino diabetic rats compared to control diabetic rats.[13] In another study, from the leaves of *A. marmelos*, Aegeline 2 was found to have antihyperglycemic activity as evidenced by lowering the blood glucose levels by 12.9% and 16.9% at 5 and 24 hours, respectively, in diabetic rats. Aegeline 2 also significantly decreased the plasma triglyceride by 55% ($p < 0.001$), total cholesterol by 24% ($p < 0.05$), and free fatty acids by 24%, accompanied with increase in HDL-C by 28% in dyslipidemic hamster model.[14]

2. *A. cepa* (onion): It is indigenous to western Asia, but it is commercially cultivated worldwide. The principal use of bulbous *A. cepa* today is to prevent age-dependent changes

in the blood vessels.[15] The hypoglycemic effects of *A. cepa* have been demonstrated *in vivo.* In addition, its inhibitory effect on platelet aggregation has also been demonstrated both *in vitro* and *in vivo*.[16,17] Platelet aggregation was inhibited in rabbits after administration of the essential oil, or a butanol or chloroform extract of the drug.[18–20] An ethanol, butanol, or chloroform extract or the essential oil (10–60 μg/mL) of the drug inhibited aggregation of human platelets *in vitro*.[21,22] Both raw onions and the essential oil increased fibrinolysis in *ex vivo* studies on rabbits and humans.[23] An increase in coagulation time was also observed in rabbits.[24] Oral administration of a butanol extract of *A. cepa* (200 mg) to subjects given a high-fat meal prior to testing suppressed platelet aggregation associated with a high-fat diet.[23] Administration of a butanol extract to patients with alimentary lipemia prevented an increase in the total serum cholesterol, -lipoprotein cholesterol, and lipoprotein and serum triglycerides.[25,26] The beneficial effects of onion extract on lipid and blood glucose are varying. In one study, fresh onion extract (50 g) did not produce any significant effects on serum cholesterol, fibrinogen, or fibrinolytic activity in normal subjects.[27,28] However, in another study, administration of an aqueous extract (100 mg) decreased glucose-induced hyperglycemia in human adults.[29] The juice of the drug (50 mg) administered orally to diabetic patients reduced blood glucose levels.[30]

3. *A. sativum* (garlic): It contains organosulfur, allicin, and ajoene, which are mainly responsible for its biological activity. It inhibits cholesterol synthesis by blocking 3-hydroxy-3 methyl-gluteryl-CoA reductase HMG-CoA reductase, squalene epoxidase, and glucose-6-phosphate dehydrogenase. Studies in moderate hypercholesterolemia in males have demonstrated that garlic produces reduction in total cholesterol and LDL cholesterol.[11,31] Allicin may reduce total cholesterol and LDL cholesterol in adults with moderate hypercholesterolemia. In a study by Jain et al. (1993), the baseline serum total cholesterol level of 262 ± 34 mg/dL was reduced to 247 ± 40 mg/dL ($p < 0.01$) after 12 weeks of standard garlic treatment (900 mg/d). One meta-analysis report incorporating data from 13 randomized, controlled trials comparing garlic with placebo (including 796 patients) on the use of garlic for hypercholesterolemia suggested that garlic is superior to placebo in reducing cholesterol levels.[32]

The antihypertensive activity of garlic has been demonstrated *in vivo*. Oral or intragastric administration of minced garlic bulbs, or alcohol or water extracts of the drug, lowered blood pressure in dogs, guinea pigs, rabbits, and rats.[33–36] The drug appeared to decrease vascular resistance by directly relaxing smooth muscle.[37] The compounds that produce the hypotensive activity of the drug are uncertain. Allicin does not appear to be involved.[38]

Aqueous garlic extracts and garlic oil have been shown *in vivo* to alter the plasma fibrinogen level, coagulation time, and fibrinolytic activity.[38] Serum fibrinolytic activity increased after administration of dry garlic or garlic extracts to animals that were artificially rendered arteriosclerotic.[39,40] Garlic inhibited platelet aggregation in both *in vitro* and *in vivo* studies. Adenosine, alliin, allicin, and the transformation products of allicin, the ajoenes; the vinyldithiins, and the dialkyloligosulfides are responsible for inhibition of platelet adhesion and aggregation.[41–45] Hypoglycemic effects of *A. sativum* have been demonstrated *in vivo*. Oral administration of an aqueous, ethanol, petroleum ether, or chloroform extract, or the essential oil of garlic, lowered blood glucose levels in rabbits and rats.[46–54] However, three similar studies reported negative results.[55–57] In one study, garlic bulbs administered orally (in feed) to normal or streptozotocin-diabetic mice reduced hyperphagia and polydipsia but had no effect on hyperglycemia or hypoinsulinemia.[57] Allicin administered orally to alloxan-diabetic rats lowered blood glucose levels and increased insulin activity in a dose-dependent manner.[46] Garlic extract's hypoglycemic action appears to enhance insulin production, and allicin has been shown to protect insulin against inactivation.[58]

A meta-analysis of the effect of *A. sativum* on blood pressure reviewed a total of 11 randomized, controlled trials (published and unpublished).[59,60] Each of the trials used dried garlic powder (tablets) at a dose of 600–900 mg daily (equivalent to 1.8–2.7 g/day fresh garlic). The results of the meta-analysis led to the conclusion that garlic may have some clinical usefulness in mild hypertension, but there is still insufficient evidence to recommend the drug as a routine clinical therapy for the treatment of hypertension.[61] Clinical studies have demonstrated that garlic activates endogenous fibrinolysis, that the effect is detectable for several hours after administration of the drug, and that the effect increases as the drug is taken regularly for several months.[38,62]

In a 3-year intervention study, 432 patients with myocardial infarction were treated with either an ether-extracted garlic oil (0.1 mg/kg/day, corresponding to 2 g fresh garlic daily) or a placebo.[63] In the group treated with garlic, there were 35% fewer new heart attacks and 45% fewer deaths than in the control group. Oral administration of garlic powder (800 mg/day) to 120 patients for 4 weeks in a double-blind, placebo-controlled study decreased the average blood glucose by 11.6%.[64]

4. *E. jambolana* (jamun): Fruit, seed, bark, and leaves of *E. jambolana* are used for medicinal purposes. Its pulp extract has been shown to be having hypoglycemic activity. The effect of pulp was seen in 30 minutes, while the seeds of the same fruit required 24 hours. The oral administration of the extract resulted in enhancement in serum insulin levels in normoglycemic and diabetic rats. Sharma et al. studied the hypoglycemic and hypolipidemic effect of ethanolic extract (100 mg/kg body weight) of its seeds in alloxan-induced diabetic rabbits. It showed a significant decrease in fasting blood glucose and glycosylated hemoglobin levels and increase in serum insulin. The ethanolic extract of seeds also exhibited significant hypolipidemic effect.[65] In another study by the same group, water extract was found to be more effective than the ethanolic extract in reducing fasting blood glucose and improving blood glucose in a glucose tolerance test.[66]

Its seed kernel has also been found to be having antihyperlipidemic effect in streptozotocin (STZ)-induced diabetic rats. The plasma lipoproteins (HDL, LDL, very low-density lipoprotein [VLDL]-cholesterol) and fatty acid composition were altered in STZ-induced diabetic rats, and these levels were reverted back to near normalcy by *E. jambolana* seed kernel treatment.[67]

5. *M. charantia* (karela): It grows throughout India. The fruits and leaves of the plant contain two alkaloids, one of them being momordicine. The plant is reported to contain a glucoside, a saponin-like substance, a resin with an unpleasant taste, an aromatic volatile oil, and mucilage. The

fruits and seeds of *M. charantia* yielded a polypeptide (mp 240°) (namely, *p*-insulin), which was considered to be similar to bovine insulin.[68] To date, close to 100 *in vivo* studies have demonstrated the blood-sugar-lowering effect of this bitter fruit. In other *in vivo* studies, bitter melon fruit and/or seed has been shown to reduce total cholesterol. Oral administration of fresh fruit juice (dose, 6 cm^3/kg body weight) lowered the blood sugar level in normal and alloxan-diabetic rabbits.[68] Various *in vivo* studies have also advocated the use of *M. charantia* as an dietary supplement for diabetic and prediabetic patients.[69,70]

Chaturvedi showed that *M. charantia* extract normalized blood glucose level, reduced triglyceride and LDL levels, and increased HDL level in diabetic rats. The animals reverted to a diabetic state once the *M. charantia* extract was discontinued.[71] Chen et al. observed slower weight gain and less visceral fat when rats fed a high-fat diet were supplemented with freeze-dried bitter melon juice.[72]

6. *O. sanctum* (tulsi): It is a herbaceous plant found throughout India. Its leaves, which are used for medicinal purposes, have numerous pharmacological activities: hypoglycemic immunomodulatory, antistress, analgesic, antipyretic, anti-inflammatory, antiulcerogenic, antihypertensive, radioprotective, antitumor, and antibacterial. The principal constituent is a bright yellow volatile oil. It also contains alkaloids, glycosides, saponins, tannins, ascorbic acid, and carotene. Administration of fresh leaves of *O. sanctum* for 4 weeks in normal albino rabbits resulted in significant lowering in serum total cholesterol, triglyceride, phospholipids, and LDL cholesterol levels and significant increase in the HDL cholesterol.[73] Antihyperlipidemic and antioxidant effect of *O. sanctum* seed oil was also studied by Gupta and coworkers (2006) in cholesterol-fed rabbits. They found significant decreased serum cholesterol, triacylglycerol, and LDL + VLDL cholesterol compared to an untreated cholesterol-fed group.[74] It has recently been reported that extract of its leaves works at all levels of antioxidant action.[75]

7. *P. amarus* (amla): It grows widely in the tropical parts of all countries except Australia. Principal compounds are phyllanthin (bitter constituent) and hypophyllanthin (nonbitter compound) isolated from the leaves. Srividya et al. assessed the diuretic, hypotensive, and hypoglycemic effects of *P. amarus* on human subjects. Nine (9) patients with mild hypertension (4 of them also with diabetes mellitus) were treated with a preparation of the whole plant of *P. amarus* for 10 days. A significant reduction in systolic blood pressure in nondiabetic hypertensive patients and female subjects was noted. Blood glucose was also significantly reduced in the treated group, with no harmful side-effects.[76] The lipid-lowering activity of *P. amarus* has been studied in triton- and cholesterol-fed hyperlipemic rats by Khanna et al.[77] Chronic feeding of this drug in animals for 30 days caused lowering in the lipids and apoprotein levels of VLDL and LDL in experimental animals. In another study, Rajak et al. orally administered fresh fruit homogenate to Wistar albino rats of either sex daily for 30 days. There was a reduction in basal myocardial lipid peroxidation, and augmentation of myocardial endogenous antioxidants. The results indicated that chronic *P. amarus* administration causes myocardial adaptation by augmenting endogenous antioxidants and protects hearts from oxidative stress.[78]

8. *T. foenum graecum* (methi): It is an aromatic herb, commonly known as fenugreek, and is cultivated in many parts of India. The seeds, which are used for medicinal purposes, contain four flavonoids and two steroidal saponins. A pure hypoglycemic component from the water extract of *T. foenum graecum* has been isolated by Puri et al. in 2002.[79] The oral administration of *T. foenum graecum* in the cholesterol-induced hyperlipidemic and diabetic rabbits for 15 days showed significant hypocholesterolemic and hypotriacylglycerolemic effects, restoring the normal serum lipid levels and substantial lowering of tissue lipids. An unusual amino acid, 4-hydroxyisoleucine 5, which has been isolated from the seeds of *T. foenum graecum*, significantly decreased the plasma triglyceride levels by 33%, total cholesterol by 22%, and free fatty acids by 14%, in the dyslipidemic hamster model.[80] In a recent study, compared with the diabetic group, rats treated with T. *foenum graecum* extract had lower blood glucose, triglycerides, total cholesterol, and higher HDL cholesterol in a dose-dependent manner.[81]

T. foenum graecum seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic, and lipogenic enzymes.[82] The water extract of the methanol extractive-free residue of the seed powder has been shown to possess significant hypoglycemic activity at different prandial states.[83] The experimental and clinical antidiabetic activity of *T. foenum graecum* has been further studied by Jung et al. in T2DM.[84]

9. *T. arjuna* (arjun): Commonly known as arjun, it is mainly found near the major riversides in India. It is a large deciduous tree. Its bark has been used as a medicine in heart disease since 500 BC. The main constituent of bark powder includes glycoside (arjunine, arjunetin, arjunoside I, arjunoside II, trityepene-*o*-glycoside). It possesses large quantities of both flavonoids and phytosterols that exert antioxidant, anti-inflammatory, and lipid-lowering effects. It increases coronary blood flow, produces mild diuresis, increase left ventricular ejection fraction, and reduces left ventricular mass. In a study comprising 30 patients with coronary artery disease, *T. arjuna* was found to modify various known coronary risk factors such as obesity, hypertension, diabetes mellitus, and circulating catecholamines. No significant side-effects were reported in this study.[85] Later on, Dwivedi and coworkers further studied the effect of *T. arjuna* in 15 stable angina cases and found it effective in reducing intensity and frequency of angina pectoris and improvement in effort tolerance. The drug lowered systolic blood pressure and body mass index and increased HDL cholesterol. There were no deleterious effects on liver or kidney function.

T. arjuna possesses antihypertensive and antiarrhythmic activity. It delays myocardial ischemia in *T. arjuna* pretreated animals. It has been found to have negative inotropic and negative chronotropic action on isolated spontaneously beating rat atrium. *T. arjuna* has been shown to reduce lipoprotein (a) (Lp(a)). Significant reduction in Lp(a) levels amounting to 24.71% following the administration of *T. arjuna* in a patient who exhibited β-thalassemia minor and hyperlipoproteinemia(a) was observed by Dwivedi and Kumar.[86]

Conclusions

Tight control of hyperglycemia, correction of endothelial dysfunction, maintenance of hypertension to an optimal

level, and ideal levels of lipids—particularly HDL cholesterol and triglycerides—are the key points of ideal therapeutic interventions to forestall development of IHD in diabetics. Based on the above criterion, *A. marmelos, A. sativum, C. domestica, E. jambolana, Murraya koenigii, T. foenum graecum*, and *T. arjuna* have been found to be useful in T2DM associated with IHD. Their active biomolecules have been identified. They have also been found to be safe in long-term use. However, currently they can only be used as an adjunct to lifestyle measures and conventional oral hypoglycemic therapy. Further clinical research regarding their potency and efficacy *vis-à-vis* oral hypoglycemic needs to done.

Disclosure Statement

No competing financial interests exist.

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