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Trigonelline: An Emerging Paradigm for Effective Therapy in Diabetes Mellitus

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Abstract

Diabetes Mellitus (DM) is recognized as a critical priority because of its epidemic nature. Successful diabetes treatment is not yet established and nowadays, diabetes is considered a global problem. Recent medications have not proved to be complete treating agents because, until now no one had completely cured diabetes. Current antidiabetic drugs have many undesirable side effects. So, an alternative therapy is required. Nowadays, various plant species are used worldwide as hypoglycemic, antihyperglycemic, antidiabetic and antihyperlipidemic agents. A number of plants contain active metabolites such as alkaloids, flavonoids, glycosides, carotenoids, terpenoids, etc., which are extensively used in antidiabetic drugs. About 400 plant species have been reported as having hypoglycemic activity. From these medicinal plants and their active components, various herbal drugs are being formed. This review aims to understand different plant species used to date for treating diabetes, the therapeutic potential of fenugreek, the active compounds isolated from fenugreek, the chemical structure of trigonelline, therapeutic uses of trigonelline as an antidiabetic agent. Research papers, manuscripts and review papers were searched and relevant contents were studied. One hundred sixty-three papers were included in this review. The review resulted in a better understanding of the use of trigonelline in diabetes treatment..

Keywords: Diabetes Mellitus, Fenugreek, Hypoglycemic, Trigonelline

1. Introduction

Diabetes Mellitus (DM) is probably one of the oldest disorders known to man. It was first reported in an Egyptian manuscript about 3000 years ago[1]. In 1936, the distinction between type 1 and type 2 DM was made. Diabetes is a major killer worldwide and its unprecedented rise poses a serious threat to mankind. In 2021, it is estimated that 537 million people have diabetes and this number is projected to reach 643 million by 2030 and 783 million by 2045. In addition, 541 million people are estimated to have impaired glucose tolerance in 2021. It is also estimated that over 6.7 million people aged 20–79 will die from diabetes-related causes in 2021[2].

The highest percentage of 387 million diabetic people live in low- and middle-income countries and comprise the 40–59 year age group in the population. A population survey by the Indian Council of Medical Research (ICMR) suggested that China leads the survey with an estimation of 98.4 million cases and India comes next with 65.1 million diabetes patients[3]. As per International Diabetes Federation-2021, 74.2 million adults (20-79 years) are diabetic in India, which is projected to rise to 124.9 million by the year 2045[2]. ICMR guidelines for the management of type 2 diabetes- 2018 reveal that the prevalence of diabetes in urban India, especially large metropolitan cities has increased from 2% in the 1970s to over 20% at present and the rural areas are also fast-catching up[4]. It has been seen that certain features in Asian Indians make the latter prone to diabetes and coronary artery disease[5,6] which include increased insulin resistance[7] and greater abdominal adiposity[8]. Studies revealed that a family history of Type 2 Diabetes Mellitus (T2DM), consumption of fast food, physical inactivity,

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Acanthosis nigricans, and being overweight are the most significant potential risk factors for diabetes mellitus[9]. Quantifying the prevalence of diabetes and the number of people affected by diabetes, now and in the future, is important to allow rational planning and allocation of resources.

Currently, no complete cure for T2DM is available. The disorder is managed with the help of medicinal involvement and certain lifestyle modifications. The recent treatment for diabetes includes some oral anti-diabetic drugs like sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, etc., which do not meet the needs of all diabetic patients. Some antidiabetic compounds recently available to treat T2DM are as follows:

1. Sulfonylurea: It reduces fasting and postprandial blood glucose level by increasing insulin secretion by β-cells of the pancreas.
2. Biguanide (Metformin): It helps in insulin sensitivity and its mechanism. It also improves insulin secretion by β-cells of the pancreas. Metformin inhibits the function of mitochondrial enzyme glycerol-3-phosphate dehydrogenase, which further blocks gluconeogenesis in the liver[10] and kidney[11].
3. Alpha-glucosidase inhibitor (Acarbose): Inhibits the breakdown of disaccharides in the upper gastrointestinal tract (GIT) thus resulting in reduced absorption of glucose.
4. Thiazoldinediones: The mechanism of thiazoldinediones is similar to biguanides. They play an important role in insulin-mediated blood glucose uptake by cells without increasing insulin secretion.

However, all these antidiabetic drugs exert some side effects like excessive hypoglycemia, vomiting, headache, weight gain, nausea, hyponatremia, flatulence, gastrointestinal disturbance, pernicious anaemia, lactic acidosis, dizziness, dyspepsia joint pain, etc. Sulfonylurea shows limited and short glycemic control with an increased risk of hypoglycemia and weight gain. While thiazoldinediones are linked with an increased risk of edema, heart failure and weight gain[12]. Therefore, instead of allopathic drugs for the management of diabetes, herbal drugs are considered a good option and show negligible side effects.

Management of this disorder may include lifestyle modifications, diet exercise, and long-term use of oral hypoglycemic agents or insulin therapy[13]. Available treatment option for diabetes mellitus is insulin therapy which shows glycemic control in diabetes, yet its shortcomings, such as ineffectiveness on oral administration, short shelf life, the requirement of constant refrigeration, fatal hypoglycemia in the event of excess dosage, the reluctance of patients to take insulin injections and above all the resistance due to prolonged administration, limit its usage[14].

2. Medicinal Plants with Antidiabetic and Related Beneficial Effects

For the last few decades, phytochemistry has been making rapid progress and herbal products are becoming more popular. There has been a dramatic rise in the sale of herbal products. Herbal medicines are produced by a number of distinguished researchers and due to their accessibility to traditions, it is still practised even by practitioners. Ayurveda, the ancient healing system of India, flourished in the Vedic era in India. According to historical facts, the classical texts of Ayurveda, Charaka Samhita and Sushruta Samhita were written around 1000 B.C. The Ayurvedic Materia Medica includes 600 medicinal plants along with therapeutic uses. The ayurvedic formulations incorporate a single herb or two or more herbs (polyherbal formulations).

It has been investigated that for a long time, plants-based herbal medicines or their extracts have been the major source of drugs for the treatment of diabetes mellitus in Indian medicine and other systems in the world[15], because plant products are frequently considered to be less toxic and freer from side effects than modern synthetic drugs[16]. Ethnobotanical information suggests that about 800 medicinal plants have become more important, and the search for more effective and safer hypoglycemic agents has continued to be an important area of active research. Many herbs and plants have been described as possessing hypoglycemic activity when taken orally[17]. However, many florae still wait for an investigation into their medicinal properties. There are many plants which possess antidiabetic properties like fenugreek, bitter melon, turmeric, giloy, gudmar, garlic, vijayasar, ashwagandha, amla, ginger, red sandalwood, chiretta, etc., (Table 1).

Table 1. List of plants showing antidiabetic and other activities

Sr. No.	Scientific Name of the Plant	Common/Ayurvedic Name	Antidiabetic and other Activities	References
1.	*Allium sativum*	Garlic	α-amylase inhibitor, hypoglycemic, α-glucosidase inhibitor, antihyperglycemic	18-25
2.	*Annona squamosa*	Sugar apple or Custard apple	Increase in plasma insulin level, hypoglycemic and antihyperglycemic	26-28
3.	*Areca catechu*	Betel-nut palm or Supari	Hypoglycemic	29
4.	*Artemisia pallens*	Davana	Increases peripheral glucose utilization or inhibits glucose reabsorption, hypoglycemic	30
5.	*Boerhavia diffusa*	Punarnava	Hypoglycemic, increase in plasma insulin level, antioxidant, increase in hexokinase activity, decrease in glucose-6-phosphatase and fructose bis-phosphatase activity	31-35
6.	*Bombax ceiba*	Semul	Hypoglycemic	36
7.	*Butea monosperma*	Palas	Anti-hyperglycemic	37
8.	*Caesalpinia bonducella*	Sagargota or Fevernut	Hypoglycemic, hypolipidemic	38-40
9.	*Camellia sinensis*	Tea	Antihyperglycemic, antioxidant	41,42
10.	*Capparis decidua*	Karir	Hypoglycemic, hypolipidemic, antioxidant	43
11.	*Coccinia indica*	Bimb or Kanturi	Hypoglycemic	44
12.	*Curcuma longa*	Turmeric	Hypoglycemic, antioxidant, glucosidase inhibitory activity	45,46
13.	*Emblica officinalis*	Amla	Hypoglycemic, antioxidant, decreases lipid peroxidation	47-49
14.	*Enicostema littoral*	Nahi	Hypoglycemic, increase in hexokinase activity, decrease in glucose 6-phosphatase and fructose 1,6 bisphosphatase activity	50,51
15.	*Eugenia uniflora*	Pitanga	Hypoglycemic	52
16.	Ficus benghalenesis	Banyan	Hypoglycemic, antioxidant	53
17.	*Gymnema sylvestre*	Gudmar or Merasingi	Antihyperglycemic, hypolipidemic	54,55
18.	*Momordica charantia*	Bitter melon	Hypoglycemic	56,57
19.	*Momordica cymbal aria*	Kadavanchi	Hypoglycemic, hypolipidemic	58,59
20.	Murraya koenigii	Curry patta	Hypoglycemic, increases glycogenesis, decreases gluconeogenesis and glycogenolysis	60
21.	*Musa sapientum*	Banana	Antihyperglycemic, antioxidant	61-63

Table 1 to be continued...

22.	*Phaseolus vulgaris*	Hulga or common bean	Hypoglycemic, hypolipidemic, inhibit alpha-amylase activity, antioxidant.	64-66
23.	*Pterocarpus marsupium*	Malabar kino or Indian kino or Vijayasar	Hypoglycemic, antihyperlipidemic	67-70
24.	*Pterocarpus santalinus*	Red sandalwood	Antidiabetic, antioxidant	71
25.	*Punica granatum*	Pomegranate or Anar	Antihyperglycemic, antioxidant,	72
26.	*Scoparia dulcis*	Sweet broomweed	Antihyperlipidemic, hypoglycemic, antioxidant	73-75
27.	*Swertia chirayita*	Chiretta	Stimulates insulin release from islets	76
28.	*Syzygium alternifolium*	Shahajire	Antihyperglycemic, hypoglycemic	77
29.	*Terminalia bellirica*	Behada	Hypoglycemic, antibacterial	78
30.	*Terminalia chebula*	Hirda	Hypoglycemic, antibacterial	78
31.	*Tinospora cordifolia*	Guduchi or giloy	Hypoglycemic, antihyperglycemic, α-amylase inhibitors	18, 79-85
32.	*Trigonella foenum graecum*	Fenugreek	Hypoglycemic, antioxidant, decreased glucose-6-phosphatase and fructose –1,6-biphosphatase activity	86-90
33.	*Withania somnifera*	Ashvagandha	Hypoglycemic, hypocholesterolemic	91
34.	*Zea mays*	Maize or corn	Antioxidant, hypolipidemic	92
35.	Zingiber officinale	Ginger	Hypoglycemic, α-amylase inhibitor	18,79,93,94

3. Therapeutic Uses of Fenugreek

One of the medicinal plants having antidiabetic activity is fenugreek. *Trigonella foenum-graecum* L. (fenugreek) originated from East Asia and Northern Africa and it is one of the medicinally important plants known historically[95]. About 260 species of fenugreek have been described, of which *Trigonella foenum-graecum* is the only one cultivated widely. All parts of fenugreek, such as leaves, seeds and whole plant extract have been used as antidiabetic[96,97] and antiaging[98-102]. Fenugreek seed extract administration on alloxan-induced diabetic mice revealed histopathological and ultrastructural changes in the pancreas by decreasing oxidative stress and preserving pancreatic β cell integrity[103]. Previously, it has been reported that the seed powder of fenugreek shows hypoglycemic and hypolipidemic effects in human as well as animal models[104]. It has been commonly used to treat a variety of diseases including fever, abdominal colic, boils, etc[98,105,106] (Table 2).

4. Active Compounds of Fenugreek

Most of the medicinal research has aimed to evaluate the therapeutic value of plants and identify the related active compounds that can be extracted. Many medicinal plants have antidiabetic potential and bioactive compounds such as glycosides, alkaloids, terpenoids, carotenoids and flavonoids have been confirmed to be effective in both preclinical and clinical studies[125,126]. Fenugreek is an important medicinal plant. Its leaves and seeds contain a variety of bioactive compounds like alkaloids, amino acids, coumarins, flavonoids, saponins, etc. (Table 3), which are beneficial in the treatment of diabetes.

5. Structure of Trigonelline

Trigonelline, a plant alkaloid, was first isolated from *Trigonella foenum-graecum* L. In fenugreek seeds, the percentage of trigonelline is approximately 0.1-0.15 %

Table 2. Fenugreek plant parts and their pharmacological activities

Sr. No.	Plant parts/ phytochemicals	Pharmacological activities	References
1.	Seed	Decrease in blood glucose and triglyceride levels	107
2.	Seeds	Hypoglycemic, hypolipidemic	108-110
3.	Seeds	Reduction in blood glucose, serum total cholesterol, LDL and VLDL cholesterol and triglyceride levels	111
4.	4-Hydroxyisoleucine extracted from seeds	Increase in insulin secretion	86
5.	Seeds	Increased number of insulin receptors	112
6.	Alkaloids, flavonoids, and saponins from seeds	Decrease of lipidemia, glycemia and cholagogic for treating diabetes mellitus	113
7.	Seed extract rich in saponins	Reduction in plasma cholesterol in rats	114
8.	Seeds	Antidiabetic effects	115
9.	Seeds	Antiulcer potential	116
10.	Seeds	Protection against ethanol toxicity	117
11.	Seeds	Hypocholesterolemic effect	118,119
12.	Total aqueous extract	Immunostimulatory effect	120
13.	Seeds	Anti-hyperthyroid effect	121
14.	Seeds	Anticancer effect	122-124

Table 3. Biologically active compounds of fenugreek

Sr. No.	Chemical Group	Compounds	References
1.	Alkaloids	Trigonelline, choline	127
2.	Amino Acids	Aspartic acid, glutamic acid, lysine, phenylalanine, histidine, leucine, 4-hydroxyisoleucine, tryptophan, tyrosine, cysteine, arginine, canavanine	128-131
3.	Coumarins	Trigocumarin, trimethyl coumarin	132-133
4.	Flavonoids	Naringenin, kaempferol, vecenin-1, vecenin-2, tricin, isovitexin, isoorientin. orientin, vitexin, luteolin, quercetin, 7, 4'-dimethoxy flavanones	132, 134-137
5.	Saponins	Fenugrin, foenugracin, glycoside, yamogenin, trigonoesides, smilagenin, gitogenin, sarsasapogenin, yuccagenin, hederagin, diosgenin, tigonenin, neotigogenin	138
6.	Others	Folic acid, ascorbic acid, thiamine, riboflavin, biotin, nicotinic acid, β-Carotene, minerals	127

of the total seed weight[86]. It is commonly used as a spice throughout India[139]. The chemical name of trigonelline is N-methylnicotinic acid the empirical formula of which is $C_7H_7NO_2$. Chemically, trigonelline is derived from vitamin B6. Trigonelline has a zwitterionic structure similar to that of a substrate D-amino acid and is a useful

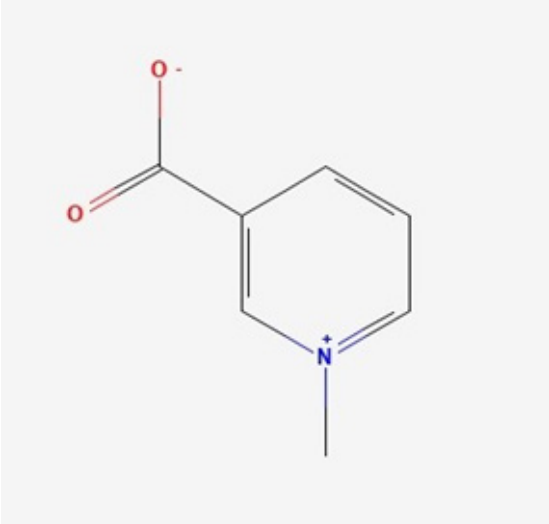

Figure 1. Structure of trigonelline.
(Source:https://pubchem.ncbi.nlm.nih.gov)

active site probe for D-amino acid oxidase[104]. The affinity of trigonelline for D-amino acid oxidase at the enzyme-bound flavin adenine dinucleotide 3-iminogroup is higher than in the deprotonated state in the neutral state, unlike benzoate, which is a monoanionic competitive inhibitor[140].

6. Therapeutic Uses of Trigonelline in Diabetes

Trigonelline is believed to be a plant hormone that is generally distributed in a variety of plant species of the subclass dicotyledonae[141]. Moreover, it has been demonstrated in several animals also such as arthropods, coelenterates, crustaceans, molluscs, echinoderms, marine poriferans, marine fishes, etc. It is also present in the seeds of various legume species and also appears in the urine of mammals after administration of nicotinic acid[104]. In green coffee beans, trigonelline content is about 0.6-1%. Trigonelline contributes to bitterness in coffee and it is easily soluble in water. Consumption of coffee helps in glucose homeostasis[142]. Trigonelline has demonstrated that it has sedative[143], antimigraine[144], antibacterial[145], antiviral[146], anti-platelet aggregation[147], anti-tumor[148,149], memory retention enhansion[150], hypoglycemic[151,152], hypolipidemic etc., effectx[153].

The hypoglycemic effect of trigonelline was seen in STZ-HFD (Streptozotocin-High Fat Diet) induced T2DM rats after administration of trigonelline for 28 days[151]. In another diabetic rat model (Sabra albino) trigonelline showed a good hypoglycemic effect in alloxan-induced diabetes[152]. In KK-Ay mice (genetically modified T2DM mice model), after administration of trigonelline and nicotinic acid, the level of serum TNF-α (Tumor Necrosis Factor-alpha) has been lowered compared to diabetic mice[154]. Also, the activity of glucokinase has been increased after trigonelline administration and conversely, the activity of G-6p-ase decreased in KKAy mice[154]. It is seen that trigonelline has the ability to inhibit sodium-dependent glucose uptake in the intestinal brush border of rabbit[155].

In another study by Goto-Kakizaki, it has been observed that trigonelline improves glucose tolerance after one hour of the Oral Glucose Tolerance Test[154]. Trigonelline and nicotinic acid have shown hypoglycemic effects after Oral Glucose Tolerance Test, which suggests that trigonelline improves glucose tolerance in diabetes as well as in obesity. These observations suggest that a diet containing trigonelline helps improve glucose tolerance[154]. Trigonelline-administrated rats showed increased insulin levels and improved insulin sensitivity[153]. Similar observations recorded that the trigonelline has the ability to regenerate β-cells[151]. Studies showed that trigonelline helps in reducing cholesterol levels in plasma in rat model[156]. Trigonelline also decreases fatty acid synthase activity in the liver and, conversely, it increases the activity of carnitine palmitoyl transferase and glucokinase, enzymes responsible for the inhibition of trigonelline in diabetes[153]. The antioxidative effect of trigonelline was studied in HT-29/Caco-2 cells in which trigonelline was involved in the reduction of Reactive Oxygen Species (ROS) levels[157]. It has been demonstrated that after treatment with trigonelline for 28 days, the diabetic rats showed decreased NO (Nitric Oxide) and MDA (Malondialdehyde) but conversely raised the level of SOD (Superoxide Dismutase), CAT (Catalase) and GPx (Glutathione Peroxidase) in the pancreas. These observations suggest that trigonelline has the ability to up-regulate antioxidative enzyme activities by decreasing lipid peroxidation[151]. Trigonelline also induces an antioxidant effect on liposome peroxidation[158]. The alkaloid trigonelline has possible antidiabetic effects and its treatment through food is considered to decrease oxidative stress in T2DM rats confirming its antioxidative effect[159]. Further nano-scaling of trigonelline reduces oxidative stress and improves antioxidative status in diabetic mice[160].

7. Present Scenario and Future Perspectives

Diabetes mellitus is routinely treated by a variety of synthetic antidiabetic drugs like sulphonylureas, biguanides, thiazoldinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, glinides, etc.[161]. Despite the widespread use of these drugs, they cause various adverse effects[162]. Researchers are looking for antidiabetic medications made from plants that have a better safety and efficacy profile. Bioactive compounds isolated from medicinal plants show prominent antidiabetic action. Therefore, potential bioactive compounds from medicinal plants, which have been shown to be effective in both preclinical and clinical studies and used to treat diabetes, can be considered potential compounds for the development of new antidiabetic drugs.

The clinical evidence for fenugreek is stronger than for other medicinal plants. World Health Organization monographs as well as the European Medicines Agency supported the use of fenugreek and officially published assessment reports on it[163]. One of the important bioactive compounds isolated from fenugreek is trigonelline. It is also derived from coffee beans, garden peas, hemp seeds and oats. Plants containing trigonelline at levels of more than 1000 ppm include fenugreek and coffee. The use of trigonelline is a potential treatment for certain disorders related to diabetes such as hyperglycemia, hyperlipidemia, insulin resistance and diabetic auditory neuropathy. However, further study of trigonelline's pharmacological activities and the exact molecular mechanism is needed, which would facilitate its development as a drug. This can also guide the recognition of complex and novel molecular pathways. Hence, further research on trigonelline will enable the discovery of several targets for therapeutic intervention against diabetes mellitus.

8. Conclusion

This review provides comprehensive information about the promising antidiabetic plant – fenugreek, and its bioactive compound – trigonelline. Trigonelline from fenugreek seeds reduces blood glucose by regenerating β-cells in islets of Langerhans of the pancreas, and thus insulin secretion also increases. Further, the glucose uptake by muscle and liver cells also increases which ultimately leads to a lowering of blood glucose levels. So, in order to treat diabetes, regular intake of fenugreek seeds is good, and if one is taking trigonelline, it is the best way to treat diabetes. Trigonelline can be explored further to develop pharmaceutical drugs against diabetes and diabetes-related complications.

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10. References

1. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002; 23(4):373-78.
2. IDF Diabetes Atlas, 10thEd. International Diabetes Federation; 2021.
3. Madras Diabetes Research Foundation (India), 2014. http:// mdrf.in.
4. ICMR Guidelines for Management of Type 2 Diabetes, Indian Council of Medical Research; 2018.
5. Joshi SR. Metabolic syndrome—emerging clusters of the Indian phenotype. J Assoc Physi Ind. 2003; 51:445–6.
6. Deepa R, Sandeep S, Mohan V, *et al*. Abdominal obesity, visceral fat and type 2 diabetes—Asian Indian phenotype, in Type 2 Diabetes in South Asians: Epidemiology, Risk Factors and Prevention. Jaypee Brothers Medical Publishers, New Delhi, India; 2006. pp. 138–52.
7. Chandalia M, Abate N, Garg AJ, *et al*. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. J Clin Endocrinol Metab. 1999; 84(7):2329–35. https://doi.org/10.1210/jc.84.7.2329
8. Ramachandran A, Snehalatha C, Viswanathan V, *et al*. Risk of non-insulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites. Diab Res Clin Pract. 1997; 36(2):121–5. https://doi.org/10.1016/S0168-8227(97)00040-5
9. Hannan MA, Selim S, Saha M, Miah MA. Screening the Risk Factors of Diabetes Mellitus in 1st year MBBS

and BDS Students of a Medical College in Bangladesh. J Endocrinol Reprod. 2022; 26(2):119-26.
10. Madiraju AK, Erion DM, Rahimi Y, *et al*. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature. 2014; 510:542–6. https://doi.org/10.1038/nature13270
11. Kiersztan A, Modzelewska A, Jarzyna R, *et al*. Inhibition of gluconeogenesis by vanadium and metformin in kidney-cortex tubules isolated from control and diabetic rabbits. Biochem Pharmacol. 2002; 63:1371–82. https://doi.org/10.1016/S0006-2952(02)00861-4
12. Cornell S. Type 2 Diabetes Treatment Recommendations Update: Appropriate Use of Dipeptidyl Peptidase-4 Inhibitors. J Diabetes Metab. 2014; 05:8. https://doi.org/10.4172/2155-6156.1000414
13. Lawal HA, Atiku MK, Khelpai DG, Wannang NN. Hypoglycaemic and hypolipidaemic effect of aqueous leaf extract of Murraya koenigii in normal and alloxan-diabetic rats. Niger J Physiol Sci. 2008; 23:37–40. https://doi.org/10.4314/njps.v23i1-2.54919
14. Kasiviswanath R, Ramesh A, Kumar KE. Hypoglycemic and antihyperglycemic effect of Gmelina asiatica Linn. in normal and in alloxan induced diabetic rats. Biol Pharm Bull. 2005; 28(4):729–32. https://doi.org/10.1248/bpb.28.729
15. Akhtar FM, Ali MR. Study of the anti diabetic effect of a compound medicinal plant prescription in normal and diabetic rabbit. J Pakistan Med Assoc. 1984; 34:239-44.
16. Brinker FJ. Herb contraindications and drug interactions: With appendices addressing specific conditions and medicines. 2nd ed. Oregon (USA): Eclectic Medical Publications; 1998.
17. Pepato MT, Baviera AM, Vendramini RC, *et al., Cissus sicyoides* (princess vine) in the long-term treatment of streptozotocin-diabetic rats. Biotechnol Appl Biochem. 2003; 37:15-20. https://doi.org/10.1042/BA20020065
18. Sudha P, Zinjarde SS, Bhargava SY, Kumar AR. Potent α-amylase inhibitory activity of Indian Ayurvedic medicinal plants. BMC Complement Altern Med. 2011; 11(5):1-10. https://doi.org/10.1186/1472-6882-11-5
19. Mootoosamy A, Mahomoodally MF. Ethnomedicinal application of native remedies used against diabetes and related complications in Mauritius. J Ethnopharmacol. 2014; 151:413–44. https://doi.org/10.1016/j.jep.2013.10.069
20. Roman-Ramos R, Flores-Saenz JL, Alarcon-Aguilar FJ. Anti-hyperglycemic effect of some edible plants. J Ethnopharmacol. 1995; 48:25–32. https://doi.org/10.1016/0378-8741(95)01279-M
21. Sukandar EY, Adnyana IK, Nurfitria RS. Antioxidant potential of garlic and turmeric mixture - A traditional Indonesian formulation. Indian J Trad Knowl. 2015; 14:632–6.
22. Moradabadi L, Kouhsari SM, Sani MF. Hypoglycemic effects of three medicinal plants in experimental diabetes: Inhibition of rat intestinal α-glucosidase and enhanced pancreatic insulin and cardiac GLUT-4 mRNAs expression. Iran J Pharm Res. 2013; 12:385–97.
23. Mesa MG. Hypolipidemic potential of plants used in Cuba. Pharmacologyonline 2014; 1:73–80.
24. Karou SD, Tchacondo T, Tchibozo MAD, *et al*. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus and hypertension in the Central Region of Togo. Pharm Biol. 2011; 49:1286–97. https://doi.org/10.3109/13880209.2011.621959
25. Xie W, Du L. Diabetes is an inflammatory disease: Evidence from traditional Chinese medicines. Diabetes Obes Metab. 2011; 13:289–301. https://doi.org/10.1111/j.1463-1326.2010.01336.x
26. Kaleem M, Asif M, Ahmed QU, Bano B. Antidiabetic and antioxidant activity of *Annona squamosa* extract in streptozotocin-induced diabetic rats. Singapore Med J. 2006; 47:670–5.
27. Gupta RK, Kesari AN, Murthy PS, *et al*. Hypoglycemic and antidiabetic effect of ethanolic extract of leaves of *Annona squamosa* L. in experimental animals. J Ethnopharmacol. 2005; 99:75–81. https://doi.org/10.1016/j.jep.2005.01.048
28. Gupta RK, Kesari AN, Watal G, *et al*. Nutritional and hypoglycemic effect of fruit pulp of *Annona squamosa* in normal healthy and alloxan-induced diabetic rabbits. Ann Nutr Metab. 2005; 49:407-13. https://doi.org/10.1159/000088987
29. Chempakam B. Hypoglycemic activity of arecoline in betel nut *Areca catechu* L. Indian J Exp Biol. 1993; 31:474–5.
30. Subramonium A, Pushpangadan P, Rajasekharan A, *et al*. Effects of *Artemisia pallens* Wall. On blood glucose levels in normal and alloxan-induced diabetic rats. J Ethnopharmacol.1996; 50:13–7. https://doi.org/10.1016/0378-8741(95)01329-6
31. Pari L, Amarnath Satheesh M. Antidiabetic activity of *Boerhavia diffusa* L. effect on hepatic key enzymes in experimental diabetes. J Ethnopharmacol. 2004; 91:109–13. https://doi.org/10.1016/j.jep.2003.12.013
32. Satheesh MA, Pari L. Antioxidant effect of *Boerhavia diffusa* L. in tissues of alloxan induced diabetic rats. Indian J Exp Biol.2004; 42:989–92.

33. Pari L, Amarnath Satheesh M. Antidiabetic effect of *Boerhavia diffusa*: effect on serum and tissue lipids in experimental diabetes. J Med Food. 2004; 7:472–6. https://doi.org/10.1089/jmf.2004.7.472
34. Arora S, Haldar C, Basu P, *et al*. Oral Administration of Root Extract of *Boerhaavia diffusa* Mitigates Diabetes-induced Kidney Damages in the Golden Hamster *Mesocricetus auratus*. J Endocrinol Reprod. 2022; 26(3):163-170.
35. Arora S, Haldar C. Diabetes: Rescue by *Boerhaavia diffusa*. J Endocrinol Reprod. 2018; 22(2):1-3.
36. Saleem R, Ahmad M, Hussain SA, *et al*. Hypotensive, hypoglycemic and toxicological studies on the flavonol C-glycoside shamimin from *Bombax ceiba*. Planta Med. 1999; 5:331–4. https://doi.org/10.1055/s-1999-14060
37. Somani R, Kasture S, Singhai AK. Antidiabetic potential of *Butea monosperma* in rats. Fitoterapia. 2006; 77:86–90. https://doi.org/10.1016/j.fitote.2005.11.003
38. Chakrabarti S, Biswas TK, Seal T, *et al*. Antidiabetic activity of *Caesalpinia bonducella* F. in chronic type 2 diabetic model in Long-Evans rats and evaluation of insulin secretagogue property of its fractions on isolated islets. J Ethnopharmacol. 2005; 97:117–22. https://doi.org/10.1016/j.jep.2004.10.025
39. Chakrabarti S, Biswas TK, Rokeya B, *et al*. Advanced studies on the hypoglycemic effect of *Caesalpinia bonducella* F. in type 1 and 2 diabetes in Long Evans rats. J Ethnopharmacol. 2003; 84:41–46. https://doi.org/10.1016/S0378-8741(02)00262-3
40. Sharma SR, Dwivedi SK, Swarup D. Hypoglycemic, antihyperglycemic and hypolipidemic activities of *Caesalpinia bonducella* seeds in rats. J Ethnopharmacol. 1997; 58:39–44. https://doi.org/10.1016/S0378-8741(97)00079-2
41. Gomes A, Vedasiromoni JR, Das M, *et al*. Antihyperglycemic effect of black tea (*Camellia sinensis*) in rats. J Ethnopharmacol. 1995; 45:223– 226. https://doi.org/10.1016/0378-8741(95)01223-Z
42. Devasagayam TPA, Kamat JP, Mohan H, Kesavan PC. Caffeine as an antioxidant: Inhibition of lipid peroxidation induced by reactive oxygen species in rat liver microsomes. Biochim Biophys Acta. 1996; 1282:63–70. https://doi.org/10.1016/0005-2736(96)00040-5
43. Agarwal V, Chauhan BM. A study on composition and hypolipidemic effect of dietary fiber from some plant foods. Plant Foods Human Nutr. 1988; 38:189–97. https://doi.org/10.1007/BF01091723
44. Kamble SM, Kamlakar PL, Vaidya S, Bambole VD. Influence of *Coccinia indica* on certain enzymes in glycolytic and lipolytic pathway in human diabetes. Indian J Med Sci. 1998; 52:143–6.
45. Kuroda M, Mimaki Y, Nishiyama T, *et al*., Hypoglycaemic effects of turmeric (*Curcumalonga* L. rhizomes) on genetically diabetic KK-Ay mice. Biol Pharm Bull. 2005; 28:937-9. https://doi.org/10.1248/bpb.28.937
46. Lekshmi PC, Arimboor R, Nisha VM, *et al*. *In vitro* anti-diabetic and inhibitory potential of turmeric (*Curcuma longa* L.) rhizome against cellular and LDL oxidation and angiotensin converting enzyme. J Food Sci Technol. 2014; 51(12):3910-7. https://doi.org/10.1007/s13197-013-0953-7
47. Bhattacharya A, Chatterjee A, Ghosal S, Bhattacharya SK. Antioxidant activity of active tannoid principles of *Emblica officinalis* (amla). Indian J Exp Biol. 1999; 37:676–80.
48. Kumar KCS, Muller K. Medicinal plants from Nepal, II. Evaluation as inhibitors of lipid peroxidation in biological membranes. J Ethnopharmacol. 1999; 64:135–9. https://doi.org/10.1016/S0378-8741(98)00117-2
49. Devasagayam TPA, Subramanian M, Singh BB, *et al*. Protection of plasmid pBR322 DNA by flavonoids against single-strand breaks induced by singlet molecular oxygen. J Photochem Photobiol. 1995; 30:97–103. https://doi.org/10.1016/1011-1344(95)07159-Y
50. Maroo J, Vasu VT, Gupta S. Dose-dependent hypoglycemic effect of aqueous extract of *Enicostemma littorale* blume in alloxan-induced diabetic rats. Phytomedicine. 2003; 10:196–9. https://doi.org/10.1078/094471103321659933
51. Vijayvargia R, Kumar M, Gupta S. Hypoglycemic effect of aqueous extract of *Enicostemma littorale* Blume (chhota chirayata) on alloxan induced diabetes mellitus in rats. Indian J Exp Biol. 2000; 38:781–4.
52. Arai I, Amagaya S, Komatzu Y, *et al*. Improving effects of the extracts from *Eugenia uniflora* on hyperglycemia and hypertriglyceridemia in mice. J Ethnopharmacol. 1999; 68:307–14. https://doi.org/10.1016/S0378-8741(99)00066-5
53. Augusti KT, Daniel RS, Cherian S, *et al*. Effect of Leucoperalgonin derivative from *Ficus benghalensis* Linn. on diabetic dogs. Indian J Med Res. 1994; 99:82–6.
54. Chattopadhyay RR. A comparative evaluation of some blood sugar lowering agents of plant origin. J Ethnopharmacol. 1999; 67:367–72. https://doi.org/10.1016/S0378-8741(99)00095-1
55. Preuss HG, Jarrell ST, Scheckenbach R, *et al*. Comparative effects of chromium, vanadium and *Gymnema sylvestre* on sugar-induced blood pressure elevations in SHR. J

Am Coll Nutr. 1998; 17:116–23. https://doi.org/10.1080/07315724.1998.10718736
56. Khanna P, Jain SC, Panagariya A, Dixit VP. Hypoglycemic activity of polypeptide-p from a plant source. J Nat Prod. 1981; 44:648–55. https://doi.org/10.1021/np50018a002
57. Shibib BA, Khan LA, Rahman R. Hypoglycemic activity of *Coccinia indica* and *Momordica charantia* in diabetic rats: Depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1, 6-biphosphatase and elevation of liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. Biochem J. 1993; 292:267–70. https://doi.org/10.1042/bj2920267
58. Nagaraju N. Biochemical studies on some medicinal plants of Rayalaseema region. PhD thesis. SV University, Tirupathi, 1992.
59. Rao BK, Kessavulu MM, Giri R, Apparao C. Antidiabetic and hypolipidemic effects of *Momordica cymbalaria* Hook fruit powder in alloxan-diabetic rats. J Ethnopharmacol. 1999; 67:103–9. https://doi.org/10.1016/S0378-8741(99)00004-5
60. Khan BA, Abraham A, Leelamma S. Hypoglycemic action of *Murraya koenigii* (curry leaf) and *Brassica juncea* (mustard) mechanism of action. Indian J Biochem Biophys. 1995; 32:106–108.
61. Dhanabal SP, Sureshkumar M, Ramanathan M, Suresh B. Hypoglycemic effect of ethanolic extract of *Musa sapientum* on alloxan induced diabetes mellitus in rats and its relation with antioxidant potential. J Herb Pharmacother. 2005; 5:7–19. https://doi.org/10.1080/J157v05n02_02
62. Pari L, Umamaheswari J. Antihyperglycaemic activity of *Musa sapientum* flowers: effect on lipid peroxidation in alloxan diabetic rats. Phytother Res. 2000; 14:136–138. https://doi.org/10.1002/(SICI)1099-1573(200003)14:2<136::AID-PTR607>3.0.CO;2-K
63. Pari L, Maheswari JU. Hypoglycemic effect of *Musa sapientum* L. in alloxan-induced diabetic rats. J Ethnopharmacol. 1999; 68:321–5. https://doi.org/10.1016/S0378-8741(99)00088-4
64. Tormo MA, Gil-Exojo I, Romero de Tejada A, Campillo JE. Hypoglycemic and anorexigenic activities of an alpha-amylase inhibitor from white kidney beans (*Phaseolus vulgaris*) in Wistar rats. Br J Nutr. 2004; 92:785– 90. https://doi.org/10.1079/BJN20041260
65. Pari L, Venkateswaran S. Protective role of *Phaseolus vulgaris* on changes in the fatty acid composition in experimental diabetes. J Med Food. 2004; 7:204–9. https://doi.org/10.1089/1096620041224120
66. Knott RM, Grant G, Bardocz S, *et al*., Alterations in the level of insulin receptor and GLUT-4 mRNA in skeletal muscle from rats fed a kidney bean (*Phaseolus vulgaris*) diet. Int J Biochem. 1992; 24:897–902. https://doi.org/10.1016/0020-711X(92)90094-H
67. Haranath PSRK, Ranganathrao K, Anjaneyulu CR, Ramnathan JD. Studies on the hypoglycemic and pharmacological actions of some stilbenes. Indian J Med Sci. 1958; 12:85–89.
68. Joglekar GV, Chaudhary NY, Aiaman R. Effect of Indian medicinal plants on glucose absorption in mice. Indian J Physiol Pharmacol. 1959; 3:76–7.
69. Chakravarty BK, Gupta S, Gambhir SS, Gode KD. Pancreatic beta cell regeneration. A novel antidiabetic mechanism of *Pterocarpus marsupium* Roxb. Indian J Pharmacol. 1980; 12:123–7.
70. Jahromi MA, Ray AB, Chansouria JPN. Antihyperlipidemic effect of flavonoids from *Pterocarpus marsupium*. J Nat Prod. 1993; 56:989–94. https://doi.org/10.1021/np50097a001
71. Pagadala JC, Yenugu S, Gudipalli P. Anti-diabetic Activity of Partially Purified Santalin A from the Heartwood of *Pterocarpus santalinus* L.f. in Alloxan-induced Diabetic Wistar Rat J Endocrinol Reprod. 2021; 25(1):65-78.
72. Jafri, M.A., Aslam, M., Javed, K., and Singh, S.: Effect of *Punica granatum* Linn. (flowers) on blood glucose level in normal and alloxan induced diabetic rats. J Ethnopharmacol. 2000; 70:309–14. https://doi.org/10.1016/S0378-8741(99)00170-1
73. Pari L, Latha M. Antidiabetic effect of *Scoparia dulcis*: effect on lipid peroxidation in streptozotocin diabetes. Gen Physiol Biophys. 2005; 24:13–26.
74. Pari L, Latha M. Antihyperlipidemic effect of *Scoparia dulcis* (sweet broomweed) in streptozotocin diabetic rats. J Med Food. 2006; 9:102–107. https://doi.org/10.1089/jmf.2006.9.102
75. Latha M, Pari L, Sitasawad S, Bhonde, R. Insulin secretagogue activity and cytoprotective role of the traditional antidiabetic plant *Scoparia dulcis* (Sweet Broomweed). Life Sci. 2004; 75:2003–14. https://doi.org/10.1016/j.lfs.2004.05.012
76. Saxena AM, Bajpai MB, Murthy PS, Mukherjee SK. Mechanism of blood sugar lowering by a Swerchirin containing hexane fraction (SWI) of *Swertia chirayita*. Indian J Exp Biol. 1993; 31:178–81.
77. Rao BK, Rao CH. Hypoglycemic and antihyperglycemic activity of *Syzygium alternifolium* (Wt.) Walp. seed extracts in normal and diabetic rats. Phytomedicine.

2001; 8: 88–93. https://doi.org/10.1078/0944-7113-00015
78. Sabu MC, Kuttan R. Antidiabetic activity of medicinal plants and its relationship with their antioxidant property. J Ethnopharmacol. 2002; 81:155–60. https://doi.org/10.1016/S0378-8741(02)00034-X
79. Kar A, Choudhary BK, Bandyopadhyay NG. Comparative evaluation of hypoglycaemic activity of some Indian medicinal plants in alloxan diabetic rats. J Ethnopharmacol. 2003, 84:105–8. https://doi.org/10.1016/S0378-8741(02)00144-7
80. Dineshkumar B, Analava M, Manjunatha M. Antidiabetic and hypolipidaemic effects of few common plants extract in type 2 diabetic patients at Bengal. Int J Diabetes Metabol. 2010; 18:59–65. https://doi.org/10.1159/000497694
81. Marwat SK, Fazal UrR, Khan EA, *et al*. Useful ethnophytomedicinal recipes of angiosperms used against diabetes in South East Asian countries (India, Pakistan and Sri Lanka). Pak J Pharma Sci. 2014; 27:1333–58.
82. Tanaka M, Kishimoto Y, Saita E, *et al*. *Terminalia bellirica* extract inhibits low-density lipoprotein oxidation and macrophage inflammatory response *in vitro*. Antioxidants. 2016; 5(2):20. https://doi.org/10.3390/antiox5020020
83. Sharma R, Amin H, Galib, Prajapati PK. Antidiabetic claims of *Tinospora cordifolia* (Willd.) miers: Critical appraisal and role in therapy. Asian Pac J Trop Biomed. 2015; 5:68–78. https://doi.org/10.1016/S2221-1691(15)30173-8
84. Patel MB, Mishra S. Hypoglycemic activity of alkaloidal fraction of *Tinospora cordifolia*. Phytomedicine. 2011; 18:1045–52. https://doi.org/10.1016/j.phymed.2011.05.006
85. Thomas A, Rajesh EK, Kumar DS. The significance of *Tinospora crispa* in treatment of diabetes mellitus. Phytother Res. 2016; 30:357–66. https://doi.org/10.1002/ptr.5559
86. Sauvaire Y, Petit P, Broca C, *et al*. 4-hydroxyisoleucine: A novel amino acid potentiator of insulin secretion. Diabetes. 1998; 47(2):206–10. https://doi.org/10.2337/diab.47.2.206
87. Khosla P, Gupta DD, Nagpal RK. Effect of *Trigonella foenum graecum* (fenugreek) on blood glucose in normal and diabetic rats. Indian J Physiol Pharmacol. 1995; 39:173–4.
88. Gupta D, Raju J, Baquer NZ. Modulation of some gluconeogenic enzyme activities in diabetic rat liver and kidney: Effect of antidiabetic compounds. Indian J Exp Biol. 1999; 37:196–9.
89. Ravikumar P, Anuradha CV. Effect of fenugreek seeds on blood lipid peroxidation and antioxidants in diabetic rats. Phytother Res. 1999; 13:197–201. https://doi.org/10.1002/(SICI)1099-1573(199905)13:3<197::AID-PTR413>3.0.CO;2-L
90. Dixit PP, Ghaskadbi SS, Hari M, Devasagayam TPA. Antioxidant properties of germinated fenugreek seeds. Phytother Res. 2005; 19:977–83. https://doi.org/10.1002/ptr.1769
91. Adallu B, Radhika B. Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (*Withania somnifera*, Dunal) root. Indian J Exp Biol. 2000; 38:607–9.
92. Arora S, Haldar C. Phytomelatonin (*Zea mays*) Supplementation Restores the Damage Caused by Induced-Diabetes in the Golden Hamster *Mesocricetus auratus.* J Endocrinol Reprod. 2020; 24(2):81-6.
93. Ranilla LG, Kwon YI, Apostolidis E, Shetty K. Phenolic compounds, antioxidant activity and *in vitro* inhibitory potential against key enzymes relevant for hyperglycemia and hypertension of commonly used medicinal plants, herbs and spices in Latin America. Bioresour Technol. 2010; 101:4676–89. https://doi.org/10.1016/j.biortech.2010.01.093
94. Morakinyo AO, Akindele AJ, Ahmed Z. Modulation of antioxidant enzymes and inflammatory cytokines: Possible mechanism of anti-diabetic effect of ginger extracts. Afr J Biomed Res. 2011; 14:195–202.
95. Prajapati ND, Purohit SS, Sharma AK, Kumar T. A Handbook of Medicinal Plants: A Complete Source Book. Jodhpur (India): Agrobios Publisher; 2003. 523 p.
96. Sharma R. Effect of fenugreek seeds and leaves on blood glucose and serum insulin responses in human subjects. Nutr Res. 1986; 6:1353-64. https://doi.org/10.1016/S0271-5317(86)80020-3
97. Petropoulos GA. Fenugreek: the genus Trigonella. CRC. 2002; 11:1-201. https://doi.org/10.1201/9780203217474
98. Deshmukh VM, Walvekar MV, Desai SR. Modulatory effect of fenugreek (*Trigonella foenum graceum)* seed extract on salivary glands lipofuschinogenesis in aging accelerated male mice. Int J Pharm Bio Sci. 2014; 5(2):83-9.
99. Deshmukh VM, Walvekar MV, Khairmode SP. Protective role of *Trigonella foenum graceum* (fenugreek) seed extract on oxidative stress in salivary glands of aging accelerated mice. Arch Appl Sci Res. 2014; 6(1):92-6.

100. Walvekar MV, Deshmukh VM, Pol SB. Structural and cytochemical study of salivary glands after fenugreek seed extract administration in oxidatively stressed mice. Int J Pharmacogn Phytochem Res. 2015; 7(3):395-400.
101. Deshmukh VM, Walvekar MV, Desai SS. Effect of *Trigonella foenum graceum* (fenugreek) -loaded PLGA nanoparticles on non-specific esterase enzyme activity in salivary glands of aging accelerated mice. J Endocrinol Reprod. 2015; 19(1):34-39. https://doi.org/10.18519/jer/2015/v19/86058
102. Deshmukh VM, Walvekar MV, Ghadage YK, Deshpande VY. Protective effect of fenugreek seed extract on lipofuscinogenesis and antioxidative profile in reproductive system of aging accelerated male mice. Int J Curr Biotechnol. 2020; 8(4):1-6.
103. Walvekar MV, Pol SB, Chandrashekhar Sagar BK. Histopathological and ultrastructural studies of the effect of fenugreek seed extract on pancreas of alloxan induced diabetic mice. Int J Pharm Sci Res. 2014; 5(7):1-16.
104. Zhou J, Chan L, Zhou S. Trigonelline: a Plant Alkaloid with Therapeutic Potential for Diabetes and Central Nervous System Disease. Curr Med Chem. 2012; 19:3523-31. https://doi.org/10.2174/092986712801323171
105. Riyad MA, Abdul-Salam SA, Mohammad SS. Effect of Fenugreek and Lupine seeds on the development of experimental diabetes in rats. Planta Med. 1988; 54:286–90. https://doi.org/10.1055/s-2006-962434
106. Sharma RD, Raghuram TC. Hypoglycaemic effect of fenugreek seeds in non-insulin dependent diabetic subjects. Nutr Res. 1990; 10:731–9. https://doi.org/10.1016/S0271-5317(05)80822-X
107. Mitra A, Bhattacharya D. Dose-dependent effects of Fenugreek composite in diabetes with dislipidaemia. Int J Food Safety. 2006; 8:49-55.
108. Madar Z, Abel R, Samish S, Arad J. Glucose-lowering effect of fenugreek in non-insulin dependent diabetics. Eur J Clin Nutr 1988; 42(1):51-4.
109. Jain V, Jain P, Sharma S, Kakani R. Hypolipidaemic activity of syndrex, a hydroalcoholic extract of fenugreek seeds: Single blind clinical study. Int Med J. 1995; 89:1-41.
110. Sharma RD, Sarkar A, Hazra DK, *et al.* Toxicological evaluation of fenugreek seeds: a long term feeding experiment in diabetic patients. Phytother Res. 1996; 10(6):519-20. https://doi.org/10.1002/(SICI)1099-1573(199609)10:6<519::AID-PTR873>3.0.CO;2-T
111. Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Eur J Clin Nutr. 1990; 44(4):301-6.
112. Raghuram TC, Sharma RD, Sivakumar B, Sahay BK. Effect of fenugreek seeds on intravenous glucose disposition in non-insulin dependent diabetic patients. Phytother Res. 1994; 8(2):83-6. https://doi.org/10.1002/ptr.2650080206
113. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. Int J Card. 2005; 98(1):1-14. https://doi.org/10.1016/j.ijcard.2003.06.039
114. Petit PR, Sauvaire YD, Hillaire-Buys DM, *et al.,* Steroid saponins from fenugreek seeds: extraction, purification, and pharmacological investigation on feeding behaviour and plasma cholesterol. Steroids. 1995; 60(10):674-80. https://doi.org/10.1016/0039-128X(95)00090-D
115. Ribes G, Sauvaire Y, Da Costa C, *et al.* Antidiabetic effects of subtractions from fenugreek seeds in diabetic dogs. Exp Biol Med. 1986; 182(2):159-66. https://doi.org/10.3181/00379727-182-42322
116. Suja Pandian R, Anuradha CV, Viswanathan P. Gastroprotective effect of fenugreek seeds (*Trigonella foenum-graecum*) on experimental gastric ulcer in rats. J Ethnopharmacol. 2002; 81(3):393-97. https://doi.org/10.1016/S0378-8741(02)00117-4
117. Thirunavukkarasu V, Anuradha CV, Viswanathan P. Protective effect of fenugreek (*Trigonella foenum-graecum*) seeds in experimental ethanol toxicity. Phytother Res. 2003; 17:737–43. https://doi.org/10.1002/ptr.1198
118. Sowmya P, Rajyalakshmi P. Hypocholesterolemic effect of germinated fenugreek seeds in human subjects. Plan Food Hum Nutr. 1999; 53(4):359-65. https://doi.org/10.1023/A:1008021618733
119. Xue WL, Li XS, Zhang J, *et al.* Effect of *Trigonella foenum-graecum* (fenugreek) extract on blood glucose, blood lipid and hemorheological properties in streptozotocin-induced diabetic rats. Asia Pac J Clin Nutr. 2007; 1:422–6.
120. Bin-Hafeez B, Haque R, Parvez S, *et al.* Immunomodulatory effects of fenugreek (*Trigonella foenum-graecum* L.) extract in mice. Int Immunopharmacol. 2003; 3:257–65. https://doi.org/10.1016/S1567-5769(02)00292-8
121. Tahiliani P, Kar A. The combined effects of *Trigonella* and *Allium* extracts in the regulation of hyperthyroidism in rats. Phytomedicine. 2003; 10:665–8. https://doi.org/10.1078/0944-7113-00277

122. Shabbeer S, Sobolewski M, Anchoori RK, *et al.* Fenugreek: A naturally occurring edible spice as an anticancer agent. Cancer Biol Ther. 2009; 8(3):272-8. https://doi.org/10.4161/cbt.8.3.7443
123. Amin A, Alkaabi A, Al-Falasi S, Daoud SA. Chemopreventive activities of *Trigonella foenum-graecum* (Fenugreek) against breast cancer. Cell Biol Int. 2001; 29:687–94. https://doi.org/10.1016/j.cellbi.2005.04.004
124. Verma SK, Singh SK, Mathur A. *In vitro* cytotoxicity of *Calotropis procera* and *Trigonella foenum-graecum* against human cancer cell lines. J Chem Pharm Res. 2010; 2:861–5.
125. Loew D, Kaszkin M. Approaching the Problem of Bioequivalence of Herbal Medicinal Products. Phyther Res. 2002; 16:705–11. https://doi.org/10.1002/ptr.1248
126. Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. Phytomedicine. 1995; 2(2):137–89. https://doi.org/10.1016/S0944-7113(11)80059-0
127. Srinivasan K. Fenugreek (*Trigonella foenum-graecum*): A review of health beneficial physiological effects. Food Rev Intl. 2006; 22:203–24. https://doi.org/10.1080/87559120600586315
128. Hidvegi M, El-Kady A, Lasztity R, *et al*. Contributions to the nutritional characterization of fenugreek (*Trigonella foenum-graecum* L). Acta Aliment. 1984; 13:315–24.
129. Fowden L, Pratt H, Smith A. 4-Hydroxyisoleucine from seed of *Trigonella foenum-graecum*. Phytochem. 1973; 12:1707–11. https://doi.org/10.1016/0031-9422(73)80391-7
130. Sauvaire Y, Girardon P, Baccou JC, Risterucci AM. Changes in the growth, proteins and free amino acids of developing seed and pod of fenugreek. Phytochem. 1984; 23:479–86. https://doi.org/10.1016/S0031-9422(00)80363-5
131. Birdsong BA, Alston R, Turner BL. Distribution of canavanine in the family leguminosae as related to phyletic groupings. Can J Bot. 1960; 38:499–505. https://doi.org/10.1139/b60-046
132. Parmar VS, Singh S, Rathore JS. A structure revision of trigocoumarin. J Chem Res Synop. 1984; 11:378.
133. Khurana SK, Krishnamoorthy V, Parmar VS, *et al*. 3, 4, 7-Trimethylcoumarin from *Trigonella foenum-graecum* stems. Phytochem. 1982; 21:2145–6. https://doi.org/10.1016/0031-9422(82)83074-4
134. Skaltsa H, Petropoulos GA. Fenugreek—The Genus *Trigonella*. Taylor and Francis, London and New York. 2002; pp. 132–61. https://doi.org/10.1201/9780203217474
135. Seshadri TR, Varshney IP, Sood AR. Study of glycosides from *T. corniculata* Linn. and *T. foenum-graecum* Linn seeds. Curr Sci India. 1973; 42:421–2.
136. Wagner H, Iyengar MA, Horhammer L. Vicenin-1 and -2 in the seeds of *Trigonella foenum-graecum*. Phytochem. 1973; 12:2548. https://doi.org/10.1016/0031-9422(73)80481-9
137. Shang M, Cai S, Han J, *et al*. Studies on flavonoids from Fenugreek (*Trigonella foenum-graecum* L.). Zhongguo Zhong Yao Za Zhi. 1998; 23(10):614-6, 39.
138. Soliman G, Mustafa Z. The Saponin of Fenugreek Seeds. Nature. 1943; 151:195–6. https://doi.org/10.1038/151195b0
139. Zia T, Hasnain SN, Hasan SK. Evaluation of the oral hypoglycaemic effect of *Trigonella foenum-graecum* L. (methi) in normal mice. J Ethnopharmacol. 2001; 75:191–5. https://doi.org/10.1016/S0378-8741(01)00186-6
140. Nishina Y, Sato K, Shiga K. Proton release from flavoprotein D-amino acid oxidase on complexation with the zwitterionic ligand, trigonelline. Biochemistry. 1990; 107:726-31. https://doi.org/10.1093/oxfordjournals.jbchem.a123116
141. Allred KF, Yackley KM, Vanamala J, Allred CD. Trigonelline is a novel phytoestrogen in coffee beans. J Nutr. 2009; 139:1833–8. https://doi.org/10.3945/jn.109.108001
142. Tresserra-Rimbau A, Rimm EB, Medina-Remón A, *et al*. Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study. Nutr Metab Cardiovasc Dis. 2014; 24:639–47. https://doi.org/10.1016/j.numecd.2013.12.014
143. Czok G. Biopharmacological effects of coffee substances other than caffeine. Arch Sci Med. (Torino) 1974; 131(1):15-7.
144. Errol Z, Raymond T. Trigonelline. Review of Toxicological Literature. 535-83.
145. Almeida AA, Farah A, Silva DA, *et al.* Antibacterial activity of coffee extracts and selected coffee chemical compounds against enterobacteria. J Agric Food Chem. 2006; 54(23):8738-43. https://doi.org/10.1021/jf0617317
146. Ozcelik B, Kartal M, Orhan I. Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids. Pharm Biol. 2011; 49(4):396-402. https://doi.org/10.3109/13880209.2010.519390
147. Naito S, Yatagai C, Maruyama M, Sumi H. Effect of coffee extracts on plasma fibrinolysis and platelet aggre-

gation. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2011; 46(2):260-9.
148. Hirakawa N, Okauchi R, Miura Y, Yagasaki K. Anti-invasive activity of niacin and trigonelline against cancer cells. Biosci Biotechnol Biochem. 2005; 69(3):653-8. https://doi.org/10.1271/bbb.69.653
149. Anthoni U, Christophersen C, Hougaard L, Nielsen PH. Review: Quaternary ammonium compounds in the biosphere-an example of a versatile adaptive strategy. Comp Biochem Physiol. 1991; 99B(1):1-18. https://doi.org/10.1016/0305-0491(91)90002-U
150. Tohda C, Kuboyama T, Komatsu K. Search for natural products related to regeneration of the neuronal network. Neurosignals. 2005; 14(1-2):34-45. https://doi.org/10.1159/000085384
151. Zhou J, Zhou S, Zeng S. Experimental diabetes treated with trigonelline: effect on beta cell and pancreatic oxidative parameters. Fundam Clin Pharmacol. 2013; 27(3):279-87. https://doi.org/10.1111/j.1472-8206.2011.01022.x
152. Mishkinsky JS, Goldschmied A, Joseph B, *et al.* Hypoglycaemic effect of *Trigonella foenum graecum* and *Lupinus termis* Leguminosae) seeds and their major alkaloids in alloxan-diabetic and normal rats. Arch Int Pharmacodyn Ther. 1974; 210(1):27-37.
153. Yoshinari O, Sato H, Igarashi K. Anti-diabetic effects of pumpkin and its components, trigonelline and nicotinic acid, on Goto-Kakizaki rats. Biosci Biotechnol Biochem. 2009; 73(5):1033-1041. https://doi.org/10.1271/bbb.80805
154. Yoshinari O, Igarashi K. Anti-diabetic effect of trigonelline and nicotinic acid, on KK-Ay mice. Curr Med Chem. 2010; 17(20):2196-202. https://doi.org/10.2174/092986710791299902
155. Al-Habori M, Raman A, Lawrence MJ, Skett P. *In vitro* effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase A. Int Exp Diabetes Res. 2001; 2:91-9. https://doi.org/10.1155/EDR.2001.91
156. Abe S, Kaneda T. Effect of betaines and taurine and its derivatives on plasma cholesterol levels in rats. Eiyo To Shokuryo. 1975; 28:125-8. https://doi.org/10.4327/jsnfs1949.28.125
157. Bakuradze T, Lang R, Hofmann T, *et al.* Antioxidant effectiveness of coffee extracts and selected constituents in cell-free systems and human colon cell lines. Mol Nutr Food Res. 2010; 54:1734-43. https://doi.org/10.1002/mnfr.201000147
158. Yen WJ, Wang BS, Chang LW, Duh PD. Antioxidant properties of roasted coffee residues. Agric Food Chem. 2005; 53:2658-63. https://doi.org/10.1021/jf0402429
159. Yoshinari O, Takenake A, Igarashi K. Trigonelline ameliorates oxidative stress in type 2 diabetic Goto-Kakizaki rats. J Med Food. 2013; 16:34-41. https://doi.org/10.1089/jmf.2012.2311
160. Daunde JA, Desai SS, Desai PJ, *et al.* Nano-scaling of Trigonelline Improves Antioxidative Status of hfd-stz Induced Diabetic mice. Int J Res In Appl Sci Eng Technol. 2018; 6:2547-52.
161. Li GQ, Kam A, Wong KH, *et al.* Herbal Medicines for the Management of Diabetes. In: Ahmad SI, editor. Diabetes: An Old Disease, a New Insight, Advances in Experimental Medicine and Biology. New York, NY: Springer. 2013; pp. 396–413. https://doi.org/10.1007/978-1-4614-5441-0_28
162. Osadebe PO, Odoh EU, Uzor PF. Natural Products as Potential Sources of Antidiabetic Drugs. Br J Pharm Res. 2014; 4(17):2075–95. https://doi.org/10.9734/BJPR/2014/8382
163. EMA Assessment Report on Trigonella foenum-graecum L.; Semen. Available online: http://www.ema.europa. eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2011/04/WC500105228.pdf