JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/42137
REVIEW ARTICLE

A Comprehensive Drug Review on *Cuntai Varral Cūranam* for its Anti-diabetic Potential on *Matumēkam* (Type II Diabetes Mellitus)

Shunmugaram Shenbagaraj[1*], Vinodini Ramamoorthy[1], Saraswathi Balasubramanian[1], Sri Sathiya Priya Ramachandran[2], Sathiyarajeswaran Parameswaran[1] and Shyamala Rajkumar[1]

[1]Siddha Regional Research Institute (Central Council for Research in Siddha, Ministry of Ayush, Government of India) Kuyavarpalayam, Puducherry – 605013, India; dr.s.s.ram28@gmail.com
[2]Online consultant, Sri Mahalakshmi Siddha hospital, Kallakurichi - 606202, Tamil Nadu, India

Abstract

Diabetes Mellitus (DM) is a chronic metabolic disorder caused by inadequate insulin production by the pancreas or insufficient insulin utilisation by the body. WHO (World Health Organisation) estimates that Non-Communicable Diseases (NCDs) account for 75% of all worldwide fatalities and 2 million death per year account due to diabetes including kidney disease. The prevalence of DM is comparatively higher in lower and middle-income countries than in high-income countries. The IDF states that approximately 10.5% of adults aged 20 to 79 have diabetes, and half of them are unaware of their condition It is estimated that by 2045, the number of adults living with diabetes will rise to 46%. Diabetes Mellitus can be clinically correlated with signs and symptoms of *Inippu nīr* (NSMC-XGB 1.4) and *Matumēkam* and its complications stated as in *Avattaikal* in *Siddha* text. Traditional plant remedies for diabetes have been considered excellent oral therapeutic options due to their effectiveness, safety and less adverse effects. *Cuntai Varral Cūranam* (CVC) is the polyherbal formulation prescribed as a single or supplemental drug for gastrointestinal disorders and used in the management of DM and its ailments in practice. This study aims to review the Anti-diabetic efficacy of CVC through its phytochemical, pharmacological aspects, and basic *Siddha* principle (*Mukkurram, cuvai, vīriyam* and *vipākam*) for the ingredients of CVC. The pharmacological actions like anti-diabetic, hypolipidemic, hepatoprotective, nephroprotective, cardioprotective, antioxidant, and anti-microbial activities and the enzyme inhibition pathways of the ingredients were analysed. The result suggested that CVC might be an effective anti-diabetic drug in the management of DM and its complications due to its synergistic effect.

Keywords: Anti-diabetic, *Chundai Vatral Chooranam*, Diabetes Mellitus, *Madhumegam*, *Neerizhivu*, *Siddha* Medicine

1. Introduction

According to the World Health Organisation (WHO), 74% of all fatalities that occur worldwide are due to NCDs. Among those, 77% occurred in low- and middle-income countries. Among the majority of NCD deaths, cardiovascular diseases account for 17.9 million people per year, malignancies account for 9.3 million, chronic respiratory diseases cause 4.1 million, and Diabetes including kidney disease accounts for 2.0 million per year. Almost 80% of all early NCD fatalities are caused by these four illnesses[1]. The main metabolic risk factors that raise the risk of NCDs are Increased BP, Obesity, Hyperglycemia, and Hyperlipidemia. The WHO plays a vital role in coordinating and advancing the world's battle against NCDs and achieving sustainable development goals[2].

Diabetes Mellitus is a chronic metabolic disorder that is caused by inadequate production of insulin by the pancreas or by insufficient insulin utilisation by the body[3]. The two types of Diabetes Mellitus (DM) are, type I Insulin Dependent Diabetes Mellitus (Juvenile diabetes mellitus), which is hereditary and requires

*Author for correspondence

Article Received on: 20.03.2024 Revised on: 18.09.2024 Accepted on: 25.09.2024

daily administration of insulin, and type II "Adult type" Non-Insulin Dependent Diabetes Mellitus, which mostly affects the elderly and treated with oral antidiabetic drugs[4]. Recently a newly emerged diagnosis known as type 3 Diabetes mellitus (T3cDM) is diabetes of the exocrine pancreas which occurs due to pathological changes like pancreas insufficiency, lack of fat-soluble vitamins (especially vitamin D) and deficiency of incretin and fat hydrolysis secretion. The rapid increase of DM prevalence is higher in low- and middle-income countries than in high-income countries. Age-standardized death rates due to diabetes increased to 3% between 2000-2019, and it is around 13% in lower- and middle-income nations[3].

According to the International Diabetes Federation Diabetes Atlas 2021, approximately 10.5% of adults aged 20 to 79 have diabetes, and nearly half of them are unaware of their condition. The IDF estimates that by 2045, the number of adults living with diabetes will be raised to 46%. Around 783 million individuals, equivalent to 1 in 8 adults worldwide will affect[5]. Rapid urbanization, a sedentary lifestyle, visceral adiposity, a high-calorie diet, and high genetic predisposition are the main risk factors for the increased prevalence of Type II DM among the younger Indian population[6].

Diabetes Mellitus is clinically correlated with signs and symptoms of *Inippu nīr* (NSMC-XGB 1.4)[7] and *Matumēkam*. Excessive indulgence in sex, excessive food intake, sedentary life, stress, inappropriate food habits such as excessive intake of fish, meat, ghee, milk, lack of physical activity, inherited factors, and stimulation of *mūlātāram* by other *vāyukkal* are all contributing factors mentioned in *Siddha* text[8]. Obesity, tongue dryness, delirium, loss of essential fluid in urine, breathlessness, nausea, laboured breathing, carbuncle, and abscess formation, altered sensorium, emaciation with copious expectoration which result in mortality are the stage-wise complications that occur in DM that are mentioned in *Siddha* literature as *Avattaikal*[9].

Traditional plant remedies for diabetes have been considered excellent oral therapeutic options due to their effectiveness, safety, and less adverse effects[10]. Phytochemicals are compounds obtained from plants that are beneficial to human health and not needed for human nutrition. Phytochemicals found in plants exert their antidiabetic effects by enhancing glucose regulation and insulin sensitivity, combating oxidative stress, lowering the levels of inflammatory cytokines, inhibiting the activity of α-amylase and α-glucosidase enzymes, and promoting tyrosine phosphorylation of the Insulin Receptor (IR)[11].

There are numerous herbal, mineral, metallic and herbal-mineral formulations for Diabetes mellitus are commonly prescribed in *Siddha* Medicine. One such traditional polyherbal formulation listed in *Citta Vaittiya Tirattu* is *Cuntai Varral Cūranam* (CVC)[12], is prescribed as a single or supplemental drug for gastrointestinal disorders. Apart from that, CVC is also used in the management of DM and its ailments in practice. This review aims to emphasise the Anti-diabetic potential of *Cuntai Varral Cūranam* via scientific validation including phytochemical constituents, and pharmacological activities along with *Siddha* perspectives.

2. Ingredients and Standard Operating Procedure of *Cuntai Varral Cūranam*

The shown ingredients (Table 1) are to be pulverized into a fine powder and to be consumed with curd[12], dosage of 1-2 gm, twice a day (Figure 1).

Table 1. *Cuntai Varral Cūranam* – ingredients and parts used

S. No.	Name of the Ingredient	Botanical Name	Parts Used
1	*Cuntaivarral*	*Solanum torvum* Burm.	Dried Fruit
2	*Karuvēppilai*	*Murraya koenigii* Linn.	Dried leaves
3	*M*āmparuppu	*Mangiferra indica* Linn.	Dried kernel
4	Ōmam	*Trachyspermum ammi. Linn Sprague ex* Turril.	Dried seed
5	*Nellivarral*	*Emblica officinalis* Gaertn.	Dried fruit
6	*M*ātulaiōtu	*Punica granatum* Linn.	Dried fruit peel
7	*Ventayam*	*Trigonella foenum-gracecum* Linn.	Dried seed



Figure 1. Ingredients of *Cuntai Varral Cūranam*.

3. Discussion

The treatment of Diabetic Mellitus encompasses not just reducing the blood glucose level; additionally, it should focus on the complications and comorbidities as well. *Cuntai Varral Cūranam* is indicated for *Porumal, Māntam, Iraiccal, Kaliccal, Mūlam, Aticāram, Kirakani*[12] and it is prescribed for Gastrointestinal ailments by the practitioner generously. Numerous recent studies imply that altered bowel function may lead to the pathogenesis of Diabetes Mellitus. In this context, particular emphasis is given to the significance of the intestinal barrier, especially focusing on intestinal permeability, immune response, and the composition of intestinal microbiota. These changes in intestinal permeability impair the function of the intestinal barrier, allowing dietary antigens and infectious agents to easily penetrate mucosal immune elements. This can eventually trigger immune responses that damage pancreatic beta cells and increase the production of cytokine, which in turn causes insulin resistance and uncontrollable progression to Diabetes Mellitus[94]. As per the *Siddha* text, *Cuntai Varral Cūranam* is mainly given with curd as an adjuvant[12], which may increase the effectiveness of intestinal gut microbiota function and may help to reduce the blood glucose level by down hilling the pathogenesis of DM in the bowel.

Phytochemical analysis revealed that the ingredients of CVC commonly have tannins, saponins, terpenoids, flavonoids, gallic acid and ellagic acid, and all these have anti-diabetic properties on their own as follows: Tannins are water-soluble polyphenols that enhance the glucose uptake and inhibit adipogenesis, also improves the pathological oxidative state of a diabetic condition[22,23]. Saponins are triterpene glycoside that helps in reducing ROS production in DM, regulates hyperlipidaemia and enhance the insulin secretion[21]. Flavonoids are phenolic compounds that improve

Table 2. *Cuntai Varral Cūranam* – pharmacological activities and phytochemical analysis

S. No.	Ingredients and parts used	Taste	Digestive bio-transferring state	Pharmacological activity	Phytochemicals		Mode of action in DM
1	***Cuntai varral*** (*Solanum torvum* Burm.)/Dry fruits	Bitter	Pungent	Anti-diabetic activity[13,14] Antioxidant activity[15] Hepatoprotective activity[16] Nephroprotective activity[16,17] Cardioprotective activity[18] Hypolipidemic activity[19]	Alkaloids, flavonoids, tannins, glycosides, saponins, oil, tocopherol/ Vitamins E, B and C, iron salts, glycosylated compounds derived from solasodine, namely solamargine and solasonine (0.0043%)[20]	Saponins	Reduce the production of ROS in diabetes by inducing antioxidant enzymes like catalase and SOD. Modulates the expression of genes associated with lipid metabolism and controls hyperlipidaemia associated with DM. Stimulates AMPK phosphorylation, which lowers the triglyceride accumulation in HepG2 cells. Additionally, improves insulin resistance and increases insulin secretion[21].
						Tannins	It has been used as a medication to treat NIDDM because it increases the absorption of glucose and inhibits adipogenesis. In DM, tannins can ameliorate the pathological oxidative state[22,23].
2	***Māmparuppu*** (*Mangiferra indica* Linn.)/ Seed kernel	Astringent	Pungent	Anti-diabetic activity[24,25] Antioxidant activity[26] Hepatoprotective activity[27] Nephroprotective activity[28] Cardioprotective activity[29] Hypolipidemic activity[30]	Tannins, gallic acid, coumarin, caffeic acid, vanillin, mangiferin, ferulic acid, cinnamic acid, phytosterols, sitosterol, quercitin, syringic acid and ellagic acid[31].	Gallic Acid (GA)	GA and its derivatives can modulate oxidative stress, apoptosis, and inflammation in various pathophysiological scenarios. They are powerful antioxidants and free radical scavengers. The antidiabetic effects of GA facilitated by regulation of TNF-α and adipocytokines expression. It improves the function of the β-cells by inhibiting caspase 9-related cellular apoptosis. It accelerates cell migration of human keratinocytes and fibroblasts and activates wound healing due to DM. Prevent Oxidative stress-induced hepatic and renal injury in the DM[32]. Induce GLUT 4 and increases the glucose uptake. Additionally, by inhibiting the actions of pancreatic lipase and alphaglucosidase, phenolic compounds reduce blood glucose levels[33].

Table 2. Continued…

						Mangiferin	Increasing insulin sensitivity and inhibiting alpha-glucosidase activity[33].
						Quercetin	It improves endogenous antioxidant enzymes and protects against pancreatic damage[33].
						Ferulic acid	Prevent β-cells damage through a decrease in oxidative stress[33].
						Vanillin	Neonatal rats with diabetes induced by STZ showed anti-hyperglycemic activity by improving insulin sensitivity and reducing oxidative stress[34].
3	***Karuvēppilai*** (*Murraya koenigii* Linn.)/Leaves	Pungent	Pungent	Anti-diabetic activity[35,36] Antioxidant activity[37,38] Hepatoprotective activity[39,40] Nephroproductive activity[41] Cardioprotective activity[42] Hypolipidemic activity[43]	Carbazole alkaloids (Mahanine, Pyrayafoline-D and Murrayafoline –I)[45], essential oils, Polyphenols. Terpenoids - Blumenol A, loliolide, icariside B1, β-pinene, sabinene, squalene, β-sitosterol Flavonoids - Quercitine, apigenin, Kaempferol, Rutin, Catechin, Myricetin Alkaloids like Mahanine, Murrayanol, Mahanimbine, Koenimbine, Koenigicine, Murrayone, Koenigine, Mahanimbicine,	Mahanimbine	In STZ-induced diabetic rats, mahanimbine given intraperitoneally at doses of 50 and 100 mg/kg revealed anti-diabetic and hypolipidemic effects[45]
					Mukonicine, O-Methylmurrayamine, Mahanimboline, Phebalosin, Phebalosin B, Bismurrayafoline E, Mahanimbinine, Girinimbilol, Isomahanine, Pyrayafoline-D, Glycozoline, Cyclomahanimbine, Cyclomahanimbine, Isomurrayazoline, Mahanimboline, Mukonicine, Isolongifolene[44]	Mahanimbine, Isomahanine, Mahanimboline, Mahanimbinine	Anti-diabetic activity[44]
						Mahanimbine, Isomahanine, Isolongifolene, Koenigine, Mahanimboline, Mahanimbinine, Koenine, Mukonicine, O-Methyl-murrayamine	Antioxidant activity[44]

Table 2. Continued…

4	Ōmam (*Trachyspermum ammi*. Linn Sprague ex Turril.)/ Seeds	Pungent	Pungent	Anti-diabetic activity[46] Antioxidant activity[47] Hepatoprotective activity[48] Nephroproductive activity[49] Hypolipidemic activity[50]	Fiber, carbohydrates, tannins, glycosides, saponins, protein, fat, and mineral matter containing phosphorous, calcium, iron and nicotinic acid. The principal oil constituents of *T. ammi* are "carvone (46%), limonene (38%), and dillapiole (9%)"[51],	Phenol, Carvacrol.	Anti-diabetic, Antioxidant activity[52]
5	***Nellivarral*** (*Emblica officinalis* Gaertn.)/ Dry fruits	Astringent Sweet Sour	Sweet	Anti-diabetic activity[53,54] Antioxidant activity[55,56]	Ascorbic acid, ellagic acid, gallic acid, quercetin,	Ellagic acid	Anti-diabetic action by stimulating insulin secretion and reducing glucose intolerance through the action on the pancreatic β-cells[65]
				Hepatoprotective activity[57,58] Nephroproductive activity[59] Cardioprotective activity[60-62] Hypolipidemic activity[66]	rutin, catechol[63], tannins, phembembaic acid, lipids, emblicol, flavonoids, and mymic acid[64]		
6	***Mātulai*** ōtu (*Punica granatum* Linn.)/ Fruit peel	Astringent	Pungent	Anti-diabetic activity[67-69] Antioxidant activity[70,71] Hepatoprotective activity[72,73] Nephroproductive activity[74] Cardioprotective activity[74] Hypolipidemic activity[75]	They are rich in tannins, steroids, alkaloids, flavonoids, terpenoids, and saponins. Flavonoids namely flavonols, proanthocyanidins, and anthocyanidins. Dietary fibres like lignin, cellulose, uronic acid and neutral sugars[76] Nine polyphenolic constituents, including "p-coumaric acid, syringic acid, benzoic acid, ellagic acid, caffeic acid, cinnamic acid, protocatechuic acid, isoferulic acid, and quinic acid". "Gallo tannins, punicalins, punicalagins, and gallic acid" are some of the major phytochemicals present in pomegranate peel[77]	Punicalagin	Antioxidant, anti-inflammatory, and lipid metabolism regulation[78,79]
						Ellagic acid	After consuming 180 mg of ellagic acid daily for eight weeks, patients with type 2 DM showed significant reductions in "insulin, HBA1C, lipid profile, malondialdehyde, total antioxidant capacity, glutathione peroxidase and superoxide dismutase activity, C-reactive protein, TNF-α, and interleukin 6"[80]

Table 2. Continued…

7	***Ventayam*** *(Trigonella foenum gracecum* Linn.)/ Seeds	Bitter	Pungent	Anti-diabetic activity[81-83] Antioxidant activity[84] Hepatoprotective activity[85,86] Nephroproductive activity[87] Cardioprotective activity[88] Hypolipidemic activity[89]	Saponins, high fibre content, the amino acid 4 -hydroxyisoleucine and major alkaloid trigonelline[90], isoorientin, orientin, vitexin, isovitexin, pinitol, and sarsasapogenin[91]	*Trigonella*	Iso-orientin	Anti-diabetic action by reducing oxidative stress, regulating insulin secretion, and enhancing insulin resistance and glucose tolerance[92] Reduce the glucose level and ameliorate the anti-oxidative profile[93]

glucose tolerance in diabetics by binding to the receptors for glucose transporter 1 and peroxisome proliferator-activated receptor gamma (PPARγ), which stimulates lipid metabolism[95]. Terpenoids exhibit antioxidant and anti-inflammatory properties by downregulating pro-inflammatory cytokines and anti-inflammatory markers. Additionally, by upregulating the endogenous antioxidants like Superoxide Dismutases (SODs), Catalase (CAT) and Glutathione (GSH)[96]. Ellagic acid is a bioactive polyphenolic compound and a clinical study revealed that after 8 weeks of treatment at 180 mg/day, type 2 diabetic patients had significantly lower mean blood glucose, HBA1C, lipid profile, insulin, malondialdehyde, C-reactive protein, TNF-α, and interleukin 6. Additionally, the mean of total antioxidant capacity and the activity of glutathione peroxidase and superoxide dismutase enzymes significantly increased[97]. The bioactive components of each ingredient are tabulated in Table 1.

As Enzyme plays a key role in biochemical pathways, they can be a possible target of medication to control disease and their treatment. It is well-known that delaying the digestion of carbohydrates from absorbable monosaccharides leads to a decrease in postprandial hyperglycemia and inhibits the activity of intestinal α-glucosidase and pancreatic α-amylase[98]. According to this, it is clear that all ingredients of *Cuntai Varral Cūranam* are efficient in inhibiting carbohydrate-digesting enzymes like alpha-amylase and alpha-glucosidase. *In vitro* and *in vivo* studies mentioned in this review show that all the ingredients have potential anti-diabetic, hypolipidemic, hepatoprotective, nephroprotective, cardioprotective, anti-oxidant activities that can be also helpful in managing DM and diabetes-induced complications like Diabetic peripheral neuropathy, nephropathy, retinopathy, cardiovascular disease, stroke, peripheral vascular disease, dental disease, etc.

In vivo, acute, sub-acute and chronic toxicity studies have gone through for all the ingredients of CVC such as *Solanum torvum*[99], *Murraya koenigii*[100,101], *Mangiferra indica*[102], *Punica granatum*[103], *Trigonella foenum graecum*[104,105], *Emblica officinalis*[106] and *Trachyspermum ammi*[107]. The results showed that there is no elevation in the biochemical parameters. Physiological parameters like food consumption, body weight, visual, auditory and organ weight were

also normal. No gross changes were observed in the necropsy and histopathological results. The study findings showed that the drug administered at a higher dose than the recommended dose for a long period also didn't cause any ill effects.

The phytochemical study of the *Cuntai Varral Cūranam* also gives support to the claim of the presence of phytoconstituents that present in the ingredients which may give a synergistic effect to inhibit the enzyme and enhance the anti-diabetic efficacy of the drug. Karthi *et al.*, evaluate the anti-microbial and anthelmintic activity of CVC against *E. coli, K. pneumoniae, Bacillus cereus, S. Aureus,* and *Salmonella*[108]. Nisha *et al.,* evaluated the in vitro anthelmintic activity of CVC on the Pheritima posthuma model. The above results revealed that CVC has a potential anti-microbial and anthelmintic efficacy, which may help in the protection of opportunistic infection that occurs in the GI tract among the DM population[109].

In *Matumēkam*, derangement of the *Alal* and *Aiyam kurram* that affects the *vali* which is the causative factor for the further progression of disease results in diabetes and its complication[110]. The diagnosis and treatment modality in the *Siddha* system of medicine is adhered with the basic principles like *Mukkurram, Cuvai, Vīriyam, Vipākam* and *Ceykai* which play an important role in the prognosis of the disease. To balance the elevated *Alal* and *Aiyam*, the *Kaippu* (bitter), *Tuvarppu* (astringent), and *Kārppu* (pungent) taste herbs are suitable for the selection of drug. Bitter taste composed of *V*āyu (air) and Ākāyam (space), increases *Vali*, decreases *Alal* and *Aiyam*. It purifies and dries out all the secretions of the body. Bitters due to their pungent *Vipākam* (post-digestive biotransformation) help to exit out the *Aiyam* in *Alal* space and reinstate *Alal* in its place. Astringent taste composed mainly of *V*āyu (air) and *Pirutivi* (earth), increases *Vali*, decreases *Alal* and *Aiyam*. It acts as a blood purifier. A pungent taste composed of *Tēyu* (fire) and *V*āyu (air), increases *Alal* and *Vali* and decreases *Aiyam*. It acts as an appetizer, and cardiac tonic and increases all the secretions in the body[111]. All the ingredients of CVC have a bitter, pungent and astringent taste with hot potency that will change into a pungent taste in post-digestive biotransformation. Likewise, the ingredients of scientifically known Anti-diabetic formulations like Āvārai *kutinīr cūranam,* D5 *cūranam, Matumēka cūranam, Tiripalā cūranam, Cīntil cūranam* etc., also have bitter, astringent and pungent taste[112].

4. Conclusion

The phytopharmacological review provides comprehensive information on the ingredients of *Cuntai Varral Cūranam*, and it reveals their anti-diabetic, hypolipidemic, hepatoprotective, nephroprotective, cardioprotective, antioxidant and anti-microbial activities. The phytoconstituents may also have a synergistic effect to inhibit the enzyme and enhance the anti-diabetic efficacy of the drug. Hence, we postulate that CVC may be an effective anti-diabetic drug in the management of DM and its complications. This review may initiate further in-vitro, in-vivo and clinical trials to explore this scientific claim.

5. Acknowledgment

The authors express their sincere thanks to Prof. Dr. N. J. Muthukumar, Director General, Central Council for Research in *Siddha*, Ministry of Ayush, GoI, Chennai for extending his support and encouragement.

6. References

1. World Health Organization. Non communicable diseases [Internet]. [cited 2024 Mar 2]. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
2. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. World Health Organization; 2013.
3. World Health Organization. Diabetes [Internet]. [cited 2024 Mar 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes
4. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c) — Are we neglecting an important disease? Eur J Intern Med. 2013; 24(3):203-6. https://doi.org/10.1016/j.ejim.2012.12.017 PMid:23375619
5. World Health Organization. International Diabetes Federation [Internet]. [cited 2024 Mar 11]. Facts & figures. Available from: https://idf.org/about-diabetes/diabetes-facts-figures/
6. Mohan V. Why are Indians more prone to diabetes? J Assoc Physicians India. 2004; 52:468-74.

7. NAMASTE. NAMASTE - Portal [Internet]. [cited 2024 Mar 19]. Available from: https://namstp.ayush.gov.in/#/index
8. Kuppusami M. *Siddha* Maruthuvam (Pothu). Department of Indian Medicine and Homeopathy; 2012. p. 730.
9. Parvathy P, Lekha GS, Aparna S, Kanagarajan A. *Siddha* therapeutic approach to diabetic nephropathy - A review. J Nat Remedies. 2023; 1359-1371. https://doi.org/10.18311/jnr/2023/33881
10. Patel D, Kumar R, Laloo D, Hemalatha S. Natural medicines from plant source used for therapy of diabetes mellitus: An overview of its pharmacological aspects. Asian Pac J Trop Dis. 2012; 2(3):239-50. https://doi.org/10.1016/S2222-1808(12)60054-1
11. Balbaa M, El-Zeftawy M, Abdulmalek SA. Therapeutic screening of herbal remedies for the management of diabetes. Molecules. 2021; 26(22):6836. https://doi.org/10.3390/molecules26226836 PMid:34833928 PMCid:PMC8618521
12. Kuppusamy KN, Uthamarayan KS. *Siddha* vaithiyathirattu. Chennai: Department of Indian Medicine and Homeopathy, 3rd edition; 2009.
13. Manikandaselvi S, Divya RS, Thinagarbabu R. *In vitro* antidiabetic activity of aqueous fruit extract of *Solanum torvum* Sw. Int Res J Pharm. 2018; 9:145-51. https://doi.org/10.7897/2230-8407.099203
14. Gandhi GR, Ignacimuthu S, Paulraj MG. *Solanum torvum* Swartz. fruit containing phenolic compounds shows antidiabetic and antioxidant effects in streptozotocin induced diabetic rats. Food Chem Toxicol. 2011; 49(11):2725-33. https://doi.org/10.1016/j.fct.2011.08.005 PMid:21855597
15. Ramamurthy CH, Kumar MS, Suyavaran VS, Mareeswaran R, Thirunavukkarasu C. Evaluation of antioxidant, radical scavenging activity and polyphenolics profile in *Solanum torvum* L. fruits. J Food Sci. 2012; 77(8):C907-13. https://doi.org/10.1111/j.1750-3841.2012.02830.x PMid:22860581
16. Kadam V, Gangurde S, Mohan M. Protective effect of *Solanum torvum* on monosodium glutamate-induced hepatotoxicity and nephrotoxicity in rats. Indian J Nat Prod Resour. 2019; 10(1):31-42.
17. Mohan M, Kamble S, Gadhi P, Kasture S. Protective effect of *Solanum torvum* on doxorubicin-induced nephrotoxicity in rats. Food Chem Toxicol. 2010; 48(1):436-40. https://doi.org/10.1016/j.fct.2009.10.042 PMid:19883716
18. Nguelefack TB, Mekhfi H, Dimo T, Afkir S, Nguelefack-Mbuyo EP, Legssyer A, *et al*. Cardiovascular and anti-platelet aggregation activities of extracts from *Solanum torvum* (*Solanaceae*) fruits in rat. J Altern Complement Med. 2008; 5(1). https://doi.org/10.2202/1553-3840.1105
19. Wannasiri S, Chansakaow S, Sireeratawong S. Effects of *Solanum torvum* fruit water extract on hyperlipidemia and sex hormones in high-fat fed male rats. Asian Pac J Trop Biomed. 2017; 7(5):401-5. https://doi.org/10.1016/j.apjtb.2017.01.027
20. Darkwah WK, Koomson DA, Miwornunyuie N, Nkoom M, Puplampu JB. Review: phytochemistry and medicinal properties of *Solanum torvum* fruits. All Life. 2020; 13(1):498-506. https://doi.org/10.1080/26895293.2020.1817799
21. Elekofehinti OO. Saponins: Anti-diabetic principles from medicinal plants - A review. Pathophysiol. 2015; 22(2):95-103. https://doi.org/10.1016/j.pathophys.2015.02.001 PMid:25753168
22. Kumari M, Jain S. Tannins: An antinutrient with positive effect to manage diabetes. Res J Recent Sci. 2012; 1(12):70-3.
23. Ajebli M, Eddouks M. The promising role of plant tannins as bioactive antidiabetic agents. Curr Med Chem. 2019; 26(25):4852-84. https://doi.org/10.2174/0929867325666180605124256 PMid:29874989
24. Yoopum S, Wongmanee N, Rojanaverawong W, Rattanapunya S, Sumsakul W, Hanchang W. Mango (*Mangifera indica* L.) seed kernel extract suppresses hyperglycemia by modulating pancreatic β cell apoptosis and dysfunction and hepatic glucose metabolism in diabetic rats. Environ Sci Pollut Res Int. 2023; 30:123286-308. https://doi.org/10.1007/s11356-023-31066-7 PMid:37981611
25. Rajesh MS, Rajshekar J. Assessment of antidiabetic activity of *Mangifera Indica* seed kernel extracts in streptozotocin induced diabetic rats. J Nat Remedies. 2014: 33-40.
26. Pitchaon M. Antioxidant capacity of extracts and fractions from mango (*Mangifera indica* Linn.) seed kernels. Int Food Res J. 2011; 18(2).
27. Nithitanakool S, Pithayanukul P, Bavovada R. Antioxidant and hepatoprotective activities of Thai mango seed kernel extract. Planta Med. 2009; 75(10):1118-23. https://doi.org/10.1055/s-0029-1185507 PMid:19326325
28. Attia SH, Elshazly SM, Abdelaal MM, Soliman E. Reno-protective effect of mangiferin against methotrexate-induced kidney damage in male rats: PPARγ-mediated antioxidant activity. Saudi Pharm J. 2022; 30(9):1252-61. https://doi.org/10.1016/j.jsps.2022.06.026 PMid:36249937 PMCid:PMC9561181
29. Prabhu S, Jainu M, Sabitha KE, Devi CS. Cardioprotective effect of mangiferin on isoproterenol induced myocardial infarction in rats.
30. Anila L, Vijayalakshmi N. Flavonoids from *Emblica officinalis* and *Mangifera indica* — effectiveness for dyslipidemia. J Ethnopharmacol. 2002; 79(1):81-7. https://doi.org/10.1016/S0378-8741(01)00361-0 PMid:11744299
31. Asif A, Farooq U, Akram K, Hayat Z, Shafi A, Sarfraz F, *et al*. Therapeutic potentials of bioactive compounds from

mango fruit wastes. Trends Food Sci. 2016; 53:102-12. https://doi.org/10.1016/j.tifs.2016.05.004

32. Xu Y, Tang G, Zhang C, Wang N, Feng Y. Gallic acid and diabetes mellitus: its association with oxidative stress. Molecules (Basel, Switzerland). 2021; 26(23):7115. https://doi.org/10.3390/molecules26237115 PMid:34885698 PMCid:PMC8658971
33. Saleem M, Tanvir M, Akhtar MF, Iqbal M, Saleem A. Antidiabetic potential of *Mangifera indica* L. cv. Anwar Ratol leaves: Medicinal application of food wastes. Medicina (Kaunas, Lithuania). 2019; 55(7):353. https://doi.org/10.3390/medicina55070353 PMid:31323919 PMCid:PMC6681213
34. Lu G, Luo X, Liu Z, Yang L, Lin C, Xu M. Protective effect of vanillin in streptozotocin-induced diabetes in neonatal rats via attenuation of oxidative stress and inflammation. Trop J Pharm Res. 2019; 18(2):349-55. https://doi.org/10.4314/tjpr.v18i2.18
35. Kesari AN, Gupta RK, Watal G. Hypoglycemic effects of *Murrayakoenigii* on normal and alloxan-diabetic rabbits. J Ethnopharmacol. 2005; 97(2):247-51. https://doi.org/10.1016/j.jep.2004.11.006 PMid:15707761
36. Al-Ani IM, Santosa RI, Yankuzo MH, Saxena AK, Alazzawi KS. The antidiabetic activity of curry leaves "MurrayaKoenigii" on the glucose levels, kidneys, and islets of Langerhans of rats with Streptozotocin induced diabetes. Makara J Health Res. 2017; 21(2):4. https://doi.org/10.7454/msk.v21i2.7393
37. Zahin M, Aqil F, Husain FM, Ahmad I. Antioxidant capacity and antimutagenic potential of Murrayakoenigii. Biomed Res Int. 2013. https://doi.org/10.1155/2013/263509 PMid:23853769 PMCid:PMC3703397
38. Aju BY, Rajalakshmi R, Mini S. Evaluation of antioxidant activity of *Murrayakoenigii* (L.) Spreng using different in vitro methods. J Pharmacogn Phytochem. 2017; 6(4):939-42.
39. Sathaye S, Bagul Y, Gupta S, Kaur H, Redkar R. Hepatoprotective effects of aqueous leaf extract and crude isolates of Murrayakoenigii against in vitro ethanol-induced hepatotoxicity model. Exp Toxicol Pathol. 2011; 63(6):587-91. https://doi.org/10.1016/j.etp.2010.04.012 PMid:20488686
40. Desai SN, Patel DK, Devkar RV, Patel PV, Ramachandran AV. Hepatoprotective potential of polyphenol rich extract of *Murrayakoenigii* L.: An *in vivo* study. Food Chem Toxicol. 2012; 50(2):310-4. https://doi.org/10.1016/j.fct.2011.10.063 PMid:22067293
41. Mahipal P, Pawar RS. Nephroprotective effect of *Murraya koenigii* on cyclophosphamide induced nephrotoxicity in rats. Asian Pac J Trop Med. 2017; 10(8):808-12. https://doi.org/10.1016/j.apjtm.2017.08.005 PMid:28942830
42. Sandamali JA, Hewawasam RP, Jayatilaka KA, Mudduwa LK. Cardioprotective potential of *Murraya koenigii* (L.) Spreng. leaf extract against doxorubicin-induced cardiotoxicity in rats. Evid Based Complementary Altern Med. 2020. https://doi.org/10.1155/2020/6023737 PMid:32308710 PMCid:PMC7142394
43. Phatak RS, Khanwelkar CC, Matule SM, Datkhile KD, Hendre AS. Antihyperlipidemic activity of *Murraya koenigii* leaves methanolic and aqueous extracts on serum lipid profile of high fat-fructose fed rats. Pharmacogn Mag. 2019; 11(4). https://doi.org/10.5530/pj.2019.11.134
44. Balakrishnan R, Vijayraja D, Jo SH, Ganesan P, Su-Kim I, Choi DK. Medicinal profile, phytochemistry, and pharmacological activities of *Murraya koenigii* and its primary bioactive compounds. Antioxidants. 2020; 9(2):101.
45. Mitra A, Mahadevappa M. Antidiabetic and hypolipidemic effects of mahanimbine (carbazole alkaloid) from *Murraya koenigii* (Rutaceae) leaves. Int J Phytomedicine. 2010; 2:22-30.
46. Kaskoos RA. GC/MS Profile and *in vitro* antidiabetic activity of *Cinnamomum z eylanicum* Blume., Bark and *Trachyspermum ammi* (L.) Sprague, Seeds. J Essent Oil-Bear Plants. 2019; 22(2):535-44. https://doi.org/10.1080/0972060X.2019.1612281
47. Chatterjee S, Goswami N, Bhatnagar P. Estimation of phenolic components and *in vitro* antioxidant activity of fennel (*Foeniculum vulgare*) and Ajwain (*Trachyspermum ammi*) seeds. Adv Biores. 2012; 3(2):109-8.
48. Zolfaghari N, Monajemi R, Shahani Pour K, Ahadi AM. TNF-α and IL-1β in diabetes-induced liver damage: The relationship between *Trachyspermum ammi* seeds methanol extract and inflammatory cytokine inhibition. J Food Biochem. 2023. https://doi.org/10.1155/2023/5296711
49. Bilal M, Ahmad S, Rehman T, Abbasi WM, Ghauri AO, Arshad MA. Effects of *Trachyspermum ammi* L. (Apiaceae) on serum, urine and hepatic uric acid levels in oxonate-induced rats and *in vitro* xanthine oxidase inhibition assay. Indian J Tradit Knowl. 2019; 18(1):52-7.
50. Saleem U, Riaz S, Ahmad B, Saleem M. Pharmacological screening of Trachyspermumammi for antihyperlipidemic activity in Triton X-100 induced hyperlipidemia rat model. Pharmacogn Res. 2017; 9(Suppl 1):S34. https://doi.org/10.4103/pr.pr_37_17 PMid:29333040 PMCid:PMC5757323
51. Bairwa R, Sodha RS, Rajawat BS. *Trachyspermum ammi*. Phcog Rev. 2012; 6(11):56. https://doi.org/10.4103/0973-7847.95871 PMid:22654405 PMCid:PMC3358968
52. Sharma H, Yang H, Sharma N, An SS. Trachyspermum ammi bioactives promote neuroprotection by inhibiting acetylcholinesterase, Aβ-Oligomerization/fibrilization, and mitigating oxidative stress *in vitro*. Antioxidants.

2023; 13(1):9. https://doi.org/10.3390/antiox13010009 PMid:38275629 PMCid:PMC10812417

53. Elobeid MA, Ahmed EA. Antidiabetic efficacy of aqueous fruit extract of Amla (*Emblica officinalis*, Gaertn) in streptozotocin-induced diabetes mellitus in male rats. Trop J Pharm Res. 2015; 14(5):801-6. https://doi.org/10.4314/tjpr.v14i5.9
54. Tirgar PR, Shah KV, Patel VP, Desai TR, Goyal RK. Investigation into mechanism of action of anti-diabetic activity of *Emblica officinalis* on streptozotocin induced type I diabetic rat. Res J Pharm Biol Chem Sci. 2010; 1(4):672-82.
55. Middha SK, Goyal AK, Lokesh P, Yardi V, Mojamdar L, Keni DS, *et al*. Toxicological evaluation of *Emblica officinalis* fruit extract and its anti-inflammatory and free radical scavenging properties. Pharmacogn Mag. 2015; 11(Suppl 3):S427. https://doi.org/10.4103/0973-1296.168982 PMid:26929577 PMCid:PMC4745213
56. Charoenteeraboon J, Ngamkitidechakul C, Soonthorncha-reonnon N, Jaijoy K, Sireeratawong S. Antioxidant activities of the standardized water extract from fruit of *Phyllanthus emblica* Linn. Songklanakarin J Sci Technol. 2010; 32(6):599.
57. Huang CZ, Tung YT, Hsia SM, Wu CH, Yen GC. The hepatoprotective effect of *Phyllanthus emblica* L. fruit on high fat diet-induced Non-Alcoholic Fatty Liver Disease (NAFLD) in SD rats. Food Funct. 2017; 8(2):842-50. https://doi.org/10.1039/C6FO01585A PMid:28128372
58. Tung YT, Huang CZ, Lin JH, Yen GC. Effect of *Phyllanthus emblica* L. fruit on methionine and choline-deficiency diet-induced nonalcoholic steatohepatitis. J Food Drug Anal. 2018; 26(4):1245-52. https://doi.org/10.1016/j.jfda.2017.12.005 PMid:30249323 PMCid:PMC9298569
59. Malik S, Suchal K, Bhatia J, Khan SI, Vasisth S, Tomar A, Goyal S, Kumar R, Arya DS, Ojha SK. Therapeutic potential and molecular mechanisms of *Emblica officinalis* Gaertn in countering nephrotoxicity in rats induced by the chemotherapeutic agent cisplatin. Front Pharmacol. 2016; 7. https://doi.org/10.3389/fphar.2016.00350
60. Ojha S, Golechha M, Kumari S, Arya DS. Protective effect of *Emblica officinalis* (amla) on isoproterenol-induced cardiotoxicity in rats. Toxicol Ind Health. 2012; 28(5):399-411. https://doi.org/10.1177/0748233711413798 PMid:22033422
61. Fatima N, Pingali U, Pilli R. Evaluation of *Phyllanthus emblica* extract on cold pressor induced cardiovascular changes in healthy human subjects. Pharmacogn Res. 2014 Jan; 6(1):29. https://doi.org/10.4103/0974-8490.122914 PMid:24497739 PMCid:PMC3897005
62. Kanthe PS, Patil BS, Bagali SC, Reddy RC, Aithala MR, Das KK. Protective effects of ethanolic extract of *Emblica officinalis* (amla) on cardiovascular pathophysiology of rats, fed with high fat diet. J Clin Diagn Res. 2017; 11(9):CC05. https://doi.org/10.7860/JCDR/2017/28474.10628 PMid:29207698 PMCid:PMC5713720
63. Chahal AK, Chandan G, Kumar R, Chhillar AK, Saini AK, Saini RV. Bioactive constituents of *Emblica officinalis* overcome oxidative stress in mammalian cells by inhibiting hyperoxidation of peroxiredoxins. J Food Biochem. 2019. https://doi.org/10.1111/jfbc.13115 PMid:31821595
64. Hasan MR, Islam MN, Islam MR. Phytochemistry, pharmacological activities and traditional uses of Emblica officinalis: A review. Int Curr Pharm J. 2016; 5(2):14-21. https://doi.org/10.3329/icpj.v5i2.26441
65. Fatima N, Hafizur RM, Hameed A, Ahmed S, Nisar M, Kabir N. Ellagic acid in Emblica officinalis exerts anti-diabetic activity through the action on β-cells of pancreas. European journal of nutrition. 2017; 56(2):591-601. https://doi.org/10.1007/s00394-015-1103-y PMid:26593435
66. Anila L, Vijayalakshmi N. Flavonoids from *Emblica officinalis* and *Mangifera indica* —effectiveness for dyslipidemia. J Ethnopharmacol. 2002; 79(1):81-7. https://doi.org/10.1016/S0378-8741(01)00361-0 PMid:11744299
67. Khalil EA. Antidiabetic effect of an aqueous extract of Pomegranate (*Punica granatum* L.) peels in normal and alloxan diabetic rats. Egypt J Hosp Med. 2004; 16(1):92-9. https://doi.org/10.21608/ejhm.2004.18177
68. Parmar HS, Kar A. Antidiabetic potential of *Citrus sinensis* and *Punica granatum* peel extracts in alloxan treated male mice. Biofactors. 2007; 31(1):17-24. https://doi.org/10.1002/biof.5520310102 PMid:18806305
69. Mayasankaravalli C, Deepika K, Lydia DE, Agada R, Thagriki D, Govindasamy C, *et al*. Profiling the phyto-constituents of Punica granatum fruits peel extract and accessing its in-vitro antioxidant, anti-diabetic, anti-obesity, and angiotensin-converting enzyme inhibitory properties. Saudi J Biol Sci. 2020; 27(12):3228-34. https://doi.org/10.1016/j.sjbs.2020.09.046 PMid:33304128 PMCid:PMC7715522
70. Singh RP, Murthy KNC, Jayaprakasha GK. Studies on the antioxidant activity of pomegranate (*Punica granatum*) peel and seed extracts using *in vitro* models. J Agric Food Chem. 2002; 50(1):81-6. https://doi.org/10.1021/jf010865b PMid:11754547
71. Khan BH, Ahmad F, Ahmad J, Yunus SM. Hepatoprotective activity of ethanolic extract of peel of *Punica granatum*. Int J Sci Res. 2017; 6(6):1118-22.
72. Khalil EA. A hepatoprotective effect of an aqueous extract of pomegranate (*Punica granatum* L.) rind against acetaminophen treated rats. Egypt J Hosp Med. 2004; 16(1):112-8. https://doi.org/10.21608/ejhm.2004.18179
73. Emam NM, Anjum S, Okail HA, Ibrahim MA, Ahmad T. Pomegranate peel extract protects against carbon tetrachloride-induced nephrotoxicity in mice

through increasing antioxidants status. Biomed Rep. 2020; 13(3). https://doi.org/10.3892/br.2020.1320 PMid:32765852 PMCid:PMC7391291

74. Patel IB, Atar MA, Ali SA. *Punica granatum* peel extract ameliorates Doxorubicin induced cardiotoxicity. Anal Chem Lett. 2019; 9(6):835-44. https://doi.org/10.1080/22297928.2019.1708789
75. Sadeghipour A, Eidi M, Ilchizadeh Kavgani A, Ghahramani R, Shahabzadeh S, Anissian A. Lipid lowering effect of Punica granatum L. peel in high lipid diet fed male rats. Evid Based Complement Alternat Med. 2014. https://doi.org/10.1155/2014/432650 PMid:25295067 PMCid:PMC4176639
76. Mo Y, Ma J, Gao W, Zhang L, Li J, Li J, *et al*. Pomegranate peel as a source of bioactive compounds: A mini review on their physiological functions. Front Nutr. 2022; 9:887113. https://doi.org/10.3389/fnut.2022.887113 PMid:35757262 PMCid:PMC9218663
77. Singh J, Kaur HP, Verma A, Chahal AS, Jajoria K, Rasane P, *et al*. Pomegranate peel phytochemistry, pharmacological properties, methods of extraction, and its application: A comprehensive review. ACS Omega. 2023; 8(39):35452-69. https://doi.org/10.1021/acsomega.3c02586 PMid:37810640 PMCid:PMC10551920
78. Zhang Y, Tan X, Cao Y, An X, Chen J, Yang L. Punicalagin protects against diabetic liver injury by upregulating mitophagy and antioxidant enzyme activities. Nutrients. 2022; 14(14):2782. https://doi.org/10.3390/nu14142782 PMid:35889739 PMCid:PMC9319303
79. Atrahimovich D, Samson AO, Khattib A, Vaya J, Khatib S. Punicalagin decreases serum glucose levels and increases PON1 activity and HDL anti-inflammatory values in Balb/c mice fed a high-fat diet. Oxid Med Cell Longev. 2018. https://doi.org/10.1155/2018/2673076 PMid:30151068 PMCid:PMC6091419
80. Trapali M. Ellagic acid and Type 2 diabetes. JOJ Nurse Heal Care. 2021; 12(1).
81. Al-Juraisy YH. The hypoglycemic effect of Fenugreek (*Trigonella foenum-gracecum*) seed extract in experimentally diabetic rats. Al-Mustansiriyah J Sci. 2014; 25:1-8.
82. Mowl A, Alauddin M, Rahman M, Ahmed K. Antihyperglycemic effect of *Trigonella foenum-graecum* (fenugreek) seed extract in alloxan-induced diabetic rats and its use in diabetes mellitus: A brief qualitative phytochemical and acute toxicity test on the extract. Afr J Tradit Complement Altern Med. 2009; 6(3). https://doi.org/10.4314/ajtcam.v6i3.57165 PMid:20448850 PMCid:PMC2816457
83. Kumar P, Kale RK, McLean P, Baquer NZ. Antidiabetic and neuroprotective effects of *Trigonella foenum-graecum* seed powder in diabetic rat brain. Prague Med Rep. 2012; 113(1):33-43. https://doi.org/10.14712/23362936.2015.35 PMid:22373803
84. Priya V, Jananie RK, Vijayalakshmi K. Studies on anti-oxidant activity of *Trigonella foenum graecum* seed using in vitro models. Int J Pharm Sci Res. 2011; 2(10):2704.
85. Reddy RR, Srinivasan K. Hepatoprotective and antioxidant effect of fenugreek (*Trigonella foenum-graecum*) seeds in mice under lithogenic condition. J Food Biochem. 2011; 35(6):1619-26. https://doi.org/10.1111/j.1745-4514.2010.00488.x
86. Das S. Hepatoprotective activity of methanol extract of fenugreek seeds rats. Int J Pharm Sci Res. 2014; 5(4):1506.
87. Hegazy MG, Emam MA. Ethanolic extract of *Trigonella foenum graecum* attenuates cisplatin-induced nephro-and hepatotoxicities in rats. Cell Mol Biol. 2015; 61(7):81-7.
88. Bafadam S, Mahmoudabady M, Niazmand S, Rezaee SA, Soukhtanloo M. Cardioprotective effects of Fenugreek (*Trigonella foenum-graceum*) seed extract in streptozotocin induced diabetic rats. J Cardiovasc Thorac Res. 2021; 13(1):28. https://doi.org/10.34172/jcvtr.2021.01 PMid:33815699 PMCid:PMC8007891
89. Hannan JM, Rokeya B, Faruque O, Nahar N, Mosihuzzaman M, Khan AA, Ali L. Effect of soluble dietary fibre fraction of *Trigonella foenum graecum* on glycemic, insulinemic, lipidemic and platelet aggregation status of Type 2 diabetic model rats. J Ethnopharmacol. 2003; 88(1):73-7. https://doi.org/10.1016/S0378-8741(03)00190-9 PMid:12902054
90. Perera PK, Li Y. Functional herbal food ingredients used in type 2 diabetes mellitus. Phcog Rev. 2012; 6(11):37. https://doi.org/10.4103/0973-7847.95863 PMid:22654403 PMCid:PMC3358966
91. Singh P, Bajpai V, Gond V, Kumar A, Tadigoppula N, Kumar B. Determination of bioactive compounds of fenugreek (*Trigonella foenum-graecum*) seeds using LC-MS techniques. Legume Genomics: Methods and Protocols; 2020. p. 377-93. https://doi.org/10.1007/978-1-0716-0235-5_21 PMid:31893460
92. Liang Y, Dai X, Cao Y, Wang X, Lu J, Xie L, *et al*. The neuroprotective and antidiabetic effects of trigonelline: A review of signaling pathways and molecular mechanisms. Biochimie. 2023; 206:93-104. https://doi.org/10.1016/j.biochi.2022.10.009 PMid:36257493
93. Malik A, Jamil U, Butt TT, Waquar S, Gan SH, Shafique H, Jafar TH. *In silico* and *in vitro* studies of lupeol and isoorientin as potential antidiabetic agents in a rat model. Drug Des Devel Ther. 2019; 13:1501-13. https://doi.org/10.2147/DDDT.S176698 PMid:31123393 PMCid:PMC6510393
94. De Kort S, Keszthelyi D, Masclee AA. Leaky gut and diabetes mellitus: What is the link. Obes Rev. 2011; 12(6):449-58. https://doi.org/10.1111/j.1467-789X.2010.00845.x PMid:21382153

95. Singh S, Bansal A, Singh V, Chopra T, Poddar J. Flavonoids, alkaloids and terpenoids: a new hope for the treatment of diabetes mellitus. J Diabetes Metab Disord. 2022; 21(1):941-50. https://doi.org/10.1007/s40200-021-00943-8 PMid:35673446 PMCid:PMC9167359
96. Masyita A, Sari RM, Astuti AD, Yasir B, Rumata NR, Emran TB, *et al*. Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. Food Chem: X. 2022; 13:100217. https://doi.org/10.1016/j.fochx.2022.100217 PMid:35498985 PMCid:PMC9039924
97. Ghadimi M, Foroughi F, Hashemipour S, Nooshabadi MR, Ahmadi MH, Nezhad AB, Haghighian HK. Randomized double-blind clinical trial examining the Ellagic acid effects on glycemic status, insulin resistance, antioxidant, and inflammatory factors in patients with type 2 diabetes. Phytother Res. 2021; 35(2):1023-32. https://doi.org/10.1002/ptr.6867 PMid:32909365
98. Raghupathi P, Kathirvel A, Sankarnarayanan S. Amylase inhibitors: Potential source of anti diabetic drug discovery from medicinal plants. Int J Pharm Life Sci. 2012; 3(2):1407-12.
99. Kuete V, Beng VP, Etoa FX, Lontsi D, Mbiapo FT. Acute and subacute toxicities of hydroethanolic extract of the ripe fruits of *Solanum torvum* Sw. (Solanaceae). J Indian Soc Toxicol. 2005; 1(2).
100. Sakarkar DM, Tembhurne SV, More BH. 28 days repeated dose toxicity study of ethanolic extract of *Murraya koenigii* in Wistar rats. Ann Pharmacol Pharm. 2017; 2(4):1047.
101. Saini SC, Reddy GB, Birari P. Acute toxicity study of *Murraya koenigii*. Int J Pharm Sci Invent. 2012; 2:34-6.
102. Tajiri H, Tanaka W, Takashima M, Matsuyama H, Sugita T, Hidaka K, Sakakibara H. Subchronic safety evaluation of hot-water extract from thinned immature mangos (*Mangifera indica* 'Irwin'): 90-days oral toxicity study in rats. Toxicol Rep. 2021; 8:1046-53. https://doi.org/10.1016/j.toxrep.2021.05.005 PMid:34040996 PMCid:PMC8142251
103. Jahromi SB, Pourshafie MR, Mirabzadeh E, Tavasoli A, Katiraee F, *et al*. *Punica granatum* peel extract toxicity in mice. Jundishapur J Nat Pharm Prod. 2015; 10(4):e23770. https://doi.org/10.17795/jjnpp-23770
104. Khalki L, M'hamed SB, Bennis M, Chait A, Sokar Z. Evaluation of the developmental toxicity of the aqueous extract from *Trigonella foenum-graecum* (L.) in mice. J Ethnopharmacol. 2010; 131(2):321-5. https://doi.org/10.1016/j.jep.2010.06.033 PMid:20600755
105. Hinad I, S'hih Y, Elgui R, Mesfioui A, Elhessni A, OuahidiMI. Acute and subacute toxicity study of *Trigonella foenum-graecum* L. seed extract in Wistar rat. Trop J Nat Prod Res. 2023; 7(10):4912-15.
106. Jaijoy K, Soonthornchareonnon N, Lertprasertsuke N, Panthong A, Sireeratawong S. Acute and chronic oral toxicity of standardized water extract from the fruit of *Phyllanthus emblica* Linn. Int J Appl Res Nat Prod. 2010; 3(1):48-58.
107. Saraswat N, Sachan N, Chandra P. Acute and sub-acute toxicity studies and pharmacodynamic studies of standardized extract of *Trachyspermum ammi* (L.) Sprague (Fruits) against chemically induced inflammation in rats. Curr Drug Discov Technol. 2021; 18(5):e17092020186046. https://doi.org/10.2174/1570163817999200918103041 PMid:32957888
108. Karthi S, Sivakkumar S, Visweswaran S. Antimicrobial activity of polyherbal *Sidda* formulation *chundai vatral chooranam*. Ntl J Environ Sci Res. 2022; 4(9).
109. Nisha J, Kumar NJM, Visweswaran S, Anbu N, Banumathi V. An *in vitro* evaluation of the anthelmintic activity of *Siddha* drug *sundai vatral chooranam* on the Pheritimaposthuma model. Int J Curr Res Chem Pharm Sci. 2018; 5(10): 7-11.
110. Shanmugavelu M. *Noi naadal noi muthal naadal* Part II. 2010, 6th ed. Chennai: Directorate of Indian Medicine and Homeopathy.
111. Shanmugavelu M. *Noi nadal noi mudhal nadalthirattu* Part I. 1st edition. Chennai: Directorate of Indian Medicine and Homeopathy; 2014.
112. Mudhaliar KNM. *Gunapadam mooligai vaguppu*, Vol 1. 2nd edition. Chennai: Directorate of Indian Medicine & Homeopathy; 2002.