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A Review on the Therapeutic Potentials of *Ocimum Sanctum Linn:* In the Management of Diabetes Mellitus (Madhumeha)

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Abstract
Diabetes Mellitus is a health burden with high morbidity and mortality and becoming a pandemic. Management of diabetes without complications is seems to be unachievable goal. In Ayurveda, *Ocimumm sanctum* (Tulasi) has been included in the treatment plan of prameha including Madhumeha. Its therapeutic potentials have been identified through scientific researches. In this study, research findings that favorable for the management of diabetes were collected and reviewed with Allopathy and Ayurvedic aspects. *Ocimum sanctum* was found to act oppose to the pathological process of diabetes. Antidiabetic, antioxidant, antilipidemic, antihypertensive, antistress, anticataract, anti-inflammatory, cardioprotective, immunomodulating and wound healing properties were found to play a major role in the management of diabetes. Its antioxidant property seems to be very important in the prevention of diabetes as well. *Ocimum sanctum* is a cheaper, better, safer solution for an effective management of diabetes.

Keywords: Complications, Morbidity, Mortality, Pandemic, Antioxidant.

1. Introduction
Diabetes Mellitus and Madhumeha are well known similar clinical entities in two different disciplines. It has been identified as a life style disorder since antiquity. According to Ayurveda, Madhumeha is one of the eight maha rogas (incurable diseases) [1] in which all three body humors (vata, pitta and kapha) are involved but vata is predominant. If not treated properly in due period, all twenty pramehas will be end up with Madhumeha where urine becomes sweet and smells like honey. Sedentary life style and kapha (phlegm) aggravated food are concerned as the initiative factors of Madhumeha. It is of two distinct types. One is due to the aggravation of vata dosa because of tissue depletion (dhatu kshaya). Such patients are lean and similar to Type 1 Diabetes. The other is due to the blockage of channels (srotas) and patients are obese which similar to Type 2 Diabetes. Channels blockage and tissue depletion are inter- related as a vicious circle. Impairment of digestion and metabolism is the main reason behind the pathological process of Madhumeha and its complications.
According to Allopathy medicine, "Diabetes Mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin" [2]. Macro and micro vascular complications such as ischemic heart disease, stroke, nephropathy, neuropathy, retinopathy, lower extremities amputations make it a major health burden throughout the world. Medical expenses are two times higher among people with diabetes than none.
According to the IDF Diabetes Atlas 2013 [3], diabetes prevalence in South East Asia (SEA) region was 8.3% and only second to the Western Pacific (WP) where it was 8.5%. World diabetic population was 382 million and expected to reach up to 592 million by 2035. It's an alarming signal for effective measures for the prevention, early diagnosis and better management. It will benefit country's economical status as well as productivity.
As per the scientific researches, *Ocimum sanctum* (OS) has been identified as a plant with diversified therapeutic effects such as antidiabetic, antioxidant, antihyperlipidemic, antihypertensive, antistress, anticataract, antimicrobial, anti-inflammatory, antiarthritic, cardioprotective, hepatoprotective, immunomodulating and wound healing properties etc. It seems to be a rare event that a single plant with all the capabilities that can address almost all the complications of diabetes. Review of those findings through the basic principles of Ayurveda and Allopathy medicine may further confirm the suitability of OS in the management of diabetes. Therefore, this type of study was undertaken.

2. Materials and Methods

Data were collected from Sri Lankan traditional and authentic Ayurvedic texts and other relevant texts, scientific journals and other web sources. Then the collected data were reviewed.

3. Results

Madhumeha is a kshaya janya disease (causes tissue depletion). According to Madhava Nidana[4], kaphaja pramehas (10 types), pittaja pramehas (06 types) and vataja pramehas (04 types) are progressive stages of the same disease process (Diabetes Syndrome). Its pathological process is described using a flow chart below Fig.1.

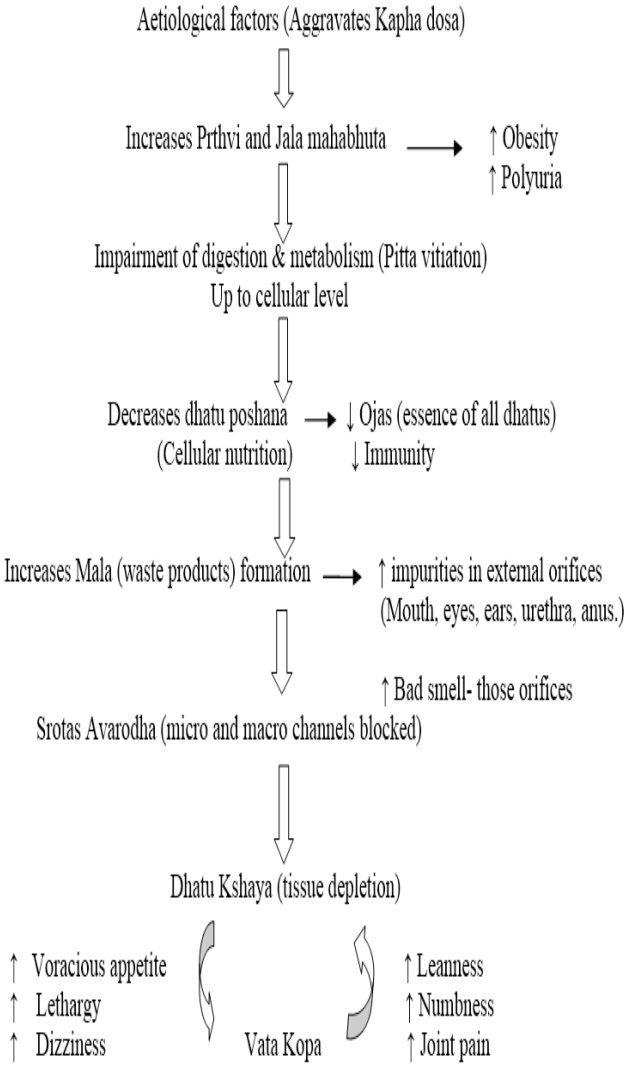

Fig 1: Pathological process of Madhumeha

According to the basic principles of Ayurveda, pharmacodynamics of specific medicinal plant generally depend on its rasa (taste), guna (qualities), virya (general potency), vipaka (transformed state after digestion) and prabhava (specific potency). Generally, until the herbal drug is assimilated and metabolized, its therapeutic effect will not occur. Those properties of OS and their panchabhautika status (composition of 5 basic elements) have been tabulated as follows Table 1.

Table1. Determinants of therapeutic potentials of *Ocimum sanctum*[5-8]

General properties of *Ocimum sanctum*		Predominant mahabhuta(s)
Rasa	Katu (pungent) Tikta (bitter)	Vayu- Agni Vayu - Akasha
Guna	Laghu (lightness) Ruksha (roughness) Tiksna (sharpness)	Vayu - Agni Vayu - Agni Vayu – Agni - Akasha
Virya	Usna (hot)	Agni
Vipaka	Katu (pungent)	Vayu - Agni
Prabhava	Krimighna (anthelmintic)	Not determined in Authentics

Predominance of agni and vayu mahabhutas are seen in the properties of OS which have catabolic effect. In contrast, kleda dhatus (liquid portion) which are predominant of parthiva and jala mahabhutas have anabolic effect and excessively increased in the pathological process of madhumeha. In Ashthanga Hradaya Samhita, surasā is included in 'Katukaskandhaya' which consists of the drugs predominant in katu rasa (pungent taste). Its therapeutic uses have been tabulated below Table 2.

Table 2: Functions of pungent taste and its therapeutic indications [9]

Functions of pungent taste	Therapeutic indications
Reduce wound's inflammation	Skin diseases
Widens the channels	Urticaria
Absorbs sneha (oil), fat and moisture and bulk reducing, purifies dosa.	Oedema
	Pruritis
Removes stiffness of joints (by breaking hard obstructions)	Obesity
	Diabetes
Alleviates kapha, resuscitator	Cough, Coryza, Asthma
Sharpens the sense organs, Mouth cleaning	
Removes obstructions	Dyspepsia
Nervous stimulant	Cardiac disorders
Anthelmintic	Dysentry and sprue
Promotes bleeding (anticoagulant)	
Enhances hunger (by increasing agni), and is digestive, appetizer and assimilates food.	Kapha - vataja diseases

Further, medicines as well as food with bitter taste are especially indicated for the management of madhumeha. Functions and therapeutic indications of Bitter taste are tabulated below Table 3.

Table 3: Functions of bitter taste and its therapeutic indications [10]

Functions of bitter taste	Therapeutic Indications
Cures worms (bacteria, parasites etc)	Obesity
Antidotal to poison	Poisoning
Dries up moisture (water, fat, marrow, lymph, pus, sweat, urine, feces, bile and mucous)	Diabetes
	Fever
	Itching
Febrifuge Blood purifier	Anorexia
Narrow the channels	Fainting
Appetiser, easily digestible	Thirst
Cleanses the breast milk and throat	Gastritis
Increases intelligence	Burning sensation
Causes dryness	Loss of consciousness
Imparts firmness to the skin and flesh	Excessive discharges, puss etc.
Removes pus, toxins, serous discharges	
Cold in potency and dry	Leprosy and other skin diseases

OS is a divine plant with diversified therapeutic effects. Its pharmacodynamic properties and therapeutic indications have been tabulated in Table 4 [11-14].

Table 4: Medicinal properties and therapeutic indications of *Ocimum sanctum* according to Ayurvedic aspect

Pharmacodynamic properties	Therapeutic indications
Kapha-vatashamaka (pacifying kapha & vata dosas) Twagdoshahara (alleviate disorders in skin) Jantughna, Krimighna (anti-microbial) Vedanahara (pain reliever) Shotahara (anti-inflammatory) Shirovirechana (removes disorders in the head) Akshepashamaka (anti convulsant) Raktashodhak (blood purifier) Deepana (appetizer) Pacana (digestive) Anulomana (carminative) Kasahara (anti-tussive, bronchial sedetives) Shwasahara (antidyspnic) Hrdyottejaka (cardiac stimulant) Kshayanashaka (anti TB, alleviate tissue depletion) Mootrala (diuretic) Shukrala(increases volume of semen) Jwaraghna (antipyretic) Vishaghna (anti poisonous) Sheetaprashamana (anti-cooling) Balya (tonic) Durgandhanasaka (deoderent)	Kacchu, Dadru (skin disorders) Siroroga (head disorders) Daurbalya (debility) Vedana (pain) Visha (poison) Kasa (cough) Shwasa (dyspnoea) Parshwasula (pain in flanks) Yakshma (TB) Mutrakricchra (dysuria) Sukrameha (spermaturia) Twagvikara (skin disorders) Karnashoola (pain in ears) Jwara (fever) Pratishyaya (common cold) Vishamajwara (malaria) Sheetajwara (fever with coldness) Vatashlaishmika (alleviates vata & kapha disorders) Prameha (obstinate urinary disorders including diabetes mellitus) Akshepayuktavikara (diseases with convulsions)

Pharmacodynamic properties that have been identified through scientific experiments

OS is known as 'Queen of the Herbs', Elixir of Life', Panacea which reflect its therapeutic value. According to scientific researches, OS was found to possess Antiasthmetic, Antirheumatc, Antistress, Antibacterial, Antifungal, Antifertility, Antiviral, Anti implantation, Abortifacient, Hypoglycemic, Antispasmodic, Anticataract, Antipyretic, Antimutagenic, Antitumour, Antigenotoxic, Anticoagulase, Nematicidal, Larvicidal, Antioxidant, Anticancer, Hypotensive, Antirheumatic, Immunostimulant, antiulcer activity and Anti-inflammatory properties [11-14].

Leaves, seeds, roots, inflorescence, whole plant and extracts of OS have been used for different medicinal purposes. Leaves are commonly used in fresh and dried form as well. Phytochemicals that have been identified in different parts of the plant are tabulated below Table 5 [11-14].

Table 5: Chemical constituents that identified in different parts of the *Ocimum sanctum*

Part(s)	Chemical constituents
Roots	β – sitosterol and three triterpenes
Whole plant	Ascorbic acid, carotene, alkaloids, glycosides, saponins and tannins
Leaves	Bornyl acetate, cadinine, camphene, camphor, carvacrol, β – caryophyllene, 1:8- cineole, decylaldehyd, eugenol, eugenol methyl ether, humelene, limonene, methylchavicol, nerol, α and β- pinenes, γ-selinene, terpen-4-ol, ascorbic acid, β-carotene, apigenin and its 7-0-glucuronide, luteolin and its 7-0-glucuronid, molludistin, oreantin, Cirsilineol, cirsimartin, isothymusin, isothymosin, apigenin, ursolic acid, rosmarinic acid, linoleic acid, gallic acid, vanillic acid, caffeic acid and flavonoids like luteolin, orientin and vicenin. Traces of zinc, manganese and sodium
Seed oil	Sitosterol, palmitic, stearic, oleic, linoleic and linolenic acids

Tulasi is commonly known as 'Surasa' in Aurveda Authentics. Surasa represents the properties and actions of Surasadi gana which cures kapha (phlegm), fat, worms, cold, anorexia, dyspnoea, cough and cleanses wounds. It is specially indicated for the following ailments.

Table 6. Therapeutic uses of Surasadi gana in different ailments [15-17]

Therapeutic indications	Mode of application of surasadi gana
Prameha cikitsa (including madhumeha)	Asthapana vasti
When vata is associated with kapha	Hot fermentation
Medoja vrddhi cikitsa	Fermentation
Kaphaja karna sula	Ear drops, dusting powders
Dusta vrna (vitiated ulcer) and those of diabetes and leprosy	Seven types of therapies such as kshālana, ālepa, ghrta, taila, rasakriyā, curna and varti.

Anti-Diabetic Effect

Ethanol extract (70%) of OS leaves showed a significant blood sugar lowering effect in normal and streptozotocin induced diabetic model rats and was dose dependant. It improved oral glucose tolerance and potentiated the activity of exogenously injected insulin [18].

OS inflorescence found to show hypoglycemic effect which depends on its organic as well as inorganic parts. Inorganic parts being glucose tolerance factor play an indirect role in the management of diabetes. The mechanism behind is some specific mineral elements that cause releasing of insulin from β cells of Islets of Langerhans [19].

Antihyperglyemic effect of OS is at least partially dependent upon insulin release from the pancreas since the ethanol extract of OS showed a greater anti-hyperglycemic effect in milder form of diabetes but a lower response in moderate form of diabetes [20].

Tetracyclic triterpenoid isolated from hydro alcoholic extract of the aerial part of OS has a great antidiabetic effect [21].

OS leaf extracts exert prominent stimulatory effects on insulin secretion from the β cells via physiological pathways. In vivo

studies also indicate that the ethanol extract decreased blood glucose and increased plasma insulin in type 2 diabetic rats [22].

Antioxidant Effect

OS showed strongest overall antioxidant activity among five medicinal plants namely Pterospermum acerifolium, Achyranthes aspera, Delonix regia and Mentha spicata with impressive super oxide anion scavenging activity. Total Poly phenolic content was quite high in OS (methanol extract) and it is related with high free radical scavenging property. Hydroxyl groups directly responsible for the elimination of free radicals and stabilizing lipid peroxidation. Low IC50 value is due to the high content of polyphenolics and flavonoids. Low absorbance value of OS further confirmed its high level of antioxidant activity [23].

Methanolic extract of OS (200 mg/kg/day for 15 days) found to prevent oxidative stress during reperfusion injury. Further it attenuates behavioral deficits and histopathological changes resulted in hypoperfusion [24].

Antilipidemic Effect

In vitro, OS extracts and their fractions are strong inhibitors of lipid peroxidation of erythrocytes' membranes. In vivo, they showed powerful anti-lipid peroxidative effects both in normal as well as hypercholesterolemia-induced stress condition [25].

Anti-Hypertensive Effect

OS fixed oil showed hypotensive effect that appears to be due to its vasodilator action. It also showed anticoagulatory effect that comparable to Aspirin and seems to be due to inhibition of platelet aggregation [26].

Anti-Stress Effect

OS found to limit the harmful effects of stress on rat heart through its unique action on the damaging factors involved in chronic stress, which seems to be helpful in minimizing the overall cardiovascular risk associated with psychological stress [27].

Pre-treatment with Ethanol extract of OS for 7 days appears to prevent noise- induced changes in total acetylcholine content and the activity of acetylcholinesterase in all the four areas of brain [28].

Anticataract Effect

Aqueous extracts of *Ocimum sanctum* (OS), *Withania somnifera* (WS), *Curcuma longa* (CL), *Azadirachta indica* found to inhibit lens Aldose Reductase (AR) activity at different levels. OS was found to be the most effective AR inhibitor followed by CL, AI and WS. In vitro, OS showed an impressive anti cataract activity and it seems to be related with AR inhibitory effect. The most effective AR inhibitory concentration of OS was 100g/ml [29].

Anti-Inflammatory Effect

Cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid and appreciable quantities of eugenol were identified in the extract of fresh leaves and stems of OS. They were found to responsible for its anti-inflammatory activity or cyclooxygenase inhibitory activity. Eugenol showed 97% cyclooxygenase-l inhibitory activity [30].

In vivo, fixed oil of OS found to a potent anti-inflammatory agent that blocks both the pathways cyclooxygenase and lipoxygenase of arachidonic acid metabolism in rats [31].

Cardio Protective Effect

In vivo, infusion of OS leaves juice was found to restore cardiac activity of the hypodynamic frog heart showing greater cardiotonic and cardiac stimulant effect. It caused positive ionotropic and negative chronotropic action on the myocardial muscles of the perfused frog heart. Nifidipine as well as Timolol didn't block the stimulant effect of Os leaves juice. It indicates the mechanism behind is neither mediate through Ca^{+2} ions nor β_1 1 adreno receptors [32].

The order of cardiac stimulant activity of plants juice is as follows:

O. tenuiflorum > T. ammi > Alangium salvifolium flowers >Neem flower > O. sancium > C. quadrangularis

Immuno Modulatory Effect

In a cross over study, group in which OS capsules (300mg of 70% ethanolic extract of OS leaves) were administered empty stomach for 4 weeks showed an impressive immune response [33].

OS seed oil was found to modulate both humoral as well as cell-mediated immune responsiveness and these immunomodulatory effects may be mediated by GABAergic pathways [34].

Anti Ulcerogenic and Ulcer Healing Effect

OS was found to possess potent anti-ulcerogenic as well as ulcer healing properties. Cyto-protective ability of OS seems to be due to its free radical scavenging effect rather than anti secretary effect. It could be used as a potent therapeutic agent against peptic ulcer disease [35].

Faster wound healing property of OS appears to be due to its antioxidant property. Both alcoholic and aqueous extracts of OS may be useful in the management of abnormal healing as well as hypertrophic scars [36].

4. Discussion

Rasa (taste), guna (quality), virya (general potency), vipaka (transformed state after digestion) and prabhava (specific potency) are the factors which determine therapeutic potential(s) of herbal plant. In general, guna supercedes the rasa and responsible for its ultimate resultant action. Sometimes, guna helps rasa and facilitate its action by way of synergism. Vipaka also more or less depends on gunas.

Ocimum sanctum is primarily pungent and secondarily bitter in tastes. Both have an absorbing and anti-diuretic effect and causes sroto shodhana (channel cleaning). They enhance digestion and metabolism through different mechanisms.

Bitter taste consists of vayu and akasha mahabhutas (micro elements). Vayu make the bitter taste rough. It absorbs kapha (phlegm/excessive mucous secretion) which initiates and facilitates the pathological process of diabetes. Further, it depletes medas (fat), vasa (muscle fat), majja (marrow) and lasika (lymph) which are liquid in nature and invariably get vitiated in madhumeha. Due to akasha which has sukshma (minute) quality, reaches even to the minutest channels. It

indicates that bitter taste has the ability to reach not only into the cells but up to the level of micro organelles.

Pungent taste is a potent appetizing and digestive factor. It absorbs fluid and expels the obstructive materials. This quality is known as 'Pramathi [37] (eliminating obstruction by churning) which contradict to the abhishyandi quality. Due to increased fat utilization in diabetes, high amount of cholesterol which has abhishyandi quality is resulted. It paves the way for atherosclerosis which leads to micro and macro vascular complications. This srtotas shodhana property of tikta and katu are very useful in correcting atherosclerosis in diabetes.

According to Caraka Samhita, [38] alleviation and aggravation of all dosas (body humors) are dependent upon agni (power of digestion and metabolism). To keep a balance state of body humors, it is always necessary to maintain a good digestion and metabolism and to avoid factors which responsible for the disturbance of agni. Pungent (katu) and bitter (tikta) tastes have positive effects to correct the digestion and metabolism in diabetes.

A single drug with all the properties such as antidiabetic, antioxidant, antihyperlipidemic, antihypertensive, antistress, anticataract, antimicrobial, anti-inflammatory, antiarthritic, cardioprotective, hepatoprotective, immunomodulating and wound healing would be helpful in the management of diabetes effectively.

According to the scientific researches, antioxidant property was found to be the major therapeutic effect of OS and it potentiates other properties as well. It promotes digestion, metabolism and circulation of rasa (nutrition) through its unique properties. Hence it indicates that OS is a Rasayana drug (rejuvenator) [39] which delays decaying of the body and prolong the span of life.

5. Conclusion (s)

Therapeutic potentials of OS may helpful in the management of diabetes with minimum complications.

It may useful in the prevention of diabetes and other degenerative diseases and to be subjected for further researches.

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