WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Evidential Results for Optimized Dose of Ocimum Sanctum in Management of Metabolic Syndrome

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ABSTRACT

Human societies constantly endure in contact with their environment since the beginning of an era, which makes us depended on plants source to obtain food and medicine. Medicinal plants are beheld as a cure for innumerable diseases in almost all cultures. Safeguarding the safety, quality and efficiency of herbal plants very recently became a hotspot in the developing countries. Phytotherapy has long been a foundation of medicinal products and over the years there have been numerous attempts to use herbal medicines for the treatment of various diseases including metabolic syndrome. The metabolic syndrome which is a result of unbalanced metabolism and the environmental condition has become like an epidemic. Therefore, the various trail is performed to investigate *Ocimum Sanctum* role in metabolic syndrome. This review focusses on evidential dose related research trial conducted in various part of world to determine the quantity and efficiency of Ocimum sanctum to manage diabetes and related disorders.

Keyword: Metabolic syndrome, Phytotherapy, hyperglycaemic, Ocimum sanctum.

Introduction:

In the last decade, the concept of metabolic syndrome (MS) has been comprehensively debated by the scientific community [1,2,3]. Metabolic syndrome, which is also known as syndrome X, is defined by WHO (World health organization) as a pathologic condition characterized by abdominal obesity, insulin resistance, Diabetes, hypertension, and hyperlipidemia. The urban population of developing countries has an excessive prevalence of metabolic syndrome. The elementary reason for the spread of metabolic syndrome is an upsurge in consumption of high calorie-low fiber fast food and the diminution in physical activity.

The guidelines issued from the ncepatp iii guidelines that at least three of the hypothesized following criteria for asserting as the metabolic syndrome:

1. Abdominal obesity: For Asian, the cut-off values are ≥90 cm (35 in) in men or ≥85 cm in women
2. Serum triglycerides value be 150 mg/dl or above.
3. HDL cholesterol value is 40mg/dl or lower in men and 50mg/dl or lower in women.
4. Blood pressure of 130/85 or more.
5. Fasting blood glucose value be 100 mg/dl or above.

In this contemporary hectic world where utmost of the pharmacological drugs derived through synthetic means. Though the drug might offer a promising effect to patients it also leads to numerous types of side effects. Thus, to cope up with such type of side effects modern world is focussing on "Phytotherapy" and as a result, these are attaining more attractiveness due to their natural origin their absence from side effects.
Phytotherapy has long been a foundation of medicinal products and there have been many endeavours to use herbal medicines for the treatment of diabetes over the years [4, 5]. Furthermore, the number of scientific publications concerning herbal medicine and type 2 diabetes is endlessly increasing at exponential rates [6]. The various mechanism has been suggested to control diabetes such as inhibition of α-glucosidase and α-amylase, the upshot on glucose uptake and glucose transporter, activities enhancement of insulin section by pancreatic β-cell, the inhibition of protein tyrosine phosphatase 1B activity have been sharing out in detail [7].

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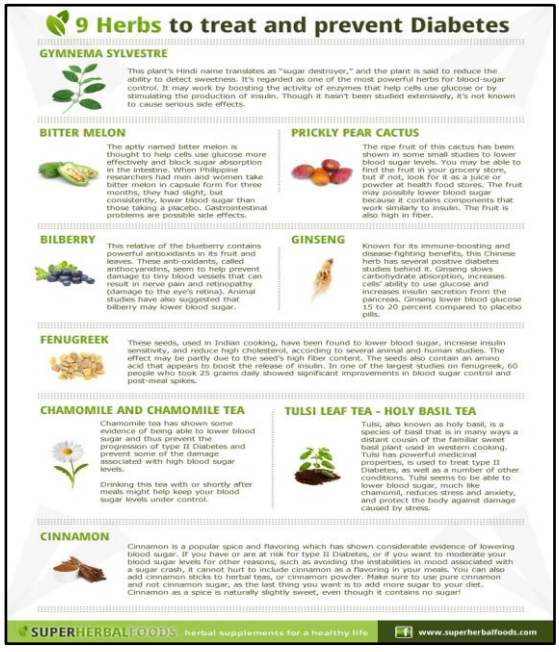
The World Health Organization (WHO) has enumerated 21,000 plants, which are used for medicinal purposes around the world. India being the crucial producer of medicinal herbs and is called a botanical garden of the world [8]. The World Health Organization assessed that 80 percent of the population of developing countries still count on to traditional medicines, mostly plant drugs for their primary health care needs. (WHO, 2000).
There is a fact that nearly 25% of drugs which are derived in the contemporary pharmacopeia are from natural sources. Modern medicine is using ethano-botanical traditions using indigenous flora to treat human diseases. [9]



Innumerable studies on medicinal plant species have gone through botanically, pharmacognostically, chemically and lastly clinically. Herbal products are biodegradable and eco-friendly products [10]. It is well acknowledged that plants are the richest source of bioactive phytochemicals and antioxidant nutrients [11]. Numerous deadly diseases can be healed by certain classes of plant-based compounds such as dietary fiber, flavonoids, vitamins, phenolic compounds, and antimicrobial agents [12]. Strong antioxidant and antimicrobial activities have been acknowledged in phenolic compounds of plants, especially those belonging to the Lamiaceae family [13] Among all the predominant families of the plant kingdom, the family Lamiaceae have exposed to be very beneficial in folk medicine.

Ocimum sanctum- A family to know about:

Ocimum sanctum (OS; Lamiaceae) is an extensively grown, sacred plant of India. It is universally known as Tulsi in Hindi, Tulasi in Telugu and Holy basil in English. It is grown as a perennial plant in tropical and subtropical regions of Asia, Africa, Central and South Africa [14]. The plant is a shrub attaining to a height of 0.5 to 1.5 m. The leaves attain 2-4 cm in length. There are numerous varieties of the plant. The one with dark foliage, on the other hand, is the most commonly utilised. Essential oil added to the leaves and blossom. Antibacterial, anti-yeast, and insecticidal properties are found in this essential oil. Both the seeds and the oil have been discovered to have minor antibacterial properties.

Chemical constituents:

Vitamins C and A, minerals like calcium, zinc, and iron, and phytonutrients like chlorophyll and many others. 30 kcal, 4.2 g protein; 0.5 g fat; 2.3 g carbohydrate; 25 mg calcium; 287 mg phosphorus; 15.1 mg iron; and 25 mg vitamin C per 100 g edible portion [15]

Pharmaceutical Properties:

Pharmaceutical Properties: Tulsi has a complex chemical makeup that includes various nutrients and other biologically active substances, while there is some fluctuation between strains due to seasonal variations, differing growing practises, harvesting, and storing methods.The plant has been considered ethnobotanically significant because of its usage in the traditional health care system [16]. The synergistic interactions of several different bioactive phytochemicals indicate to varied pharmacological properties of the whole herb in its native form. As a result, due to the inherent botanical and biochemical complexity of Tulsi, its overall qualities cannot be properly recreated with isolated chemicals or extracts, and Tulsi standardisation has eluded modern science thus far.
The leaf contains eugenol, euginol, urosolic acid, methylcharicol, limatrol, and caryophylline [18], which are bioactive components that sustain pharmacological characteristics. The leaves are diaphoretic and antiperiodic, and are used to treat bronchitis, stomach and liver diseases, and other

ailments. Tulsi leaves are commonly used for coughs, colds, mild indigestion, decreased appetite, and malaise. It's utilised as an anti-helmintic, anti-inflammatory deodorant, cardiotonic, blood purifier, and antipyretic, especially in malarial fevers. It is advantageous in abdomen pain, nausea, cough, worms, allergic rhinitis, and respiratory disorders. It is externally applied to chronic nonhealing ulcers, inflammation, skin disorders. The seeds contain oil composed of fatty acid and sitosterol. Chinese medicine uses basil for kidney conditions, stomach spasms, promote blood circulation, and to treat snake and insect bites [19]. Tulsi needs a comprehensive evaluation for it has immense therapeutic possibilities [20].

Diabetes mellitus and pharmaceutical synthetic drug:

Diabetes mellitus has emerged as a worldwide health issue affecting millions of people in both developing and developed countries. According to the **International Diabetes Federation's Diabetes Atlas (8th edition), it was estimated that 425 million people of which 123 million above 65 years age and 327 million in 20-65 years of age have diabetes in the year 2017 worldwide, and this is expected to increase to 629 million in 2045.** Diabetes mellitus is a syndrome with disordered metabolism leading to hampering in glucose balance due to either an inappropriate functioning of insulin secretion or insulin resistance condition

There are various type of diabetes as type 1 diabetes (T1DM), type 2 diabetes (T2DM) and the third type ofMaturity-onset diabetes of young MODY).

Type 1 diabetes, an autoimmune disease that mainly affects children, is characterized by the loss of insulin-producing beta cells. Genome-wide association studies and single nucleotide polymorphisms made possible to understand this disease. Although 40 immune response related genes have been implicated in type 1 diabetes, we are still lacking in understanding how these genes are susceptible to this complex disorder.

Type 2 diabetes is common among people 30 years of age or above and characterized by the lack of serum autoantibody, progressive insulin-resistance, and beta-cell insufficiency.

Regardless of the cause, both type 1 and type 2 diabetes are linked to microvascular problems such diabetic nephropathy, neuropathy, and retinopathy, as well as macrovascular complications like cardiovascular disease and atherosclerosis. The hyperglycaemic memory3 or legacy effect refers to the fact that tight glycaemic control for 3 to 5 years may prevent cardiovascular disease but not all diabetes-related outcomes.

Type 2 diabetes mellitus combined with multiple sclerosis increases the risk of diabetic complications when compared to T2DM without MS.

The Risk factor to diabetes:

Obesity and Overweight: Insulin resistance is linked to obesity, and many mechanisms have been proposed to explain how obesity and diabetes interact. The adipocyte produces a variety of circulating hormones, cytokines, and metabolic fuels, such as non-esterified (free) fatty acids (NEFA), which modify insulin activity. Increased triglyceride storage, particularly in visceral or deep subcutaneous adipose depots, results in big adipocytes that are resistant to insulin's capacity to regulate lipolysis.

Sedentary behaviour: A lack of physical activity is linked to diabetes complications and mortality. In the genetically vulnerable, components of MS such as increased adipose tissue lowered HDL-cholesterol, resulting in higher triglycerides, blood pressure, and glucose.

Diabetes mellitus: It is estimated that metabolic syndrome affects 75% of patients with type 2 diabetes or impaired glucose tolerance. When compared to individuals with type 2 diabetes who do not have metabolic syndrome, patients with type 2 diabetes who do not have the syndrome have a higher risk of cardiovascular disease (CVD).

Commonly acclaimed Anti-diabetic drugs.

Metformin and thiazolidinedione suppress gluconeogenesis, lowering hepatic glucose production and, to a lesser extent, improving insulin sensitivity in hepatic and peripheral tissues. They also help you lose weight and improve your lipid profile. In circumstances such as cardiogenic or septic shock, congestive heart failure, severe liver illness, and pulmonary insufficiency with hypoxemia or severe tissue hypoperfusion, metformin therapy should be avoided.

Metformin's side effects can include hypoglycemia and gastrointestinal issues. Mal-absorption of vitamin B12 and anemia are less common adverse effects. Thiazolidinedione appears to act by binding to PPARY (peroxisome proliferator-activated receptor gamma) in adipocytes to promote adipogenesis. It lowers FFA (free fatty acids) levels by lowering fats transfer from liver and muscles it increases insulin sensitivity. Like fibrates, they lower triglyceride level and raise HDL cholesterol level. Reduction of insulin resistance is necessary to improve the blood glucose level in type-2 diabetic patients with obesity and insulin resistance.

Role of Aspirin in MS:

Aspirin significantly shrinks the risk of a first Myocardial Infarction approximately by one-third, stroke by approximately one- fourth and Cardiovascular Disease by approximately one-sixth. The usual recommended dose is 75 to 325 mg daily (Antithrombotic Trialists' Collaboration, 2002).

Other Anti-diabetic drugs:

Currently used anti-diabetic drugs which are ramparted in the market are sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and the oral dipeptidyl-peptidase-4 inhibitor sitagliptin can merely be used for patients with type 2 diabetes. They are mainly used to replace insulin deficiency or to enhance the action of insulin or decrease the insulin resistance for the treatment of diabetes and management of its complications.

Glibenclamide is an anti-diabetic drug in a class of sulfonylureas. The mode of action of the drug is by inhibiting sulfonylurea receptor 1 (SUR1) which is a regulating subunit of the ATP-sensitive potassium 3 channels (KATP) in pancreatic beta cells. This inhibition cause depolarization which leads to calcium uptake in beta cell and finally leads to release of insulin.

Current drugs used for diabetes therapy are not free from side effects and do not restore normal glucose homeostasis by keeping this view current world is shifting towards tradition medicinal plant, to extract their medicinal properties for mankind.

For various reasons in recent years, the popularity of complementary medicine has increased. Dietary measures and Phytotherapy as prescribed by Ayurvedic.

Biguanides developed from prototypic plant molecule is an excellent example of anti-diabetic drug development from plants. Thus, it is prudent in the current context to look for new and if possible, more efficacious hits from the vast reserves of Phytotherapy. Therefore, it has become necessary to find cost-effective along with highly therapeutically effective treatment should be discovered especially for developing and under-developed nations.

Management of diabetes by *Ocimum sanctum*:

This review on the management of metabolic syndrome especially focussing on Diabetes related problems illustrates various scientific research conducted and their achievements in proving the beneficial effect of Tulsi.

More recently, the effect of Tulsi extract on metabolic and biochemical parameters in 30 young overweight/obese participants was studied in a randomised, parallel group, open-label pilot trial. When compared to the control, supplementation with Tulsi extract (250 mg twice daily for 8 weeks) reduced plasma insulin and insulin resistance by 28.49 percent and 24.79 percent, normalised blood lipid profile, and reduced body weight and BMI. Plasma insulin (28.49 percent; p = 0.021), HOMA-IR (24.79 percent; p = 0.049) (Homeostasis Model Assessment for Insulin Resistance), and BMI (Body Mass Index) (1.98 percent; p = 0.005) all decreased significantly. The control group's plasma glucose levels increased significantly (10.25 percent; p = 0.012), whereas the intervention group's plasma glucose levels did not change significantly (p = 0.070). [21].

In another study, the author used a randomised, placebo-controlled, crossover single-blind trial to investigate the effects of holy basil leaf administration on fasting and postprandial blood glucose and serum cholesterol levels in people. The results showed that when holy basil leaves were used instead of placebo leaves, fasting and postprandial blood glucose levels were significantly lower. Fasting blood glucose decreased by 21.0 mg/dl (p 0.001), while postprandial blood glucose decreased by 15.8 mg/dl (p 0.02). The decreased glucose results corresponded to reductions in fasting and postprandial blood glucose of 17.6% and 7.3 percent, respectively. The glucose levels in urine followed a similar pattern. During the basil therapy period, mean total cholesterol levels decreased somewhat. [22].One of the animal studies showed that the oral administration of Tulsi aqueous extracts (200 mg/kg) can postpone the onset of insulin resistance. Indeed, the study proved an improvement in fasting blood glucose and glucose tolerance, abnormal lipid profile through a reduction in serum, LDL cholesterol levels. [23,24,25]. Similar study conducted with Ethanol (80% w/w) extracts obtained from Tulsi leaves were highly effective in lowering blood glucose levels in normal, glucose fed hyperglycemic and streptozocin-induced diabetic rats, also potentiating the action of exogenous insulin in normal rats [26].

Another study used the perfused rat pancreas, isolated rat islets, and the clonal rat BRIN-BD11 cell line to investigate Tulsi's insulinotropic effects. During a 10-minute perfusion, an ethanol extract of Tulsi generated a significant (P0•001) biphasic rise in insulin release, with a peak 21-fold over the basal level. Following a 5-minute exposure to 11 mM glucose, insulin release rose sharply from 0•05 0•01 ng/ml to 1•120 0•08 ng/ml (P0•001). In comparison to the 3 mM glucose control, ethanol extract enhanced insulin release by 61–99 percent (P0•01). Insulin release was increased by twofold when glucose concentration was increased from 3 to 11•1 mM. On ex vivo rat pancreas and in BRIN-BD11 rat clonal-cells, the glucose-lowering benefits were discovered to be mediated by its insulin secretagogue actions [27].

The administration of 500 mg/kg of Tulsi ethanolic (95 percent w/w) leaves extract for 15 days to other streptozocin-induced diabetic rats resulted in a reduction in hepatic lipids and reversion of the diminution of lipoprotein lipase, plasma post-heparin lipolytic, and lecithin cholesterol acyl transferase activities [28]. The fixed oil derived from Tulsi leaves (46.54 mg/kg/day for three weeks) has been suggested to be responsible for the free radical scavenging activity, decrease in plasma glucose, and increase in insulin release observed in streptozocin-induced diabetic rats [29].

In one study, a bioactive component of Tulsi called "Tetracyclic triterpenoid, 16-hydroxy-4,4,10,13-tetramethyl-17-(4-methyl-pentyl)-hexadecahydro-cyclopenta[a]phenanthren-3-one, isolated from the aerial part of Tulsi, was able to lower serum glucose levels, total cholesterol, triglycerides, and HDL cholesterol, while increasing

Tulsi extract given to normal rats fed fructose for 30 days significantly reduced serum glucose levels compared to the control group in a study [31]. According to the findings, Tulsi L. lowers cortisol and glucose levels in the blood and has an antiperoxidative impact. As a result, Tulsi may be able to control diabetes mellitus caused by corticosteroids.

When 300 mg of Tulsi leaf extract was given combined with the anti-diabetic medicine glibenclamide for a 12-week study of type 2 diabetes patients, there was a significant reduction in both glycaemic index and HbAc1 levels, compared to controls who were solely on the anti-diabetic drug [32]. Similarly, a controlled experiment of diabetic patients revealed that consuming 2 g of Tulsi powdered leaves for two weeks resulted in a significant improvement in the glycemic index [33]. In a 12-week randomised trial in diabetic patients, 2 g of Tulsi leaf extract alone or in combination with neem leaf extract reduced diabetes symptoms significantly, with the combination having the largest benefit [34].

Tulsi's effect on people with metabolic syndrome has been studied in six different studies [21, 35, 36]. Two studies found significant improvements in blood pressure in hypertensive subjects given 30 mL of fresh Tulsi leaf juice once day or 30 mL twice daily for 10 and 12 days, respectively [37], with a third study finding blood pressure stabilisation in hypotensive adult females [38]. Another study found that giving 3 g of whole plant Tulsi extract twice daily for 12 weeks improved lipid profiles in older persons (60–80 years) with psychosomatic symptoms [39].

Obese patients who were given 250 mg capsules of Tulsi leaf extract twice daily for 8 weeks improved their lipid profiles and BMI, according to a recent study [40].

Tulsi's effect on three carbohydrate metabolism enzymes [glucokinase (GK), hexokinase (HK), and phosphofructokinase (PFK)] as well as glycogen content of insulin-dependent (skeletal muscle and liver) and insulin-independent tissues (kidneys and brain) in streptozotocin (STZ, 65 mg/kg)-induced diabetes rats was studied for 30 days in another study [41]. On the 15th and 30th days after receiving Tulsi extracts 200 mg/kg for 30 days, plasma glucose levels dropped by 9.06 and 24.4 percent, respectively. Tulsi partially restored glucokinase (GK), hexokinase (HK), and phosphofructokinase (PFK) activities that had been disrupted in diabetic management.

Tulsi leaf powder was fed to normal and diabetic rats at a concentration of 1% for one month, and the results showed a significant reduction in fasting blood sugar, urogenic acid, and total amino acids levels. This finding reveals that Tulsi has a hypoglycemic impact in diabetic rats. [42]

One of the studies was conducted in 2013 on 4 groups of rats each to evaluate the hypoglycaemic effect of ethanolic extract of Tulsi. The test group was given ethanolic extract in a dose of 400 mg/kg body weight of rat model shows that mean fasting blood glucose levels on day1 shows reduction in glucose levels were 33%, which later increased to 51.0% reduction on the 3rd day and it sustained after 3rd day to 45% [43]

Conclusion:

Despite enormous impressive advancements in western medical science, the fragmented approach of modern allopathic medicine is unable to cope with the growing database of chronic degenerative environmental, lifestyle and personal stress-related disorders that plague modern society. Traditional herbal medicines are emerging as holistic approaches to health in the prevention and treatment of the passive illness of modern civilization. The comprehensive outline of the researches evidently substantiated that Phytotherapy has enormous potential in controlling glucose levels, but they lack alternative drugs to mono-molecular ones for type II diabetic patients. Recognizing prominence of enlarging western medical perspective, the World Health Organization recommended that traditional health and folk medicine be incorporated with modern medical therapies to address health problems worldwide more effectively. Substantial evidence has accumulated that, in addition to Tulsi's many specific therapeutic applications, the herb's powerful general adaptogenic properties offer significant preventive and curative potential with respect to the stress-related degenerative diseases endemic to industrialized societies.

Widespread clinical trials are needed using modern standardized extracts to better investigate correlations between hypoglycaemic activity and chemical composition of herbal preparations, with the aim of optimizing extracts by investigating metabolic pathways and, most imperative one is its dose optimization.

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