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Mechanistic Interventions of Selected *Ocimum* Species in Management of Diabetes, Obesity and Liver Disorders: Transformative Developments from Preclinical to Clinical Approaches

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Abstract: Metabolic disorders are usually categorized as inborn metabolism defects, including carbohydrate metabolism deficits in enzymes, amino acids derived from proteins, and fatty acids released from lipids. A metabolic disorder, which arises from elevated body weight, diabetes, and obesity, has reached epidemic proportions in countries. This review discusses the metabolic disorders with respect to diabetes, obesity and liver disorders and their therapeutic management with selective *Ocimum* species. *Ocimum* genus contains more than 200 species and is one of the richest sources of diverse phytoconstituents, including fatty acids, saponins, flavonoids, terpenoids, phenols, tannins, etc. that are documented to be *beneficial* in the management of various metabolic disorders. The potential of selected *Ocimum* species in metabolic disorders is discussed by reviewing available preclinical and clinical studies and associated mechanisms of action and their effect on gene expression.

Keywords: *Ocimum*; metabolic disorders; diabetes; liver disorder; obesity; gene expression.

1. Introduction

Metabolic disorders are usually categorized as inborn metabolism defects, which also include carbohydrate metabolism deficits in enzymes, amino acids derived from proteins, and fatty acids released from lipids. Insulin resistance, elevating fasting glucose level, up down in liver and lipid markers are the major causes that result in a metabolic disorder like diabetes, obesity, and liver ailments which have reached epidemic proportions in countries [1,2]. It is estimated that up to 2030, out of ten adults, one will have diabetes mellitus. People who are overweight have a relatively higher risk for developing colon cancer, gastric cardia, and cholangiocarcinoma, whereas diabetic patients are prone to neuropathy, nephropathy, and retinopathy that could affect the quality of patient's life and is associated with intense morbidity [3-5]. Though the drugs are available to treat metabolic disorders like liver disorders, obesity, diabetes, etc., as mentioned in tables given below (Tables 1, 2, & 3), these drugs only resolve symptoms and fail to cure the disorder permanently. Therefore, people rely on herbal therapies that are considered relatively safer and devoid of side effects.

1.1. Methodology.

A systematic literature review of PubMed, Bentham, Scopus, and EMBASE (Elsevier) databases was carried out with the help of the keywords like *Ocimum* Metabolic disorders, Diabetes,

liver disorder, and obesity till October 2020. This review focuses on clinical and preclinical interventions linked to selected species of *Ocimum* in metabolic disorders and their mechanistic approaches.

2. Drugs Used in Metabolic Disorders and their Side Effects

As shown in the tables below (Tables 1, 2, and 3), drugs are available to treat metabolic disorders such as liver disorders, obesity, diabetes, etc. However, these drugs only treat symptoms and do not cure the disorder permanently. As a result, people rely on herbal therapies, which are thought to be safer and have fewer side effects.

Table 1. Conventional drugs and side effects in diabetes.

S. No	Drug class	Representative Drug	Mechanism of Action	Side effects	Ref.
1.	Insulin analogs	Insulin	Lower the blood glucose level by enhancing the uptake of peripheral glucose by skeletal muscle cell and adipocyte cell	Weight gain, insulin allergies, hypoglycemia	[9]
2.	Sulphonylureas	Glyburide	These drugs enhance the pancreatic beta cells for the secretion of insulin, i.e., shows the Hypoglycemic effect.	Hypoglycemia, weight gain, CVS disorders, rashes, itching, damage to bone marrow, a stomach infection	[9]
3.	GLP-1 agonists	Exenatide	Increases the secretion of glucose dependent insulin from beta cells in pancreatic.	GIT effects, cancer risks also the cardiovascular disorders	[10]
4.	DPP-4 inhibitors	Saxagliptin	It degrades the levels of glucagon hence low down the secretion of glucagon	Risk of cancer, kidney damage	[9]
5.	Thiazolidinediones	Pioglitazone	Stimulates the transcription of genes for glucose control	Weight gain, hepatitis, water retention	[11]
6.	Dual PPAR agonists	Saroglitazar	It has both actions to improve the insulin resistance as well as decreases the high blood triglycerides	Pyrexia	[9]
7.	Alpha Glucosidase inhibitors	Acarbose	Reduces the synthesis the blood glucose	GIT disorders, hepatitis	[9]
8.	Amylin analogs	Pramlintide	Helps in blood glucose control by reducing gastric emptying, by encouraging satiety through hypothalamic receptors	Allergic reactions	[11]
9.	SGLT-2 inhibitors	Canagliflozin	It helps to reduce the glucose reabsorption in the kidney, which results in an increase inthe excretion of urinary glucose and reduces the glucose in the plasma	Glycosuria	[9]
10.	Biguanides	Metformin	It lowers the production of hepatic glucose and lowers the absorption of glucose in the intestine	Lactic acidosis	[11]

2.1. Statins.

Statins are the active hydrolyzed drugs which are the HMG-CoA reductase inhibitors for lowering cholesterol levels, so we can say these are the cholesterol-lowering agent. Statins also had an influence on the LDL and HDL secretion in patients with high cholesterol levels.

2.1.1. Simvastatin.

Simvastatin is a more potent compound to increase the apoA1 synthesis. It is also clinically proved that it might increase the plasma HDL concentration levels, but it decreases the LDL cholesterol concentrations.

2.1.2. Atorvastatin.

It helps to elevate the overproduction of hepatic lipoproteins [6] also enhances hepatic insulin signaling and sensitivity.

2.2. Ezetimibe.

It inhibits the dietary and biliary cholesterol intestinal absorption also reduces the LDL-C levels [7].

2.3. Insulin sensitizing agents.

2.3.1. Rosiglitazone.

It enhances hepatic insulin signaling but decreases lipoprotein overproduction [8].

2.3.2. Metformin.

It decreases the rates of more hepatic glucose production. It helps to improve its use of insulin-stimulated glucose through the extra liver tissue. It lowers diabetes development in those with obese and overweight insulin-resistant personal. It is the mainly preferred drug in patients with diabetes mellitus type 2.

2.4. GLP receptor agonists.

2.4.1. Exenatide.

It inhibits apoptotic beta cells. It enhances the rate of blood pressure, lipids, and also hepatic transaminase levels in the body. The most common side effect is that it gives reduction to the infiltration of liver fat.

2.5. DPP 4 inhibitors.

2.5.1. Sitagliptin.

It improves the blood glucose controls of diabetes 2 in adults. It ameliorates the secretion of insulin by improving the secretion of proinsulin ratio.

Table 2. Conventional drugs and side effects in liver disorders.

S. No	Drug	Mode of action	Adverse effects	Reference
1.	Metadoxine	It is a serotonin receptor antagonist that acts on the GABA transaminase enzyme and reduces its activity	Nausea, fatigue, headache	[9]
2.	Ondansetron	It is a 5HT3 receptor antagonist which is used in various therapies like cancer therapy, radiation, or surgery to prevent vomiting and nausea	Constipation, drowsiness, diarrhea, fatigue	[9]

S. No	Drug	Mode of action	Adverse effects	Reference
3.	Silymarin	It has a hepatoprotective and antioxidant activity on the liver also inhibits the fibrogenesis in liver	Abdominal bloating, itching, indigestion also some allergic reactions	[12]
4.	L- Ornithine L-Aspartate	It stimulates the urea cycle	Weight loss, wound healing, etc.	[9]

Table 3. Conventional drugs and side effects in obesity.

S. No	Drug	Mode of action	Adverse effects	Reference
1.	Phentermine	It suppresses the Sympathomimetic amine activity	Insomnia increases the blood pressure and the pulse rate, constipation, severe headache	[13]
2.	Diethylpropion	Sympathomimetic appetite suppressant	Palpitation, headache, constipation increases the B.P. as well as the pulse rate	[13]
3.	Zonisamide	Having an anticonvulsant activity	Sweating, tremors, GIT effects, insomnia, and fatigue	[13]
4.	Topiramate	Also anticonvulsant activity	Fatigue, memory impairment, somnolence, stomach pain	[13]
5.	Orlistat	It inhibits the pancreatic lipase	Stomach pain, oily stools, low down the absorption of the fat-soluble vitamins	[13]

3. Importance of Herbal Drugs in the Management of Metabolic Disorders like Obesity, Liver Disorder, and Diabetes

Natural products are being utilized as traditional medicinal products from ancient times. These resources have contributed significantly to drug discovery. Indeed herbal formulations have been developed from natural products for health-promoting effects. Herbal formulations are affordable and can be associated with having a pharmacological effect with minimal side effects, so they are used as alternatives to conventional therapies [14,15]. Herbal products are rich sources of flavonoids; terpenoids, saponins, fatty oils, glycosides, etc., are used to treat diabetes, obesity and liver disorders, etc. The herbal formulations can be used as anti-diabetic, anti-obesity agents, and hepatoprotective for more effectiveness and few side effects in preclinical and clinical studies, as the herbal formulations have no side effects. The current therapeutic approaches (such as just four major groups of oral hypoglycaemic drugs viz: sulfonylurea and pioglitazone, biguanide, glucosidase inhibitors) are largely ineffective. These are also chemically synthetic drugs with certain significant side effects, such as liver disorders, lactic acidosis, and diarrhea. Many of the researchers move towards nature for the collection of some of the herbals with their less toxic effects more solutions. One of the traditionally used medicinal plant genus is the *Ocimum* species of *Ocimum* genus in Tropical and subtropical areas of Africa, Tropical Asia, and tropical portions of America's level an altitude of over 1700 m from water level [16]. These are used traditionally in the management of metabolic disorders like diabetes, liver disorders, obesity. It contains a diverse class of phytoconstituents possessing antioxidants, antidiabetics, anti-obesity, hepatoprotective activities (Table 4). The present review discusses the role of selected & potentially important *Ocimum* species in managing metabolic disorders like obesity, diabetes, and hepatoprotection (Figure 1). Also, various preclinical and clinical studies and their mechanism of action are discussed to develop *Ocimum* species as anti-obesity, anti-diabetic, and hepatoprotective drugs (Figure 2).

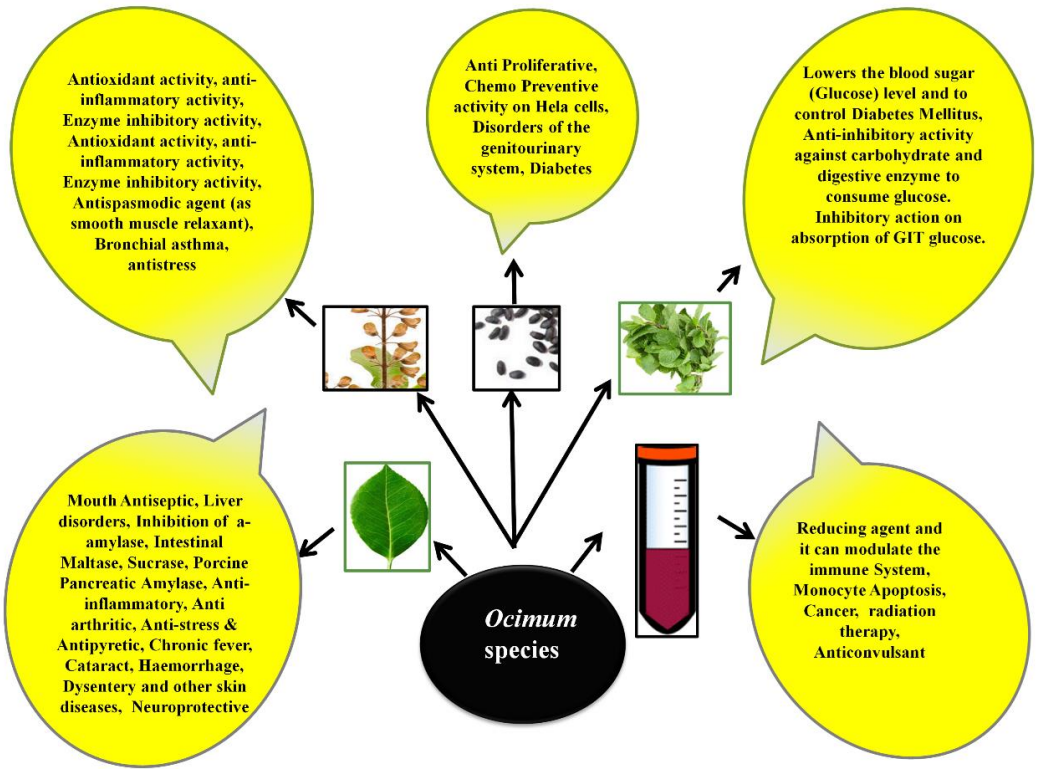

Figure 1. Pharmacological role of the *Ocimum* species in metabolic disorders preclinical studies on *Ocimum* species with their reported mechanisms.

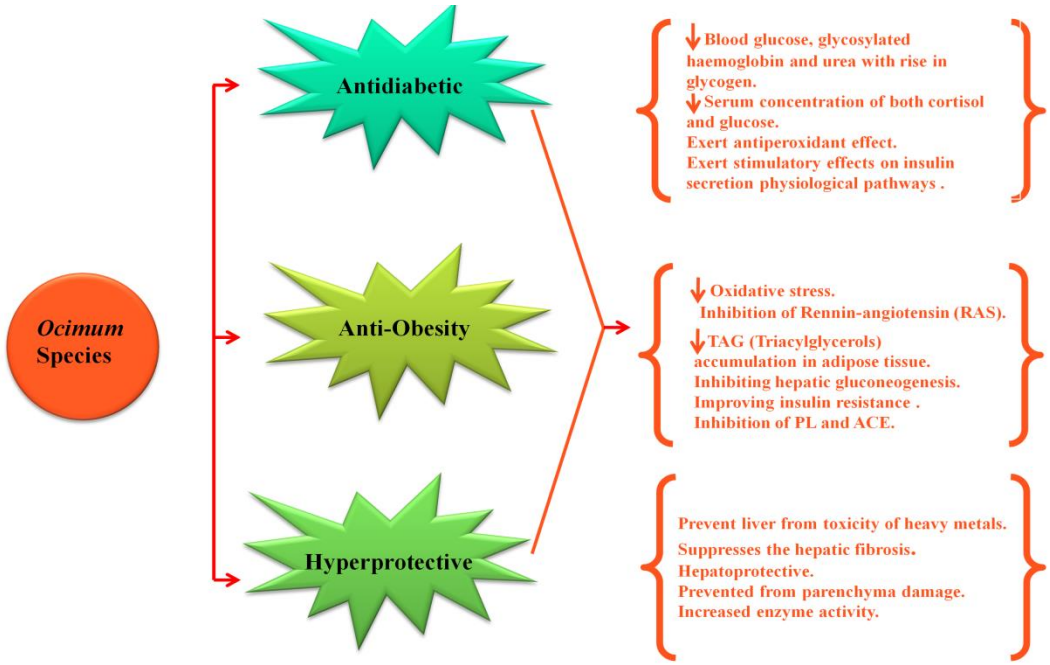

Figure 2. Role of *Ocimum* species in metabolic disorders as anti-diabetic, anti-obesity, and hepatoprotective.

3.1. Obesity.

Increasing the incidence of overweight obesity is a global health issue because excessive weight gain poses an increased risk for different diseases, such as cardiovascular diseases, diabetes, liver disorders, and cancers[17]. Epidemiologically, in lower economy countries, obesity primarily affects middle-aged people, whereas relatively high-economy countries affect all age groups[18]. This increased rate of obesity also leads to an economic burden on a country [19]. The body mass index (BMI), which was measured as weight in kilograms divided by the height in square

meters, closely correlates with excessive fatty tissue and is therefore used for obesity measurement. Based on the percentage of the body fat and the morbidity data, the normal BMI limits for the Asians are lower (Normal BMI: 18.0–22.9 kg/m^2, Overweight: 23.0–24.9 kg/m^2, Obesity: >25 kg/m^2) [20]. Both obesity and metabolism-related with the highest mortality, mainly related to cardiovascular disease (CVS) [21]. Recently, obesity and metabolism have emerged as solid, main risk factors for chronic kidney disease (CKD) and renal end-stage disease (ESRD). The pancreatic lipase (PL) plays an important role in the digestion of lipids, as bulk hydrolysis is caused by pancreatic lipase (50-70%) of total dietary fats [22]. The activation of the rennin-angiotensin system (RAS) has one of the possible mechanisms reported through which obesity may lead to high blood pressure, i.e., hypertension and higher cardiovascular risk [23]. Thus, obesity is associated with further disorders, and thus, finding a treatment strategy for obesity is of prime importance.

3.2.Diabetes.

The two major types of diabetes mellitus (DM), insulin-dependent diabetes mellitus (IDDM), i.e., Type I DM and Non-insulin-dependent (NIDDM), i.e., Type II DM, Even with the use of clinically available insulin analogs and oral antihyperglycaemic medications, epidemiological research and clinical trials firmly support the view that frequent use of these agents cannot prevent long-term complications such as diabetic retinopathy, neuropathy, nephropathy, foot infections, atherosclerosis and other associated cardiovascular events including progression-related hypertension, obesity, dyslipidemia and hypercoagulability [24-26]. The major limitation of insulin is that its interaction with Poor patient compliance, possible dosage errors, diabetic ketoacidosis, local tissue necrosis, nerve damage, while costs and untreatable hypoglycemia remain a significant limiting factor [27]. Studies show that so many oral anti-hyperglycaemic agents have failed to maintain normal blood glucose levels for a prolonged period, especially among the elderly [24] and during pregnancy causes gestational diabetes [28]. Therefore the production of successful anti-diabetic agents remains one of the world's highest public health priorities.

3.3. Hepatic disorder.

The liver is structurally and functionally heterogeneous and contains a wide range of different types of cells, like hepatocytes, immune cells (adaptive and innate immune system), including Kupffer cells, lymphocytes stellate cells, and progenitors. The liver is at the junction of the portal blood supply from the stomach and peripheral organs. A common clinical syndrome is a non-alcoholic fatty liver disease (NAFLD), driven by causes other than alcohol use or some other well-established hepatic injury. NAFLD is pathologically distinguished by a diffuse accumulation of fat in the liver cells (steatosis) while also being a significant factor in developing insulin resistance, type 2 diabetes, and cardiovascular disease.A certain proportion of NAFLD patients was developed to non-alcoholic steatohepatitis (NASH) and eventually to cirrhosis and hepatocellular carcinoma [29]. Studies have shown that intestinal microbiota modification can play a significant role in NAFLD growth and progression. Changing microbiota composition using prebiotics such as inulin-type fructans reduces hepatic steatosis and de novo lipogenesis [30]. Genetics, immunity, dietary components and intestinal microbiota may be the cause of the complex clinical image of alcoholic liver disease (ALD)[31].

4. Role of Herbal Drugs in Managing Metabolic Disorder

Plants are one of the main medicinal sources. Today the vast number of medicines used comes from plants, like Morphine from *Papaver somniferum*, Aswagandha from *Withania somnifera*, Ephedrine from *Ephedra vulgaris*[32], Atropine from *Atropa belladonna*, Reserpine from *Roulphia serpentina*[33], etc. The medicinal plants are secondary plant metabolites (potential drug sources) and essential oils of therapeutic value. The main benefits assumed for medicinal plants' therapeutic use in metabolic disorders are their protection and being economical, effective, and easy to access. In traditional therapeutic methods, medicinal plants were used to effectively regulate the various disease conditions such as bronchial asthma, chronic fever, cold, cough, malaria, dysentery, epilepsy, diabetes, diarrhea, arthritis, emetic syndrome, skin diseases, the bite of insects, etc. also to treat intestinal, hepatic, cvs and immunological disorders [34-36]. Eventually, medicinal plants' properties and therapeutic uses were studied in detail and experimental data documented by the ancient practitioners in Ayurveda (an indigenous medicinal system), which is a fundamental basis of ancient medical science in India [37].

4.1. Ocimum species a valuable medicinal genus.

The Sanskrit term *Ocimum* connotes 'the incomparable ones' with tremendous potential for disease treatment and prevention [38]. It is a mainly valued culinary aromatic genus of the Lamiaceae family with medicinal properties, which is the Indian subcontinent indigenous and has been used for more than 3000 years in Ayurvedic medicine [39]. For its healing powers, *Ocimum* is sometimes referred to as the “Elixir of Life” in the Indian Ayurveda and also has been known for its treating properties in many health problems.

4.1.1. Prominent species of *Ocimum* genus.

4.1.1.1. Ocimum gratissimum Linn.

It is mainly found in warm and temperate Indian regions also known as Vana, or wild *Ocimum* (dark green leaves). The plant grows to one to two feet tall and the stem and branches are light yellow or green. The leaves are sharp, oval, pointing and one to two inches long. It stimulates nerve endings which cause a sensation of tingling. The leaves taste like cloves; hence they are widely used for vegetable flavouring etc. [40].

4.1.1.2. Ocimum americanum Linn.

It is found throughout India in fields and wastelands. A pubescent erect, heavily branched herb, 15-60 cm high with branches of sub quadrangular striations. Whitish pink flowers grow in elongated racemes. The fruit is small; when wetted, the nutlets are pitted and mucilaginous [41].

4.1.1.3. Ocimum sanctum Linn.

Known as *Ocimum tenuiflorum, Ocimum* is being used in Ayurveda for centuries for its rich healing properties. *Ocimum*, the Queen of Herbs, India's legendary 'Incomparable One,' is one of the most saintly and cherished of the many healthy and healing herbs of the oriented [42]. It is an erect herb 30-75 cm tall that may be grown in most parts of India. The leaves are long 2.5-5 cm and wide 1.6-3.2 cm, oblong and elliptical. The smell and taste are aromatic and strong.

4.1.1.4. Ocimum basilicum Linn.

Known as sweet basil, it belongs to the family of Lamiaceae and is commonly cultivated in African, Asian, and South American countries for its medicinal properties and culinary use. Sweet basil extracts are used to treat diabetes also in cardiovascular diseases [43]. Although distinct species with *Ocimum tenuiflorum* have DNA six times less than *Ocimum gratissimum* [44], they are traditionally used in the same manner for treating similar diseases

Table 4. Phytoconstituents and pharmacological uses of *Ocimum* genus.

***Ocimum* species**	**Plant Part**	**Active Constituents**	**Pharmacological uses**	**References**
O. gratissimum	Leaves	Eugenol, methyl eugenol, cis-ocimene, trans-ocimene, pinene, camphor, germacrene- D, trans-caryophyllene, farnesene and l-bisabolene, oleanolic acid	Mouth antiseptic, liver disorders, hypoglycemic effect, antioxidant, anti-inflammatory, antimicrobial, neuroprotective	[45]
O. gratissimum	Seed	Pentoses, hexoses, uronic acid and lipids and thymol	Anti-proliferative as well as chemopreventive activity	[46]
O. gratissimum	aqueous extract of leaves	Tannins, steroids, triterpinoids, carbohydrates	Reducing agent and it can modulate the immune System, Monocyte apoptosis	[46]
O. basilicum	Leaves	Estragole, 3,7-dimethyl, trans-alpha-bergamotene, citral, eucalyptol, levomenthol, and beta-myrcene.	Inhibition of alpha-amylase intestinal maltase and Sucrase, porcine pancreatic amylase	[47]
O. sanctum	Leaves	Ursolic acid flavonoids such as apigenin, polyphenols, anthocyanins and luteolin, eugenol, thymol, or sesquiterpene alcohols	Anti-inflammatory, anti-arthritic, anti-stress, antipyretic, chronic fever, cataract, hemorrhage, dysentery, other skin diseases	[48]
O. sanctum	Whole Plant	Eugenol, thymol, palmitic acid, saponins, flavonoids, tannins etc.	Lowers the blood glucose level	[49]
O. sanctum	Flower Tops	Cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmeric acid	Antispasmodic agent (as a smooth muscle relaxant), bronchial asthma, anti-stress	[14]
O. sanctum	Seeds	Fatty oils, palmitic acid, stark acid, linolenic acid and linoleic acid, also contains oleic acid	Disorders of the genitourinary system	[14]
O. americanum	Flowers and leaves	Gallic acid, quinic acid, caftaric acid, caffeic acid, ellagic acid, jasmonic acid, palmitic acid, oleic acid, arachidic acid	Antioxidant activity, anti-inflammatory activity, enzyme inhibitory activity	[50]

4.2. Anti-diabetic Potential of Selected Ocimum species.

Herbal medicines are constantly being studied using the animal disease model in expectation of the development of a relatively safe anti-diabetic plant-based drug. *Ocimum sanctum* ethanolic extracts substantially decrease blood glucose, glycosylated hemoglobin, and urea with such a subsequent increase in streptozotocin (STZ) induced diabetic rats throughout glycogen and hemoglobin [42]. The extract has increased insulin and peptide levels and resistance to glucose [41]. The Phytoconstituents of *Ocimum sanctum* leaf extracts has stimulating effects on insulin secretion

that may underlie its reported anti-diabetic action [52]. Grover proposed treating*Ocimum sanctum* extract for 30 days to normal rats fructose-fed considerably lowered serum glucose level [53]. However, *Ocimum sanctum* does not affect hyperinsulinemia in any significant way. A possible mechanism for lowering blood glucose levels by *Ocimum sanctum* in male mice could be via reducing both serum cortisol and glucose concentration and antiperoxidant effect. In another study, the effect *Ocimum sanctum* on three major carbohydrate metabolism enzymes Glucokinase (GK), Hexokinase (HK), and Phosphofructokinase (PFK), along with insulin-dependent (skeletal muscle and liver) glycogen content and insulin-independent tissue (kidney and brain), were studied [54] in STZ (65 mg/kg) model of diabetes in rats. The administration of extracts at 200 mg/kg for 30 days leads to a reduction of approximately 9.06 and 24.4% in plasma glucose levels on the 15th and 30th day. *Ocimum sanctum* leaf powder was fed for a duration of one month at one percent in normal as well as diabetic rats; also, the test shows a significant decrease in fasting blood sugar urogenic acid, total amino acids levels. This indicates the hypoglycaemic impact of *O. sanctum* in diabetic rats.

Ocimum gratissimum leaf fractions had an anti-diabetic activity which was recorded in a newly designed Type 2 diabetic (T2D) model [55]. The *O. gratissimum* plant comprises active Phytoconstituents attenuating the increased glucose level and thus indicating a potent therapy for type 1 diabetes [56,57]. The leaf fractions of *Ocimum gratissimum were* used for the Type 2 diabetic model in diabetic rats [55]. The latest animal model T2D provided evidence-based data indicating the anti-diabetic effect of *O. gratissimum* leaf aqueous fractions, comprising Phytoconstituents n-hexane, chloroform, ethyl acetate, and n-butanol, resulted in decreasing the blood glucose levels. The potential benefits of the *O. gratissimum* leaf fractions may be attributable to enhanced insulin sensitivity and beta-cell function due to alkaloids, flavonoids, saponins and/or tannins present within *O. gratissimum* leaf [58] fractions and the effective therapeutic dose is 250 mg/kg oral. It was observed that this dose decreased hyperglycemia among diabetic rats by 29.3% at 4 h after oral administration [55]. The aqueous extract of the leaves of the *O. gratissimum* boosts up the hematological properties in the diabetic rats caused by the alloxan at the dose rate of 400 mg/kg orally and low down the blood glucose level also inhibits the anemia with their antioxidant properties [59].The anti-hyperglycemic function of *O. gratissimum* leaves with their inhibitory ability against carbohydrate and SGLT1-mediated digestive enzymes to consume glucose. The α-starch in the diet is metabolized into glucose, especially by α-amylase and maltase in the digestive tract. The inhibitory ability of *O. gratissimum* leaves extract on the absorption of gastrointestinal (GIT) glucose and provides the theoretical evidence for *O. gratissimum* extract's anti-hyperglycemic impact [60]. The elevated blood glucose level in mice following oral administration in α-starch and glucose was blocked by pre-administering *O. gratissimum* leaves extract, although the maltase and amylase were less inhibited by the *O. gratissimum* extract [61]. The extract of *O. basilicum* treatment substantially ($P<0.05$) reduced the concentration of fasting blood glucose at dose levels 100 and 200 mg/kg and significantly enhance the average body weight in the treated groups [62]. The extract induced a dose-dependent enhancement in the volume of glycogen in the liver, although it lowered levels of alanine transferase and aspartate transferase in a non-dose-dependent manner. The *Ocimum basilicum* extract hasthe ability to inhibit the endogenous release of glucose, also glycogenolysis inhibition, or it may stimulate glycogenesis. *Ocimum basilicum* is also confirmed to have preventive effects on the liver also have antihyperglycaemic activity. These promote the release of insulin and inhibit glucose production from the pancreas in the liver; also, glycogen synthesis increases. Extract of *O. basilicum* leaves [63] demonstrated a statistically significant reduction in blood glucose between both the diabetic control group and the treatment group metformin or *O. basilicum* in 100, 200, 400 mg/kg body weights, so the leaves of *O. basilicum*

can be used to reduce the blood sugar level and the advanced end products with glycation in diabetic rats [64]. Furthermore, *Ocimum* plants are reported to be beneficial in managing diabetic complications. The compounds caffeic acid, oleanolic acid, linalool, eugenol, ursolic acid, saponins possessing anti-inflammatory, urea and creatinine reducers, α-glucosidase and alpha-amylase inhibitory effects, antioxidant were identified in *Ocimum* genus that might be associated with health-promoting effects in diabetic –neuropathy, -nephropathy and -retinopathy (Table 5, Figure 3).

Table 5. Role of *Ocimum* species in managing diabetic secondary complications.

Diabetic Complications	Species	Plant extracts	Constituents	Activity	Reference
Diabetic Retinopathy	***Ocimum sanctum***	Ethanolic extract	Oleanolic acid	Inhibit Vascular Endothelial Growth Factor Receptor- 2 (VEGFR2)	[84]
Diabetic Neuropathy	***Ocimum gratissimum***	Hexane extract	Linalool, Eugenol	Inhibit α- amylase and α-glucosidase, Antioxidant.	[85]
	Ocimum sanctum	Methanolic extract	Saponin	Antioxidant and reducing calcium levels	[66]
	Ocimum basilicum	Hexane extract	Linalool, Eugenol	Inhibit α- amylase and α-glucosidase, Antioxidant.	[62,86,87]
Diabetic Nephropathy	***Ocimum gratissimum***	Alcoholic extract	Eugenol	Down regulation of Transforming growth factor-β, Reduction in urea and creatinine.	[88]
	Ocimum sanctum	Ethanolic extract	Ursolic acid	Antioxidant and anti-inflammatory	[89]
	Ocimum basilicum	Phenolic extract	Caffeic acid	suppression of autophagy regulatory miRNAs	[90]

4.2.1. Mechanistic interventions of selected *Ocimum* species in diabetes.

Diabetes, one of the most common metabolic disorders, is mainly characterized by insulin secretion or insulin action defects. With insulin deficiency, the body tissues, the liver, and adipose tissues use glucose from the blood circulation. This leads to increased blood glucose levels, known as hyperglycemia [65]. *Ocimum* species known to have a strong therapeutic potential, i.e., anti-hyperglycemic effect, and eugenol, a phenolic compound of the essential oils, are found in different *Ocimum* species been found to lower the blood glucose level. A diabetic study was done *in vivo* showing that eugenol reduced blood glucose levels via inhibiting α-glucosidase, activation of PKC pathway, RAS & increase of TGF-β and non-enzymatic glycation. The polyphenols, caffeic acid, p-coumaric acid of aqueous extracts of *Ocimum sanctum* leaves, Chicoric acid show an anti-diabetic effect as reported [66]. Pathophysiology of diabetes suggests the involvement of free radicals in the development of diabetic complications, [67] as free radicals are capable of damaging cellular molecules, DNA, proteins, and lipids leading to altered cellular functions. Many recent studies reveal that *Ocimum species* capable of neutralizing free radicals effectively decrease Ca2+ levels attributed to its antioxidant effects and reduce the severity of diabetic complications, e.g., neuropathy [65]. *Ocimum* may also increase insulin receptor sensitivity and stimulate B-cells releasing insulin, resulting in decreased glucose levels. Significant reduction in “fasting blood

glucose, total amino acid, total lipid, uronic acid, total cholesterol, and triglyceride" indicated the hypoglycemic and hypolipidemic effects of *Ocimum*in diabetic rats. [62, 66] (Figure 3).

4.3. Anti-obesity potential of selected Ocimum species.

In obesity, *O. basilicum* plays a role as an antispasmodic, carminative, stomachic, and also *O. basilicum*, along with *O. gratissimum* leaves may be consumed as food supplements to treat obesity and obesity-related hypertension and to avoid oxidative stress. Pancreatic lipase (PL) plays a vital role in efficient lipid digestion as it is primarily for the hydrolysis of total dietary fats. It is the main enzyme that hydrolyzes triglyceride into glycerol and fatty acids, thus facilitating its uptake. Consequently, it is widely used as an index to assess therapeutics' potential effectiveness as anti-obesity agents [68]. Rennin-angiotensin (RAS) activation has been described as one of the possible mechanisms by which obesity may lead to hypertension and higher cardiovascular risk [22]. Experimental evidence has shown that the rennin angiotensin system (RAS) is triggered in obesity; it has also been reported to be involved in the pathophysiology of obesity-related hypertension [69].

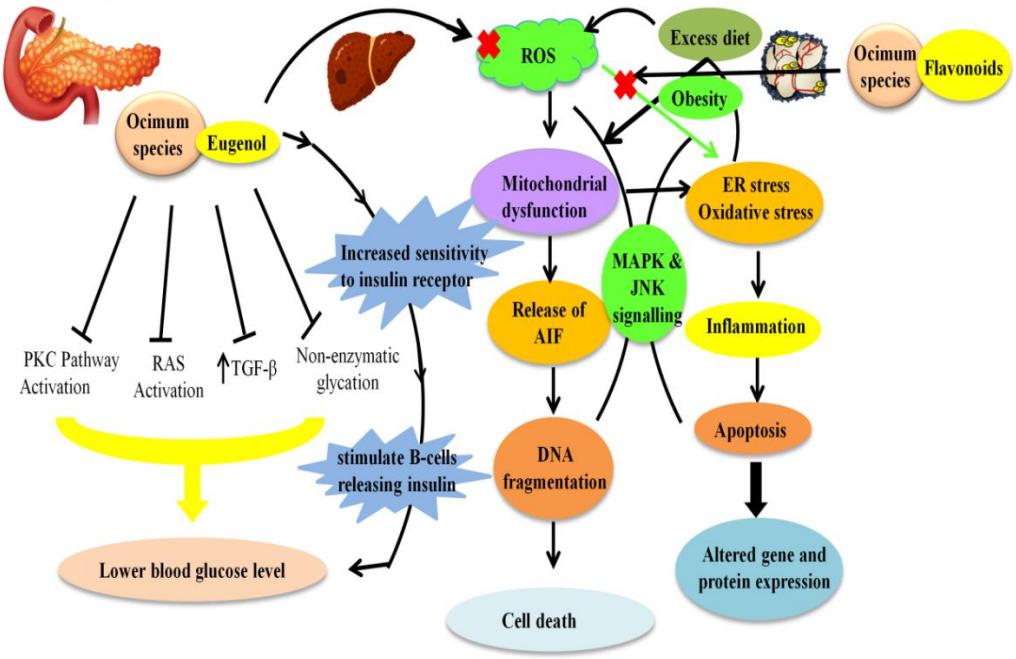

Figure 3. Pictorial presentation of various Tranduction pathways modulated by *Ocimum* species in metabolic disorders as Antidiabetic, Anti-Obesity and Hepatoprotective.

The angiotensin 1-converting enzyme (ACE) plays a key role in blood pressure control and normal cardiovascular function in the RAS. It catalyzes the transformation of angiotensin I into angiotensin II, which is known to raise blood pressure. Consequently, inhibition of ACE is an effective strategy for treating and managing obesity-induced hypertension [68]. *O. basilicum* and *O. gratissimum* are documented to have inhibitory effects on two main enzymes (PL and ACE) involved *in vitro* in obesity and hypertension. *O. gratissimum* had an ACE inhibitor activity greater than *basilicum.* This may be attributed to the presence of a large amount of luteolin (flavonoid) occurring in *O. gratissimum* (2.01 mg/g) and ellagic acid (phenolic acid) not identified in *O. basilicum* [69] as luteolin had better ACE inhibitor activity. Thus, *O. santum* and *O. gratissimum* leaves should be consumed as food supplements to control obesity-related hypertension and avoid oxidative stress that characterizes both disorders. The administration of *O. sanctum* decoction lowering the body weight, which was associated with lowering the triacylglycerols (TAG)

accumulation in adipose tissue, decreased hypertrophy of adiposities, and diminished intestinal TAG digestion and absorption, as shown in increased TAG fecal excretion, and *O. sanctum* exerted the most beneficial effect. These results indicate that *O. sanctum* decoction decreases fasting blood glucose by inhibiting hepatic gluconeogenesis and improving insulin resistance [71].

4.3.1 Mechanistic interventions of selected *Ocimum* species in hepatotoxicity.

The liver carry ou tbody's normal metabolic homeostasis as well as biotransformation, detoxification and excretion of various endogenous and exogenous compounds and is a major organ attacked by *ROS*. Liver damage caused by natural, industrial toxins [72, 73] or drugs is common but hardly recognized. Eugenol, flavonoid, and ursolic acid components present in *Ocimum sanctum* leaves have free radical scavenging and anti-lipoperoxidation effects**.** Free radicals are capable of mitochondrial dysfunctioning, which initiate AIF release and cause DNA fragmentation resulting in cell death. On the other hand, ROS may also lead to activation of some pathways such as MAPK & JNK, causing a decrease in Bcl2 & Bclxl damaging cellular molecules [74]. *Ocimum* species contribute to discontinue this entire process and prevent cell death. The hepatoprotective effect of *Ocimum sanctum* is due to the antioxidant properties of its constituents &membrane-stabilizing property [75]. Moreover, the fixed oil of *Ocimum sanctum* comprises linoleic acid, which is responsible for its anti-inflammatory activity and reversing the inflammatory features associated with hepatic injury. Administration of the alcoholic extract of *Ocimum sanctum* leaves showed significant hepatoprotective activity, as shown previously in other studies[74] (Figure 3).

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4.4. Hepatoprotective potential of Selected Ocimum species.

O. Sanctum leaf extracts may prevent the liver from the toxicity of heavy metals. CCl_4 causing the liver injury is dependent on its metabolism to the highly reactive radical trichloromethyl ($\cdot CCl_3$), which initiates lipid peroxidation. This results in the hepatotoxicity of the CCl_4 by initiating lipid peroxidation in the membranes [76]. The current findings indicate that the *O. sanctum* has strengthened the histological changes and increased enzyme activity caused by CCl_4 in liver function. This shows that *O. sanctum* has effectiveness in the prevention of hepatotoxicity to CCl_4. *O. Sanctum* hepatoprotective effects on experimental liver damage appeared in the study [77], and it also reported that *O. santum*in case of CCl_4-induced parenchymal damage may suppress hepatic

fibrosis and protects the liver. However, the data obtained indicates that CCl_4-induced liver fibrosis in rats has resulted in a significant reduction in serum albumin and a significant rise in overall protein; these are clinically effective synthetic hepatic functionalmarkers[76]. A triterpene-rich extract from hairy root cultures *O. basilicum* has been evaluated for hepatoprotective action against extracts from the aerial parts and normal explant roots. Recently, it has been shown that triterpenes such as oleanolic, ursolic, and glycyrrhetinic acids and their derivatives are active in inhibiting CCl_4-induced experimental hepatotoxicity. CCl_4, a well-known model compound for chemical hepatic injury induction, [78] oral administration of a hairy root extract at doses of 200 mg/kg lowered the liver oxidative stress. MDA (malondialdehyde) is a large lipid peroxidation agent which is used as a marker for oxidative liver damage. The hairy root extract's protective impact on the liver injury was not statistically different from Silymarin (milk thistle extract), a commonly used natural hepatoprotective agent. It has been evaluated that *O. americanum* leaves at medium dose 200 mg/kg and high dose 400 mg/kg show the hepatoprotective effects on the liver or hepatic damage in rats caused by the paracetamol [79]. The *O. americanum* leaves may increase the total protein [69] and albumin in the serum [80], and also there is an increase in the levels of the total bilirubin (TBIL), alkaline phosphate (ALP), aspartate transaminase(AST), alanine transaminase [81-83] (ALT) were reported.

4.4.1. Mechanistic interventions of selected *Ocimum* species in obesity.

Excess diet leads to obesity which further causes mitochondrial dysfunction, ER stress, oxidative stress, inflammation, and apoptosis, altering gene & protein expression via MAPK & JNK signaling. Systemic oxidative stress isa common feature of obesity and obesity-related hypertension, liver disorder, and diabetes [91]. Oxidative stress arises due to increased generation of free radicals and reactive oxygen species (ROS), with the attendant reduction in the antioxidant defense system, in the obese, further damaging DNA, lipids, and protein. Angiotensin II (AG-II) also induces oxidative stress, which plays a key role in developing hypertension [67]. Though, various previous studies have demonstrated that *Ocimum* species are rich in flavonoids, and phenolic acids can scavenge free radicals. The ability of the *O. basilicum* and *O. gratissimum* leaves extracts to scavenge free radicals is a sign that they could help alleviate oxidative stress in obesity and obesity-related other disorders [91] (Figure 3).

5. Effect of Selected *Ocimum* Species on Gene Expression

The chief phenolic elements extracted from *O. gratissimum* and *O. basilicum* have been reported to significantly affect the gene expression of the insulin regulatory & proliferative genes and glucose transporter 2 in treated islets, explaining its ability in reducing the blood glucose level [92]. *O. basilicum L.* exerts an anti-inflammatory effect in adipocytes via suppressing the inflammatory signaling pathway through a decrease in Tnfrsf9 gene expression. Also, Nfκb1 gene expression was low with *O. basilicum L.*, suggesting that the *Ocimum* extracts influenced TLR4-NF-κB signaling [93, 94]. The genes that play a direct role in atherogenesis are “LDRL, LxRalpha [95], PPARs, CD-36”, as these genes regulate cytotoxin production, lipid metabolism, and cellular activity within the arterial wall. Polyphenols extracted from *O. sanctum* L. have a direct effect on the transcription of these genes in cultured human mononuclear cells (HMC) in the presence of polyphenols extracted from *O. sanctum* L. These polyphenolic extracts have shown an inherent capacity to prevent the transcriptional expression of such genes in metabolic disorders [96].

6. Conclusions

Ocimum species are highly revered for their health-promoting effects in the traditional system of medicines. Preclinical and clinical investigations showed that *Ocimum* species, particularly *O. basilicum*, *O. sanctum*, *O. gratissimum* and *O. americanum* are devoid of any toxic effects and have the potential to normalize blood glucose levels and lipid profile, inhibit lipase activity, ameliorate chemical-induced hepatotoxicity, and treat diabetic –neuropathy, -nephropathy and –retinopathy. Also, the *Ocimum* genus contains phenols, terpenoids, flavonoids, tannins, and steroids documented to be responsible for the observed biological effects of these species. However, more rigorous studies with larger sample sizes and longer durations giving insights into the further mechanism of action and development of standardized formulations are certainly required to develop these species as drugs for managing metabolic disorders and related comorbidities.

Table 6. Clinical studies of selected *Ocimum* species in metabolic disorders.

S. No	Study Title	Participants	*Ocimum* Formulations	Outcome measures	References
1	Randomized controlled	40 male adults T2DM (45–55 years)	Leaves	fasting blood glucose activity	[97]
2	Randomized parallel-group	30 adults Obesity (17–30 years)	Leaves	Enhances body mass index and lipid levels	[91]
3	Controlled parallel-group	30 adults T2DM	Leaf powder	Significant post-prandial glucose & fasting blood	[98]
4	Randomized single-blind parallel-group	200 adults Gouty arthritis	Tincture of plant	Reduces the serum uric acid levels	[99]
5	Randomized, placebo-controlled	100 adults (≥40 years)	Aqueous Leaves	Enhances lipid levels, increases blood glucose, and rise BP	[100]
6	Randomized, controlled parallel	60 adults T2DM (30–65 years)	Leaves + glibenclamide drug	Significant fasting blood & postprandial glucose reduced HBA1c	[101]
7	Randomized placebo-controlled	40 adults T2DM (45–55 years)	Aqueous leaves	Significant improvement in lipid profile	[44]
8	Randomized, clinical trial	90 male adults T2DM (40–60 years)	Powder *Ocimum* leaves	Improved T2DM symptoms: polydipsia, polyphagia, & BP	[44]
9	Randomized control	22 healthy adults (22–37 years)	Ethanolic extract	Reduction in lipid profile	[44]
10	Randomized control	5 adults psychosomatic (60–80 years)	Powder whole plant	Significant improvement in lipid profile	[102]
11	Clinical study open-label	50 Female adults hypotensive (18–30 years)	Fresh juice of leaves	Significant decrease in Blood pressure	[103]

S. No	Study Title	Participants	*Ocimum* Formulations	Outcome measures	References
12	Controlled group	27 adults T2DM/MeS (45–65 years)	Powder of leaves	Enhances lipid levels, blood glucose levels, glycated proteins (HbA1c) & UA	[44]
13	Randomized, single-blind, Placebo-controlled cross-over	40 adults T2DM (41–65 years)	Powder of leaves	Significant decrease in fasting blood glucose, post-prandial glucose and urine glucose	[44]
14	Randomized placebo-controlled cross-over	20 adults, hypertension (45–64 years)	Fresh Juice of leaves	Significant decrease in blood pressure	[44]
15	Randomized placebo-controlled	16 adults, hypertension (45–64 years)	Fresh Juice of leaves	Significant decrease in blood pressure	[44]

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Conflicts of Interest

There are no conflicts of interest.

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