Article Information

Article Type:	systematic-review
Journal Title:	Critical Reviews in Food Science and Nutrition
Publisher:	Taylor & Francis
DOI Number:	10.1080/10408398.2023.2170320
Volume Number:	0
Issue Number:	0
First Page:	1
Last Page:	20
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A systematic [Correction file uploaded] review on anti-diabetic plant essential oil compounds: Dietary sources, effects, molecular mechanisms, and safety

Left running head: G. R. GANDHI ET AL.

Short title : Critical Reviews in Food Science and Nutrition

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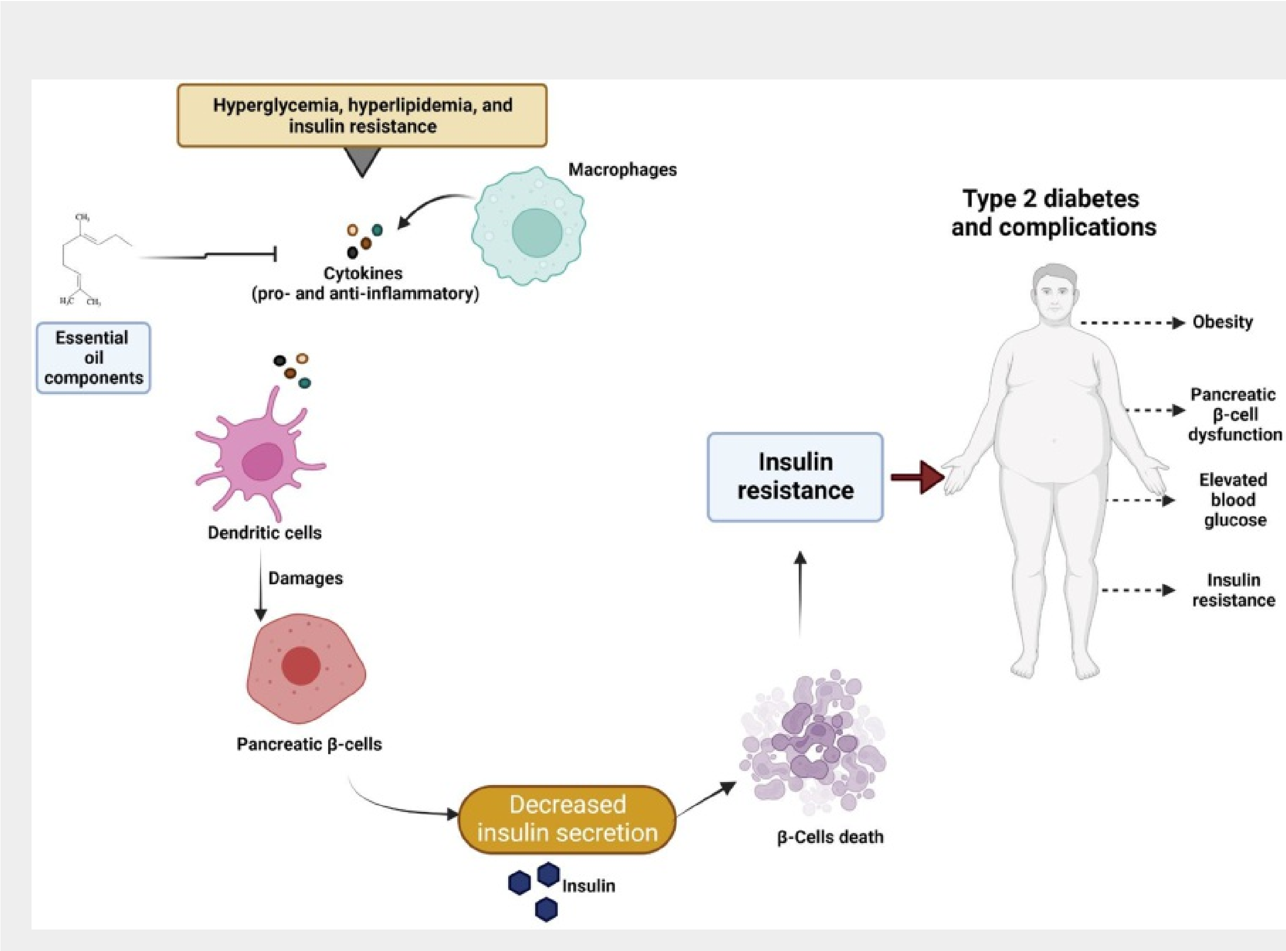
ABSTRACT

Type 2 diabetes mellitus (T2DM) is a multifaceted metabolic syndrome defined through the dysfunction of pancreatic β-cells driven by a confluence of genetic and environmental elements. Insulin resistance, mediated by interleukins and other inflammatory elements, is one of the key factors contributing to the progression of T2DM. Many essential oils derived from dietary plants are beneficial against various chronic diseases. We reviewed the anti-diabetic properties of dietary plant-derived essential oil compounds, with a focus on their molecular mechanisms by modulating specific signaling pathways and other critical inflammatory mediators involved in insulin resistance. High-quality literature published in the last 12 years, from 2010 to 2022, was collected from the Scopus, Web of Science, PubMed, and Embase databases using the search terms "dietary plants," "essential oils," "anti-diabetic," "insulin resistance," "antihyperglycemic," "T2DM," "anti-diabetic essential oils," and anti-diabetic mechanism." According to the results, the essential oil compounds, including cinnamaldehyde, carvacrol, zingerone, sclareol, zerumbone, myrtenol, thujone, geraniol, citral, eugenol, thymoquinone, thymol, citronellol, α-terpineol, and linalool have been demonstrated to contain strong anti-diabetic effects via modulating various signal transduction pathways linked to glucose metabolism. Additionally, in diabetes-related animal models, they can also considerably reduce the expression of TNF-α, IL-1β, IL-4, IL-6, iNOS, and COX-2. The main signaling molecules regulated by these compounds include AMPK, GLUT4, Caspase-3, PPARγ, PPARα, NF-κB, p-IκBα, MyD88, MCP-1, SREBP-1c, AGEs, RAGE, VEGF, Nrf2/HO-1, and SIRT-1. They can also significantly inhibit the generation of TBARS and MDA, reduce oxidative stress, increase insulin levels, adiponectin, and glycoprotein enzymes, boost antioxidant enzymes like SOD, CAT, and GPx, as well as reduce glutathione and vital glycolytic enzymes. Besides, they can significantly lower the levels of liver enzymes and lipid profile markers. Moreover, most essential oil compounds are generally safe based on animal studies. In conclusion, dietary plant-derived essential oil compounds have potential anti-diabetic effects by influencing different signaling pathways and molecular targets linked to glucose metabolism, and should be safe and beneficial against diabetes and related complications.

GRAPHICAL ABTSRACT



KEYWORDS

Essential oil; insulin resistance; interleukins; dietary plants; type 2 diabetes mellitus

Note: Any change made here needs to be made in the corresponding section at the end of the article.

The author(s) reported there is no funding associated with the work featured in this article.AQ11

IntroductionAQ2

Type 2 diabetes (T2DM) is a chronic metabolic syndrome induced through pancreatic β-cell dysfunction, and is featured with insulin resistance, hyperglycemia, and hyperlipidemia, in the target organs (Galicia-Garcia et al. 2020). It is a multi-factorial condition that is influenced by a variety of genes and lifestyle variables, including aging, stress, and obesity, and can promote the threat of vascular complications in diabetic patients (Kaku 2010). T2DM affects approximately 462 million people worldwide and accounts for more than 90% of all diabetic patients (Khan et al. 2020). It is estimated that 193 million people live with undiagnosed diabetes (Kaushik, Kaushik, and Parvez 2022; Maurya and Qamar 2022). It impairs the proper functions of critical organs, such as the pancreas, liver, kidney, brain, small intestine, skeletal muscle, and adipose tissues. Moreover, it can cause pathological complications, such as retinopathy, diabetic neuropathy, nephropathy, and cardiomyopathy (DeFronzo 2009).

The recommended first-line treatment for T2DM is a combination of healthy lifestyle changes and monotherapy, preferably metformin (Garber et al. 2017). However, insulin therapy remains the most effective glucose-lowering strategy for diabetic patients with high glycated hemoglobin (HbA1c) levels. Still, intensive insulin administration inevitably results in an increased rate of hypoglycemia (Swinnen, Hoekstra, and DeVries 2009). The most often used medications are sodium-glucose cotransporter-2 (SGLT-2) inhibitors, biguanides, insulin sensitizers, amylin analogs, glucagon-like peptide-1 (GLP-1) agonists, alpha-glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors, and peroxisome proliferator-activated receptor (PPAR) agonists (Padhi, Nayak, and Behera 2020).

Insulin resistance plays an important role in the etiology and pathophysiology of T2DM by increasing the levels of inflammatory mediators, like interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α), chemokines, and adipocytokines (Kochumon et al. 2019). The chronic exposure of cytokines and other inflammatory mediators activates several cytokine signaling, inhibiting the stimulation of insulin signaling receptors (Rehman and Akash 2016). Additionally, when β-cells are exposed to free fatty acids (FFAs) and glucose for a long time, IL-1β is activated by different molecular pathways controlled by transcription. When IL-1β is active, it binds to the IL-1 receptor type I (IL1R1), termed as cluster of differentiation 121a (CD121a), which includes nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and myeloid differentiation primary response 88 (MYD88). It causes the pancreatic β-cells to slowly develop amyloidosis, apoptosis, and fibrosis (Donath and Shoelson 2011).

Aromatherapy, a complementary and alternative therapy in which essential oils are used as the primary therapeutic agent against various diseases, has recently received much attention (Ali et al. 2015). Essential oils are extracted from different plant parts such as leaves, stems, flowers, fruits, seeds, rhizomes, and bark. These essential oils have volatile constituents that belong to the class of monoterpenes, terpenes, terpenoids, phenols, and sesquiterpene hydrocarbons. In addition, they also have biological and pharmaceutical properties such as antimicrobial, antimutagenic, anticancer, anti-inflammatory, analgesic, anti-diabetic, and antiviral properties (Raut and Karuppayil 2014; Mehdizadeh and Moghaddam 2018). Limited evidence is available on the anti-diabetic potential of dietary plant-derived essential oil compounds (Hamid, Aiyelaagbe, and Usman 2011). Therefore, this review focuses on the constituents of essential oil compounds derived from dietary plants and how they regulate the key signaling pathways and related inflammatory mediators involved in T2DM.

Materials and methods

Search strategy

The procedures stated in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al. 2009) were followed in conducting this systematic review. The Scopus, Web of Science, PubMed, and Embase databases were used for the literature search. Searches were done using a combination of the terms "dietary plants," "essential oils," "antidiabetic," "insulin resistance," "antihyperglycemic," "T2DM," "antidiabetic essential oils," and "antidiabetic mechanism." A total of 32 animal model studies published between 2010 and 2022 were finally selected to constitute the study.

Criteria for inclusion and exclusion

The inclusion and exclusion criteria are as follows. (1) Recent high-quality literature was included based on studies with animals treated with compounds derived from dietary plant essential oils for experimentally-induced T2DM. (2) Studies containing information on cytokine-mediated signaling factors and critical biomarkers associated with glucose metabolism were selected for the following round of screening. (3) Studies from all regions and countries were included. (4) All the selected studies have been peer-reviewed and published. (5) Due to insufficient evidence of treating T2DM, *in-vitro* studies were excluded. (6) Papers without experimental or numerical data on glycemic response were also excluded from this review.

Data analysis

All titles and abstracts identified by manual reference list searches and online searches were evaluated for inclusion by three independent reviewers (N.M.K., G.H., and D.Y.). The full-text versions were retrieved and examined if any titles or abstracts lacked sufficient details to decide whether to reject or include them in the research. When a conflict arose in deciding on the inclusion or exclusion of any study, it was settled by the fourth reviewer (G.R.G.).

Data extraction

The information was taken from the retrieved original research articles and put into a table. This included the name of the author, the publication year, the study region, the animal strains, the type of study, the effectiveness of the essential oil compounds, the biochemical and molecular markers, and the likely mechanisms.

Results and discussion

Search results

Using related keywords, the initial search from the databases identified 878 articles (Pubmed, 374; Embase, 80; Scopus, 278; and Web of Science, 146). After using the inclusion and exclusion criteria in this review study, we collected 120 articles for further reading and screening after removing any duplicates. Our manual search failed to add any new articles to the selection. Finally, 32 articles that met all the eligibility criteria were selected and included in this systematic review. Figure 1 illustrates the flowchart of study selection for this systematic review. This review article primarily consolidated the in vivo studies on the anti-diabetic potential of main dietary plant-derived essential oil compounds (Figure 2) and discussed their related mechanisms of action (Table 1).

Figure 1. The flowchart illustrates an overview of the study search and inclusion process. The initial search was performed in PubMed, Web of Science, Embase, and Scopus databases. The inclusion criteria were in vivo studies of diabetic-induced animals treated with dietary plant-derived essential oil compounds.

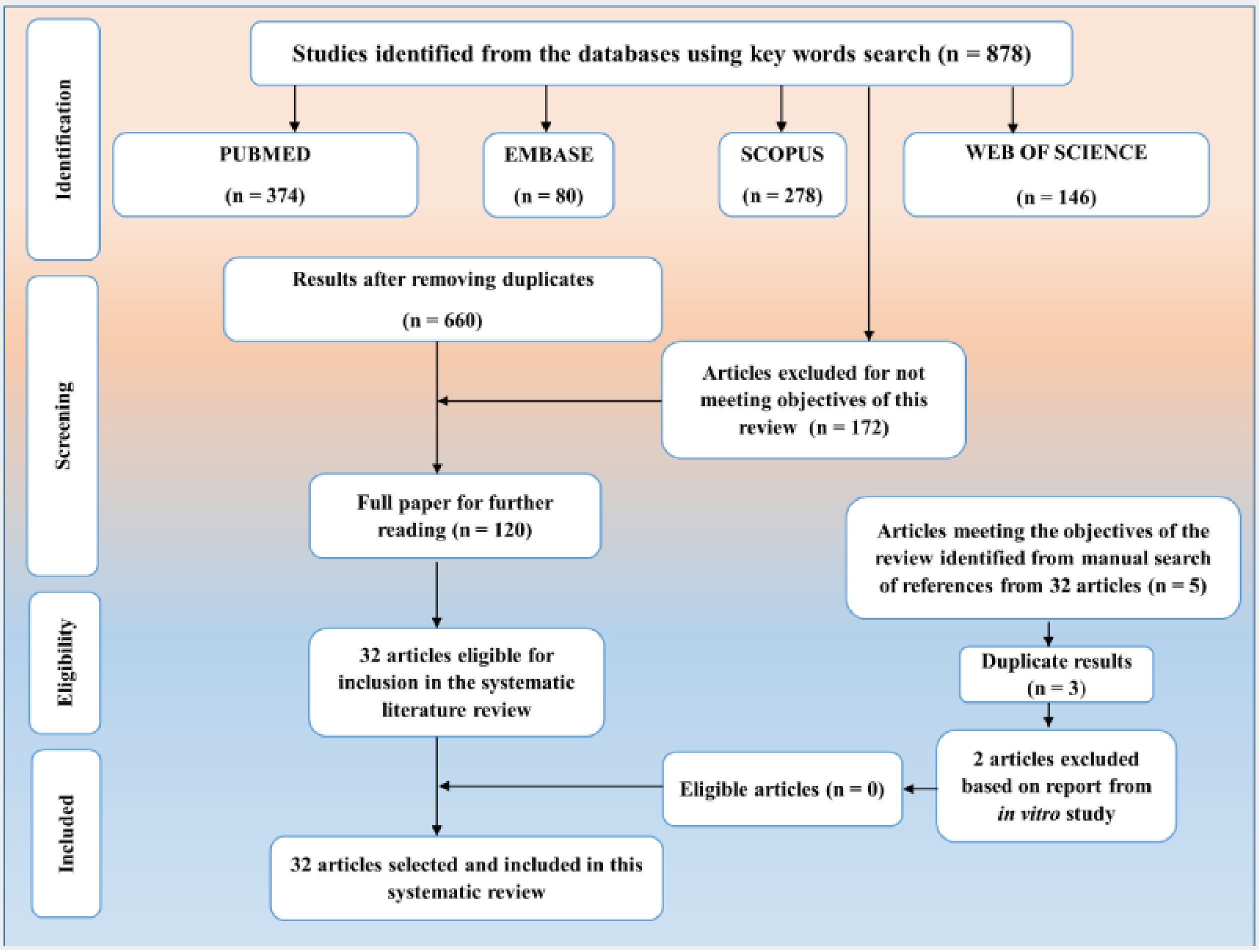


Figure 2. The chemical structures of main dietary plant-derived essential oil compounds with anti-diabetic effects.

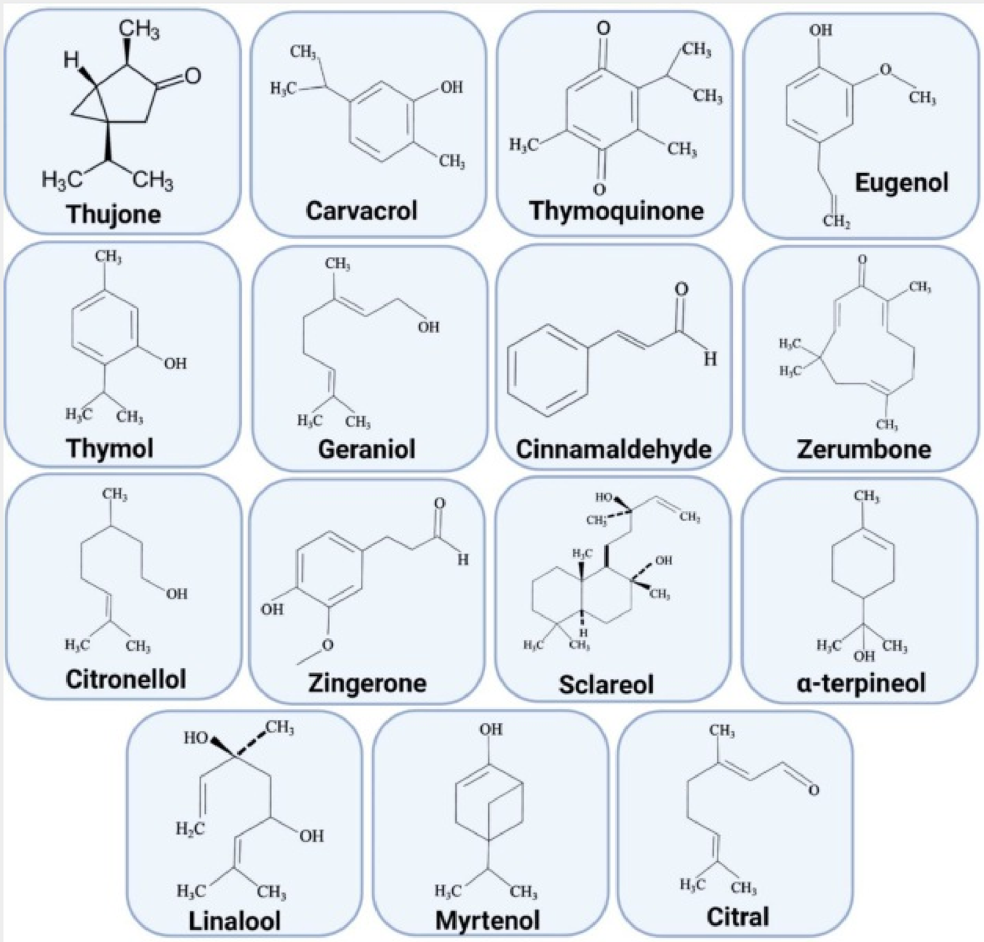


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Table 1. The anti-diabetic effects and molecular mechanisms of dietary plant-derived essential oil compounds.

Essential oil compounds	Animal/Strain	Dose/Route	Effects and molecular mechanisms	References

Thujone	Sprague-Dawley rats	0.1 mg/mL	↑ GLUT4 intrinsic activity; ↑ AMPK phosphorylation; rescues insulin-stimulated glucose transport by restoring AS160 phosphorylation; regulates palmitate oxidation	(Alkhateeb and Bonen 2010)
Citral	Sprague-Dawley rats	10, 15, and 20 mg/kg	↓ fasting blood glucose levels; ↑ glucose tolerance and increased metabolic rate	(Modak and Mukhopadhaya 2011)
Carvacrol	Wistar rats	25, 50, and 100 mg/kg *intraperitoneal*	↓TNF-α-induced NF-κB pathway; ↓ Caspase-3; reduced oxidative stress	(Deng, Lu, and Teng 2013)
Thymoquinone	Sprague-Dawley rats	Thymoquinone (5 mg/kg) *intraperitoneal*	↓ COX-2 expression, malondialdehyde levels; ↑ level of SOD	(Al Wafai 2013)
Eugenol	Wistar rats	2.5, 5, and 10 mg/kg *intragastric*	↓ ALP, AST, ALT; ↓ CK and BUN; regulate plasma glucose levels, insulin, HbA1C; ↑ glycogen level in the liver; ↓ glycolytic enzymes	(Srinivasan et al. 2014)
Clove oil and Eugenol microemulsions	Sprague-Dawley rats	40 mg/kg (Clove essential oil); 40 mg/kg (Clove essential oil microemulsion); 31 mg/kg eugenol *oral*	↓ Triglycerides, cholesterol, AST, ALT; significant regulation on steatohepatitis and dyslipidemia; prevention of cardiovascular disease	(Al-Okbi et al. 2014)
Thymol	C57BL/6J mice	10, 20, and 40 mg/kg *intragastric*	↑ LCAT and LPL; ↓ in HMG-CoA reductase; ↓ in plasma glucose, insulin, TGs, total cholesterol, LDL, HDL, FFAs; ↑ adiponectin; ↓ leptin	(Saravanan and Pari 2015)
Geraniol	Wistar rats	250 mg/kg *oral*	↑ PPARγ and suppression of RAGE activated NF-κB; ↑ insulin sensitivity; ↓ pro-inflammatory mediators RAGE and HbA1C; ↓ liver NO and lipid peroxides; ↓ AST and ALT activities; ↑ adiponectin	(Ibrahim, El-Denshary, and Abdallah 2015)
Thymol	C57BL/6J mice	40 mg/kg *intragastric*	↓ TGF-β1 and VEGF; ↑ SOD, catalase, GPx, GSH, vitamins C & E; ↑ insulin secretion and ↓ SREBP-1; ↓ blood glucose and insulin	(Saravanan and Pari 2016)
Cinnamaldehyde	Sprague-Dawley rats	25, 50, and 100 nM/L	↓ NF-κB, p-IκBα, TNF-α and IL-6	(Yang et al. 2016)
Zerumbone	Wistar rats	40 mg/kg *oral gavage*	↓ retinal TNF-α, IL-1β, IL-6; blocks AGEs, RAGE, NF-κB pathways; ↓ plasma glucose and glycosylated Hb; ↓ elevated AGEs and RAGE	(Tzeng et al. 2016)
Eugenol	BALB/c mice	100 mg/kg *intraperitoneal*	↓ α-glucosidase facilitating reduced blood glucose and AGEs formation; ↓ binding of sugar to albumin by binding with lysine residues	(Singh et al. 2016)
Citronellol	Wistar rats	25, 50, and 100 mg/kg *oral*	↓ ALP, ALT, AST; ↑ insulin, Hb, and hepatic glycogen; ↓ glucose and HbA1C levels; reduced the elevated levels of urea, uric acid, and creatinine	(Srinivasan and Muruganathan 2016)

Cinnamaldehyde	Sprague-Dawley rats	10, 20, and 40 mg/kg *oral*	↓ IL-6 and TNF-α in hippocampus and cortex; ↑ acetylcholine esterase and glutamate and GABA; ↓ IL-6 and TNF-α; ↓ Plasma glucose and HbA1C	(Jawale et al. 2016)
Thymol	C57BL/6 mice	20 and 40 mg/kg *gavage*	↑ Nrf2/HO-1 signaling; improving brain insulin resistance	(Fang et al. 2017)
Zerumbone	C57BL/6 mice	0.025%	Induce AMPK activation and ↓ miR-146b; ↑SIRT-1 expression; ↓ adipocyte size and improved hyperleptinemia, hyperinsulinemia, and hyperglycemia	(Ahn et al. 2017)
Geraniol	Wistar rats	100, 200, and 400 mg/kg *oral*	↑ insulin level; ↓ plasma glucose and HbA1C; ameliorated glucose metabolic pathway enzymes; restored pancreatic acini with the absence of dilatation	(Babukumar et al. 2017)
Isomalto-oligosaccharides and cinnamaldehyde	Swiss albino mice	1 g/kg and 10 mg/kg *oral*	↓ LPS, TNF-α, IL-1, IL-1β, MCP-1; ↑ gut lining and mucin content; ↑ glucose and lipid metabolism with reduced ectopic fat deposition	(Singh et al. 2017)
Citral	NMRI mice	5, 10, and 20 mg/kg *intraperitoneal*	↑ adiponectin; ↓TNF-α; ↑ PPARα; ↓ serum leptin levels; ↑anti-oxidant enzyme levels; eliminated liver fibrosis	(Vaezi et al. 2018)
Zingerone	Wistar rats	50 and 100 mg/kg	Abrogate ROS; ↓ NF-κB activation; ↓ TNF-α, IL-1β, IL-6; ↓ kidney toxicity markers (Kim-1, BUN, creatinine); ↓ LDH, TGF-β	(Rehman et al. 2019)
Eugenol	Sprague Dawley rats	10 mg/kg *oral*	↑ GLUT4 and AMPK; ↓ insulin, TGs, cholesterol, LDL, malondialdehyde and IL-6	(Al-Trad et al. 2019)
Sclareol	Swiss Mice	1 mg/kg *intraperitoneal*	↓ NF-κB, MCP-1, SREBP-1; ↓ adiposity; ameliorating insulin sensitivity and glucose tolerance; ↑ plasma HDL	(Cerri et al. 2019)
Citral	Sprague-Dawley rats	30 mg/kg *oral*	↑ activity of GK/HK and PK; ↓ activity of LDH; ↓ activity of SOD, GPX and catalase; ↑ glucose absorption and insulin production; ↓ HbA1C; restored the changes in TGs, LDL and FFAs	(Mishra et al. 2019)
α-terpineol	Sprague Dawley rats	25, 50, and 100 mg/kg	↓ TNF-α, IL-1β; ↓ serum thiobarbituric acid reactive substances (TBARS); ↑ insulin sensitivity	(Sousa et al. 2020)
Carvacrol	C57BL/6 mice	10, 20, and 40 mg/kg *intraperitoneal*	↑ glucose tolerance and ↓ plasma TGs; ↓ LDH; ↑ HK and PFK; ↓ random plasma glucose	(Li et al. 2020)
Linalool	Rats	25 mg/kg *oral gavage*	↓ fasting glucose, insulin resistance, dyslipidemia, glycation oxidative stress, inflammatory markers, renal dysfunction indices;↑ GLO-I	(Mahdavifard and Nakhjavani 2020)
Eugenol	NMRI mice	50, 100, and 200 µM	↑ insulin secretion; ↑ contents of islets cells	(Oroojan 2020)
Carvacrol	Wistar rats	75 mg/kg *gavage*	↑ glutathione peroxidase, catalase and Bcl-2, Nrf-2 and HO-1; ↓ malondialdehyde, Bax, COX-2, NF-κB, Bax/Bcl-2 ratio	(Arkali, Aksakal, and Kaya 2021)

Myrtenol	Wistar rats	50 mg/kg *oral*	↑ enzymatic actions of CAT, SOD, GST, GPx; ↓ IL-1β and TNF-α; ↓ expression of TLR4, MyD88, NF-κB; ↓ blood glucose and lipid profile	(Xuemei et al. 2021)
Cinnamaldehyde	Wistar rats	20 mg/kg *gavage*	Reduced and normalized plasma NOx levels; ↓ iNOS activity	(Ataie et al. 2021)
Citral	Wistar rats	300 mg/kg *gavage*	↓ inflammatory genes IL-6 and TNF-α and related cytokines	(Zarandi et al. 2021)
Eugenol	C57BL/6 mice	500 mg/kg	Improved gut microbiota by ↑ *Actinobacteria phylum*; ↓ *Proteobacteria phylum*; prevents liver fat accumulation	(Rodrigues et al. 2022)

Abbreviations: Advanced glycation end products (AGE); Akt substrate (AS160); Alanine transaminase (ALT); Alkaline phosphatase (ALP); AMP activated protein kinase (AMPK); Aspartate transaminase (AST); B-cell growth inhibitory factor (BIF); B-cell lymphoma-2 (Bcl-2); Bcl-2 associated X protein (Bax); Blood urea nitrogen (BUN); Creatine kinase (CK); Cyclooxygenase-2 (COX-2); Free fatty acid (FFA); Gamma amino butyric acid (GABA); Glucokinase (GK); Glucose transporter type 4 (GLUT4); Glutathione (GSH); Glutathione peroxidase (GPx); Glyoxylase-1 (GLO-1); Heme oxygenase - 1 (HO-1); Hemoglobin (Hb); Hemoglobin A1C (HbA1c); Hexokinase (HK); High density lipoprotein (HDL); Hydroxymethylglutaryl-coenzyme A (HMG-CoA); Inducible nitric oxide synthase (iNOS); Interleukin (IL); Lactate dehydrogenase (LDH); Lecithin cholesterol acyltransferase (LCAT); Lipoprotein lipase (LPL); Lipopolysaccharide (LPS); Low density lipoprotein (LDL); Monocyte chemoattractant protein-1 (MCP-1); Myeloid differentiation primary response 88 (MYD88*)*; Nitric Oxide (NO); Nuclear factor erythropoietin-2-related factor 2 (Nrf2); Nuclear Factor Kappa B (NF-κB); Peroxisome proliferator-activated receptor-α (PPARα); Peroxisome proliferator-activated receptor-γ (PPARγ); Phosphofructokinase (PFK); Post-translational modifications of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (p-IκBα); Pyruvate kinase (PK); Reactive oxygen species (ROS); Receptor for advanced glycation end products (RAGE); Sirtuin 1 (SIRT-1); Sterol regulatory element-binding protein-1 (SREBP-1); Super Oxide Dismutase (SOD); Thiobarbituric acid Reactive Substances (TBARS); Toll-like receptor 4 (TLR4); Transforming Growth Factor-β (TGF-β); Triglycerides (TGs); Tumor Necrosis Factor-α (TNF-α); Vascular Endothelial Growth Factor (VEGF).

Modulation of NF-κB signaling and mitigation of other inflammatory mediators

Cinnamaldehyde

Cinnamaldehyde is an important essential oil compound abundant in some culinary flavor spices, such as cinnamon bark and *Cinnamomum zeylanicum* Blume (Lauraceae), *Cinnamomum verum* J. Presl (Lauraceae), and *Cinnamomum cassia* Presl (Lauraceae), have been reported in studies to possess therapeutic potential for the prevention and treatment of T2DM (Yin, Zhang, and Ye 2008; Zhang et al. 2008; Cabello et al. 2009). It has anti-obesity and anti-hyperglycemic properties (Camacho et al. 2015). In streptozotocin (STZ)-induced diabetic rats, cinnamaldehyde exerted an antioxidant effect against reactive oxygen species (ROS)-induced hyperglycemic conditions (Subash-Babu, Alshatwi, and Ignacimuthu 2014).

In another study, cinnamaldehyde protected the damaged neurons by reducing apoptosis in the dorsal root ganglion neurons after exposure to high glucose. Nrf2-associated oxidative stress and NF-κB inflammatory cascades are significant pathophysiological mediators in experimental diabetic peripheral neuropathy. The authors reported that cinnamaldehyde could boost the therapeutic response against diabetes mellitus (DM) by inhibiting the NF-κB activity and lowering ROS production (Yang et al. 2016).

Gut microbiota plays a vital role in health and disease (Sekirov et al. 2010). The unfavorable impact on gut health can be overcome by combining non-digestible isomalto-oligosaccharides (IMOs) with cinnamaldehyde. In a study, the combination of IMOs and cinnamaldehyde prevented its adverse effects on gut microbiota and related metabolic outcomes in high-fat diet (HFD)-treated mice. Furthermore, the co-supplementation of cinnamaldehyde with IMOs showed a promising effect against HFD-induced histological, biochemical, and genomic alterations in the liver, visceral white adipose tissue, and gastrointestinal tract. Additionally, the administration of cinnamaldehyde with IMOs significantly reversed the increase in peroxisome proliferator-activated receptor gamma (PPARγ), toll-like receptor 4 (TLR4) and NF-κB, and decrease in mucin synthesis genes (mucin 2 and 4), caused by the HFD (Singh et al. 2017). Therefore, the authors concluded that the potential prebiotic IMOs and metabolic health benefits of cinnamaldehyde could synergistically enhance the overall gut health and they could be beneficial dietary supplements in functional foods to treat obesity and associated complications.

In the lipopolysaccharide-activated BV2 microglia culture system, Ho, Chang, and Chang (2013) showed that the anti-neuroinflammatory activity of cinnamaldehyde from cinnamon may be caused through the inhibition of NF-κB-mediated transcription of pro-inflammatory cytokine release. In this regard, Jawale et al. (2016) investigated the behavioral and neurochemical effects of cinnamaldehyde on reversing diabetes-induced cognitive deficits. The results showed the potential health benefits of cinnamaldehyde in neuroinflammation, improvement in neurotransmitter levels, and consequent progress in behavioral deficits of diabetic rats. Its positive mode of action in improving the neurological impairments of diabetic rats could be via decreasing the levels of IL-6 and TNF-α, along with improving the levels of acetylcholine esterase, glutamate, and gamma-aminobutyric acid (GABA). The results indicate that the enhanced level of IL-6-induced inflammation in the hippocampus and cortex of diabetic rats may alter the neurotransmitter homeostasis and cognitive deficits by modulating the GABA-glutamate-glutamine cycle. Therefore, it could be concluded that cinnamaldehyde possesses many bioactivities relating to the anti-diabetic, cognitive enhancer, anti-inflammatory, behavioral, and neurochemical health benefits.

Nitric oxide (NO) levels and insulin secretions are altered in obesity and insulin resistance conditions, respectively (Choromańska et al. 2020; Gluvic et al. 2017). Cinnamaldehyde enhanced islet insulin secretion, restored NO levels, decreased insulin resistance, and improved plasma glucose levels in rats fed an HFD (Ataie et al. 2019; Farrokhfall et al. 2014; Khare et al. 2016; Zuo et al. 2017). Ataie et al. (2021) also demonstrated the influence of cinnamaldehyde on inducible nitric oxide synthase (iNOS) activity and NO-induced islet insulin secretion in rats receiving HFD. HFD-fed rats showed increased iNOS activity in islets. In contrast, a diet supplemented with cinnamaldehyde stabilized iNOS, serum nitrate, and nitrite levels, restoring the stimulatory effect of NO on insulin secretion. Therefore, the authors concluded that by lowering the islet iNOS activity, cinnamaldehyde positively affected glucose metabolism via modulating the NO pathway.

Carvacrol

Carvacrol (2-methyl-5-isopropyl phenol), a naturally occurring phenolic monoterpene, is a substantial component of essential oils produced by the mint family (Lamiaceae), which includes the genus *Origanum*, *Thymus*, and *Ocimum* (Raja 2012). Carvacrol has been documented to exhibit numerous biological functions (Baser 2008). In addition to its known effects on the peripheral nervous system (PNS), studies reveal that DM may harm the central nervous system (CNS) and result in cognitive impairment (Biessels and Reagan 2015; Dobretsov, Romanovsky, and Stimers 2007).

Diabetes causes a multifactorial cognitive dysfunction known as diabetes-associated cognitive decline (DACD), characterized by altered neurochemical processes and structural abnormalities (Kodl and Seaquist 2008). DM-related cognitive impairment is often closely associated with cardiovascular diseases and triggered by disturbed glucose homeostasis and disrupted insulin signaling in the CNS (Elias et al. 2005; Reagan, Grillo, and Piroli 2008). Besides causing morphological abnormalities and memory deficits in the brain, osmotic impairment and oxidative stress caused by diabetic-hyperglycemia also damage neurons (Sharma and Singh 2011). Furthermore, hyperglycemia stimulates the uncontrolled production of pro-inflammatory cytokines (TNF-α and IL-1β), activation of NF-κB signaling pathway, and generation of free oxygen radicals, leading to DACD (Kuhad et al. 2009; Umegaki 2010) and apoptosis in neuronal cells (Mastrocola et al. 2005).

In a diabetic rat model, Deng, Lu, and Teng (2013) examined the neuroprotective effects of carvacrol on DACD and investigated its probable molecular mechanisms. Administration of carvacrol substantially and dose-dependently reversed the behavioral, biochemical, and molecular alterations linked with diabetes. The findings also showed that carvacrol was used to treat DACD and lower oxidative stress, inflammation, and apoptotic cascades that are caused by DM. The mechanism of action suggests that carvacrol could be further explored as a promising treatment against hyperglycemia-associated oxidative stress, inflammation, and DACD.

Studies have also demonstrated that diabetes has significant adverse effects on the male reproductive system, leading to sexual dysfunctions and infertility in both STZ-induced diabetic male animal models and male diabetic patients, who have notable reductions in spermatological parameters (Alves et al. 2013; Bener et al. 2009; Jain and Jangir 2014; Tsounapi et al. 2017). According to Nna et al. (2019), DM-induced excessive ROS production and oxidative stress lead to infertility through lipid peroxidation, germ cell apoptosis, dysfunctional spermatogenesis, and insufficient androgenic hormone production (Aitken and Baker 2006; Kanter, Aktas, and Erboga 2013), and improper spermatozoa maturation in the epididymis (Agarwal et al. 2014).

The activation of the transcription factor, nuclear factor-erythroid 2 associated factor 2 (Nrf2) in response to the oxidative stress regulates the transcription of genes, namely catalase (CAT), quinone oxidoreductase (NQO-1), superoxide dismutase (SOD), glutathione peroxidase (GPx), and haemoxygenase-1 (HO-1), which are responsible for protecting the body against the oxidative stress (Ha et al. 2006; Itoh et al. 1997; Ma 2013). Spermatogenesis and sperm maturation are impaired by the oxidative stress that occurs in the testicles and epididymis due to alterations in the Nrf2 gene expression (Nakamura et al. 2010). According to reported studies, DM may cause apoptosis and inflammation in the testicular tissue, and NF-κB regulates a wide range of cellular functions and prevents chronic inflammation (Kushwaha and Jena 2012; Maremanda, Khan, and Jena 2016; Biswas and Bagchi 2016). In the pathogenesis of inflammatory illnesses, cyclooxygenases are key polyunsaturated fatty acid enzymes for converting arachidonic acid to prostaglandin (PG) and cyclooxygenase-2 (COX-2). (Shanmugam, Gaw Gonzalo, and Natarajan 2004). Besides, the Bcl-2-associated X (Bax) protein (pro-apoptotic protein) to B-cell lymphoma-2 (Bcl-2) (anti-apoptotic protein) ratio is important in the regulation of cell survival and rate of apoptosis.

Carvacrol therapy provided significant protection against diabetes-induced testicular damage in rats by dramatically enhancing antioxidant activity, sperm quality, testicular apoptosis, and inflammation by lowering oxidative stress. It substantially impacted GPx, CAT activities, Bcl-2, Nrf2, HO-1 protein expression levels, malondialdehyde (MDA) levels, Bax, COX-2, and NF-κB expression levels, and Bax/Bcl-2 ratio. It also showed a significant MDA-lowering impact (Arkali, Aksakal, and Kaya 2021). The treatment of carvacrol improved sperm quality, decreased NF-κB-mediated apoptosis and inflammation through modifying the Nrf2/HO-1 pathway, and diminished oxidative stress induced by diabetes.

An alternative study showed that carvacrol treatment reduced blood sugar levels significantly and dose-dependently. Carvacrol-treated diabetic mice also improved glucose tolerance and decreased the level of triglycerides (TGs) when compared to the vehicle-treated diabetic mice. When compared to the diabetic control group, carvacrol significantly reduced plasma levels of lactate dehydrogenase (LDH), but not aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP). Besides, carvacrol treatment increased the activity of HK, 6-phosphofructokinase (PFK), and citrate synthetase (CS) in diabetic mice (Li et al. 2020).

Zingerone

Oxidative stress and inflammation play a key role in the development of diabetic nephropathy, and these markers can be important targets for therapeutic intervention. Dry or cooked ginger contains the major flavor component zingerone, also known as vanillyl acetone (Ahmad et al. 2015). Fresh ginger contains no zingerone, however, cooking or drying fresh ginger converts gingerol to zingerone via the reverse aldol reaction (Takizawa et al. 2012). Rehman et al. (2019) evaluated the renal protective efficacy of zingerone in controlling oxidative burst and inflammation in HFD/STZ-treated experimental diabetic nephropathy of rats. The treatment enhanced renal function by ameliorating the levels of the kidney toxicity markers, such as kidney injury molecule-1 (KIM-1), blood urea nitrogen (BUN), creatinine, and LDH. Besides suppressing transforming growth factor beta (TGF-β), it also significantly lowered the ROS levels, blocked the NF-κB activation, and reduced levels of other downstream inflammatory molecules, like TNF-α, IL-6, and IL-1β. Therefore, the authors concluded that zingerone is a bioactive molecule with anti-hyperglycemic, anti-oxidant, and anti-inflammatory potential. It could be further investigated for its treatment of diabetic nephropathy by improving kidney function.

Sclareol

The essential oil extracted from *Salvia sclarea* Linn. (Lamiaceae) contains a significant quantity of sclareol, a bioactive hydrophobic diterpene widely used as a flavoring agent for wines and alcoholic drinks (Cerri et al. 2019). Sclareol is well known for its anti-inflammatory and antioxidant properties. However, due to various factors, such as its low solubility in water, high tendency to accumulate in adipose tissue, and high lipophilicity, the use of sclareol is restricted (Cerri et al. 2019; Hatziantoniou et al. 2006). Hence, lipid nanocarriers may be used to effectively overcome these drawbacks and increase its bioavailability (Aditya et al. 2014).

Cerri et al. (2019) evaluated the effects of sclareol in nanoparticle formulations (solid-lipid nanoparticles) on the metabolic profile of obese mice. In obese mice, sclareol-loaded lipid nanoparticles increased high-density lipoprotein cholesterol (HDL-C) levels in plasma, reduced adiposity, improved insulin sensitivity, and ameliorated glucose tolerance. It reduced the expression of sterol regulatory element-binding protein-1c (SREBP-1c), monocyte chemoattractant protein-1 (MCP-1), and NF-κB. The combination of sclareol and lipid nanocarriers may hold promise in treating metabolic disorders by decreasing the proportion of adipose tissue.

Zerumbone

In obese patients, adipose tissue is a storage site for excess fat, which alters the lipid metabolism of adipose tissue, leading to fatty acid uptake, *de novo* lipogenesis, and lipolysis. Zerumbone, a prominent cyclic sesquiterpene found in the rhizomes of the wild ginger *Zingiber zerumbet* (L.) Smith (Zingiberaceae), has been shown to repair defective lipid metabolism in the white adipose tissues of C57BL/6 mice and ameliorate HFD-induced obesity (Ahn et al. 2017). It is also present in other food plants, like *Curcuma amada* Roxb.*,* (Zingiberaceae), *Alpinia galangal* (L.) Willd. (Zingiberaceae), and *Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae) (Tanaka et al. 2001; Rahman et al. 2014). Additionally, zerumbone suppressed adipocyte development and consequently prevented obesity caused by increased HFD intake. It was also found that by enhancing fatty acid oxidation and lowering lipogenesis through 5′ adenosine monophosphate-activated protein kinase (AMPK) activation, zerumbone improved the impaired lipid metabolism. In the same study, zerumbone administration downregulated microRNA-146b (miR-146b) expression, which further caused an increase in the mRNA and sirtuin (SIRT)-1 protein production. Therefore, the findings showed that zerumbone might be a potent bioactive molecule for preventing and treating metabolic diseases, particularly diet-induced obesity, by inhibiting adipogenesis with the molecular mechanism related to AMPK and the microRNA-146b/SIRT-1 pathway.

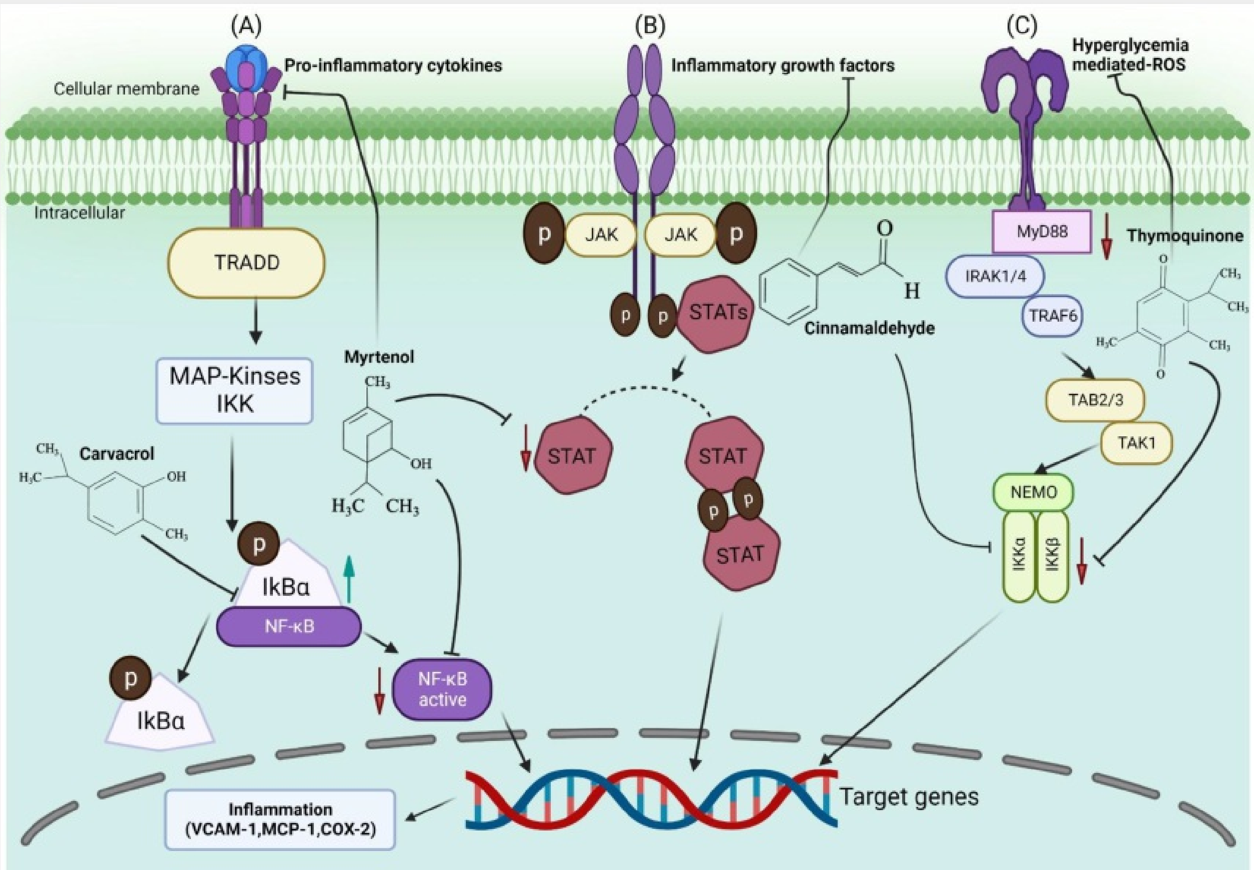
Uncontrolled hyperglycemia in DM may result in a number of complications, including ischemia, endothelial cell failure, blood-retinal barrier disruption, diabetic retinopathy, and vascular abnormalities (Antonetti, Klein, and Gardner 2012; Nentwich and Ulbig 2015). Tzeng et al. (2016) evaluated the protective effect of zerumbone against diabetic retinopathy in STZ-induced diabetic rats. The study suggested that zerumbone possesses retinal protective effects by lowering TNF-α, IL-1, and IL-6 via inhibiting NF-κB activation in diabetic rats. Therefore, the authors concluded that the antiapoptosis and retinal protective effects of zerumbone might be associated with the inhibition of advanced glycation end products (AGEs) and receptors for AGEs (RAGEs) signaling.

Myrtenol

Tansy and *Myrtus communis* Linn. (Myrtaceae) contain the monoterpene component known as myrtenol, which has a variety of therapeutic properties and can be used as a flavoring agent in a variety of foods (Özek, Demirci, and Baser 2000; Mockute and Judzentiene 2003). A study evaluated the protective effects of myrtenol in rats with STZ-induced gestational diabetes mellitus (GDM). The result revealed that in the hepatic and pancreatic tissues of the STZ-induced GDM rats, myrtenol significantly reduced oxidative stress and inflammatory responses and restored histological damage. The mRNA expression of the signaling proteins for the TLR4, MyD88, and NF-κB was also significantly reduced by myrtenol. Myrtenol thereby reduced inflammation and oxidative stress in diabetic pregnant rats through the TLR4/MyD88/NF-κB signaling pathway (Xuemei et al. 2021). The findings demonstrate the therapeutic value of the bioactive compound myrtenol for the treatment of GDM.

The development of DM-related vascular complications is significantly influenced by NF-κB. Chronic hyperglycemia stimulates NF-κB, which in turn causes the expression of many cytokines, chemokines, and inflammatory molecules (Suryavanshi and Kulkarni 2017). The subsequent effect of dietary essential oil components regulating NF-κB and its related inflammatory mediators in T2DM is shown in Figure 3.

Figure 3. Schematic diagram showing the possible inhibition/suppression of nuclear factor kappa B (NF-κB) pathway in type-2 diabetes using essential oil compounds. NF-κB regulates the pro- and anti-inflammatory immune reactions, promoting the development of insulin resistance. Essential oils compounds downregulate the NF-κB signaling and its related inflammatory mediators. NF-κB synergistically regulates a collective set of inflammatory factors.



Regulation of PPAR receptors, glucose transporters, cytokines, and insulin signaling markers

Thujone

Thujone, a monoterpene, is a bioactive component of essential oils primarily derived from the *Salvia*, *Thuja*, and *Artemisia* species and has been used in beverages, food additives, and herbal medicine for the treatment of T2DM (Lopes-Lutz et al. 2008; Raal, Orav, and Arak 2007; Sirisoma, Höld, and Casida 2001). Palmitate-induced insulin resistance in skeletal muscle is a crucial feature of T2DM in humans and rodents and is often caused by impaired insulin sensitivity of the insulin signaling pathway (Alkhateeb et al. 2007). Consequently, it is reflected in the reduction of palmitate oxidation, AMPK/acetyl-CoA carboxylase (ACC) phosphorylation, protein kinase B (PKB), and AS160 phosphorylation, besides impairing the insulin-stimulated glucose transport and plasmalemmal glucose transporter type 4 (GLUT4) translocation (Alkhateeb et al. 2009; Savage, Petersen, and Shulman 2007). AMPK activation in skeletal muscles increases lipid oxidation and glucose transport, which is supported by enough literature (Hardie 2007; Schimmack, DeFronzo, and Musi 2006).

Thujone, a principal constituent of aromatic medicinal plants, which treated palmitate-induced insulin-resistant rat model and exhibited improved skeletal muscle insulin sensitivity in diabetic-treated rats, restored insulin-stimulated AS160 phosphorylation, enhanced insulin-mediated GLUT4 translocation to the cell surface, and preserved insulin-driven glucose transport. Besides, by increasing the GLUT4 intrinsic activity, thujone also restored palmitate oxidation (Alkhateeb and Bonen 2010). Thus, the authors came to the conclusion that the anti-diabetic activity of thujone, which is manifested by an increase in insulin sensitivity in skeletal muscle, may be related to an AMPK-dependent mechanism that involves the substantial reversal of insulin-stimulated GLUT4 translocation.

Geraniol

Geraniol belongs to the class of acyclic monoterpene alcohols. It is commonly found in rose oil, palmarosa oil, ninde oil, citronella oil, and essential oils derived from geranium and lemon (Baser, Kürkcüoglu, and Demirci 2005). It is traditionally used for several medical purposes, such as DM. The antihyperglycemic potential of geraniol on the activities of enzymes involved in glucose production and utilization in STZ-induced diabetic rats was examined by Babukumar et al. (2017). The study found that administering geraniol at its effective dose (200 mg/kg) to diabetic rats restored carbohydrate metabolic enzyme activities to near normal levels, improved critical enzymes of glucose homeostasis, increased hepatic glycogen content, preserved the normal histological appearance of pancreatic β-cells and demonstrated significant insulinotrophic acitivity. These results suggest the strong anti-hyperglycemic and anti-diabetic potentials of geraniol in diabetic rats.

A study investigated the anti-inflammatory and anti-oxidative stress potential efficacy of geraniol, alone and in combination with pioglitazone, in modulating the metabolic syndrome induced by fructose in rats. The authors reported that the supplementation of geraniol increased PPARγ transcriptional activity in lowering inflammatory mediators and free radical injury and in modified cardiovascular risk variables associated with metabolic syndrome. Therefore, to combat metabolic syndrome, the combined treatment of geraniol with pioglitazone could be beneficial in enhancing insulin sensitivity by lowering the fasting insulin level. The positive effect of the co-administration of geraniol could be linked to the synergistic interactions of the receptor for AGEs and serum TGs (Ibrahim, El-Denshary, and Abdallah 2015). In light of this, the authors concluded that geraniol treatment, both in its pure form and in combination with pioglitazone, alleviated fructose-induced metabolic syndrome in rats by reducing inflammatory and oxidative stress markers.

Citral

Insulin deficiency and insulin insensitivity may result in hyperglycemia and develop insulin resistance. Hyperlipidemia occurs in diabetic conditions due to an increase in the plasma levels of FFAs, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), plasma TGs, and plasma insulin (PI). Diabetes results in an increase in the transport of FFAs from adipose cells, which causes lipotoxicity and excessive fat buildup in various tissues, including the liver, adipose, and pancreas (Yang and Li 2012). In hyperglycemia, excessive generation of free radicals results in lipid peroxidation and membrane damage (Tangvarasittichai 2015). In diabetic conditions, disturbed glucose homeostasis is a crucial factor in the progression of the illness. In the liver, a variety of enzymes are involved in the processes of converting glucose to pyruvate (glycolysis) and producing glucose from non-carbohydrate substrates (gluconeogenesis). In DM, insulin deficiency leads to a decrease in the activities of hexokinase (HK), glucokinase, and pyruvate kinase (PK) and an upsurge in the activity of glucose-6-phosphatase (G6P), which is the key enzyme in gluconeogenesis (Jiang et al. 2020).

The principal aliphatic aldehyde monoterpene present in the majority of *Citrus* species is citral, which is produced by the enantiomers neral (cis) and geranial (trans). Plants containing a significant concentration of citral include bushy matgrass, lemongrass, lemon myrtle, olive tea tree, lemon tea tree, marsh honey myrtle, gulbarn, petitgrain lemon tree, and lemon ironbark (Southwell 2021). In diabetic-dyslipidemic rats, STZ and a HFD were used to create the condition. Citral treatment showed a lowered glycemic index and an increased PI level. Citral treatment also improved the oxidative markers and anti-oxidative enzyme activities in the liver, adipose, and pancreas of T2DM rats. Furthermore, it regulated the glucose-metabolizing enzymes activity in the liver. These interpretations were comparable to glibenclamide, a common oral diabetes drug. Hence, the authors concluded that citral has potent antidyslipidemic and anti-diabetic properties and can regulate the glycolytic and gluconeogenic enzyme activities in the liver (Mishra et al. 2019).

The elevation often reflects T2DM in serum glucose and FFAs, which leads to increased production and release of pro-inflammatory cytokines, and the activities of mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) (King 2008). Pro-inflammatory cytokines, such as IL-6, IL-1, and TNF-α, promote inflammation and remain vital for diabetic complications (Qu et al. 2014). Additionally, increased levels of haptoglobin (Hp) and α2-macroglobulin (α2-MG) proteins in the plasma indicate the acute stage of DM (Kuribayashi et al. 2015). In this regard, Zarandi et al. (2021) investigated the effects of citral on the reduction of inflammatory markers in DM rats. Citral restored the inflammatory components, such as pro-inflammatory cytokines (IL-6 and TNF-α), and acute-phase proteins (Hp and α2-MG), to normalcy in diabetic animals when compared to the untreated diabetes control group. The reduction of inflammation in citral-treated diabetic animals might be due to the protective effect of citral, which reduced oxidative stress and inflammatory mediators. According to the study findings, citral could be used as an appropriate ingredient to decrease diabetes-related complications. In another study, antiadipogenic effects of citral was evaluated in an HFD-induced model of obesity and reported that the compound inhibited adipogenesis by blocking retinaldehyde metabolism due to its structural closeness to retinaldehyde and high affinity to its receptor. Citral's administration showed a dose-dependent reduction in body weight gain and a reduction in the abdominal fat mass in a diet-induced model of Sprague-Dawley (SD) obese rats. It also prevented insulin resistance and glucose intolerance by reducing lipid accumulation (Modak and Mukhopadhaya 2011). Therefore, the authors concluded that citral, an aliphatic aldehyde of terpene (3,7-dimethyl-2,6-octadienal), could be a novel phytochemical in treating HFD-induced obesity-linked DM.

Vaezi et al. (2018) investigated the anti-hyperlipidemic, insulin sensitizing and anti-inflammatory effects of citral in an HFD-induced nonalcoholic steatohepatitis (NASH) mouse model. The study revealed that HFD-induced fibrosis in the mouse liver tissues impaired lipid profile, developed high glucose levels, exhibited insulin resistance, and disturbed liver enzymes, antioxidants, adiponectin, and leptin. In contrast, citral therapy led to dose-dependent improvement in the disease condition and an increase in the PPARα level. Based on these data, the authors suggested that citral could be potentially effective in the therapeutic improvement of nonalcoholic fatty liver disease (NAFLD) through improving the activities of antioxidant enzymes, inhibiting inflammatory cytokines, and increasing the PPARα gene expression. These results indicate that citral could be an effective therapeutic intervention in treating diseases related to its antihyperlipidemic and anti-inflammatory effects and it may be also able to reduce the adverse effect of NAFLD and DM.

Eugenol

Eugenol (4-allyl-2-methoxyphenol) is a naturally existing phenolic secondary metabolite found in various fruits, vegetables, and other plant-based foods that can help manage or prevent DM. Cloves, turmeric, oregano, basil, black pepper, and nutmeg are the primary sources of eugenol, a widely occurring fragrant oil component (Srinivasan and Pari 2013; Raja et al. 2015). In STZ-induced diabetic rats, the anti-hyperglycemic potential of eugenol was investigated by monitoring the activity of the key enzymes involved in glucose metabolism. The administration of eugenol in the STZ-induced diabetic rats significantly increased the PI level, decreased the blood glucose and HbA1c levels, and restored the altered activities of crucial enzymes involved in carbohydrate metabolism, such as HK, PK, glucose-6-phosphate dehydrogenase (G6PD), G6P, fructose-1,6-bisphosphatase (F1,6P), as well as the liver marker enzymes, creatine kinase (CK), and BUN in the serum. Additionally, the anti-hyperglycemic potential of eugenol in diabetic rats was shown by improving the body weight and hepatic glycogen content following the eugenol treatment. These results imply that eugenol may improve the vital enzymes involved in glucose metabolism in diabetic animals and could be explored further to reduce the adverse consequences of DM (Srinivasan et al. 2014).

According to a study led by Soares et al. (2017), flavonoids like quercetin and rutin can regulate the amount of insulin released by β-cells by increasing intracellular Ca^{2+} in a mechanism that stimulates L-type Ca^{2+} channels in the endoplasmic reticulum. Eugenol also increased insulin secretion and enhanced islet function in the pancreas. Oroojan (2020) investigated the effect of eugenol on insulin secretion and β-cells function in male mice. Eugenol stimulated moderate insulin production at a dose level of 100 µM and a maximum level of insulin content at 200 µM throughout the glycemic condition. Hence, the study indicated that eugenol at 100 µM was suitable for prediabetes and eugenol at 200 µM was appropriate for the mature phase of the disease (Oroojan 2020).

The pathogenesis of obesity is greatly influenced by the gut microbiome. In HFD-fed mice, eugenol was studied for its beneficial effects on the gut microbiota, hepatic lipid accumulation, body weight, adipose tissue weight, and lipid and glycemic profile. Although eugenol did not prevent weight gain or beneficially affect the lipid and glycemic profiles, it prevented hepatic lipid accumulation and positively modified the gut flora by stimulating a rise in the *Actinobacteria* phylum and a decline in the *Proteobacteria* growth (Rodrigues et al. 2022).

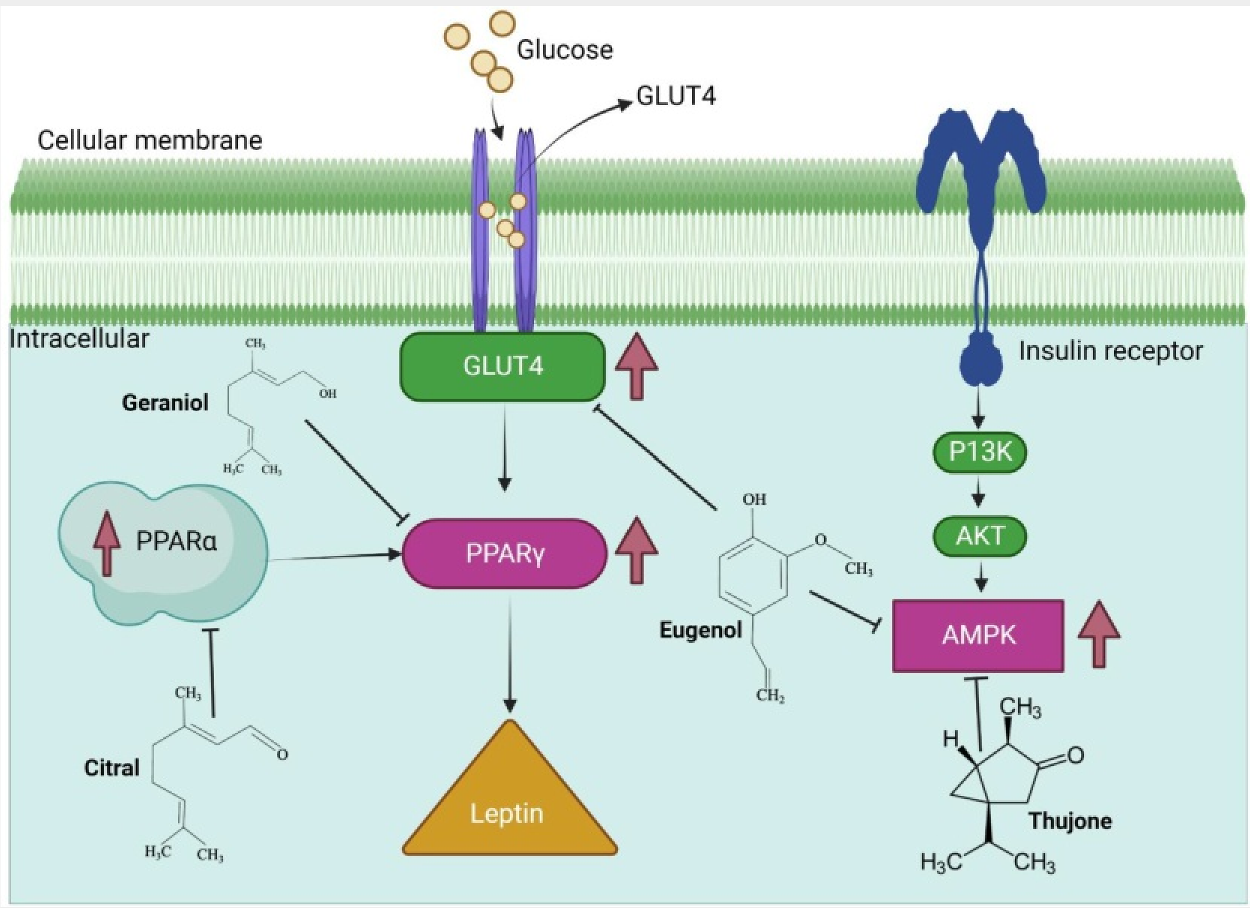
Enhancing insulin sensitivity and thereby stimulating glucose absorption in the skeletal muscles in T2DM may be achieved by activating the AMPK/GLUT4 pathway. Oxidative stress and heightened levels of IL-6, a major proinflammatory cytokine, are important indicators in the pathogenesis of insulin resistance and β-cell failure in the developing stage of T2DM (Chang and Chuang 2010). Finally, diabetic dyslipidemia contributes to the increased production of ROS, activates inflammatory pathways, induces peripheral tissue insulin resistance, and accelerates macrovascular and microvascular diseases in diabetic patients (Vijayaraghavan 2010). Eugenol treatment in HFD/STZ-induced diabetic rats showed a significant reduction in serum glucose, TG, TC, LDL-C, MDA, and IL-6 compared to the diabetic group. Furthermore, eugenol treatment restored decreased serum insulin levels and glutathione in diabetic-induced rats. In addition, the eugenol-treated groups had enhanced skeletal muscle protein levels of GLUT4 and AMPK compared to the diabetic control group. (Al-Trad et al. 2019). Thus, the authors suggested potent antioxidant and anti-inflammatory effects of eugenol in HFD/STZ-induced diabetic rats, mainly by facilitating insulin sensitivity and stimulating skeletal muscle glucose absorption via activation of the GLUT4/AMPK signaling pathway.

Singh et al. (2016) evaluated the anti-diabetic activity of eugenol, a phenylpropanoid, and reported the inhibitory effect of AGEs. Eugenol treatment in diabetic-induced mice prevented intestinal-glucosidase from converting carbohydrates to glucose, lowered blood sugar levels, and decreased AGEs production. Additionally, eugenol showed a higher binding affinity to the surface-exposed amine group of lysine residues via its reactive 4′-OH group, inhibiting sugar binding to serum albumin. Therefore, the authors proposed that eugenol could combat T2DM by lowering blood glucose levels via inhibiting α-glucosidase and preventing the AGEs formation via binding to the ε-amine group of lysine, protecting it from glycation.

By administering the clove essential oil containing eugenol and eugenol conventional microemulsion separately to animals, inflammatory fatty liver disease (steatohepatitis) and dyslipidemia were significantly lessened. As a result, cardiovascular diseases and other steatohepatitis complications were prevented (Al-Okbi et al. 2014). The authors suggested that the clove oil with high eugenol content may have potential health benefits for different metabolic syndromes, such as inflammatory fatty liver (steatohepatitis), dyslipidemia, and DM-induced cardiovascular disease and other complications of steatohepatitis.

Figure 4 displays a pictorial representation explaining how essential oil compounds from plant-based foods enhance the translocation of the GLUT4 protein and stimulate the insulin signaling pathway. They improve GLUT4 translocation by promoting PPARα/PPARγ activity predominantly through an AMPK-dependent mechanism involving phosphoinositol 3-kinase (PI3K) and protein kinase B (AKT).

Figure 4. Essential oil compounds accelerate glucose transporter-4 (GLUT4) protein translocation via activation of insulin signaling cascades. Pancreatic hormones trigger the translocation of the GLUT4 from an intracellular location to the cell surface and activate the insulin-dependent glucose uptake and storage in muscle and fat tissues. Essential oil phytochemicals stimulate GLUT4 translocation and subsequently improve PPARα/PPARγ activity via an AMPK-dependent mechanism including PI3K-AKT, which in turn increases glucose absorption.



Modulation of reactive oxygen species and vital biochemical markers

Thymoquinone

Thymoquinone is a bioactive phytochemical mainly found in the seeds of *Nigella sativa* Linn. (Ranunculaceae), which is also known as black cumin or black seeds (Taborsky et al. 2012). The effects of thymoquinone on intracellular adhesion molecule-1, COX-2, and oxidative stress in the pancreas of STZ-induced type 1 diabetic rats were investigated. The results showed that thymoquinone reduced COX-2, intracellular adhesion molecule-1 mRNA expression in the pancreas, and the oxidative stress associated with increased inflammation. The outcome supported the potential benefits of thymoquinone in reducing oxidative stress and inflammation symptoms during diabetes and preserving β-cell damage (Al Wafai 2013).

Thymol

Thymol (2-isopropyl-5-methyl phenol), a dietary monoterpene, is rich in the oils of thyme and medicinal herbs, like *Thymus vulgaris* Linn. (Lamiaceae), *Thymbra spicata* Linn. (Lamiaceae), *Trachyspermum ammi* (L.) Sprague ex Turrill (Apiaceae), *Monarda fistulosa* Linn. (Lamiaceae), and *N. sativa* seeds (Saravanan and Pari 2016). Thymol has been reported with anti-diabetic activity. A protective effect of thymol on HFD-induced diabetic nephropathy in C57BL/6J mice was investigated by Saravanan and Pari (2015). The results revealed that thymol reduced kidney weight, regulated biochemical markers in urine and serum, and improved glucose homeostasis in HFD-induced diabetic mice. It also restored the TGF-β and vascular endothelial growth factor (VEGF) proteins. Furthermore, thymol retained renal architecture and prevented renal fibrosis while drastically lowering the lipid profile by suppressing the expression of the SREBP-1c protein. The authors have proposed the protective effect of thymol on HFD-induced diabetic nephropathy after their study showed the beneficial impact of thymol on HFD-induced diabetic nephropathy.

Saravanan and Pari (2015) studied the role of thymol on hyperglycemia and hyperlipidemia in HFD-induced T2DM mice and reported its potential benefits as an antihyperglycemic and antihyperlipidemic drug against obesity-induced T2DM. In addition to regulating the lecithin cholesterol acyltransferase (LCAT) and hepatic lipid-metabolism enzymes, thymol administration drastically decreased various diabetic-related parameters such as plasma glucose, insulin resistance (IR), HbA1c, TG, TC, FFAs, LDL, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, leptin, and adiponectin.

Impaired insulin signaling causes DM-induced Alzheimer's disease (AD). Two key elements of AD development are defective insulin receptor substrate-1 (IRS-1) and elevated oxidative stress. Enhancing the insulin signaling pathway can reduce tau hyperphosphorylation, restore hippocampal synaptic plasticity, and protect against neuroplasticity deficits produced by intrahippocampal delivery of amyloid-β (Aβ) (Biessels and Reagan 2015). The dendritic spine, the development of synapses, and synaptic plasticity were all modified by the PI3K/AKT pathway (Yin et al. 2015). The activity of glycogen synthase kinase 3β (GSK3β) controlled the deposition of Aβ and the phosphorylation of tau protein (Chen et al. 2016; Phiel et al. 2003), which are the significant pathological markers of AD. Thymol increased insulin resistance in the brain and lowered Aβ deposition and tau phosphorylation in the hippocampus (Fang et al. 2017). In addition, thymol therapy significantly enhanced Nrf2 and HO-1 expression while reducing oxidative stress, inflammation, and other deleterious effects. Therefore, the authors suggest that thymol administration could be essential in treating AD and T2DM.

Citronellol

Citronellol (3,7-dimethyl-6-octen-1-ol) is a commonly found linear monoterpene alcohol in nearly 70 essential oils, especially in the citrus pulp (Rajeswara Rao et al. 2004). It is widely used in the food and flavor industries. It has been recommended by the Council of Europe (COE) in the list of safe food additives (COE No. 59). Citronellol as an anti-diabetic agent was assessed by Srinivasan and Muruganathan (2016) by determining the activities of key enzymes responsible for the metabolism of carbohydrate in the liver of STZ-induced diabetic rats. The results revealed that the oral administration of citronellol normalized the activities of HK, PK, G6PD, G6P, and F1,6P, which control the glucose metabolism in the liver, and regulated the kidney damage biomarkers in STZ-induced diabetic rats. Besides, citronellol administration in STZ-induced diabetic rats reversed the cellular damage in the hepatic and the β-cells. As a result, the authors concluded that citronellol could reduce hyperglycemia in diabetic rats by normalizing the activity of glucose metabolism enzymes in the liver and improving the function of β-cells to stimulate insulin secretion in STZ-induced diabetic rats.

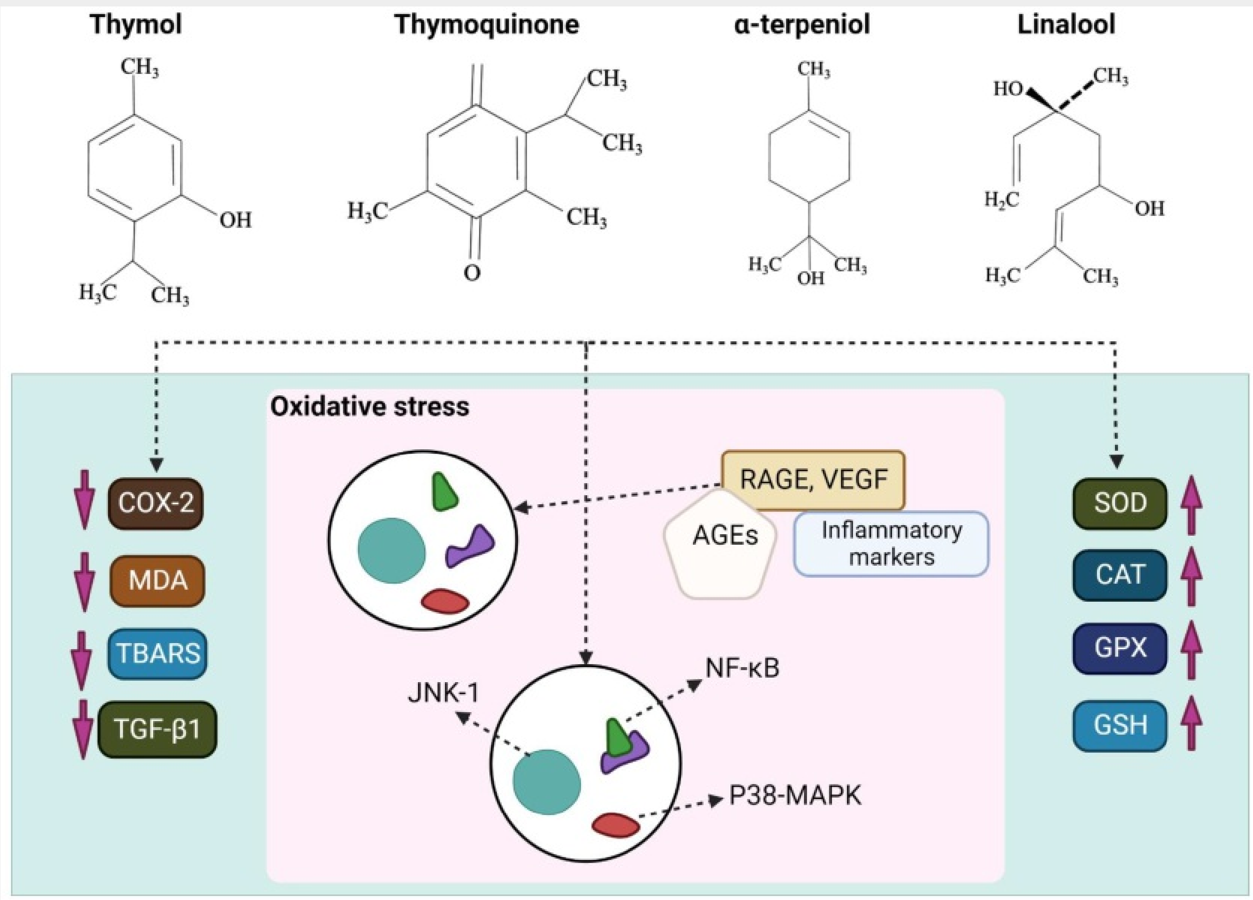
α-terpineol

α-terpineol is found in many aromatic essential oils with antioxidant and anti-inflammatory activities. The most prevalent monoterpene in nature is limonene, and its R-(+)-enantiomer is the primary component of the orange peel oil, while its S-(−)-enantiomer is present in modest proportions in mentha and pine oils (Surburg and Panten 2016). *Sphingobium* sp. could biotransform R-(+)- and S-(−)-limonene to produce R-(+)- and S-(−)-α-terpineol, respectively (Molina et al. 2019). Sousa et al. (2020) evaluated the effect of supplementation of α-terpineol enantiomers on the biomarkers of rats fed an HFD. Compared to the diabetic control group, the consumption of α-terpineol at 50 mg/kg concentration restored insulin sensitivity. It also lowered serum levels of the pro-inflammatory cytokines TNF-α and IL-1β. Additionally, it reduced hepatic and serum levels of thiobarbituric acid reactive substances (TBARS). Therefore, the authors concluded that α-terpineol enantiomers are potentially beneficial in treating different disease conditions linked to HFD-induced obesity.

Linalool

Linalool, a naturally occurring terpene alcohol, is categorized as an acyclic monoterpenoid and comprised of two enantiomers found in many flowers and spice plants. (S)-linalool is the major constituent of the essential oils obtained from coriander (*Coriandrum sativum* Linn., Apiaceae), cymbopogon (*Cymbopogon martinii* Roxb. Wats.; Poaceae), and sweet oranges (*Citrus sinensis* L. Osbeck; Rutaceae), while (R)-linalool is present in lavender (*Lavandula officinalis* Chaix ex Vill; Lamiaceae), bay laurel (*Laurus nobilis* Linn. Lauraceae), and sweet basil (*Ocimum basilicum* Linn.; Lamiaceae) (Said-Al Ahl and Mahmoud 2010; Said-Al Ahl et al. 2010). Hyperglycemia contributes to DM-linked vascular complications by reducing the activity of glyoxalase-I (GLO-I) and increasing glycation, oxidative stress, and inflammatory markers. Linalool has been shown to have a variety of protective effects in reducing the risk of developing DM-mediated vascular complications by lowering fasting serum glucose, insulin resistance, dyslipidemia, glycation, oxidative stress, inflammatory markers, and renal dysfunction indices in nicotinamide and STZ-induced T2DM rats (Mohammadi Bytamar et al. 2017). Therefore, it could be concluded that linalool effectively reduces the risk of developing diabetic complications by increasing GLO-I activity, enhancing antioxidant, antiglycation, and anti-inflammatory properties, and improving glucose and lipid metabolism. In Figure 5, it is indicated that the components of essential oils greatly reduce the overexpression of pro-inflammatory molecules like TBARS, TGF-β, COX-2, and MDA, while increased the levels of antioxidant enzyme biomarkers like SOD, CAT, GPX, and GSH.

Figure 5. Essential oil compounds regulate oxidative stress. They significantly downregulate the overexpression of pro-inflammatory elements including TBARS, TGF-β1, COX-2, and MDA, and enhance the antioxidant enzymes markers such as SOD, CAT, GPX, and GSH.



Bioavailability of essential oil components

This study found that monoterpenes (α-terpineol, thymoquinone, thujone, geraniol, linalool, citral, citronellol, myrtenol, eugenol, thymol, and carvacrol), diterpenes (sclareol), sesquiterpenes (zerumbone), aldehydes (cinnamaldehyde); and ketones (zingerone) have potentially beneficial insulin-sensitizing properties. To exert various antidiabetic functions, these bioactive molecules modulated NF-κB signaling, oxidative stress-related enzyme activites, PPAR receptors, glucose transporters, pro- and anti-inflammatory cytokines. In addition, essential oil components may easily penetrate the epithelial cell membrane and bioaccumulate in fatty tissues in the body, since they are volatile, small, and lipophilic (fat-soluble) (Sadgrove et al. 2021).

Studies evaluated in this review mostly preferred oral, intra-gastric, or intra-peritoneal modes of administration in various animal models. Michiels et al. (2008) have demonstrated that, upon oral administration, the half-life (t1/2) of carvacrol, thymol, eugenol, and trans-cinnamaldehyde in the bloodstream ranged between 1.84 and 2.05 h. Mason et al. (2017) established that the essential components of *Oregano* and *Thyme* plant species were present in dairy cattle for up to 13 days. A previous study about the metabolism of thymol in rabbits and humans showed that thymol was converted to functional metabolites like thymol sulfate, thymol glucronide, and thymol thymohydroquinone sulfate, and it was excreted in urine as glucuronic acid and sulfuric acid metabolites (Takada et al. 1979). Similarly, an investigation with healthy humans revealed that eugenol was rapidly absorbed and metabolized after oral administration, and was cleared in the urine as eugenol glucuronide and eugenol sulfate within 24 h. The results also revealed that less than 1% of the administered dose was excreted non-metabolized in the urine (Fischer et al. 1990).

Guenette et al. (2007) suggested that in rats, the half-life (t1/2) of eugenol in plasma is about 14 h and in blood is 18 h. Pavan et al. (2018) observed that after the oral administration, geraniol was highly stable in the whole blood of humans and rodents and showed high bioavailability of geraniol in terms of absorption rate and absorbed amounts (peak of blood concentration at 30 min and absolute bioavailability of 92%). Moreover, the study showed that geraniol was capable of infiltrating directly from the bloodstream to the central nervous system and was detected in the cerebrospinal fluid of rats. Thujone metabolism was studied in vivo by Höld et al. (2000), and two neutral urinary metabolites have been reported as 3-β-hydroxy-α-thujane and 3-β-hydroxy-β-thujane following the oral administration of a mixture of α- and β-thujone at a dose of about 650-800 mg/kg to male rabbits.

The components of essential oils have been shown to effectively enter the skin and bioaccumulate in fatty tissues (Adorjan and Buchbauer 2010; Baser and Buchbauer 2020). A study conducted in humans showed that with a single dose of a Bronchipret® TP tablet, which is equivalent to 1.08 mg/person of thymol, the peak plasma concentration reached 0.093 µg/mL and only about 16% was eliminated as thymol sulfate and glucuronide via renal excretion, indicating its effective bio-accumulation in the body (Kohlert et al. 2002). Therefore, sufficient literature supports the bioavailability of essential oil components in animal and human models. Hence, the use of dietary essential oil components may be recommended as a new strategy for the prevention and treatment of metabolic diseases, such as obesity-induced T2DM.

Safety of essential oil compounds

In this review, the acute toxicity studies of 15 essential oil compounds, including cinnamaldehyde, carvacrol, zingerone, sclareol, zerumbone, myrtenol, thujone, geraniol, citral, eugenol, thymoquinone, thymol, citronellol, α-terpineol, and linalool supported the repeated dose safety by oral administration of them for 4-6 weeks in animal models. In addition, no adverse effects were reported with the specified doses tested in animal studies. Briefly, no adverse effects were reported for cinnamaldehyde in SD rats at 100 nM/L (Yang et al. 2016), on Wistar rats at 20 mg/kg (Ataie et al. 2021), and on SD rats at 40 mg/kg (Jawale et al. 2016), cinnamaldehyde in Swiss albino mice at 10 mg/kg (Singh et al. 2017), carvacrol in Wistar rats at 75 and 100 mg/kg (Arkali, Aksakal, and Kaya 2021; Deng, Lu, and Teng 2013), and in C57BL/6 mice at 40 mg/kg (Li et al. 2020), zingerone in Wistar rats at 100 mg/kg (Rehman et al. 2019), sclareol in Swiss mice at 1 mg/kg (Cerri et al. 2019), zerumbone in Wistar rats at 40 mg/kg (Tzeng et al. 2016) and in C57BL/6 mice at 0.025% (Ahn et al. 2017), myrtenol in Wistar rats at 50 mg/kg (Xuemei et al. 2021), thujone in SD rats at 0.1 mg/mL (Alkhateeb and Bonen 2010), geraniol in Wistar rats at 250 mg/kg (Ibrahim, El-Denshary, and Abdallah 2015) and at 400 mg/kg (Babukumar et al. 2017), citral in SD rats at 20 and 30 mg/kg ((Modak and Mukhopadhaya 2011; Mishra et al. 2019) and in NMRI mice at 20 mg/kg (Vaezi et al. 2018), and in Wistar rats at 300 mg/kg (Zarandi et al. 2021), eugenol in Wistar rats at 10 mg/kg (Srinivasan et al. 2014), in BALB/c mice at 100 mg/kg (Singh et al. 2016), in SD rats at 10 mg/kg (Al-Trad et al. 2019), in NMRI mice at 200 μM (Oroojan 2020), and in C57BL/6 mice at 500 mg/kg (Rodrigues et al. 2022), clove oil and eugenol microemulsions in SD rats at 40 mg/kg and 31 mg/kg respectively (Al-Okbi et al. 2014), thymoquinone in SD rats at 5 mg/kg (Al Wafai 2013), thymol in C57BL/6J mice at 40 mg/kg (Fang et al. 2017; Saravanan and Pari 2015), citronellol in Wistar rats at 100 mg/kg (Srinivasan and Muruganathan 2016), α-terpineol in SD rats at 100 mg/kg (Sousa et al. 2020), linalool in rats at 25 mg/kg (Mahdavifard and Nakhjavani 2020). On the other hand, their administration showed no significant abnormalities in experimental animals in their clinical chemistry, hematology, or urinalysis. Besides, histopathological analysis of target organs showed no toxicities, nor has it been reported to cause undesirable outcomes.

Since they mainly exist in spicy plants and are traditionally used as taste enhancers for cooking worldwide, essential oil compounds together with related spicy plants may be generally recommended for various human ailments. Studies have also proposed the encapsulation of essential oil compounds to optimize their target release, transdermal transfer, enhance permeability, and tissue targeting (Franklyne et al. 2016)**AQ3**. At the same time, clinical trials still are needed to verify their dose-dependent and long-term safety. Moreover, the suitability of the oral route must also be examined, as their antimicrobial properties may have an undesirable effect on the gut microbiota (Modak and Mukhopadhaya 2011; Dan et al. 2020).

Conclusion and perspectives

Dietary plant-based essential oil compounds are potential anti-diabetic agents because they act as modulators of cytokines and influence the key inflammatory signaling markers in the treatment of insulin resistance. We summarized main aromatic compounds, including cinnamaldehyde, carvacrol, zingerone, sclareol, zerumbone, myrtenol, thujone, geraniol, citral, eugenol, thymoquinone, thymol, citronellol, α-terpineol, and linalool with potential anti-diabetic effects on animal models by influencing key insulin-dependent signaling pathways. The crucial anti-diabetic mechanisms of these compounds include the inhibition of the production of TBARS and MDA, the reduction of oxidative stress, the increase of insulin, adiponectin, glycoprotein enzymes, antioxidant enzymes, and glycolytic key enzymes, the decrease of the elevated levels of liver marker enzymes and lipid profile parameters, and the inhibition of the expression of TNF-α, IL-1β, IL-4, IL-6, TGF-β, iNOS, and COX-2. The key signaling pathways modulated by these compounds include AMPK, GLUT4, Caspase-3, PPARγ, NF-κB, p-IκBα, TLR4, MyD88, MCP-1, SERBP-1, AGE, RAGE, VEGF, Nrf2/HO-1, and SIRT-1 signaling. Therefore, these dietary plant-derived essential oil compounds can be promising dietary bioactive compounds with the potential to manage diabetes and related complications under the control of well-designed clinical trials.

Acknowledgments

The authors thank Rajagiri College of Social Sciences (Autonomous), Kalamaserry, Kochi, for providing total research assistance. Rajagiri College of Social Sciences (Autonomous) offered financial support for this project in the category of seed money for faculty Minor Research Projects (MRP).

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Conceptualization, GRG, EH, PJA, and NMK; data curation, GRG, YG, NMK and EH; formal analysis, GRG, RYG, and SAC; funding acquisition, GRG and SAC; project administration, GRG and SAC; supervision, SAC, RYG, and GRG; writing original draft, GRG, PJA, NMK, and YG; writing review and editing, GRG, RYG, LLDZ, NMK, EH, SAC, and PJA. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

ACC = acetyl-CoA carboxylaseAD = Alzheimer's diseaseAGEs = advanced glycation end productsALP = alkaline phosphataseALT = alanine transaminaseα2-MG = α2-macroglobulinAMPK = AMP-activated protein kinaseAST = aspartate transaminaseAβ = amyloid-βBax = Bcl-2 associated X proteinBcl-2 = B-cell lymphoma-2BUN = blood urea nitrogenCAT = catalaseCD121a = cluster of differentiation 121aCK = creatine kinaseCNS = central nervous systemCOE = Council of EuropeCOX-2 = cyclooxygenase-2CS = citrate synthetaseDACD = diabetes-associated cognitive declineF1,6P = fructose-1,6-bisphosphataseFFAs = free fatty acidsGABA = gamma-aminobutyric acidG6P = glucose-6-phosphataseG6PD = glucose-6-phosphate dehydrogenaseGDM = gestational diabetes mellitusGLO-1 = glyoxylase-1GLP-1 = glucagon-like peptide-1GLUT4 = glucose transporter type 4GPx = glutathione peroxidaseGSK3β = glycogen synthase kinase 3βHp = haptoglobinHbA1c = glycated hemoglobinHFD = high-fat dietHK = hexokinaseHMG-CoA = hydroxymethylglutaryl-coenzyme AHO-1 = haemoxygenase-1IL1R1 = interleukin 1 receptor type IIL-1β = interleukin 1 betaIMOs = isomalto-oligosaccharidesiNOS = inducible nitric oxide synthaseIRS-1 = insulin receptor substrate-1KIM-1 = kidney injury molecule-1LCAT = lecithin cholesterol acyltransferaseLDH = lactate dehydrogenaseLDL-C = low density lipoprotein cholesterolMAPK = mitogen-activated protein kinaseMCP-1 = monocyte chemoattractant protein-1MDA = malondialdehydeMYD88 = myeloid differentiation primary response 88NAFLD = nonalcoholic fatty liver diseaseNAS = nonalcoholic steatosisNF-κB = nuclear factor kappa BNO = nitric oxideNQO-1 = quinone oxidoreductaseNrf2 = nuclear factor erythropoietin-2-related factor 2PFK = phosphofructokinasePG = prostaglandinPI = plasma insulinPK = pyruvate kinasePI3K = phosphatidylinositol 3-kinasePKB = protein kinase BPKC = protein kinase-CPNS = peripheral nervous systemPPARγ = peroxisome proliferator-activated receptor γPRISMA = Preferred reporting items for systematic reviews and meta-analysisRAGE = receptor for advanced glycation end productsROS, reactive oxygen speciesSERBP-1 = sterol regulatory element-binding transcription factor-1SGLT-2 = sodium-glucose cotransporter-2SIRT-1 = sirtuin 1STZ = streptozotocinSREBP-1c = sterol regulatory element-binding protein 1cSD = Sprague-DawleySOD = superoxide dismutaseTG = triglycerideT2DM = Type 2 diabetes mellitusTBARS = thiobarbituric acid reactive substancesTC = total cholesterolTGF-β = transforming growth factor-βTGs = triglyceridesTLR4 = toll-like receptor 4TNF-α = tumor necrosis factor-αVEGF = vascular endothelial growth factor

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