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REVIEW ARTICLE

An Updated Review on Possible Antidiabetic and Hypolipidemic Molecular Action Mechanisms of Medicinal Plants

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SUMMARY

The prevalence of diabetes mellitus and its related diseases has been increasing. It is common to use natural resources to support medical treatments for endocrine diseases. The aim of this study was to discuss the possible molecular mechanisms of action of medicinal plants and their secondary metabolites, which have been proven to be effective in diabetes mellitus and dyslipidemia by clinical studies. Literature searches were conducted using international databases (Science Direct, Scopus, and Web of Science), academic search engines (Google Scholar), and the Cochrane Library. Studies published between 2015 and 2023 are included in the manuscript. The most prominent herbs for diabetes mellitus and dyslipidemia were garlic, cinnamon, turmeric, ginseng, walnut, flaxseed, bitter melon, black cumin, pomegranate, fenugreek, and ginger. These plants were effective in diabetes mellitus and dyslipidemia by modulating different signaling pathways [(adenosine monophosphate activated protein kinase (AMPK), nuclear factor kappa B (NF-κB), and c-Jun N-terminal kinases (JNK), etc.)], and by their biological activities, including antioxidant, anti-inflammatory, and antiapoptotic effects. This review elaborates on the mechanisms of action of extracts prepared from medicinal plants and their secondary metabolites regarding glucose and lipid metabolism in the treatment of diabetes mellitus. Medicinal herbs treat diabetes mellitus or ameliorate its progression by acting on multiple targets via different enzymes, receptors, and mediators. However, investigations to elucidate the mechanism of action were conducted in vitro and in vivo. The mechanisms identified in preclinical studies must be corroborated by extensive and multicenter clinical trials. The clarification of the effects and mechanisms of action of medicinal plants by preclinical and clinical studies will contribute to the development of antidiabetic drugs.

Keywords: *Diabetes mellitus, dyslipidemia, medicinal plants, molecular mechanism.*

Tıbbi Bitkilerin Olası Antidiyabetik ve Hipolipidemik Moleküler Etki Mekanizmaları Üzerine Güncellenmiş Bir İnceleme

ÖZ

Diabetes mellitus ve ilişkili hastalıkların prevalansı giderek artmaktadır. Endokrin hastalıklara yönelik tıbbi tedavileri desteklemek için doğal kaynakların kullanımı oldukça yaygındır. Bu çalışmanın amacı, diabetes mellitus ve dislipidemide etkili olduğu klinik çalışmalarla kanıtlanmış olan tıbbi bitkilerin ve sekonder metabolitlerinin olası moleküler etki mekanizmalarını tartışmaktır. Literatür taramaları uluslararası veri tabanları (Science Direct, Scopus ve Web of Science), akademik arama motorları (Google Scholar) ve Cochrane Kütüphanesi kullanılarak yapılmıştır. 2015-2023 yılları arasında yayımlanan çalışmalar makaleye dahil edilmiştir. Diabetes mellitus ve dislipidemi için en çok öne çıkan tıbbi bitkilerin sarımsak, tarçın, zerdeçal, ginseng, ceviz, keten tohumu, acı kavun, çörek otu, nar, çemen otu ve zencefil olduğu görülmektedir. Bu bitkiler, farklı sinyal yolaklarını [adenozin monofosfat ile aktifleştirilen protein kinaz (AMPK), nükleer faktör-κB (NF-κB) ve c-Jun N-terminal kinaz (JNK) vb.] modüle ederek, antioksidan, antienflamatuvar ve antiapoptotik etkileri içeren biyolojik aktiviteleri ile diyabetes mellitus ve dislipidemide etkili olmuştur. Bu derlemede, tıbbi bitkilerden hazırlanan ekstrelerin ve bu ekstrelerin bileşimindeki sekonder metabolitlerin diyabetes mellitus tedavisinde glukoz ve lipit metabolizması üzerindeki etki mekanizmaları ayrıntılı olarak ele alınmıştır. Tıbbi bitkiler farklı enzimler, reseptörler ve mediyatörler üzerinden çok sayıda hedefe etki ederek diyabetes mellitusu tedavi etmekte veya progresyonunu hafifletmektedir. Bununla birlikte etki mekanizmasını belirlemeye yönelik çalışmalar in vitro ve in vivo olarak gerçekleştirilmiştir. Preklinik çalışmalarda elde edilen mekanizmaların büyük ölçekli ve çok merkezli klinik çalışmalarla desteklenmesine ihtiyaç vardır. Preklinik ve klinik araştırmalarla tıbbi bitkilerin etki ve etki mekanizmalarının aydınlatılması antidiyabetik ilaç geliştirme çalışmalarına katkı sunacaktır.

Anahtar Kelimeler: *Diabetes mellitus, dislipidemi, tıbbi bitkiler, moleküler mekanizma.*

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INTRODUCTION

Diabetes mellitus is defined as a chronic and broad-spectrum metabolic disorder characterized by hyperglycemia resulting from insulin deficiency and/or defects in insulin action, affecting many organs, and causing multisystemic involvement (Petersmann et al., 2019). Diabetes mellitus is classified into four clinical forms, including Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes mellitus, and other specific types (TEMD, 2020). Type 2 diabetes mellitus, which accounts for 90–95% of all diabetes mellitus cases, is associated with a progressive insulin secretion defect accompanied by a background of insulin resistance (Hoogwerf, 2020). In the 10th edition of the "Diabetes Atlas" published by the International Diabetes Federation (IDF) in 2021, it was reported that 537 million adults aged 20–79 (prevalence: 10.5%) worldwide have diabetes mellitus. It is estimated that the number of people with diabetes mellitus among adults in this age group will reach 643 million in 2030 (prevalence: 11.3%) and 783 million in 2045 (prevalence: 12.2%) (IDF, 2021). Dyslipidemia is a clinical condition characterized by plasma lipoprotein levels outside normal ranges or the dysfunction of lipoproteins. Dyslipidemia is one of the most important etiologies of cardiovascular disease risk in diabetes mellitus. In diabetic dyslipidemia, also known as atherogenic dyslipidemia, low HDL-c, high TG, and LDL-c levels are also accompanied by a predominance of small dense LDL particles (Bahiru, Hsiao, Phillipson, & Watson, 2021). The prevalence of diabetic dyslipidemia is quite high in patients with Type 2 diabetes mellitus, with a prevalence ranging between 72% and 85%. A global survey showed that 65% of patients with diabetes mellitus had LDL-c levels greater than 100 mg/dL at the time of diagnosis and should receive medication for dyslipidemia (Athyros et al., 2018).

Medicinal plants and the secondary metabolites in their composition have important roles in the protection of health and the treatment of diseases. Medicinal plants are an important source of raw materials for the development of antidiabetic drugs (Lee et al., 2022). Medicinal plants may help in the treatment of the disease or improve its progression through modifying multiple pathways involved in the pathogenesis of diabetes mellitus. Previous studies have identified the mechanisms of action of hypoglycemic plants, including the enhancement of insulin secretion, an increase in glucose uptake by adipose and muscular tissues, inhibition of intestinal glucose absorption, and suppression of glucose synthesis by hepatocytes (Hui, Tang, & Go, 2009). Some of these mechanisms are mediated by PPAR receptors. PPARs are encoded by different genes that generate nuclear receptor isoforms: PPAR-γ, PPAR-α, and PPAR-δ. PPAR-γ regulates the expression of several factors released from adipose tissue that enhance insulin sensitivity, including adiponectin and leptin, or diminish it, such as resistin and TNF-α. In differentiated adipocytes, PPAR-γ impacts the expression of genes related to glucose homeostasis. PPAR-γ upregulates the expression of GLUT-4 and CAP, which are encoded by the GLUT-4 and c-CAP genes, respectively. PPAR-γ, triggered during the differentiation of preadipocytes into adipocytes, is crucial for lipid metabolism and other pathways, such as inflammation, immunity, and glucose homeostasis. Many medicinal plants affect diabetes mellitus by activating PPAR-γ receptors (Ríos, Francini, & Schinella, 2015).

Incretins are hormones produced by the gut that are secreted in response to the ingestion of food, mainly glucose and lipids. There are two intestinal hormones, GIP and GLP-1, which have the effect of incretin. GLP-1 and GIP are rapidly degraded by the enzyme DPP-4. Extending the half-life of GLP-1, inhibiting DPP-4, or using GLP-1 analogues resistant to DPP-4 degradation are two key goals in antidiabetic drug development studies. Medicinal plants are known as having antidiabetic properties, which are mediated through the modulation of incretin levels or the inhibition of the enzymes α-glucosidase and

α-amylase in the gastrointestinal tract (Ríos et al., 2015).

Recent studies have demonstrated that medicinal plants may effectively treat diabetes mellitus by suppressing inflammation and reducing oxidative stress. The increased production of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, causes damage to pancreatic β cells, resulting in diminished insulin secretion and insulin resistance by decreasing the efficiency of insulin utilized by peripheral tissues. Inhibition of inflammatory cytokines is an important target for the treatment of Type 2 diabetes mellitus. Inhibiting the NF-κB-mediated inflammatory signaling pathway reduces the synthesis of pro-inflammatory cytokines. The inactivation of the IκBα protein, which inhibits NF-κB, decreases the inflammatory response triggered by the NF-κB-mediated signaling pathway by effectively inhibiting NF-κB expression (Pang et al., 2019). JNK is a protein kinase that is a member of the mitogen-activated protein kinase family. It is triggered in response to multiple cellular and environmental challenges, including DNA damage, inflammatory cytokines, radiation, oxidative stress, cell proliferation, and apoptosis. JNK activation has been related to diabetes mellitus, insulin resistance, and obesity. TNF-α can activate several signaling cascades, including the NF-κB and JNK pathways. Inhibition of the JNK pathway significantly enhances insulin sensitivity and improves glucose tolerance (Yung & Giacca, 2020). Previous studies have demonstrated that medicinal plants inhibit NF-κB, JNK, IL-1β, TNF-α, and Toll-like receptor 4 in the management of Type 2 diabetes mellitus (Pang et al., 2019).

Oxidative stress damages human pancreatic cells, resulting in the onset or progression of Type 2 diabetes mellitus. SOD, GSH, and CAT are antioxidant enzymes that efficiently neutralize free radicals in the human body. NO is an important bioactive product that can exacerbate oxidative stress in the human body. iNOS triggers the synthesis of the NO. MDA is a byproduct of lipid peroxidation that elevates oxidative stress in the organism. Medicinal plants are recognized for their efficacy in diabetes mellitus treatment by enhancing antioxidant enzyme levels such as SOD, GSH, and CAT; diminishing MDA and NO levels; and suppressing iNOS (Hui et al., 2009; Pang et al., 2019; Rios et al., 2015). Recent studies have demonstrated a correlation between gut microbiomes and Type 2 diabetes mellitus. Diseases in the gut microbiome have been revealed to be closely associated with insulin resistance and the development of Type 2 diabetes mellitus. It has been noted that microorganisms such as *Roseburia*, *Blautia*, and *Clostridium* are effective in Type 2 diabetes mellitus by altering the composition of the gut microbiota (Pang et al., 2019).

The absorption, synthesis, transport, and metabolism of lipids are primarily mediated by ABCA1, NPC1, LDLR, HMGCR, SREBP-2, ACLY, PPAR, CETP, CYP7A1, FAS, ACC, AMPK, CPT1A, ChREBP, HSL, ATGL, and LXR-α pathways, targets, and their downstream genes, which are essential for these mechanisms. Among them, the inhibition of ACC reduces free fatty acid concentrations in the bloodstream. ACAT2 is an important enzyme in the production and metabolism of triglycerides, and its inhibition can decrease triglyceride levels in serum. The pathways regulated by AMPK can be classified into four main categories, including protein metabolism, lipid metabolism, glucose metabolism, autophagy, and mitochondrial homeostasis. Activated AMPK decreases lipid synthesis by inhibiting the expression of downstream targets, serving as a crucial mechanism in the control of hyperlipidemia. Medicinal plants regulate these targets and pathways, treating hyperlipidemia related to diabetes mellitus (Liu et al., 2022).

The use of medicinal plants for the management of diabetes mellitus and dyslipidemia is common. Plant-derived extracts and their isolated secondary metabolites have demonstrated efficacy in diabetes mellitus and dyslipidemia in many experimental models (Adel Mehraban et al., 2021; Marmitt, Shahrajabian, Goettert, & Rempel, 2021; Ota & Ulrih, 2017; Rios et al., 2015; Zhao & Chen, 2018). Considering the increasing prevalence of diabetes mellitus

and dyslipidemia in the community and the importance of medicinal plants as a therapeutic resource for these illnesses, it is key to evaluate the clinical effects of medicinal plants on these diseases and elucidate their potential mechanisms of action. This review aims to clarify the possible mechanisms of action of medicinal plants and their secondary metabolites that have been clinically examined in diabetes mellitus and dyslipidemia, based on current studies.

MATERIALS AND METHODS

Systematic reviews, meta-analyses, and traditional reviews on the use of medicinal plants in diabetes mellitus and dyslipidemia were searched using international databases (Science Direct, Scopus, and Web of Science), academic search engines (Google Scholar), and the Cochrane Library. The medicinal plants and secondary metabolites with the most emphasis and clinically studied efficacy in these publications were determined (Adel Mehraban et al., 2021; Marmitt, Shahrajabian, Goettert, & Rempel, 2021; Ota & Ulrih, 2017; Rios et al., 2015; Zhao & Chen, 2018). Possible molecular mechanisms of action of the identified medicinal plants and secondary metabolites in the disease group were evaluated. Preclinical studies published between 2015 and 2023 were identified by using the name of the medicinal plant/secondary metabolite, the endocrine disease in which its activity was studied, and the keyword "molecular mechanism of action".

RESULTS AND DISCUSSION

Allium sativum L. (Garlic)

Allium sativum (Amaryllidaceae) is an aromatic herbaceous annual plant used as a spice, food, and traditional medicine in different regions of the world. Garlic bulbs mainly contain sulfurous compounds such as alliin, allicin, ajoene, diallyl sulfide and its derivatives, allyl methyl sulfide, *S*-propyl-cysteine-sulfoxide, allicin, and *S*-methyl cysteine-sulfoxide. Previous studies have reported that *A. sativum* and its components are effective in diseases such as Alzheimer's, diabetes mellitus, obesity, hypertension, and dyslipidemia (El-Saber Batiha et al., 2020).

High-fat/sucrose diet-fed male Sprague-Dawley rats were treated with aged black garlic extract ($ABG10^{+*}$; 250 mg/kg, orally) rich in *S*-allyl cysteine and melanoidins for 8 weeks. $ABG10^{+*}$-treated rats were found to have elevated POMC gene expression and diminished ObR mRNA levels in the hypothalamus. $ABG10^{+*}$ overexpressed the β3-ADR in visceral adipose tissue. The treatment with $ABG10^{+*}$ downregulated the gene expression of PPAR-γ, LPL, ObR, and HSL in subcutaneous adipose tissue. It significantly reduced the levels of PPAR-γ mRNA while overexpressing InsR, GLUT-4, UCP-1, and β3-ADR in brown adipose tissue. Moreover, the obesity-induced rise in IL-1β, TNF-α, and iNOS gene expression was suppressed in $ABG10^{+*}$-treated rats (Amor et al., 2019). It has been demonstrated that water extract prepared from garlic bulbs (150 mg/kg, 6 weeks, orally) boosted protein levels of ABCA1, HMGCR, and CYP46A1, which play a role in cholesterol homeostasis in the brain and isolated astrocytes of C57BL/6J mice. Similar outcomes were observed in cultured astrocytes that had been treated with allicin (Nazeri, Azizidoost, Cheraghzadeh, Mohammadi, & Kheirollah, 2021). The administration of garlic and fermented garlic (for both products: 300 mg/kg, 1 month, orally) to male Sprague-Dawley rats fed a cholesterol-rich diet significantly inhibited collagen and ADP-induced platelet aggregation and ATP secretion. These effects were seen to be more pronounced in rats treated with fermented garlic. Furthermore, SREBP-2, ACAT-2, and HMG-CoA reductase expressions were downregulated in garlic-treated rats (Irfan et al., 2019). Taken together, garlic extracts and sulfur compounds in its composition are effective in metabolic diseases by modulating pathways regulating appetite, lipid metabolism, and insulin sensitivity, suppressing inflammation, and inhibiting platelet aggregation.

Cinnamomum sp. (Cinnamon)

The dried stem bark of *Cinnamomum verum* J.S. Presl. (syn: *Cinnamomum zeylanicum* Nees, Ceylon

cinnamon), *Cinnamomum cassia* Blume (syn: *Cinnamomum aromaticum* Nees, Chinese cinnamon), *Cinnamomum burmanni* (Nees & T.Nees) Blume (Indonesian cinnamon), and *Cinnamomum loureiroi* Nees (Saigon cinnamon, Vietnamese cinnamon) (Lauraceae) are used medicinally (İşcan, Bektaş Sarıaltın, Soyseven, & Arli, 2022). The essential oils responsible for biological activity consist of cinnamic acid and its derivatives, phenylpropanoid compounds, and terpenes. The major component of *C. verum* and *C. cassia* essential oils is cinnamaldehyde, which has a phenylpropanoid structure. Moreover, compounds with oligomeric proanthocyanidin, glycoside, lignan, lactone, and coumarin structures were isolated from cinnamon species. Previous studies have demonstrated that different cinnamon species and their secondary metabolites have a wide range of pharmacological effects, including antitumoral, anti-inflammatory, analgesic, antidiabetic, antiobesity, antimicrobial, anti-tyrosinase, cardioprotective, immunomodulatory, cytoprotective, and neuroprotective activities (Hariri & Ghiasvand, 2016; Yanakiev, 2020; Zhang et al., 2019).

Vijayakumar et al. tested the antidiabetic and hypolipidemic mechanisms of action of different extracts prepared from the bark of *C. cassia* in different experimental models, including *in vitro*, *in vivo*, and *in silico*. In the *in vitro* study, water, ethanol, and methanol extracts inhibited α-amylase with IC_{50} values of 0.79, 0.62, and 0.77 mg/mL, respectively (acarbose: 0.56 mg/mL). Water, ethanol, and methanol extracts inhibited the α-glucosidase enzyme with IC_{50} values of 0.91, 0.57, and 0.78 mg/mL, respectively (acarbose: 0.50 mg/mL). In the STZ-induced diabetic rat model, ethanol extract (300, 400, and 500 mg/kg b.wt doses, 28 days, oral) decreased glucose-6-phosphatase and fructose 1,6-bisphosphatase levels while increasing glucokinase levels. The results of molecular docking studies revealed that 9-octadecenoic acid was the compound with the highest affinity for PPAR-α/γ among the active constituents of cinnamon (Vijayakumar et al., 2023). In an HFD-fed obese mouse model, male C57BL/6 mice were administered 100 or 300 mg/kg of water extract prepared from *C. cassia* bark for 16 weeks. The extract dose-dependently enhanced MyHC, PGC-1α protein expressions, and AMPK phosphorylation in HFD mice. In the continuation of the study, C2C12 myoblasts were incubated with 0.1 or 0.2 mg/ml extract for 24 hours. The extract significantly raised ATP levels in C2C12 myoblast cells by stimulating mRNA expression of mitochondrial biogenesis-related factors such as PGC-1α, Nrf-1, and Tfam, inducing phosphorylation of AMPK, and upregulating expression of ACC. These results suggested that *C. cassia* extract controls weight gain by upregulating mitochondrial biogenesis in skeletal muscle cells (Song et al., 2017). The results of another *in vivo* study have shown that administration of *C. zeylanicum* powder (5%, 28 days, orally) boosted pancreatic SOD, CAT, and GPx activities in an alloxan-induced mouse model (Beji, Khemir, Wannes, Ayari, & Ksouri, 2018). Kaur et al. reported that treatment with *C. zeylanicum* (2 mg powder/fish/day, 4 weeks, orally) exhibited positive effects on lipid metabolism by downregulating SREBF1, SREBF2, LDLR, and NR2F2 gene expression and upregulating FOXO1 expression in a diet-induced zebrafish model (Kaur et al., 2019). Polyphenol-rich *C. zeylanicum* hydroalcoholic extract was administered to HFD-fed Wistar rats at a dose of 100 mg/kg b.wt diet for 12 weeks. The extract decreased serum and liver MDA concentrations and elevated serum TAC, liver SOD, CAT, and GPx activities. In extract-treated rats, hepatic SREBP-1c, LXR-α, ACLY, FAS, and NF-κB p65 expression were suppressed, while PPAR-α, IRS-1, Nrf2, and HO-1 expression were induced. Cinnamon polyphenol may ameliorate hyperlipidemia by activating transcription factors and the antioxidant defense signaling pathway in the livers of rats on an HFD (Tuzcu, Orhan, Sahin, Juturu, & Sahin, 2017). Khare et al. studied the effects of cinnamaldehyde, which is the active component of cinnamon, on fasting-induced hyperphagia and related hormone levels, adipose tissue lipolysis, and inflammation in mice fed a high-fat diet. Cinnamal-

dehyde was administered orally at doses of 5 and 10 mg/kg/b.wt for 7 days. Treatment with cinnamaldehyde at both doses reduced serum leptin levels. Cinnamaldehyde administration at 10 mg/kg increased total ghrelin serum levels, although not statistically significant compared to HFD-fed mice. It enhanced the expression of POMC and urocortin in the hypothalamus, while BDNF, CARTPT, and CCK were not affected at a 5 mg/kg dose. At high doses, it significantly raised the expression level of these genes in the hypothalamus. Cinnamaldehyde downregulated the expression of the adipogenic marker gene (CCAAT/enhancer-binding protein; C/EBP-α) and upregulated the expression of the DLK-1 and lipolysis-inducing genes (PNPLA2 and MGLL) at a dose of 10 mg/kg. Cinnamaldehyde treatment at this dose was detected to induce the expression of BMP4, PRDM16, and FOXC2. Cinnamaldehyde is concluded to diminish hunger-induced hyperphagia by enhancing lipolysis in adipose tissue, restoring the circulating leptin/ghrelin ratio to normal levels, and mitigating inflammation. Moreover, cinnamaldehyde at a dose of 10 mg/kg suppressed the inflammatory process by lowering the level of IL-1β and the expression of COX, MCP1, TNF-α, and IL-6. In the continuation of the study, the effect of cinnamaldehyde on cecal microbiota (*Lactobacillus*, *Bifidobacteria*, and *Roseburia* species) was assessed. It was determined that cinnamaldehyde did not affect the abundance of these bacterial genera (Khare et al., 2016). In an *in vitro* study, trans-cinnamic acid (tCA, 0-200 μM, 6–8 days) was demonstrated to upregulate the expression of brown adipose tissue-specific markers (PGC-1α, PRDM16, UCP1) and beige adipose tissue-specific genes (Cd137, Cidea, Cited1, Tbx1, Tmen26) in 3T3-L1 white adipocytes. Similarly, tCA boosted the expression of PGC-1α, PRDM16, and UCP1 in HIB1B brown adipocytes. Expression of tissue-specific genes (Lhx8, Ppargc1, Prdm16, Ucp1, and Zic1) was induced in HIB1B brown adipocytes incubated with tCA. The expression levels of adipogenic transcription factors (e.g., C/EBPα and PPAR-γ) were measured in both tissues. C/EBPα and PPAR-γ expression was diminished in white adipocytes while elevated in brown adipocytes. tCA upregulated the expression of mitochondrial biogenic genes such as Cox4, Nrf1, MtDNA, and Tfam in both tissues. In addition to these findings, treatment of 3T3-L1 cells with tCA decreased the expression levels of lipogenic markers (ACC and FAS) through the activation of AMPK and β3-AR signaling pathways. Further, tCA increased lipolysis by increasing the expression levels of pHSL and ATGL. tCA treatment also significantly enhanced the mitochondrial protein levels of ACOX1 and CPT1. In conclusion, the results revealed that tCA may be effective in the treatment of obesity by reducing adipogenesis and lipogenesis and increasing fat oxidation (Kang *et al*., 2019). Mechanisms such as increasing glucose uptake in muscle and adipose tissue by inducing GLUT-4 production and translocation, stimulating glycogen synthesis in the liver by inhibiting GSK 3β, and downregulating PEPCK gene expression are thought to be responsible for the positive effects on diabetes mellitus (Silva *et al*., 2022). Research suggests that cinnamon and cinnamic acid-derived compounds affect diabetes, obesity, and related metabolic disorders by decreasing carbohydrate digestion, reducing hepatic glucose production, enhancing cellular glucose uptake, inhibiting lipogenesis, facilitating lipolysis, augmenting energy expenditure, and through mechanisms including potent antioxidant and anti-inflammatory properties.

***Curcuma longa* L. (Turmeric)**

The rhizomes of *Curcuma longa* (Zingiberaceae), known as turmeric, are used for therapeutic purposes. Curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, are responsible for the pharmacological effects. The essential oil extracted from the rhizomes of *C. longa* contains various monoterpene and sesquiterpene compounds such as zingiberene, curcumin, and α- and β-turmerone. Previous studies have reported that *C. longa* and its active component, curcumin, exhibit a wide range of pharmacological effects involving anti-inflammatory, antioxidant, antidiabetic, antiangiogenic, anti-

mutagenic, antimicrobial, and anticancer activities. In recent years, clinical studies have been conducted to evaluate the efficacy of *C. longa* and curcumin in cancer, autoimmune diseases, metabolic diseases, neurological diseases, cardiovascular diseases, lung diseases, liver diseases, and other inflammatory diseases (Karlowicz-Bodalska, Han, Freier, Smolenski, & Bodalska, 2017; Kocaadam & Şanlier, 2017).

STZ-induced diabetic rats were administered curcumin-loaded PLA-PEG copolymer nanoparticles (20 mg/kg b.wt/day, orally). Curcumin decreased oxidative stress markers such as MDA and NO while elevating glutathione levels. It reduced serum NF-κB, TGF-β, and COX-2 levels. It also upregulated PPAR-γ mRNA expression levels in rats (El-Naggar, Al-Joufi, Anwar, Attia, & El-Bana, 2019). Zhong et al. administered curcumin at a dose of 100 mg/kg/day orally for 4 weeks to C57BL/6J mice fed a high-fat diet. Curcumin upregulated insulin-stimulated Akt phosphorylation levels in peripheral tissues. It suppressed the expression of genes involved in hepatic gluconeogenesis (Pck1 and G6pc) and de novo lipogenesis (SREBF1) in HFD mice. It upregulated the expression of FGF15, which is a gut-derived hormone. The observed effects were attributed to the modulation of the gut microbiota (Zhong et al., 2022). Curcumin (50 mg/kg/day, 8 weeks, orally) induced the expression of adipose triglyceride lipase, hormone-sensitive lipase, PPAR-γ/α, and C/EBP-α in the adipose tissue of male C57BL/6J obese mice fed a high-fat diet. Besides, it stimulated lipolysis and improved glycolipid metabolism. In a second study, differentiated 3T3-L1 adipocytes were incubated with curcumin (10, 20, and 35 μM) for 48 hours. Curcumin lowered glycerol release and increased glucose uptake by upregulating PPAR-γ and C/EBP-α (Pan et al., 2017). Maithilikarpagaselvi et al. determined that curcumin treatment (200 mg/kg/b. wt, orally, for 10 weeks) improved insulin resistance in male Wistar rats fed a high fructose diet by decreasing IRS-1 serine phosphorylation and enhancing IRS-1 tyrosine phosphorylation in skeletal muscles. It decreased the expression of the proteins COX-2 and PKC-θ, as well as TNF-α and CRP levels. It promoted GPx activity while inhibiting MDA and total oxidant status. Further, curcumin suppressed ERK1/2 and p38 protein expression in the skeletal muscle of rats. The study indicated that curcumin ameliorates glucose intolerance and insulin resistance by exerting its antioxidant and anti-inflammatory properties (Maithilikarpagaselvi, Sridhar, Swaminathan, & Zachariah, 2016). In a diet-induced obesity model, male C57BL/6 mice were given curcumin at doses of 40 and 80 mg/kg/day by oral gavage for 12 weeks. It significantly diminished the hepatic mRNA expression of SREBP-1 and SREBP-2. Hepatic mRNA expression of genes involved in cholesterol biosynthesis, such as HMGCR, FDPS, DHCR24, DHCR7, LSS, MVK, Sc4mol, SS, proprotein convertase subtilisin/kexin type 9, and LDLR, was downregulated by curcumin administration. Expression of genes playing a role in fatty acid metabolism, such as ACC1, ACL, ACS, FAS, FADS1, FADS2, SCD-1, and GPAT, was also suppressed with curcumin. It did not affect hepatic ATP-binding cassette, ABCA1, ABCG5, or ABCG8 mRNA levels. Taken together, this study concluded that curcumin improves lipid and glucose homeostasis through the regulation of SREBP and important downstream target genes (Ding *et al*., 2016). The authors suggest that *C. longa* and curcuminoids affect diabetes mellitus by enhancing insulin sensitivity, diminishing hepatic glucose production, suppressing oxidative stress and inflammation, and regulating lipid metabolism.

Ginseng

Panax ginseng C.A.Mey. (Asian ginseng, Korean red ginseng) and *Panax quinquefolius* L. (American ginseng) (Araliaceae) are two important ginseng species that are prominent for their effects on diabetes mellitus and other endocrine system diseases. Previous phytochemical studies have shown that roots and rhizomes contain saponins, polysaccharides, polyacetylene, phenol, and alkaloid compounds. "Ginsenosides", classified in three different forms as dammaran (protopanaxadiol and protopanaxatriol), ocotillol, and oleanane type, are compounds with a saponin

structure that are responsible for the pharmacological effects of ginseng plants. Ginseng has been the subject of many preclinical and clinical studies with its cardioprotective, cerebrovascular protective, neuroprotective, antitumoral, anti-inflammatory, hemostatic, anticoagulant, antidiabetic, anti-aging, and immunomodulatory effects (Chen, Balan, & Popovich, 2019; Liu, Lu, Hu, & Fan, 2020).

Shin *et al*. documented that water extract prepared from *P. ginseng* roots (GE, 5%, eight-week diet) decreased body weight, adipose tissue, and adipocyte size without affecting food intake in a testosterone-deficient castrated C57BL/6J mouse model fed a high-fat diet. GE suppressed the mRNA expression of adipogenesis-related genes (SREBP1C, PPAR-γ, FAS, SCD1, and ACC1) in visceral adipose tissues. In a second study, 3T3-L1 adipocytes were incubated with 10 μg/ml GE and 10 μM ginsenosides (Rb1 and Rg1) for 24 hours. The extract and ginsenosides inhibited lipid accumulation and mRNA expression of PPAR-γ, C/EBP-α, and SCD1. These effects were potentiated by co-administration of the extract or ginsenosides with testosterone. These results suggested that ginseng exhibits positive effects on obesity and dyslipidemia by inhibiting adipogenic gene expression and acting like testosterone (Shin & Yoon, 2018). Nagar et al. injected an ethanol extract of *P. ginseng* roots (KRG) and KRG enriched with ginsenoside Rg3 into the jugular vein of SHRs at a dose of 3 mL/kg. The results showed that endothelial nitric oxide synthase phosphorylation levels in the aorta and NO production in plasma were induced (Nagar, Choi, Jung, Jeon, & Kim, 2016). The mechanism of the antidiabetic effect of hydromethanolic extract rich in malonyl ginsenosides (PQ-MGR) prepared from *P. quinquefolius* roots was studied in an HFD/STZ-induced Type 2 diabetes mellitus model. C57BL/6J male mice were administered dietary PQ-MGR at doses of 100 and 300 mg/kg/day for 5 weeks. PQ-MGR administration upregulated protein expression of *p*-PI3K, *p*-AKT, *p*-AMPK, *p*-ACC, PPAR-*y*, and GLUT-4 in liver and skeletal muscle while downregulating protein expression of *p*-IRS1 and *p*-JNK. This study demonstrated that PQ-MGR improved insulin resistance through inhibition of the JNK signaling pathway and activation of the IRS1/PI3K/AKT signaling pathway (Liu *et al*., 2021). The activity of the ginsenoside Rb2 on glucose metabolism and fat accumulation in the insulin-sensitive cell line 3T3-L1 adipocytes and high-fat diet-induced obesity mice was investigated. Ginsenoside Rb2 induced glucose uptake in 3T3-L1 adipocytes by activating the PI3K/AKT signaling pathway at a concentration of 25 μM. Ginsenoside Rb2 suppressed TNF-α-induced activation of JNK, ERK, and P38 and phosphorylation of IRS-1 at Ser307. It also inhibited TNF-α-induced IKK α/β phosphorylation and IKK α/β activation. It reduced the expression of IL-6 and suppressor of SOCS-3. Administration of ginsenoside Rb2 (40 mg/kg/d, 10 days, *i.p.*) to C57BL/6J mice upregulated p-AKT (Ser473) expression, which supported the *in vitro* finding. The results indicate that ginsenoside Rb2 enhances the uptake of glucose and improves insulin sensitivity via AKT-dependent pathways. (Dai et al., 2018). Another study treated male Wistar rats with ginsenoside Re at a dose of 25 mg/kg/b.wt once daily by gastric irrigation for 30 days in an HFD/STZ-induced Type 2 diabetes mellitus model. Ginsenoside Re diminished oxidative stress by increasing SOD and CAT activities and lowering MDA levels. Ginsenoside Re was found to activate the AMPK signaling pathway by stimulating the cannabinoid type 1 receptor and CaMK II (Wang *et al*., 2021). The hypoglycemic, anti-inflammatory, and lipid-lowering effects of 25-OH-PPT (20 and 40 mg/kg, 5 weeks, orally), which is a triterpenoid saponin isolated from the stem and leaves of *P. ginseng*, were examined in STZ-induced hyperglycemic mice and DB/DB mouse models. In the STZ mouse model, 25-OH-PPT at both doses diminished the transcription levels of IL-1, IL-6, and COX-2. It did not affect the transcription of TNF-α. In the DB/DB mouse model, 25-OH-PPT decreased the transcription levels of IL-1, IL-6, and TNF-α. It significantly upregulated skeletal muscle GLUT4 and AMPK transcription levels in the STZ-in-

duced mouse model, while it did not affect transcription in DB/DB mice. In both mouse models, 25-OH-PPT treatment upregulated phosphorylated IR, IRS, and AKT protein expression but did not alter GSK 3β expression. The findings suggested that 25-OH-PPT increases insulin sensitivity by activating the insulin signaling pathway (Xu et al., 2021). Ginseng and its constituent ginsenosides have demonstrated potential in diabetes management through direct modulation of insulin sensitivity and glucose metabolism at the cellular level, as well as by regulating factors such as inflammation and oxidative stress that increase the severity of diabetes.

***Juglans regia* L. (Walnut)**

The different parts of *Juglans regia* (Juglandaceae), including leaf, fruit (husk, nut), bark, inflorescence, and root, have been used for medicinal purposes for many years. Different parts of the plant contain phenolic compounds (3- and 5-caffeoylquinic acid, 3- and 5-p-coumaroylquinic acid, quercetin and derivatives, taxifolin-pantocid, syringetin-*O*-hexoside, myricetin-3-O-glucoside, myricetin-3-*O*-pantocid, and epicatechin), naphthalene derivatives (juglone), and organic compounds (citric acid, malic acid, phosphate, and calcium oxalate). The most important secondary metabolites detected in the leaves and green husk of the walnut are juglone and phenolic compounds. Walnut oil is rich in polyunsaturated fatty acids, tocopherols, and phytosterols. Previous studies have stated that walnuts and their secondary metabolites have broad pharmacological effects, including antioxidant, antimicrobial, anticancer, antidiabetic, antihypertensive, and lipid-lowering activities (Bhat et al., 2023; Delaviz, Mohammadi, Ghalamfarsa, Mohammadi, & Farhadi, 2017).

The effect of an ethanol extract prepared from *J. regia* leaves (200 mg/kg, 21 days, orally) on STZ^{+} nicotinamide-induced Type 2 diabetes mellitus was evaluated using Wistar albino rats. The extract alleviated insulin resistance by increasing ADP and FNDC5 levels. It suppressed inflammation by reducing serum TNF-α levels (Atila Uslu & Uslu, 2022). *J. regia* oil-derived polyunsaturated fatty acid was administered orally to male Wistar rats at doses of 225, 450, and 900 mg/kg b.wt for 18 days in a model of STZ-induced gestational diabetes mellitus. PUFA administration ameliorated oxidative stress by elevating hepatic SOD, GSH, and CAT activities and lowering MDA content. PUFA suppressed the enhanced expression of SREBP-1, SCD-1, ACC, and FAS mRNA in the liver tissue of gestational diabetes mellitus. rats. The observed effects were found to be dose-dependent (Sun et al., 2020). Treatment with walnut-derived peptides (fractions 3–10 kDa and LP5) boosted SOD and GSH activities and inhibited TNF-α, IL-6, and IL-1β secretion in mice with Type 2 diabetes mellitus induced by STZ and HFD. Walnut-derived peptides augmented liver mitochondrial ATP, COX, SDH, and MMP levels. It upregulated LC3-II/LC3-I and Beclin-1 expression while downregulating p62 expression, which may be associated with activation of the AMPK/mTOR/ULK1 pathway. In conclusion, walnut-derived peptides promoted autophagy through activation of the AMPK/mTOR/ULK1 pathway to ameliorate hyperglycemia in mice with Type 2 diabetes mellitus (Hou et al., 2023). In another study, male Sprague-Dawley rats fed an HFD were given orally walnut meal peptides at doses of 200, 400, and 800 mg/kg for 4 weeks. Walnut meal peptides increased Apo-1 levels while decreasing Apo-B levels. Expression of FAS and HMGR was significantly inhibited in the livers of rats treated with walnut meal peptides. Moreover, walnut meal peptides induced the expression of LCAT and CYP7A1 (Yang, Zhong, Wang, Zhang, & Zhang, 2021). Walnuts and their components are effective in diabetes by improving insulin sensitivity, reducing inflammation and oxidative stress, regulating fat metabolism, and promoting autophagy and mitochondrial function.

***Linum usitatissimum* L. (Flaxseed)**

Linum usitatissimum is used for food and medicinal purposes in four common types: whole flaxseed, ground flaxseed, flaxseed oil, and partially defatted flaxseed meal. Flaxseed is particularly enriched in

α-linolenic acid (ALA), fiber, and lignans (mainly secoisolariciresinoldiglucoside). Flaxseed and its isolated secondary metabolites prevent, regress, and slow the progression of cardiovascular diseases such as lipid-induced coronary artery disease, peripheral artery disease, and stroke by lowering serum lipid levels. Secoisolariciresinoldiglycosides, which are responsible for the biological effects, act by being converted into enterolignans such as enterodiol and enterolactone by intestinal bacteria through biotransformation. Many studies have shown that flaxseed increases the diversity of the gut microbiota and the relative abundance of beneficial bacteria (Parikh et al., 2019; Prasad, Khan, & Shoker, 2020).

Bouzghaya et al. reported that treatment with flaxseed extract (1 mL of aqueous extract per mouse, five weeks, oral) ameliorated oxidative stress in alloxan-induced diabetic mice by decreasing hepatic and renal TBARS content and increasing GP_x, SOD, and CAT activities. Phytochemical analysis has revealed that the water extract contained four phenolic compounds (gallic acid (GA), vanillic acid, resveratrol, and coumaric acid) and three flavonoids (kaempferol, apigenin, and luteolin). The secondary metabolite with the highest amount was detected as GA. In the continuation of the study, GA was treated in mice by gavage at a dose of 50 mg/day for 5 weeks. GA significantly improved the activity of antioxidant markers in the liver and kidney, similar to the findings obtained in the water extract. These results suggested that flaxseed water extract has antihyperglycemic and antioxidative activities associated with its high GA content (Bouzghaya, Amri, & Homblé, 2020). Wholegrain flaxseeds (7.5 g/kg rat/day, 90 days, orally) significantly enhanced the levels of catalase, SOD, GPx, GR, GST, and cellular antioxidant enzymes in heart and liver tissues in male Wistar albino mice fed a high cholesterol diet. Although it did not reach statistical significance, reductions in TBARS levels have been observed in heart and liver tissues (Naik et al., 2018). Ground flaxseed (16.7%) was coadministered with a diet for 6 weeks to C57BL/6J male mice in a model of STZ-induced diabetes mellitus. Treatment with flaxseed decreased glucose tolerance in the OGTT and raised glycogen levels in the liver. It reduced TNF-α levels in the liver but did not affect IL-1β or IL-6 levels. It also downregulated proinflammatory gene expression, including TLR4, MyD88, and NF-κB. Moreover, there was a significant increase in the number of some beneficial bacteria in the gut microbiota of the mice in the treatment group. Taken together, these results demonstrate that it is effective in treating diabetes mellitus by suppressing the TLR4/NF-κB signaling pathway and improving the gut microbiota (Xia et al., 2022). Zhu et al. showed that flaxseed oil (10% w/w, 5 weeks, oral) lowered plasma lipopolysaccharide, IL-1β, TNF-α, IL-6, IL-17A, and MDA levels and boosted SOD levels in male Sprague-Dawley rats in a STZ-nicotinamide-induced Type 2 diabetes mellitus model. As a result of the intestinal microbiota analysis, it was found that there was a decline in the relative abundance of *Firmicutes* and *Blautia* and the ratio of *Bacteroidetes* to *Firmicutes* in the intervention group. There was an increase in the relative abundance of *Bacteroidetes* and *Alistipes*. Treatment with flaxseed oil has enhanced the levels of intestinal microbiota metabolites of short-chain fatty acids such as acetic acid, propionic acid, and butyric acid (Zhu et al., 2020). Another study assessed the potential mechanism of action of flaxseed oil on obesity and metabolic disorders in mice fed an HFD. Flaxseed oil was fed to rats for 5 days at three different concentrations: 30% (m/m, LFO), 60% (m/m, MFO), and 90% (m/m, HFO). Flaxseed oil lowered the concentrations of conjugated bile acids such as cholic acid, tauro-α-muricholic acid, and tauro-ursodesoxycholic acid in feces. It improved intestinal microbial dysbiosis by increasing the abundance of Clostridiales and Ruminococcaceae and community diversity. It decreased the expression of the FXR and FGF-15 proteins in the colon. These effects were observed to be more pronounced in the HFO group. In the continuation of the study, the effect of flaxseed oil administration on FXR-related lipid metabolism genes in the liver was tested. It up-

regulated the mRNA expression of bile acid receptors (FXR and SHP) and the expression of lipolysis-related genes (CPT-1α and ATG5). The mRNA expression of the lipogenesis-related SREBP-1c and PPAR-α genes diminished, while the mRNA expression of FAS was not altered. It induced the mRNA expression of CYP7A1 in the liver but did not change the expression of another bile acid synthesis gene, CYP8B1. Taken together, these findings suggested that flaxseed oil improved serum lipid concentrations in metabolic diseases by regulating the gut microbiota, modulating the FXR-FGF15 signaling pathway, and affecting bile acid metabolism (Yang et al., 2023). The effect of herbacetin (10, 20, and 40 mg/day, intragastric, 5 weeks), a flavonoid isolated from flax seeds, on obesity induced by a fatty diet in male C57BL/6J mice was investigated. Herbacetin significantly reduced body weight, plasma glucose, plasma insulin, and HOMA-IR activity in obesity-associated insulin-resistant mice. It significantly suppressed the mRNA expression of SREBP-1c and 2. It also decreased FAS, hepatic fatty acid β-oxidation, and G6PD activity, whereas it enhanced malic enzyme and CPT activity (Veeramani et al., 2018). In summary, flaxseed presents potential therapeutic benefits for diabetes mellitus and obesity through multiple pathways, including antioxidant and anti-inflammatory properties, modulation of gut microbiota and metabolites, enhancement of lipid metabolism and weight management, and improvement of glucose tolerance.

***Momordica charantia* L. (Bitter Melon or Bitter Gourd)**

The fruits of *Momordica charantia* (Cucurbitaceae), known as bitter melon or bitter gourd, are used for therapeutic purposes. Secondary metabolites in the structure of sterol (daucosterol, β-sitosterol, campesterol, and stigmasterol), terpenoid (charantin A and B, charantagenins D and E, kuguaosides A, B, C, and D, charantoside A, momordicosides I, F1, F2, K, L, and U, momordicine I, II, VI, VII, and VIII), phenolic acid (caffeic, coumaric, ferulic, and gallic acids), flavonoid, amino acid, vitamin, peptide, and protein, ribosome-inactivating proteins, polypeptide-P, inhibitory proteins, and P-insulin were isolated from the fruit and other parts of *M. charantia*. The hypoglycemic effect of *M. charantia* fruits and their isolated secondary metabolites comes to prominence. The hypoglycemic effect has been particularly related to charantin, polypeptide-P, and visin. It also has anti-inflammatory, antioxidant, antimicrobial, antitumoral, immunomodulatory, and hepatoprotective effects (Oyelere et al., 2022; Pahlavani et al., 2019). Ethanol extract prepared from *M. charantia* fruits (MCE) was administered orally for eight weeks at three different doses (100, 200, and 400 mg/kg/day) in a rat model of Type 2 diabetes mellitus induced by an HFD and STZ injection. In a dose-dependent manner, serum levels of TNF-α and IL-6 were significantly decreased in all groups treated with MCE. MCE treatment dose-dependently upregulated Akt-2 gene expression levels while downregulating mRNA expression of PTP-1B, SOCS-3, and JNK. MCE elevated GLUT-4 protein levels in skeletal muscle and liver tissues (Ma, Yu, Xiao, & Wang, 2017). In rats with Type 2 diabetes mellitus induced by an HFD and STZ, treatment with ethanol extract prepared from wild bitter gourd fruits (150 and 300 mg/kg, 4 weeks, orally) enhanced the content of antioxidant enzymes such as SOD, CAT, and GSH in serum and diminished the levels of inflammatory parameters including CRP, TNF-α, and IL-6. In molecular mechanism studies, it upregulated hepatic protein expression levels of p-AKT and *p*-IRS but downregulated *p*-GSK3β (Ser9) protein expression. It exerted its effect by activating the AMPK signaling pathway and inducing protein expression of GLUT-2. All effects were dose-dependent (Sun et al., 2023). Yang *et al*. treated male OLETF rats fed an HFD with freeze-dried *M. charantia* fruit powder at concentrations of 1% and 3% for 6 weeks. It reduced the expression of the proinflammatory cytokine TNF-α and the levels of IL-6 and CCL2 in the liver, muscle, and epididymal adipose tissue. It suppressed the activation of NF-κB in the liver and muscle. Administration of *M. charantia* at 3% concentration upregulated phospho-insulin receptor substrate-1 (Tyr612) and phospho-Akt

(Ser473) levels while downregulating phospho-NF-κB (p65) (Ser536) and JNK (Thr183/Tyr185) levels. Taken together, the molecular mechanism mediating the antidiabetic effect of *M. charantia* fruits appeared to be the modulation of NF-κB and JNK signaling pathways (Yang et al., 2015). Wang et al. administered saponin (L-SMC: 20 mg/kg, M-SMC: 40 mg/kg, H-SMC: 80 mg/kg) and polysaccharides (PMC, 500 mg/kg) isolated from *M. charantia* fruits by oral gavage to male Kunming mice for five weeks in an STZ-induced Type 2 diabetes mellitus model. SMC and PMC improved antioxidant capacity by increasing SOD levels and decreasing MDA levels in the liver. M- and H-SMC treatment suppressed NF-κB levels. M-SMC induced hepatic AMPK phosphorylation. PMC did not affect AMPK phosphorylation or NF-κB levels. These results suggested that the *M. charantia* saponin fraction was more effective than polysaccharides, and the possible antidiabetic mechanism of action was related to the regulation of the AMPK/NF-κB signaling pathway (Wang, Wu, Shi, & Liu, 2019). The effect and mechanism of action of four different cucurbitane types (C1–C4) triterpenoid compounds isolated from ethanol extract prepared from *M. charantia* fruits on diabetes mellitus were evaluated. Among these secondary metabolites, C2 (1.68 mg/kg, *i.v.*) significantly boosted glycogen storage in skeletal muscles in an STZ-induced diabetes mellitus model. The hypoglycemic effect of C2 in diabetic mice was found to be associated with the activation of IRS-1 and its downstream signaling pathways, including Akt, GSK-3β, Erk1/2, and PKC ζ /λ. It did not have any effect on AMPK or ACC (Han et al., 2018). In another study, 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al, a cucurbitane triterpenoid isolated from *M. charantia*, was demonstrated to activate PPAR-γ (Noruddin et al., 2021). Bitter melon displays significant antidiabetic properties by enhancing insulin sensitivity and glucose absorption through the activation of insulin signaling pathways (Akt, IRS-1, PPAR-γ) and AMPK. It also mitigates inflammation (via NF-κB, JNK) and oxidative stress (through the modulation of antioxidant enzymes) that facilitate diabetes progression.

***Nigella sativa* L. (Black cumin or Black seed)**

The dried seeds of *Nigella sativa* (Ranunculaceae), known as black cumin, are used for therapeutic purposes. Thymoquinone, the major component of the essential oil, is responsible for its pharmacological effects. The essential oil also contains compounds such as thymol, carvacrol, phellandrene, α-pinene, and β-pinene. Phenolic acids, flavonoids, alkaloids, saponins, and fatty acids were isolated from different parts of the plant. Previous studies have demonstrated that various extracts from seeds and thymoquinone exhibit antioxidant, anti-inflammatory, antihepatotoxic, analgesic, antineoplastic, antimutagenic, antinephrotoxic, immunomodulatory, hypoglycemic, antiulcer, and antimicrobial activities (Dalli et al., 2021; Gürel & Çiçek Polat, 2025).

Balbaa *et al*. administered black cumin oil at a dose of 100 mg/day for 21 days intragastrically to male albino Sprague-Dawley rats in an experimental diabetes mellitus model induced by HFD and STZ. Black cumin oil reduced serum TBARS, hepatic TBARS, serum NO, hepatic NO, and serum TNF-α levels in diabetic rats. It upregulated the gene expression of IGF-1, PI3K, and IR while suppressing the expression of ADAM-17 (Balbaa, El-Zeftawy, Ghareeb, Taha, & Mandour, 2016). *N. sativa* seed polysaccharides were administered at three different doses of 35, 70, and 140 mg/kg for 4 weeks intragastrically to Kunming mice in an STZ- and HFD-induced Type 2 diabetes mellitus model. The high dose lowered MDA, TNF-α, IL-6, and IL-1β levels while elevating total antioxidant capacity, SOD, and CAT levels in the skeletal muscle tissues of mice. It also stimulated *p*-AKT and GLUT-4 protein levels and expression. Gut microbiota analysis showed that the abundance of *Muribaculaceae* unclassified and *Bacteroides* suppressed by diabetes mellitus was significantly boosted by black cumin treatment. This study revealed that *N. sativa* seed polysaccharides are effective in treating diabetes mellitus by modulating the gut microbiota and activating the PI3K/AKT signaling pathway (Dong et al., 2020). The hydroalcoholic extract prepared from *N.*

sativa seeds (100, 200, and 400 mg/kg, 6 weeks, orally) significantly improved vasorelaxant responses to acetylcholine at all doses in male Wistar rats in the STZ-induced diabetes mellitus model. It upregulated eNOS mRNA expression while downregulating VCAM-1 and LOX-1 mRNA expression in vascular cells of aortic tissue. These results suggested that *N. sativa* ameliorated vasoreactivity, endothelial dysfunction, and vascular inflammation in the aorta of diabetic rats (Abbasnezhad et al., 2019). Adult female Wistar rats were treated intraperitoneally with black seed oil at a dose of 0.2 mg/kg/day for 6 days a week for 30 days in an STZ-induced diabetes mellitus model. It significantly inhibited the expression of Bax and caspase-3 in abdominal and thoracic aortic sections (Cüce et al., 2016). In another study, black cumin seed oil treatment (400 mg/kg, orally, for 21 days) overexpressed Bcl2 in female Wistar albino rats in a model of STZ-induced diabetes mellitus (Altun, Avci, Yildirim, & Yildirim, 2019). These studies concluded that the cardiovascular effects of black seed oil are associated with suppression of apoptosis (Cüce et al., 2016; Altun et al., 2019). Black cumin oil (2.5 mg/kg/day, 8 weeks, orally) reversed L-NAME-induced high blood pressure in adult male Sprague-Dawley rats. The effects of black cumin oil on blood pressure have been associated with a lowering of the content of the cardiac lipid peroxidation product MDA, inhibition of cardiac NADPH oxidase and angiotensin-converting enzyme activities, and a reduction in plasma nitric oxide, as well as an elevation of HO-1 activity in the heart (Jaarin et al., 2015). Collectively, black cumin and thymoquinone have been proposed to exert antidiabetic effects through various mechanisms of action, such as reducing insulin resistance, accelerating β-cell proliferation, augmenting pancreatic insulin secretion and glucose uptake, and attenuating oxidative stress. It inhibited hepatic gluconeogenesis through the reduction of gluconeogenic precursors such as glycerol, alanine, and lactate. The other possible mechanism is the activation of the insulin signaling pathway, the AMPK signaling pathway, and the PPAR-γ pathways in skeletal muscle cells, hepatocytes, and adipocytes (Maideen, 2021). Previous studies stated that it exhibits antihyperlipidemic activity by strongly inhibiting the hepatic HMG-CoA reductase enzyme, inducing arylesterase activity, and playing a regulatory role in genes affecting cholesterol metabolism. Furthermore, the positive effect on the lipid profile is attributed to the high antioxidant activity of the plant (Mollazadeh, Mahdian, & Hosseinzadeh, 2019). Collectively, black cumin seed and its phytochemicals seem to improve the management of diabetes and its related complications by augmenting insulin sensitivity, facilitating glucose uptake and secretion, inhibiting hepatic glucose production, reducing oxidative stress and inflammation, positively modulating gut microbiota, and balancing lipid metabolism.

***Punica granatum* L. (Pomegranate)**

The seeds, seed oil, roots, stem bark, leaves, flowers, fruit, and fruit peels of the Punica granatum (Punicaceae), also known as pomegranate, are medicinally valuable. Different parts of the plant contain alkaloids (pelletierin, pseudopelletierin, *N*-methylpelletierin, isopelletierin, 1-pelletierin), anthocyanins (delphinidin, cyanidin, pelargonidin), tannins (punicalagin, punicafolin, punicalin α, and β- catechin, ellagitannins), flavonoids, phenolic acids (punicalin, gallic acid, ellagic acid, pyrogallol), sterols, terpenes, lignans, fatty acids, and organic acids. Previous preclinical studies have reported that it has pharmacological effects, including antimicrobial, anticancer, anti-inflammatory, antidiabetic, and antiobesity activities (Maphetu, Unuofin, Masuku, Olisah, & Lebelo, 2022).

In an STZ-NAD-induced Type 2 diabetes mellitus model, rats were orally administered 100 and 300 mg/kg b.wt of pomegranate aril juice equivalent to punicalagin at a dose of 2.6 and 7.8 mg/kg b.wt, respectively, for 6 weeks. High-dose pomegranate juice ameliorated oxidative stress by significantly reducing serum TNF-α concentration, liver MDA concentration, and NOx production and enhancing GST activity in the liver. It upregulated the mRNA expression of hepat-

ic IRS1 while downregulating the mRNA expression of hepatic JNK in both doses administered (El-Beih, Ramadan, El-Husseiny, & Hussein, 2019). In another study, Sprague-Dawley rats were treated with fresh pomegranate juice (1 mL, 21 days, oral) or powdered pomegranate seeds (100 mg, 21 days, oral) in a STZ-NAD-induced diabetes mellitus model. Pomegranate juice reduced plasma IL-6, TNF-α, and NF-κB levels (Taheri Rouhi, Sarker, Rahmat, Alkahtani, & Othman, 2017). *P. granatum* flowers were administered to male Sprague-Dawley rats by oral gavage at doses of 50 and 100 mg/kg for 4 weeks in an STZ-induced diabetes mellitus model. It boosted the level of glycogen in the liver and muscles. It increased CAT, SOD, and GSH levels while decreasing MDA levels. It suppressed ER stress by downregulating the expression levels of IRE1α, eIF2α, XBP1-s, and CHOP, which are ER stress markers. In conclusion, it has been demonstrated that polyphenol extract prepared from pomegranate flowers reduces insulin resistance through the activation of the Akt-GSK3β signaling pathway and inhibition of ER stress (Tang et al., 2018). Punicalagin administration (20 mg/b.wt/day, 4 weeks, orally) upregulated the expression of autophagy-related proteins, including PU, LC3B, and p62, in male C57BL/6J mice in an STZ-induced diabetes mellitus model. It significantly reversed the diabetes mellitus-induced increase in phosphorylated Akt/total Akt and phosphorylated FoxO3a/total FoxO3a protein ratios (Zhang et al., 2019). Punicalagin (100, 150, and 200 mg/kg, 4 weeks, orally) decreased gluconeogenesis and augmented glycogenesis by stimulating the PI3K/AKT signaling pathway and regulating the HMGB-1/TLR4/NF-κB signaling pathway in C57BL/6J mice in the STZ-induced Type 2 diabetes mellitus model (Jin, Zhang, Li, & Zhou, 2020). Treatment with pomegranate ellagic polyphenols (PEP; 50, 150, and 300 mg/kg/day, 14 days, orally) was found to enhance 11β-HSD2 protein and mRNA levels in the placental tissue of rats with gestational diabetes mellitus in an STZ-induced model. It inhibited cell apoptosis in pancreatic and placental tissues by suppressing *p*-PI3K and *p*-AKT expressions. It downregulated ANP and chemerin expressions in pancreatic tissue, which are associated with insulin resistance and inflammation. Moreover, it downregulated the mRNA and protein levels of CRP, TNF-α, and IL-6 in pancreatic tissue. It also markedly upregulated the protein and mRNA levels of PPAR-α, TRB3, AKT2, *p*-FOXO1, and GLUT-2. All these effects were stated to be dose-dependent (Sun, Zhou, & Wang, 2019). Ellagic acid-rich pomegranate peel extract (44, 88, and 177 mg/kg/b.wt, week, oral) improved the lipid profile in hamsters by upregulating LXR-α, PPAR-α, PPAR-γ, and their downstream gene ABCA1 (Liu et al., 2015). In addition to these mechanisms, it is stated that the possible mechanisms of action of pomegranate juice may be increased β-cell function, induction of insulin secretion, inhibition of α-amylase, α-glucosidase, and dipeptidyl peptidase-4 enzymes, and protective effects against DNA damage (Virgen-Carrillo, Martínez Moreno, & Valdés Miramontes, 2020). In summary, pomegranate and its components influence diabetes mellitus by enhancing insulin sensitivity and glucose utilization, reducing oxidative stress and inflammation, suppressing endoplasmic reticulum stress, promoting cellular health and survival (through autophagy and anti-apoptotic effects), and improving lipid metabolism.

***Trigonella foenum-graecum* L. (Fenugreek)**

The seeds of the *T. foenum graecum* (Fabaceae) are used for therapeutic purposes. The seeds contain pyridine alkaloids (trigonellin, choline, gentianine, and carparine), steroidal saponins (diosgenin, yamogenin, tigogenin, neotigogenin), flavonoids (apigenin, orientin, luteolin, quercetin, vitexin, and isovitexin), free amino acids (4-hydroxyisoleucine, arginine, lysine), essential oil (n-alkane and sesquiterpene compounds), galactomannan, protein, and fixed oil. It has been reported that fenugreek and its phytochemicals exhibit antimicrobial, anticancer, antioxidant, hypoglycemic, hypolipidemic, hypocholesterolemic, immunomodulatory, and neuroprotective activities (Visuvanathan, Than, Stanslas, Chew, & Vellasamy, 2022).

Fenugreek powder (2 or 8 g per 100 g of chow, orally, for 4 weeks) was administered to male hamsters fed a high-cholesterol diet. High-dose fenugreek seed significantly upregulated LDLR gene expression, but there was no significant change in the low-dose group. These results suggested that fenugreek may be effective in treating dyslipidemia through upregulation of LDLR gene expression (Kassaee, Goodarzi, & Kassaee, 2021). In a second study, the saponin fraction isolated from fenugreek seeds (6, 12, and 24 mg/kg doses, 9 weeks, orally) boosted CYP 7A1, SCARB1, and Niemann-Pick C1-like 1 levels in HFD-fed rats. It also decreased the level of HMG-CoA reductase in the liver and serum. In conclusion, the possible positive effects of the saponin fraction on dyslipidemia were related to accelerated cholesterol metabolism, inhibited cholesterol synthesis, and facilitated reverse cholesterol transport (Chen et al., 2017). It was determined that diosgenin (20 mg/kg b.wt, 20 days, intragastric), which is one of the active components of fenugreek seed, ameliorated oxidative stress in C57BL/KsJ-Lepdb/db/+(db/+) pregnant mice by reducing TBARS content, increasing GSH level, and inducing the activities of antioxidant enzymes such as SOD and CAT. It also downregulated the expression of SREBP-1 and its target genes, including FAS, SCD-1, and acetyl coenzyme A carboxylase (Hua, Li, Su, & Liu, 2016). In a model of STZ-induced diabetes mellitus, male Sprague-Dawley rats were treated orally with trigonelline at a dose of 40 mg/kg/day for 8 weeks. Trigonellin lowered the levels of IL-1β, IL-6, and IL-18 while elevating the level of IL-10. The protein expressions of p53 and Bax, as well as the activities of caspase-3 and caspase-9, were inhibited following trigonellin treatment. It decreased MDA levels and increased SOD, GSH, and GSH-Px levels. Moreover, it induced protein expression of PPAR-γ and GLUT-4 while suppressing protein expression of TNF-α and leptin. Taken together, it was concluded that trigonellin may act on Type 2 diabetes mellitus through antioxidative, anti-inflammatory, and antiapoptotic effects and by modulating the PPAR-*y*/GLUT-4-leptin/TNF-α signaling pathway (Li, Li, Wang, Lou, & Li, 2019). The effect of a water extract prepared from fenugreek seeds and its active component, 4-hydroxyisoleucine, on insulin resistance was tested using human liver cells (HepG2). The extract and 4-hydroxyisoleucine (for both: 100 ng/mL) markedly stimulated the phosphorylation of IR-β, Akt, GSK-3α/β, and GLUT-2 under normoglycemic and hyperglycemic conditions. Fenugreek seeds and the active ingredient were observed to exhibit insulin-like antihyperglycemic effects by inducing insulin signaling, modulating the expression of insulin signaling pathway-related genes, and increasing glucose uptake (Naicker, Nagiah, Phulukdaree, & Chuturgoon, 2016). In another study, 4-hydroxyisoleucine (10 μM for 24 h) upregulated the tyrosine phosphorylation of both IR-β and IRS-1 in TNF-α-induced C2C12 myotubes. It reduced the protein concentration of SOCS-3. It increased immunoprecipitation of the IR-β subunit with IRS-1 while decreasing coimmunoprecipitation of SOCS-3 with IR-β and IRS-1. It also activated AMPK phosphorylation. These results suggested that 4-hydroxyisoleucine ameliorates inflammation-mediated insulin resistance by activating the AMPK pathway and suppressing the co-immunoprecipitation of SOCS-3 with IR-β and IRS-1 (Gautam et al., 2016). INDUS810 isolated from fenugreek seed (200 mg/kg, 15 weeks, *i.p.*) inhibited lipid accumulation while inducing lipolysis activity in 3T3-L1 adipocytes. It upregulated PPAR-α, PPAR-γ co-activator 1β, sirtuin 1, and sirtuin three protein levels. It did not affect FAS, PPAR-γ, and CCAAT/enhancer-binding protein-α expression. Moreover, it diminished the lipid content in adipocytes by activating AMP-activated protein kinase (Cheng, Yang, Ekambaranellore, Huang, & Lin, 2018). The authors suggested that fenugreek could be effective in diabetes mellitus by improving insulin signaling and glucose uptake, exhibiting significant anti-inflammatory and antioxidant properties, protecting cells from apoptosis, and regulating lipid and cholesterol metabolism.

***Zingiber officinale* Roscoe (Ginger)**

The dried rhizomes of *Zingiber officinale* Roscoe (Zingiberaceae) are used for medicinal purposes and as a spice. Essential oils (α-zingiberene, β-sesquifellandrene, β-bisabolene, (-)-β-phellandrene, and geraniol) and gingerol analogs (gingerol, shogaol, paradol, and zingerone) in the composition of the rhizomes are responsible for the biological activity. The compounds, such as diarylheptanoids, sulfonates, steroids, and monoterpenoid glycosides, were isolated from different parts of the plant. Ginger and its isolated compounds have a wide range of pharmacological activities, including gastroprotective, anticancer, lipid-lowering, antiobesity, antihelmintic, antiallergic, neuroprotective, hepatoprotective, and neuroprotective effects (Zhang et al., 2021).

The hydroethanolic extract prepared from ginger rhizomes was administered orally to male Wistar rats at a dose of 250 mg/kg/day for 5 weeks. The extract suppressed the expression of GPAT, connective tissue growth factor, SREBP-1c, and collagen 1 in the liver. It upregulated both PPAR-α and PPAR-γ expression. Ginger treatment significantly enhanced plasma adiponectin levels while decreasing plasma leptin levels. It did not affect the protein expression of the CYP7A1 enzyme or LXR (de Las Heras et al., 2017). Ahmad et al. administered zingerone (at 50 and 100 mg/kg b.wt/day, 21 days, orally) to Wistar male albino mice in a model of alloxan-induced diabetes mellitus. Zingerone diminished inflammation by inhibiting the NF-κB signaling pathway and down-regulating the expression of inflammatory cytokines such as IL-1β, IL-2, IL-6, and TNF-α. It improved oxidative stress by boosting antioxidant enzyme activities such as SOD, CAT, and GPx and lowering MDA levels (Ahmad et al., 2018). 6-gingerol (200 mg/kg/day, 28 days, orally) augmented GLP-1 levels and reduced DPP4 levels and activity by stimulating the GLP1/cAMP/PKA/CREB pathway in Lepr db/db type 2 diabetic mice. It upregulated the gene and protein expression of Rab27a and Slp4-a. It also induced membrane translocation of GLUT-4 by upregulating Rab8 and Rab10. These results suggested that 6-gingerol increased glucose uptake in the skeletal muscles of mice (Samad et al., 2017). In another study, it was reported that administration of 6-gingerol (0.05%, 4 weeks) with a 20% casein diet suppressed hepatic gene expression of PEPCK and G6Pase in db/db mice. It upregulated the gene expression of glycogen synthase while down-regulating glycogen phosphorylase. Moreover, it significantly reduced TBARS and TNF-α levels (Son et al., 2015). In addition to these mechanisms, there is *in vitro* evidence that ginger and its constituents exert antidiabetic effects by enhancing the viscosity of gastrointestinal contents, delaying gastric emptying, forming a barrier against diffusion, and inhibiting the activities of α-amylase, α-glucosidase, and angiotensin-converting enzymes (Tran, Pham, & Le, 2020). Ginger and its phytochemicals have been shown to be effective in the management of diabetes mellitus by increasing glucose uptake and storage, reducing glucose production, suppressing inflammation and oxidative stress, regulating lipid metabolism, and balancing appetite-related hormones.

CONCLUSION

The increasing prevalence of diabetes mellitus has led to a rise in the use of medicinal plants to support medical treatment. Several studies have investigated the efficacy and mechanisms of action of medicinal plants such as cinnamon, garlic, ginseng, flaxseed, black cumin, pomegranate, and walnut in diabetes mellitus and dyslipidemia. Garlic modulates appetite through increasing POMC expression in the hypothalamus and reducing ObR mRNA levels, while also promoting energy expenditure by β3-ADR and UCP-1 expression. It also inhibits inflammatory mediators such as IL-6, IL-1β, and TNF-α. Cinnamon contributes to weight management by modulating glucose metabolism by the inhibition of α-amylase and α-glucosidase and by increasing mitochondrial biogenesis through AMPK activation. Turmeric and curcumin mitigate oxidative stress by lowering MDA and NO levels and reduce inflammation by diminish-

ing NF-κB and COX-2 levels. It augments insulin signaling by elevating Akt phosphorylation in peripheral organs. It improves glycolipid metabolism by inhibiting hepatic gluconeogenesis and lipogenesis. Ginseng is effective in weight management by downregulating adipogenic genes, including SREBP1C, PPAR-γ, FAS, SCD1, and ACC1. The ginsenosides increase glucose uptake and insulin sensitivity by activating the PI3K/AKT and AMPK signaling pathways, as well as reducing inflammation. Walnuts reduce insulin resistance by increasing ADP and FNDC5 levels. Polyunsaturated fatty acids and peptides in their composition alleviate oxidative stress and enhance hyperglycemia by promoting autophagy via the AMPK/mTOR/ULK1 pathway. Flaxseed has been demonstrated to contribute to managing diabetes by regulating gut flora and enhancing short-chain fatty acid synthesis. It improves lipid profiles by modulating bile acid metabolism by regulating the FXR-FGF15 signaling pathway. Black cumin increases insulin sensitivity and promotes glucose absorption by activating the PI3K/AKT and the AMPK pathways. The positive effects on lipid metabolism are related to the inhibition of the enzyme HMG-CoA reductase. Pomegranate reduces insulin resistance by activating the Akt-GSK3β signaling pathway and decreases gluconeogenesis and enhances glycogen production by stimulating the PI3K/AKT signaling pathway. It also mitigates inflammation and oxidative stress by modulating the HMGB-1/TLR4/NF-κB pathway. Pomegranate increases cellular viability through autophagy and anti-apoptotic mechanisms. It has been proven that these plants may be effective against the mentioned disease groups by regulating mitochondrial biogenesis-related pathways and by antioxidant, anti-inflammatory, and antiapoptotic mechanisms of action. It is extremely important that the results obtained are supported by randomized, controlled clinical trials in large populations with standardized, quality-controlled herbal products. In this regard, preclinical and clinical studies assessing the mechanisms of action of these herbal products should be increased.

ABBREVIATIONS

DM: Diabetes mellitus, HDL-c: high-density lipoprotein cholesterol, TG: triglyceride, LDL-c: low-density lipoprotein cholesterol, POMC: proopiomelanocortin, ObR: leptin receptor, β3-ADR: β3-adrenergic receptor, PPAR-γ: peroxisome proliferator-activator receptor-γ, LPL: lipoprotein lipase, HSL: hormone-sensitive lipase, InsR: insulin receptor, GLUT-4: glucose transporter type-4, UCP-1: uncoupling protein-1, IL: interleukins, TNF-α: tümor necrosis factor-alpha, iNOS: inducible nitric oxide synthase, ABCA1: ATP-binding cassette transporter A1, HMG-CR: 3-hydroxy-3-methylglutaryl-CoA reductase, CYP46A1: cholesterol-24 hydroxylase, SREBP-2: sterol regulatory element binding protein-2, ACAT-2: acetyl-CoA acetyltransferase-2, HMG-CoA: β-hydroxy β-methylglutaryl-CoA, STZ: streptozotocin, HFD: high-fat diet, MyHC: myosin heavy chain, PGC-1α: peroxisome proliferator-activated receptor-γ coactivator α, AMPK: AMP-activated protein kinase, Nrf-1: nuclear respiratory factor-1, Tfam: mitochondrial transcription factor A, ACC: acetyl-CoA carboxylase, SOD: superoxide dismutase, CAT: catalase, GPx: glutathione peroxidase, SREBF1: sterol regulatory element-binding transcription factor 1, LDLR: low-density lipoprotein receptor, NR2F2: nuclear receptor subfamily 2 group F member 2, FOXO1: forkhead box transcription factor O1, MDA: malondialdehyde, TAC: total antioxidant capacity, LXR-α: liver X receptor-α, ACLY: ATP-citrate lyase, FAS: fatty acid synthase, IRS-1: insulin receptor substrate-1, HO-1: heme oxygenase-1, BDNF: brain-derived neurotrophic factor, CARTPT: cocaine and amphetamine-related transcript, CCK: cholecystokinin, C/EBP-α: CCAAT/enhancer-binding protein, DLK-1: delta-like 1 homolog, PNPLA2: patatin phospholipase domain containing 2, MGLL: monoglyceride lipase, BMP4: bone morphogenetic protein 4, PRDM16: PR domain containing 16, COX: cyclooxygenase, MCP1: monocyte chemotactic protein 1, ATGL: adipose triglyceride lipase, ACOX1: acyl-coenzyme A oxidase 1, CPT1: carnitine palmitoyltransferase 1, GSK 3β: glycogen synthase kinase 3β, PEPCK: phosphoe-

nolpyruvate carboxykinase, TGF-β: transforming growth factor-β, FGF15: fibroblast growth factor 15, PKCθ: protein kinase theta, FDPS: farnesyl diphosphate synthetase, DHCR24: 24-dehydrocholesterol reductase, DHCR7: 7-dehydrocholesterol reductase, LSS: lanosterol synthase, MVK: mevalonate kinase, Sc4mol: sterol-C4-methyl oxidase-lik, SS: squalene synthase, SCD-1: stearoyl-coenzyme A desaturase, GPAT: glycerol-3-phosphate acyltransferase, SOCS-3: suppressor of cytokine signaling-3, FXR: farnesoid X receptor, CYP8B1: sterol 12-α-hydroxylase, XBP1-s: X box-binding protein1-s, SCARB1: scavenger receptor class B type I, HFD: high-fat diet, ADP: adinopectin, PUFA: polyunsaturated fatty acid, FNDC5: fibronectin type III domain containing 5, CYP7A1: cholesterol 7α-hydroxylase, PTP-1B: protein tyrosine phosphatase 1B, JNK: phospho-c-Jun N-terminal kinase

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Abbasnezhad, A., Niazmand, S., Mahmoudabady, M., Rezaee, S. A., Soukhtanloo, M., Mosallanejad, R., & Hayatdavoudi, P. (2019). *Nigella sativa* L. seed regulated eNOS, VCAM-1 and LOX-1 genes expression and improved vasoreactivity in aorta of diabetic rat. *Journal of Ethnopharmacology*, *228*, 142–147. doi: 10.1016/j.jep.2018.09.021.

Adel Mehraban, M. S., Tabatabaei-Malazy, O., Rahimi, R., Daniali, M., Khashayar, P., & Larijani, B. (2021). Targeting dyslipidemia by herbal medicines: A systematic review of meta-analyses. *Journal of Ethnopharmacology*, *280*, 114407. doi: 10.1016/j.jep.2021.114407.

Ahmad, B., Rehman, M. U., Amin, I., Mir, M. U. R., Ahmad, S. B., Farooq, A.,…Fatima, B. (2018). Zingerone (4-(4-hydroxy-3-methylphenyl) butan-2-one) protects against alloxan-induced diabetes via alleviation of oxidative stress and inflammation: Probable role of NF-kB activation. *Saudi Pharmaceutical Journal*, *26*, 1137–1145. doi:10.1016/j.jsps.2018.07.001.

Altun, E., Avci, E., Yildirim, T., & Yildirim, S. (2019). Protective effect of *Nigella sativa* oil on myocardium in streptozotocin-induced diabetic rats. *Acta Endocrinologica*, *15*, 289–294. doi: 10.4183/aeb.2019.289.

Amor, S., González-Hedström, D., Martín-Carro, B., Inarejos-García, A. M., Almodóvar, P., Prodanov, M.,…Granado, M. (2019). Beneficial effects of an aged black garlic extract in the metabolic and vascular alterations induced by a high fat/sucrose diet in male rats. *Nutrients*, *11*, 153. doi:10.3390/nu11010153.

Athyros, V. G., Doumas, M., Imprialos, K. P., Stavropoulos, K., Georgianou, E., Katsimardou, A., & Karagiannis, A. (2018). Diabetes and lipid metabolism. *Hormones*, *17*, 61–67. doi:10.1007/s42000-018-0014-8.

Atila Uslu, G., & Uslu, H. (2022). Evaluating the effects of *Juglans regia* L. extract on hyperglycaemia and insulin sensitivity in experimental type 2 diabetes in rat. *Archives of Physiology and Biochemistry*, *128*, 121–125. doi:10.1080/13813455.2019.1668018.

Bahiru, E., Hsiao, R., Phillipson, D., & Watson, K. E. (2021). Mechanisms and treatment of dyslipidemia in diabetes. *Current Cardiology Reports*, *23*, 26. doi:10.1007/s11886-021-01455-w.

Balbaa, M., El-Zeftawy, M., Ghareeb, D., Taha, N., & Mandour, A. W. (2016). *Nigella sativa* relieves the altered ınsulin receptor signaling in streptozotocin-induced diabetic rats fed with a high-fat diet. *Oxidative Medicine and Cellular Longevity*, *2016*, 2492107. doi:10.1155/2016/2492107.

Beji, R. S., Khemir, S., Wannes, W. A., Ayari, K., & Ksouri, R. (2018). Antidiabetic, antihyperlipidemic and antioxidant influences of the spice cinnamon (*Cinnamomum zeylanicumon*) in experimental rats. *Brazilian Journal of Pharmaceutical Sciences*, *54*, e17576.

Bhat, A. A., Shakeel, A., Rafiq, S., Farooq, I., Malik, A. Q., Alghuthami, M. E.,…Alharthy, S. A. (2023). *Juglans regia* Linn.: A natural repository of vital phytochemical and pharmacological compounds. *Life*, *13*, 380. doi: 10.3390/life13020380.

Bouzghaya, S., Amri, M., & Homblé, F. (2020). Improvement of diabetes symptoms and complications by an aqueous extract of *Linum usitatissimum* (L.) seeds in alloxan-induced diabetic mice. *Journal of Medicinal Food*, *23*, 1077–1082. doi:10.1089/jmf.2019.0205.

Chen, W., Balan, P., & Popovich, D. G. (2019). Review of ginseng anti-diabetic studies. *Molecules*, *24*, 4501. doi: 10.3390/molecules24244501

Chen, Z., Lei, Y. L., Wang, W. P., Lei, Y. Y., Liu, Y. H., Hei, J.,…Sui, H. (2017). Effects of saponin from *Trigonella foenum-graecum* seeds on dyslipidemia. *Iranian Journal of Medical Sciences*, *42*, 577–585.

Cheng, C. Y., Yang, A. J., Ekambaranellore, P., Huang, K. C., & Lin, W. W. (2018). Anti-obesity action of INDUS810, a natural compound from *Trigonella foenum-graecum*: AMPK-dependent lipolysis effect in adipocytes. *Obesity Research & Clinical Practice*, *12*, 562–569. doi: 10.1016/j.orcp.2018.08.005.

Cüce, G., Sözen, M. E., Çetinkaya, S., Canbaz, H. T., Seflek, H., & Kalkan, S. (2016). Effects of *Nigella sativa* L. seed oil on intima-media thickness and Bax and Caspase 3 expression in diabetic rat aorta. *Anatolian Journal of Cardiology*, *16*, 460–466. doi: 10.5152/AnatolJCardiol.2015.6326.

Dai, S., Hong, Y., Xu, J., Lin, Y., Si, Q., & Gu, X. (2018). Ginsenoside Rb2 promotes glucose metabolism and attenuates fat accumulation via AKT-dependent mechanisms. *Biomedicine & Pharmacotherapy*, *100*, 93–100. doi: 10.1016/j.biopha.2018.01.111.

Dalli, M., Bekkouch, O., Azizi, S. E., Azghar, A., Gseyra, N., & Kim, B. (2021). *Nigella sativa* L. phytochemistry and pharmacological activities: A review (2019-2021). *Biomolecules*, *12*, 20. doi 10.3390/biom12010020.

de Las Heras, N., Valero-Muñoz, M., Martín-Fernández, B., Ballesteros, S., López-Farré, A., Ruiz-Roso, B., & Lahera, V. (2017). Molecular factors involved in the hypolipidemic- and insulin-sensitizing effects of a ginger (*Zingiber officinale* Roscoe) extract in rats fed a high-fat diet. *Applied Physiology, Nutrition, and Metabolism*, *42*, 209–215. doi: 10.1139/apnm-2016-0374.

Delaviz, H., Mohammadi, J., Ghalamfarsa, G., Mohammadi, B., & Farhadi, N. (2017). A Review study on phytochemistry and pharmacology applications of *Juglans regia* plant. *Pharmacognosy Reviews*, *11*, 145–152. doi: 10.4103/phrev.phrev_10_17.

Ding, L., Li, J., Song, B., Xiao, X., Zhang, B., Qi, M.,… Wang, Z. (2016). Curcumin rescues high fat diet-induced obesity and insulin sensitivity in mice through regulating SREBP pathway. *Toxicology and Applied Pharmacology*, *304*, 99–109. doi: 10.1016/j.taap.2016.05.011.

Dong, J., Liang, Q., Niu, Y., Jiang, S., Zhou, L., Wang, J.,…Kang, W. (2020). Effects of *Nigella sativa* seed polysaccharides on type 2 diabetic mice and gut microbiota. *International Journal of Biological Macromolecules*, *159*, 725–738. doi: 10.1016/j.ijbiomac.2020.05.042.

El-Beih, N. M., Ramadan, G., El-Husseiny, E. A., & Hussein, A. M. (2019). Effects of pomegranate aril juice and its punicalagin on some key regulators of insulin resistance and oxidative liver injury in streptozotocin-nicotinamide type 2 diabetic rats. *Molecular Biology Reports*, *46*, 3701–3711. doi: 10.1007/s11033-019-04813-8

El-Naggar, M. E., Al-Joufi, F., Anwar, M., Attia, M. F., & El-Bana, M. A. (2019). Curcumin-loaded PLA-PEG copolymer nanoparticles for treatment of liver inflammation in streptozotocin-induced diabetic rats. *Colloids and Surfaces. B, Biointerfaces*, *177*, 389–398. doi: 10.1016/j.colsurfb.2019.02.024.

El-Saber Batiha, G., Magdy Beshbishy, A., G Wasef, L., Elewa, Y. H. A., A Al-Sagan, A., Abd El-Hack, M. E.,…Prasad Devkota, H. (2020). Chemical constituents and pharmacological activities of garlic (*Allium sativum* L.): A review. *Nutrients*, *12*, 872. doi: 10.3390/nu12030872.

Gautam, S., Ishrat, N., Yadav, P., Singh, R., Narender, T., & Srivastava, A. K. (2016). 4-Hydroxyisoleucine attenuates the inflammation-mediated insulin resistance by the activation of AMPK and suppression of SOCS-3 coimmunoprecipitation with both the IR-β subunit as well as IRS-1. *Molecular and Cellular Biochemistry*, *414*, 95–104. doi: 10.1007/s11010-016-2662-9.

Gürel, Ş., & Çiçek Polat, D. (2025). Nigella sativa L.: an overview. *Journal of Faculty of Pharmacy of Ankara University*, *49*, 133–145. https://doi.org/10.33483/jfpau.1504025.

Han, J. H., Tuan, N. Q., Park, M. H., Quan, K. T., Oh, J., Heo, K. S.,…Myung, C. S. (2018). Cucurbitane triterpenoids from the fruits of *Momordica charantia* improve insulin sensitivity and glucose homeostasis in streptozotocin-ınduced diabetic mice. *Molecular Nutrition & Food Research*, *62*, e1700769. doi: 10.1002/mnfr.201700769.

Hariri, M., & Ghiasvand, R. (2016). Cinnamon and chronic diseases. *Advances in Experimental Medicine and Biology*, *929*, 1–24. https://doi.org/10.1007/978-3-319-41342-6_1

Hoogwerf B. J. (2020). Type of diabetes mellitus: Does it matter to the clinician?. *Cleveland Clinic Journal of Medicine*, *87*, 100–108. https://doi.org/10.3949/ccjm.87a.19020.

Hou, W., Zhao, F., Fang, L., Wang, X., Wu, D., Liu, C.,…Min, W. (2023). Walnut-derived peptides promote autophagy via the activation of AMPK/mTOR/ULK1 pathway to ameliorate hyperglycemia in type 2 diabetic mice. *Journal of Agricultural and Food Chemistry*, *71*, 3751–3765. doi: 10.1021/acs.jafc.2c07112.

Hua, S., Li, Y., Su, L., & Liu, X. (2016). Diosgenin ameliorates gestational diabetes through inhibition of sterol regulatory element-binding protein-1. *Biomedicine & Pharmacotherapy*, *84*, 1460–1465. doi:10.1016/j.biopha.2016.10.049.

Hui, H., Tang, G., & Go, V. L. (2009). Hypoglycemic herbs and their action mechanisms. *Chinese Medicine*, *4*, 11. https://doi.org/10.1186/1749-8546-4-11.

International Diabetes Federation (2021). IDF Guide for Epidemiology Studies [Online]. Available from: https://diabetesatlas.org/idf-guide-for-epidemiology-studies/ [Accessed 14 July 2023]

Irfan, M., Kim, M., Kim, K. S., Kim, T. H., Kim, S. D., Hong, S. B.,…Rhee, M. H. (2019). Fermented garlic ameliorates hypercholesterolemia and ınhibits platelet activation. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 3030967. doi: 10.1155/2019/3030967.

İşcan, G., Bektaş Sarıaltın, E., Soyseven, M., & Arli, G. (2022). Türkiye'de tüketime sunulan tarçın türlerinin anatomik incelenmesi ve kumarin miktarlarının belirlenmesi. *Gıda*, *47*, 310–327. doi: 10.15237/gida.GD22014.

Jaarin, K., Foong, W. D., Yeoh, M. H., Kamarul, Z. Y., Qodriyah, H. M., Azman, A.,…Kamisah, Y. (2015). Mechanisms of the antihypertensive effects of *Nigella sativa* oil in L-NAME-induced hypertensive rats. *Clinics*, *70*, 751–757. doi: 10.6061/clinics/2015(11)07.

Jin, D., Zhang, B., Li, Q., & Zhou, B. (2020). Effect of punicalagin on multiple targets in streptozotocin/high-fat diet-induced diabetic mice. *Food & Function*, *11*,10617–10634. doi: 10.1039/D0FO01275K.

Kang, N. H., Mukherjee, S., & Yun, J. W. (2019). Trans-cinnamic acid stimulates white fat browning and activates brown adipocytes. *Nutrients*, *11*, 577. doi: 10.3390/nu11030577.

Karlowicz-Bodalska, K., Han, S., Freier, J., Smolenski, M., & Bodalska, A. (2017). *Curcuma longa* as medicinal herb in the treatment of diabetic complications. *Acta Poloniae Pharmaceutica*, *74*, 605–610.

Kassaee, S. M., Goodarzi, M. T., & Kassaee, S. N. (2021). Ameliorative effect of *Trigonella foenum fraecum* L. on lipid profile, liver histology and LDL-receptor gene expression in high cholesterol-fed hamsters. *Acta Endocrinologica*, *17*, 7–13. doi: 10.4183/aeb.2021.7.

Kaur, N., Chugh, H., Tomar, V., Sakharkar, M. K., Dass, S. K., & Chandra, R. (2019). Cinnamon attenuates adiposity and affects the expression of metabolic genes in diet-induced obesity model of zebrafish. *Artificial Cells, Nanomedicine, and Biotechnology*, *47*, 2930–2939. doi: 10.1080/21691401.2019.1641509.

Khare, P., Jagtap, S., Jain, Y., Baboota, R. K., Mangal, P., Boparai, R. K.,…Bishnoi, M. (2016). Cinnamaldehyde supplementation prevents fasting-induced hyperphagia, lipid accumulation, and inflammation in high-fat diet-fed mice. *BioFactors*, *42*, 201–211. doi: 10.1002/biof.1265.

Kocaadam, B., & Şanlier, N. (2017). Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. *Critical Reviews in Food Science and Nutrition*, *57*, 2889–2895. doi: 10.1080/10408398.2015.1077195.

Lee, M., Shin, H., Park, M., Kim, A., Cha, S., & Lee, H. (2022). Systems pharmacology approaches in herbal medicine research: A brief review. *BMB Reports*, *55*, 417–428. doi: 10.5483/BMBRep.2022.55.9.102

Li, Y., Li, Q., Wang, C., Lou, Z., & Li, Q. (2019). Trigonelline reduced diabetic nephropathy and insulin resistance in type 2 diabetic rats through peroxisome proliferator-activated receptor-γ. *Experimental and Therapeutic Medicine*, *18*, 1331–1337. doi: 10.3892/etm.2019.7698.

Liu, H., Lu, X., Hu, Y., & Fan, X. (2020). Chemical constituents of *Panax ginseng* and *Panax notoginseng* explain why they differ in therapeutic efficacy. *Pharmacological Research*, *161*, 105263. doi: 10.1016/j.phrs.2020.105263.

Liu, R., Li, J., Cheng, Y., Huo, T., Xue, J., Liu, Y., … Chen, X. (2015). Effects of ellagic acid-rich extract of pomegranates peel on regulation of cholesterol metabolism and its molecular mechanism in hamsters. *Food & Function*, *6*, 780–787. doi: 10.1039/c4fo00759j.

Liu, Y., Liu, C., Kou, X., Wang, Y., Yu, Y., Zhen, N.,… Xue, Z. (2022). Synergistic hypolipidemic effects and mechanisms of phytochemicals: a review. *Foods*, *11*, 2774. https://doi.org/10.3390/foods11182774.

Liu, Z., Qu, C. Y., Li, J. X., Wang, Y. F., Li, W., Wang, C. Z.,…Yuan, C. S. (2021). Hypoglycemic and hypolipidemic effects of malonyl ginsenosides from American Ginseng (*Panax quinquefolius* L.) on type 2 diabetic mice. *ACS Omega*, *6*, 33652–33664. doi: 10.1021/acsomega.1c04656.

Ma, C., Yu, H., Xiao, Y., & Wang, H. (2017). *Momordica charantia* extracts ameliorate insulin resistance by regulating the expression of SOCS-3 and JNK in type 2 diabetes mellitus rats. *Pharmaceutical Biology*, *55*, 2170–2177. doi: 10.1080/13880209.2017.1396350.

Maideen N. M. P. (2021). Antidiabetic activity of *Nigella sativa* (black seeds) and its active constituent (thymoquinone): A review of human and experimental animal studies. *Chonnam Medical Journal*, *57*, 169–175. doi: 10.4068/cmj.2021.57.3.169.

Maithilikarpagaselvi, N., Sridhar, M. G., Swaminathan, R. P., & Zachariah, B. (2016). Curcumin prevents inflammatory response, oxidative stress and insulin resistance in high fructose fed male Wistar rats: Potential role of serine kinases. *Chemico-Biological Interactions*, *244*, 187–194. doi: 10.1016/j.cbi.2015.12.012.

Maphetu, N., Unuofin, J. O., Masuku, N. P., Olisah, C., & Lebelo, S. L. (2022). Medicinal uses, pharmacological activities, phytochemistry, and the molecular mechanisms of *Punica granatum* L. (pomegranate) plant extracts: A review. *Biomedicine & Pharmacotherapy*, *153*, 113256. doi: 10.1016/j.biopha.2022.113256

Marmitt, D. J., Shahrajabian, M. H., Goettert, M. I., & Rempel, C. (2021). Clinical trials with plants in diabetes mellitus therapy: a systematic review. *Expert Review of Clinical Pharmacology*, *14*, 735–747. doi: 10.1080/17512433.2021.1917380.

Mollazadeh, H., Mahdian, D., & Hosseinzadeh, H. (2019). Medicinal plants in treatment of hypertriglyceridemia: A review based on their mechanisms and effectiveness. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *53*, 43–52. doi: 10.1016/j.phymed.2018.09.024.

Nagar, H., Choi, S., Jung, S. B., Jeon, B. H., & Kim, C. S. (2016). Rg3-enriched Korean Red Ginseng enhances blood pressure stability in spontaneously hypertensive rats. *Integrative Medicine Research*, *5*, 223–229. doi: 10.1016/j.imr.2016.05.006.

Naicker, N., Nagiah, S., Phulukdaree, A., & Chuturgoon, A. (2016). *Trigonella foenum-graecum* seed extract, 4-hydroxyisoleucine, and metformin stimulate proximal insulin signaling and ıncrease expression of glycogenic enzymes and GLUT2 in HepG2 cells. *Metabolic Syndrome and Related Disorders*, *14*, 114–120. doi: 10.1089/met.2015.0081.

Naik, H. S., Srilatha, C., Sujatha, K., Sreedevi, B., & Prasad, T. N. V. K. V. (2018). Supplementation of whole grain flaxseeds (*Linum usitatissimum*) along with high cholesterol diet and its effect on hyperlipidemia and initiated atherosclerosis in Wistar albino male rats. *Veterinary World*, *11*, 1433–1439. doi: 10.14202/vetworld.2018.1433-1439.

Nazeri, Z., Azizidoost, S., Cheraghzadeh, M., Mohammadi, A., & Kheirollah, A. (2021). Increased protein expression of ABCA1, HMG-CoA reductase, and CYP46A1 induced by garlic and allicin in the brain mouse and astrocytes-isolated from C57BL/6J. *Avicenna Journal of Phytomedicine*, *11*, 473–483. doi: 10.22038/AJP.2021.17834.

Noruddin, N. A. A., Hamzah, M. F., Rosman, Z., Salin, N. H., Shu-Chien, A. C., & Muhammad, T. S. T. (2021). Natural Compound 3β,7β,25-trihydroxycucurbita-5,23(*E*)-dien-19-al from Momordica charantia Acts as PPARγ Ligand. *Molecules*, *26*, 2682. doi: 10.3390/molecules26092682.

Ota, A., & Ulrih, N. P. (2017). An Overview of herbal products and secondary metabolites used for management of type two diabetes. *Frontiers in Pharmacology*, *8*, 436. doi: 10.3389/fphar.2017.00436.

Oyelere, S. F., Ajayi, O. H., Ayoade, T. E., Santana Pereira, G. B., Dayo Owoyemi, B. C., Ilesanmi, A. O., & Akinyemi, O. A. (2022). A detailed review on the phytochemical profiles and anti-diabetic mechanisms of *Momordica charantia*. *Heliyon*, *8*, e09253. doi: 10.1016/j.heliyon.2022.e09253.

Pahlavani, N., Roudi, F., Zakerian, M., Ferns, G. A., Navashenaq, J. G., Mashkouri, A.,…Rahimi, H. (2019). Possible molecular mechanisms of glucose-lowering activities of *Momordica charantia* (karela) in diabetes. *Journal of Cellular Biochemistry*, *120*, 10921–10929. doi: 10.1002/jcb.28483.

Pan, Y., Zhao, D., Yu, N., An, T., Miao, J., Mo, F.,… Jiang, G. (2017). Curcumin improves glycolipid metabolism through regulating peroxisome proliferator activated receptor γ signalling pathway in high-fat diet-induced obese mice and 3T3-L1 adipocytes. *Royal Society Open Science*, *4*, 170917. doi: 10.1098/rsos.170917.

Pang, G. M., Li, F. X., Yan, Y., Zhang, Y., Kong, L. L., Zhu, P.,…Lu, C. (2019). Herbal medicine in the treatment of patients with type 2 diabetes mellitus. *Chinese Medical Journal*, *132*, 78–85. https://doi.org/10.1097/CM9.0000000000000006.

Parikh, M., Maddaford, T. G., Austria, J. A., Aliani, M., Netticadan, T., & Pierce, G. N. (2019). Dietary flaxseed as a strategy for improving human health. *Nutrients*, *11*, 1171. doi: 10.3390/nu11051171.

Petersmann, A., Müller-Wieland, D., Müller, U. A., Landgraf, R., Nauck, M., Freckmann, G.,…Schleicher, E. (2019). Definition, classification and diagnosis of diabetes mellitus. *Experimental and Clinical Endocrinology & Diabetes*, *127*, S1–S7. https://doi.org/10.1055/a-1018-9078,

Prasad, K., Khan, A. S., & Shoker, M. (2020). Flaxseed and its components in treatment of hyperlipidemia and cardiovascular disease. *International Journal of Angiology*, *29*, 216–222. doi: 10.1055/s-0040-1709129.

Ríos, J. L., Francini, F., & Schinella, G. R. (2015). Natural products for the treatment of type 2 diabetes mellitus. *Planta Medica*, *81*, 975–994. doi: 10.1055/s-0035-1546131.

Samad, M. B., Mohsin, M. N. A. B., Razu, B. A., Hossain, M. T., Mahzabeen, S., Unnoor, N.,…Hannan, J. M. A. (2017). [6]-Gingerol, from *Zingiber officinale*, potentiates GLP-1 mediated glucose-stimulated insulin secretion pathway in pancreatic β-cells and increases RAB8/RAB10-regulated membrane presentation of GLUT4 transporters in skeletal muscle to improve hyperglycemia in Leprdb/db type 2 diabetic mice. *BMC Complementary and Alternative Medicine*, *17*, 395. doi: 10.1186/s12906-017-1903-0.

Shin, S. S., & Yoon, M. (2018). Korean red ginseng (*Panax ginseng*) inhibits obesity and improves lipid metabolism in high fat diet-fed castrated mice. *Journal of Ethnopharmacology*, *210*, 80–87. doi: 10.1016/j.jep.2017.08.032.

Silva, M. L., Bernardo, M. A., Singh, J., & de Mesquita, M. F. (2022). Cinnamon as a complementary therapeutic approach for dysglycemia and dyslipidemia control in type 2 diabetes mellitus and its molecular mechanism of action: A review. *Nutrients*, *14*, 2773. doi: 10.3390/nu14132773.

Son, M. J., Miura, Y., & Yagasaki, K. (2015). Mechanisms for antidiabetic effect of gingerol in cultured cells and obese diabetic model mice. *Cytotechnology*, *67*, 641–652. doi: 10.1007/s10616-014-9730-3.

Song, M. Y., Kang, S. Y., Kang, A., Hwang, J. H., Park, Y. K., & Jung, H. W. (2017). *Cinnamomum cassia* prevents high-fat diet-induced obesity in mice through the increase of muscle energy. The *American Journal of Chinese Medicine*, *45*, 1017–1031. doi: 10.1142/S0192415X17500549.

Sun, B., Yan, H., Li, C., Yin, L., Li, F., Zhou, L., & Han, X. (2020). Beneficial effects of walnut (Juglans regia L.) oil-derived polyunsaturated fatty acid prevents a prooxidant status and hyperlipidemia in pregnant rats with diabetes. *Nutrition & Metabolism*, *17*, 92. doi: 10.1186/s12986-020-00514-.

Sun, K., Ding, M., Fu, C., Li, P., Li, T., Fang, L., Xu, J., & Zhao, Y. (2023). Effects of dietary wild bitter melon (*Momordica charanti*a var. *abbreviate* Ser.) extract on glucose and lipid metabolism in HFD/STZ-induced type 2 diabetic rats. *Journal of Ethnopharmacology*, *306*, 116154. doi: 10.1016/j.jep.2023.116154.

Sun, Y. L., Zhou, F. M., & Wang, H. R. (2019). Mechanism of pomegranate ellagic polyphenols reducing insulin resistance on gestational diabetes mellitus rats. *American Journal of Translational Research*, *11*, 5487–5500.

Taheri Rouhi, S. Z., Sarker, M. M. R., Rahmat, A., Alkahtani, S. A., & Othman, F. (2017). The effect of pomegranate fresh juice versus pomegranate seed powder on metabolic indices, lipid profile, inflammatory biomarkers, and the histopathology of pancreatic islets of Langerhans in streptozotocin-nicotinamide induced type 2 diabetic Sprague-Dawley rats. *BMC Complementary and Alternative Medicine*, *17*, 156. doi: 10.1186/s12906-017-1667-6.

Tang, D., Liu, L., Ajiakber, D., Ye, J., Xu, J., Xin, X., & Aisa, H. A. (2018). Anti-diabetic effect of *Punica granatum* flower polyphenols extract in type 2 diabetic rats: Activation of Akt/GSK-3β and inhibition of IRE1α-XBP1 pathways. *Frontiers in Endocrinology*, *9*, 586. doi: 10.3389/fendo.2018.00586.

Tran, N., Pham, B., & Le, L. (2020). Bioactive compounds in anti-diabetic plants: From herbal medicine to modern drug discovery. *Biology*, *9*, 252. doi: 10.3390/biology9090252.

Turkish Society of Endocrinology and Metabolism (2020). TEMD Guidelines for the Diagnosis, Treatment and Monitoring of Diabetes Mellitus and Its Complications. Available from http://www.temd.org.tr [Accessed 14 July 2023]

Tuzcu, Z., Orhan, C., Sahin, N., Juturu, V., & Sahin, K. (2017). Cinnamon polyphenol extract inhibits hyperlipidemia and ınflammation by modulation of transcription factors in high-fat diet-fed rats. *Oxidative Medicine and Cellular Longevity*, *2017*, 1583098. doi: 10.1155/2017/1583098.

Veeramani, C., Alsaif, M. A., & Al-Numair, K. S. (2018). Herbacetin, a flaxseed flavonoid, ameliorates high percent dietary fat induced insulin resistance and lipid accumulation through the regulation of hepatic lipid metabolizing and lipid-regulating enzymes. *Chemico-Biological Interactions*, *288*, 49–56. doi: 10.1016/j.cbi.2018.04.009.

Vijayakumar, K., Prasanna, B., Rengarajan, R. L., Rathinam, A., Velayuthaprabhu, S., & Vijaya Anand, A. (2023). Anti-diabetic and hypolipidemic effects of *Cinnamon cassia* bark extracts: an in vitro, in vivo, and in silico approach. *Archives of Physiology and Biochemistry*, *129*, 338–348. doi: 10.1080/13813455.2020.1822415.

Virgen-Carrillo, C. A., Martínez Moreno, A. G., & Valdés Miramontes, E. H. (2020). Potential hypoglycemic effect of pomegranate juice and its mechanism of action: A systematic review. *Journal of Medicinal Food*, *23*, 1–11. doi: 10.1089/jmf.2019.0069.

Visuvanathan, T., Than, L. T. L., Stanslas, J., Chew, S. Y., & Vellasamy, S. (2022). Revisiting *Trigonella foenum-graecum* L.: Pharmacology and therapeutic potentialities. *Plants*, *11*, 1450. doi: 10.3390/plants11111450.

Wang, H., Teng, Y., Li, S., Li, Y., Li, H., Jiao, L., & Wu, W. (2021). UHPLC-MS-based serum and urine metabolomics reveals the anti-diabetic mechanism of ginsenoside Re in type 2 diabetic rats. *Molecules*, *26*, 6657. doi: 10.3390/molecules26216657.

Wang, Q., Wu, X., Shi, F., & Liu, Y. (2019). Comparison of antidiabetic effects of saponins and polysaccharides from Momordica charantia L. in STZ-induced type 2 diabetic mice. *Biomedicine & Pharmacotherapy*, *109*, 744–750. doi: 10.1016/j.biopha.2018.09.098.

Xia, H., Shi, X., Zhou, B., Sui, J., Yang, C., Liu, H.,… Sun, G. (2022). Milled flaxseed-added diets ameliorated hepatic inflammation by reducing gene expression of TLR4/NF-κB pathway and altered gut microbiota in STZ-induced type 1 diabetic mice. *Food Science and Human Wellness*, *11*, 32–40. doi: 10.1016/j.fshw.2021.07.004.

Xu, J., Liu, H., Su, G., Ding, M., Wang, W., Lu, J.,… Zhao, Y. (2021). Purification of ginseng rare sapogenins 25-OH-PPT and its hypoglycemic, antiinflammatory and lipid-lowering mechanisms. *Journal of Ginseng Research*, *45*, 86–97. doi: 10.1016/j.jgr.2019.11.002.

Yanakiev, S. (2020). Effects of cinnamon (*Cinnamomum* spp.) in dentistry: A review. *Molecules*, *25*, 4184. doi: 10.3390/molecules25184184.

Yang, C., Xu, Z., Huang, Q., Wang, X., Huang, F., & Deng, Q. (2023). Targeted microbiome metabolomics reveals flaxseed oil supplementation regulated the gut microbiota and farnesoid X receptor pathway in high-fat diet mice. *Food Science and Human Wellness*, *12*, 2324–2335. doi: 10.1016/j.fshw.2023.03.036.

Yang, S. J., Choi, J. M., Park, S. E., Rhee, E. J., Lee, W. Y., Oh, K. W.,… Park, C. Y. (2015). Preventive effects of bitter melon (*Momordica charantia*) against insulin resistance and diabetes are associated with the inhibition of NF-κB and JNK pathways in high-fat-fed OLETF rats. *The Journal of Nutritional Biochemistry*, *26*, 234–240. doi: 10.1016/j.jnutbio.2014.10.010.

Yang, X. Y., Zhong, D. Y., Wang, G. L., Zhang, R. G., & Zhang, Y. L. (2021). Effect of walnut meal peptides on hyperlipidemia and hepatic lipid metabolism in rats fed a high-fat diet. *Nutrients*, *13*, 1410. doi: 10.3390/nu13051410.

Yung, J. H. M., & Giacca, A. (2020). Role of c-Jun N-terminal Kinase (JNK) in obesity and type 2 diabetes. *Cells*, *9*, 706. https://doi.org/10.3390/cells9030706.

Zhang, C., Fan, L., Fan, S., Wang, J., Luo, T., Tang, Y.,… Yu, L. (2019). *Cinnamomum cassia* Presl: A review of its traditional uses, phytochemistry, pharmacology and toxicology. *Molecules*, *24*, 3473. doi: 10.3390/molecules24193473.

Zhang, M., Zhao, R., Wang, D., Wang, L., Zhang, Q., Wei, S.,…Wu, C. (2021). Ginger (*Zingiber officinale* Rosc.) and its bioactive components are potential resources for health beneficial agents. *Phytotherapy Research*, *35*, 711–742. doi: 10.1002/ptr.6858.

Zhang, Y., Cao, Y., Chen, J., Qin, H., & Yang, L. (2019). A New possible mechanism by which punicalagin protects against liver ınjury ınduced by type 2 diabetes mellitus: Upregulation of autophagy via the Akt/FoxO3a signaling pathway. *Journal of Agricultural and Food Chemistry*, *67*, 13948–13959. doi: 10.1021/acs.jafc.9b05910.

Zhao, Y., & Chen, Z. Y. (2018). Roles of spicy foods and their bioactive compounds in management of hypercholesterolemia. *Journal of Agricultural and Food Chemistry*, *66*, 8662–8671. doi: 10.1021/acs.jafc.8b02975.

Zhong, Y., Xiao, Y., Gao, J., Zheng, Z., Zhang, Z., Yao, L., & Li, D. (2022). Curcumin improves insulin sensitivity in high-fat diet-fed mice through gut microbiota. *Nutrition & Metabolism*, *19*, 76. doi: 10.1186/s12986-022-00712-1.

Zhu, L., Sha, L., Li, K., Wang, Z., Wang, T., Li, Y.,… Wang, H. (2020). Dietary flaxseed oil rich in omega-3 suppresses severity of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in rats. *Lipids in Health and Disease*, *19*, 20. doi: 10.1186/s12944-019-1167-4.