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Review

Assessment of the synergistic effects of bioactive molecules and antidiabetic drugs: an analytical review

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Abstract

Type 2 diabetes is a chronic metabolic disorder characterized primarily by impaired glucose regulation. While oral antidiabetic drugs (OADs) are widely used, their effectiveness is sometimes limited and they may induce adverse effects. In recent years, medicinal plants have gained increasing interest either as complementary therapies to synthetic drugs or as alternative options in prediabetic conditions. This review provides an overview of the commonly used OADs in the local population, focusing on their documented side effects. It also synthesizes data from experimental studies (in vivo and in vitro) investigating the antidiabetic potential of selected medicinal plants. Furthermore, it compiles available evidence on the possible interactions—synergistic, antagonistic, or additive—between these plants and conventional antidiabetic agents. The review highlights the therapeutic prospects of such combinations while emphasizing the need for further mechanistic studies to better understand plant–drug interactions.

Keywords:

Type 2 diabetes, oral antidiabetic, phytotherapy, synergy.

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1. Introduction

Diabetes mellitus is one of the most common chronic metabolic disorders worldwide, typically characterized by hyperglycemia, resulting either from decreased insulin secretion or resistance to insulin. This condition gradually causes damage to various body systems, leading to multiple complications, especially in the eyes, heart, kidneys, blood vessels, and nerves [1]. There are two main types of diabetes: type 1 diabetes (T1D) and type 2 diabetes (T2D).

T1D, also known as insulin-dependent diabetes (IDD), is caused by insufficient insulin production by the beta cells in the islets of Langerhans in the pancreas. This type of diabetes generally develops in children and adolescents. On the other hand, T2D, or non-insulin-dependent diabetes (NIDD), is characterized by cellular resistance to insulin [2]. This latter form of diabetes represents a major public health concern globally, as it is mainly associated with lifestyle factors such as physical inactivity, smoking, obesity, and alcohol consumption. T2D contributes to increased cardiovascular morbidity and mortality. The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% of the adult population [3]. In 2015, it was estimated that 415 million adults were living with diabetes, and this figure is expected to reach 642 million by 2040 [4].

In Algeria, diabetes is also on the rise, affecting 14.4% of the population aged 18 to 69, which corresponds to around 4 million people in 2018 [5]. This increase in diabetes prevalence is accompanied by a rise in associated risk factors such as overweight and obesity. If diabetes is not properly managed, it can lead to severe complications such as blindness, kidney failure, amputations, and other outcomes that significantly affect quality of life [6].

Among all individuals with diabetes, type 2 diabetes accounts for approximately 90% of cases. This proportion is particularly high in developing countries and continues to grow each year [1].

Oral antidiabetic drugs exert hypoglycemic effects throught various mechanisms but are often associated with side effects, underscoring the need for more effective and cost-effecient management strategies. The global use of complementary and alternative medicines (CAM) for managing diseases like diabetes has increased rapidly over the past decade. It has been reported that up to 72.8% of individuals with diabetes have used herbal medicines, dietary supplements, or other CAM therapies [7]. Additionally, research indicates that most people who use CAM therapies do so in combination with, rather than as a replacement for, conventional medicine [8]. A large number of medicinal plants are believed to have antidiabetic properties and have been used to manage diabetes [9]. However, the concurrent use of antidiabetic medicinal plants and pharmaceutical drugs raises concerns about safety. Unlike conventional drugs, whose components are well-defined and mechanisms of action well understood, medicinal plants contain a vast array of bioactive compounds. The interaction between these compounds and drugs, as well as their effects when taken simultaneously, is still poorly understood, making it challenging to predict potential interactions.

While many studies have highlighted the potentially harmful effects of interactions between medicinal plants and drugs, there are also in vivo and preclinical studies showing that certain plant components may enhance or facilitate the action of antidiabetic agents. These molecules target crucial therapeutic pathways, such as blood glucose regulation via AMPK activation, inhibition of carbohydrate enzymes, or modulation of insulin sensitivity.

The positive interactions between these natural compounds and antidiabetic drugs can lead to increased efficacy through additive or synergistic effects. Molecular docking studies have shown that these compounds can bind to essential therapeutic targets, such as AMP-activated protein kinase (AMPK), thereby providing a deeper understanding of interactions at a precise molecular level [10].

This review aims to provide an overview of studies addressing the interactions between antidiabetic plants and oral antidiabetic drugs (OADs), identifying both the positive and negative aspects of these interactions while incorporating recent advances in molecular docking to shed light on the underlying mechanisms.

2. Profile of antidiabetic drugs

The profile of synthetic oral antidiabetic drugs (OADs) includes various classes, each with unique mechanisms of action, such as stimulating insulin release and enhancing peripheral glucose absorption [1]. These medications are primarily used in managing type 2 diabetes (T2D). Recent studies highlight the prevalence and clinical implications of specific drug classes, reflecting the complex management required due to significant side effects [11] . Despite considerable progress in diabetes treatment over recent years, the outcomes remain suboptimal, with numerous adverse and even toxic effects associated with the use of these pharmaceutical agents. Table 01 below summarizes the main antidiabetic agents and their specific therapeutic targets, aiming to improve treatment efficacy while minimizing side effects. Additionally, molecular docking studies have deepened our understanding of the interactions between OADs' active compounds and their targets, opening promising avenues for developing new therapeutic agents derived from medicinal plants.

2.1. Biguanides

Biguanides, derived from guanidine extracted from Galega officinalis, have been used for centuries for their antidiabetic properties [12]. Among them, metformin (1,1-dimethylbiguanide) has become the gold standard treatment for type 2 diabetes due to its efficacy and relative safety [13 , 14]. Its mechanism of action involves multiple pathways. Metformin enters cells via organic cation transporters (hOCT1) and, in high concentrations in the intestine, inhibits complex I of the mitochondrial respiratory chain. This inhibition enhances anaerobic glycolysis, lactate production, and glucose utilization [15]. In the liver, metformin reduces gluconeogenesis and glycogenolysis by inhibiting AMPK and glycerol-3-phosphate dehydrogenase. It also alters hepatic redox states, thereby lowering ATP levels and slowing the conversion of lactate into glucose [16]. In peripheral tissues, it enhances glucose utilization, improves insulin sensitivity, and reduces intestinal glucose absorption [17].

Beyond its primary role in diabetes management, metformin has diverse therapeutic applications. It lowers the risk of cardiovascular complications, helps manage metabolic diseases like non-alcoholic fatty liver disease (NAFLD) and obesity, and has a neutral or favorable effect on body weight [18]. It is also being explored for neurodegenerative diseases, such as Alzheimer's and Parkinson's, where it modulates metabolic pathways and slows aging processes [19]. In oncology, innovative derivatives like AUTAC-Biguanides and Biguanide-PROTACs target mitochondria for their antiproliferative properties [20]. However, the use of metformin can be associated with adverse effects, including gastrointestinal disturbances, vitamin B12 deficiency, and, rarely, lactic acidosis, particularly in patients with renal impairment [21]. These characteristics make metformin a versatile drug, with impacts extending far beyond the simple regulation of blood glucose.

2.2. Glitazones

Thiazolidinediones (TZDs), also known as glitazones, are agonists of the nuclear receptors PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), which are primarily expressed in adipose tissue, muscles, the liver, and the brain. These receptors, activated by fatty acids, regulate the expression of genes involved in glucose and lipid metabolism, translating nutritional signals into metabolic responses. Glitazones improve insulin sensitivity, lower blood glucose levels, and exert beneficial effects on lipid metabolism and vascular endothelium [21]. In adipose tissue, the stimulation of PPARγ receptors promotes

adipocyte differentiation and the secretion of adiponectin, a hormone that enhances fatty acid oxidation and reduces hepatic glucose production, thereby mitigating insulin resistance. Additionally, glitazones decrease the release of pro-inflammatory signals, such as TNFα, leptin, and free fatty acids, which are often associated with insulin resistance [22]. In the liver, they suppress gluconeogenesis, reducing fasting blood glucose levels. Meanwhile, by stimulating glucose uptake in muscle tissue, they lower postprandial blood glucose levels [23]. However, the use of pioglitazone, a representative of this class, is associated with side effects. The most common include visual disturbances (notably at the beginning of treatment due to glycemic fluctuations), edema (especially macular edema), weight gain, upper respiratory tract infections, decreased bone density, and hypoesthesia (reduced sensory sensitivity) [24]. These side effects sometimes limit the long-term use of these drugs, although their metabolic benefits remain undeniable.

2.3. Other Medications

Drugs that reduce glucose absorption or promote its elimination play a significant role in managing diabetes, particularly type 2 diabetes. These treatments aim to lower blood glucose levels by targeting different stages of the digestive and renal processes.

2.3.1. α-Glucosidase Inhibitors

Acarbose, a bacterial oligosaccharide that inhibits alpha-glucosidase, was the first inhibitor introduced in 1990 for the treatment of type 2 diabetes. Isolated from Actinoplanas utahensis, it reduces postprandial blood glucose and enhances insulin secretion [25, 26]. Other inhibitors, such as voglibose, a synthetic derivative of valiolamine produced by Streptomyces hygroscopicus, delay the digestion of complex carbohydrates by blocking enzymes such as maltase and sucrase [27]. These inhibitors slow the conversion of carbohydrates into glucose in the small intestine, reducing glucose absorption, thereby lowering postprandial blood glucose and, over time, HbA1c levels, especially in cases of postprandial hyperglycemia [28]. Acarbose has also demonstrated anticancer activity by depriving tumor cells of essential glucose for their survival, thereby reducing tumor metabolism and inducing oxidative stress and apoptosis, particularly in breast cancer [29]. In metastatic renal carcinoma, it enhances immune responses through CD8+ T cells and boosts treatments such as anti-PD-1 immunotherapy, limiting tumor growth and metastases [28].

However, these drugs are associated with frequent gastrointestinal side effects (flatulence, diarrhea, abdominal pain) due to the fermentation of undigested carbohydrates. They may also cause hepatobiliary disorders (elevated liver enzymes, jaundice) and rare skin reactions (rashes, urticaria) [28].

2.3.2. Glucagon-like peptide-1 (GLP-1)

GLP-1 is a peptide hormone composed of 30 amino acids, produced in the epithelial cells of the intestine. Its release is triggered by food intake, but GLP-1 is rapidly metabolized and inactivated by the enzyme dipeptidyl peptidase IV [30]. GLP-1 acts through a beta receptor; receptor activation by GLP-1 stimulates insulin

Table1: Overview of oral Antidiabetic Drugs: pharmacological targets and clinical implications

Therapeutic Agent	Therapeutic Target	Effect	Side Effects	Other Therapeutic Applications	references
Metformin	Complex I of mitochondrial respiratory chain, AMPK.	-Increases insulin sensitivity in muscle and liver. - Reduces hepatic gluconeogenesis. -Increases fatty acid oxidation.	- Risk of lactic acidosis in patients with renal insufficiency or in the event of overdose. -Accumulation of lactate. -Gastrointestinal disturbances, vitamin B12 deficiency. - haemolytic anaemia increases creatinine and AST levels	Cancer treatment AUTAC-Biguanide and Biguanide-PROTACs these new hybrid compounds are designed to target mitochondria.superior and selective antiproliferative properties. -Neurodegenerative diseases such as Alzheimer's disease can use biguanides, in particular cycloguanil, which inhibits the NMDA receptor in hippocampal neurons. -Non-alcoholic Fatty Liver Disease (NAFLD) -Obesity Management.	[53] [54] [55] [56] [57] [58]
Glitazone	PPARγ Receptor	Improves insulin sensitivity, reduces hepatic gluconeogenesis, enhances lipid metabolism	-Weight gain, edema, risk of macular edema, reduced bone density -the risk of cardiovascular	-	[21] [22]
Acrabose	α glucosidase	Reduces postprandial blood glucose by delaying carbohydrate digestion -Augmente la sécrétion d'insuline. -Diminuer le taux HbAc1.	Gastrointestinal discomfort (flatulence, diarrhea), hepatobiliary issues, rare skin reactions	Anticancer activity (e.g., breast cancer, metastatic renal carcinoma) -Reinforcing PD-1 and Rapamycin immunotherapy treatment	[25] [27] [28] [29]
GLP-1R Agonists	GLP-1 Receptor	Enhances glucose-dependent insulin secretion, inhibits glucagon secretion, reduces appetite, slows gastric emptying	Nausea, vomiting, diarrhea, risk of pancreatitis	-	[30]

secretion, enhances insulin gene transcription, increases insulin biosynthesis, promotes cell proliferation and survival, and reduces cell death. Additionally, GLP-1 inhibits glucagon secretion [31]. The side effects include nausea, vomiting, and diarrhea, but they are generally mild and transient [30].

2. Plants used in the treatment of diabetes

Traditional remedies worldwide have always supported the use of medicinal plants in the treatment of human diseases. Alternative medicine attracts researchers to explore the biological activity of numerous potent bioactive molecules with hypoglycemic properties. In this section, we have selected only two studies for each chosen plant, whether in vivo or in vitro, from the most recent research on medicinal plants used to treat type 2 diabetes (Table 02). These studies evaluate the therapeutic strategies employed against this metabolic disease, the doses used, and the results obtained, as well as the phytochemical characteristics of the plant extracts.

Nigella sativa (Ranunculaceae family) seeds are rich in essential nutrients, vitamins, minerals, and phenolic compounds, which contribute to their therapeutic effects [32]. The main components of *N. sativa* are thymoquinone and p-cymene, which are considered the most active compounds in several studies. In (Table 02), we highlight two recent studies on the activity of N. sativa essential oil in diabetic rats. These studies demonstrated the positive pharmacological effects of *N. sativa* seeds, including antioxidant properties that improve glucose tolerance, reduce hepatic gluconeogenesis, increase insulin levels, and regulate lipid profiles and hepatorenal functions.

Additionally, markers such as PDX-1, NEUROG-3, INS-1, and INS-2 showed positive regulation, suggesting pancreatic tissue regeneration in diabetic rats. Based on this context, thymoquinone exhibits multiple mechanisms contributing to its antidiabetic effects, such as insulin-mimicking properties by influencing key enzymes like AMP-activated protein kinase (AMPK), insulin secretion stimulation and impact on carbohydrate digestion. According to Woo and *al* [33], thymoquinone has shown an ability to enhance PPAR-γ activity, suggesting it might act as a ligand for this receptor. This hypothesis was confirmed by an *in-silico* study by Megantara et *al*. [34], which revealed that thymoquinone acts as a PPAR-γ agonist, interacting similarly to pioglitazone. Moreover, due to the potentially superior safety profile of natural products compared to synthetic compounds particularly in avoiding side effects like cardiotoxicity associated with pioglitazone and/or the risk of bladder cancer in diabetic patients treated with pioglitazone, thymoquinone could represent a promising alternative [35].

Sesamum indicum, belonging to the Pedaliaceae family, has seeds rich in vitamin A, B vitamins (B1, B2, B3, B6, B9) [35], vitamin E [36], and has long been used as a nutritional product. It is known for rejuvenating the liver and kidneys, nourishing the blood, and alleviating intestinal dryness [37]. Sesame seeds also contain phenolic compounds and bioactive lignans, such as sesamin, episesamin, sesamol, and sesamolin, making sesame a unique source of health benefits [38]. Previous studies have shown that sesamin and sesamolin are the most important components contributing to the therapeutic effects of this plant [39]. Two recent studies on sesame seeds demonstrated a significant reduction in blood glucose, glycated hemoglobin (HbA1c), and an improvement in lipid profiles, along with enhanced antioxidant status in diabetic rats. These results suggest that sesame may increase insulin sensitivity and/or stimulate hepatic glycogen synthesis [40]. Additionally, an *In vitro* study revealed that sesame seeds inhibit alpha-amylase and alpha-glucosidase enzymes, resulting in reduced intestinal glucose absorption and better blood glucose management [40]. Furthermore, another study indicated that sesamin retains its activity at high temperatures, showing good thermal stability of its antioxidant properties [41].

Trigonella foenum-graecum (Fenugreek), an annual plant from the legume family [42], has been traditionally used to treat various diseases, including diabetes [43]. Its seeds and leaves contain several compounds with significant hypoglycemic effects. These isolated compounds activate AMPK and GLP-1, inhibit DPP-IV, and prevent oxidative damage. Among them, trigonelline (TRG), a major bioactive

compound in fenugreek seeds, plays a crucial role [43]. Studies by Jyothi, D. et al [44] and Yella, S. and al [44] demonstrated that ethanolic extracts of fenugreek improved blood glucose levels, lipid profiles, and promoted weight loss in diabetic rats. However, an elevation in AST and ALT levels was observed in rats treated with the extract for 21 days at a dose of 100 mg/kg. Another study by Afifi, N and *al* [46] explored the effect of trigonelline (TRG) in mitigating hepatic complications and molecular alterations associated with insulin resistance induced by a high-fat and fructose-rich diet in rats. The results showed that oral TRG treatment significantly reduced HOMA-IR ("homeostatic model assessment-IR"), hepatic lipids, oxidative stress biomarkers, and inflammatory cytokines. TRG also improved histopathological changes, DNA cytometry alterations, and molecular changes induced by the high-fat and fructose-rich diet (HFFR). Studies in rodent tissues further indicated that TRG influences multiple signaling and metabolic pathways, such as mitochondrial oxidative phosphorylation. Serum trigonelline levels were linked to NAD+ levels in skeletal muscle [47]. These findings suggest that trigonelline is a novel metabolite with potential therapeutic applications in addressing age-related mitochondrial dysfunction, mitigating hepatic complications associated with insulin resistance, and serving as a biomarker for evaluating NAD+ levels.

Aloe barbadensis (Aloe vera), a tropical plant from the Asphodelaceae family (formerly Liliaceae), thrives in parts of Africa and the islands of the Indian Ocean. It is renowned for its therapeutic properties, including anticancer activity, and anti-inflammatory, antiviral, antioxidant, and antidiabetic effects [48], attributed to phenolic compounds such as acemannan. In traditional medicine, Aloe vera is used for various conditions like fungal infections, tuberculosis, and gastric ulcers. A Canadian study Dick WR and al [49] evaluated the efficacy of Aloe vera consumption in reducing fasting blood glucose and HbA1c levels. The results indicated that Aloe vera significantly reduced blood glucose levels in individuals with glucose levels exceeding 2 g/L, suggesting its role in stimulating insulin release. Moreover, Omer et *al* [50]. Demonstrated that acemannan exhibits significant antidiabetic properties in STZ-induced diabetic rats. The study reported reductions in blood glucose levels and HbA1c, crucial markers for diabetes management. Acemannan was also shown to decrease inflammatory cytokine levels and caspase-3 activity, an enzyme involved in cell apoptosis [50]. These findings underscore Aloe vera's potential as an adjunctive natural treatment for diabetes, contributing to better glycemic control and inflammation management.

Zingiber officinale (Ginger), an essential medicinal plant in traditional Chinese medicine, is recognized for its diverse therapeutic properties, including anti-arthritic, anti-migraine, antithrombotic, anti-inflammatory, hypolipidemic, and anti-nausea effects. The bioactive compounds in ginger, primarily gingerols, have demonstrated the ability to inhibit the biosynthesis of prostaglandins and leukotrienes [51] and suppress angiogenesis [52]. Additionally, some ginger constituents exhibit serotonin receptor-blocking activity, which may contribute to its pharmacological effects [59]. Studies (summarized in Table 2) conducted on diabetic rats have revealed that ginger can significantly reduce blood glucose levels, improve lipid profiles, and decrease proteinuria. These findings suggest that the bioactive components of ginger may facilitate pancreatic β-cell regeneration and insulin production [52]. Furthermore, ginger has been shown to inhibit hepatic glucose production, promote glycogen synthesis in the liver, enhance peripheral glucose uptake, and reduce insulin resistance. Its potent antioxidant properties further support its role in mitigating oxidative stress associated with diabetes. These promising results underscore the potential of ginger as a natural adjunct therapy for improving glycemic control and overall metabolic health in diabetic patients.

Thymus vulgaris (Thyme), a medicinal plant belonging to the *Lamiaceae* family, is renowned for its richness in bioactive phenolic compounds, including steroids, terpenoids, flavonoids, alkaloids, tannins, and saponins. The essential oil (EO) of thyme is particularly abundant in thymol and carvacrol, its primary constituents [60]. Moreover, thyme is an excellent source of vitamins such as vitamin A, vitamin C, and vitamin B6, which possess significant pharmacological properties. The leaves of *Thymus vulgaris* are also rich in essential minerals, including potassium, calcium, iron, manganese, magnesium, and selenium [61]. Traditionally, thyme has been used to treat a variety of ailments, such as gastrointestinal disorders and respiratory conditions including bronchitis, asthma, and cystic fibrosis. Additionally, it is recognized for its potential in managing hypercholesterolemia, menstrual disorders, hypertension, and cardiovascular diseases

[62; 63]. Table 02 summarizes findings from *In vitro* studies evaluating the antihyperglycemic activity of three types of thyme extracts: hydromethanolic extract, aqueous extract, and essential oil. Results indicate that the hydromethanolic extract exhibits significantly higher inhibitory activity against α-glucosidase and α-amylase enzymes compared to the aqueous extract and essential oil. This enhanced activity is attributed to the high phenolic content of the hydromethanolic extract. In contrast, the essential oil, despite its bioactivity, demonstrates lower efficacy due to its predominantly lipophilic composition.

Herba-alba (Artemisia), commonly known as white wormwood and a member of the *Asteraceae* family, is rich in polyphenols, particularly dicaffeoylquinic acid. This plant is widely utilized in traditional medicine, especially in Algeria, to treat various diseases, with a notable focus on diabetes mellitus. Its use in diabetes treatment is among the most frequently documented in the scientific literature [64, 65, 66, 67]. Two studies have reported the hypoglycemic effects of aqueous and ethanolic extracts of Artemisia herba-alba Asso. These extracts were administered at doses of 0.39 g/kg and 0.4 g/kg of body weight, respectively, in alloxan-induced diabetic rats. Additionally, Yujie Huang et *al* [68] demonstrated that dicaffeoylquinic acid, the major bioactive compound in Artemisia herba-alba, effectively improved glucose-lipid metabolism disorders and reduced inflammation in diabetic mice when administered at a dose of 200 mg/kg. Interestingly, this dose proved more beneficial than a higher dose of 400 mg/kg. The beneficial effects are attributed to the regulation of gut microbiota, increased levels of conjugated bile acids, and the inactivation of the enterohepatic FXR-FGF15 signaling axis. These findings highlight the therapeutic potential of Artemisia herba-alba in diabetes management, particularly through its action on metabolic and inflammatory pathways.

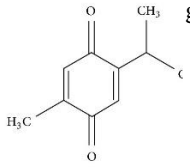
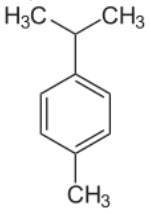
Eucalyptus, particularly the species *Eucalyptus camaldulensis* and *Eucalyptus globulus*, is widely recognized in traditional medicine for its numerous therapeutic benefits, especially in managing metabolic disorders such as diabetes. These species are rich in bioactive compounds, notably gallic acid and chlorogenic acid, which play a pivotal role in their antidiabetic activity [69]. These molecules exhibit strong antioxidant properties, inhibit digestive enzymes like alpha-amylase, and enhance insulin sensitivity, thereby aiding in blood glucose regulation. A recent study by Akinmoladun et *al* [70] evaluated the effects of a hydroethanolic extract of Eucalyptus at a dose of 400 mg/kg in diabetic animal models. The results demonstrated a significant reduction in blood glucose levels, improved hematological parameters, enhanced antioxidant activity, and a favorable weight loss. Furthermore, Uadia et *al* [71] reported that a diet enriched with 10% Eucalyptus camaldulensis leaves over 14 days led to notable improvements in lipid profiles, as well as kidney and liver function. These findings underscore the therapeutic potential of Eucalyptus extracts in treating metabolic disorders associated with diabetes, highlighting their impact on both glycemic control and overall metabolic health.

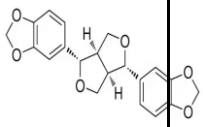
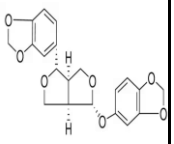
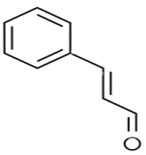
Citrus aurantium, also known as bitter orange and belonging to the Rutaceae family, is a plant with numerous therapeutic properties [72]. Its juice is recognized for its antiseptic, anti-bilious, and hemostatic effects. Traditionally, it has been used to treat gastrointestinal disorders such as intestinal ulcers, diarrhea, and constipation [73]. Additionally, *Citrus aurantium* has shown significant potential in reducing blood glucose levels in diabetic patients, regulating lipid profiles, improving cardiac circulation, purifying the blood, and managing hepatic and biliary disorders. These effects are attributed to its bioactive compounds, notably hesperetin and naringenin, which contribute to its antidiabetic and antihypercholesterolemic properties [74]. [75] demonstrated the antidiabetic properties of an aqueous extract of Citrus aurantium administered at a dose of 0.5 ml in C57BL/KsBom-db (db/db) mice over 45 days. The treatment resulted in body weight loss, normoglycemia, increased plasma triglycerides (indicating enhanced fatty acid mobilization), and improved insulin sensitivity, suggesting a favorable metabolic regulation and enhanced β-cell responsiveness. Similarly, Sharma et *al* [76] investigated the effects of an alcoholic extract at doses of 300 and 500 mg/kg/day over 21 days. The extract significantly reduced blood glucose, total cholesterol, triglycerides, and LDL levels while increasing HDL levels, with more pronounced effects at the higher dose. These findings highlight the dose-dependent efficacy of *Citrus aurantium* extracts in improving glycemic and lipid parameters, supporting its potential role in enhancing insulin sensitivity and stimulating

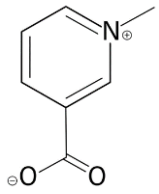
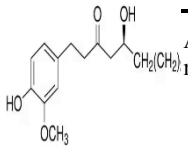
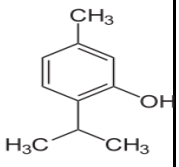
β-cell insulin secretion. Collectively, these results position *Citrus aurantium* as a promising candidate for the management of metabolic disorders such as diabetes and dyslipidemia.

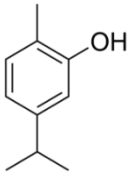
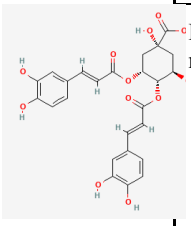
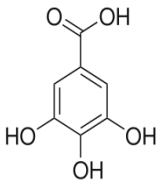
Cinnamomum cassia possesses potential therapeutic properties and has been used since ancient times in traditional medicine. Numerous pharmacological and clinical effects have been observed throughout its usage. Cinnamaldehyde, one of its most active compounds, exhibits significant antidiabetic properties. A study by Cordero-Pérez et *al* [81] on the antidiabetic activity of cinnamon oil administered for five days demonstrated normalized blood glucose levels in diabetic rats. Additionally, Vijayakumar et *al* [84]. investigated the effects of alcoholic extracts and found that this treatment induces hypoglycemia, enhances the activity of tricarboxylic acid (TCA) cycle enzymes, and improves liver and kidney profiles while regenerating beta cells. Other studies on cinnamaldehyde show that treatment with cinnamaldehyde for two months increases glycogen content in skeletal muscle by restoring GLUT4 levels in STZ-induced rats [82]. Furthermore, Juan et *al* [83]. revealed that cinnamaldehyde treatment increases GLUT4 mRNA expression by enhancing phospho-Akt (Thr308) expression in the skeletal muscle of C57BLKS db/db mice [83]. These findings suggest that cinnamaldehyde improves glucose homeostasis, optimizes lipid profiles, and modulates autophagy in various tissues [84], making it a promising adjunctive treatment for diabetes management [85].

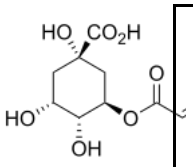
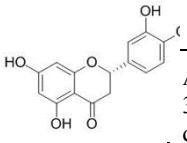
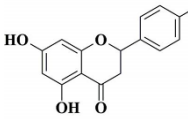
Table 2: Medicinal plants and their extracts in diabetes management

Plant	Molecule	Method	Results	References
Black seed *Nigella sativa*	Thymoquinone ($C_{10}H_{12}O_2$) 	Oil obtained by cold pressing. Dose: 4 mg/kg/day via oral gavage for 21 days.	↓ [Glycemia] and ↑ [Insulinemia], ↓ Oxidative stress, ↓ [LDL]; [TG]; [Cholesterol]. Upregulation of PDX-1, NEUROG-3, INS-1, and INS-2, indicating pancreatic regeneration..	[78]
	p-cymene $C_{10}H_{14}$ 	Oil: 5 ml/kg/day, Seeds: 150 mg/kg/day for 28 days.	Improvement in glucose levels, lipid profiles, hepatic, and renal functions. Histological preservation of islets of Langerhans compared to untreated diabetic rats.	[79]

Sesame *Sesamum indicum*	Sesamin $C_{20}H_{18}O_6$  Sesamoulin $C_{20}H_{18}O_7$ 	Doses: 20 and 60 mg/kg/day for 50 days (form not specified).	↓ [Glycemia], [HbA1c], [ALT], [AST], [Triglycerides]; ↑ [Insulin]. Enhanced antioxidant activities (SOD, CAT, GPx) in the liver.	[80]
		les doses de l'huile utilisées sont 350 et 700 mg/kg/j P.O., le SSO contient 150 -300 mg de ω- 6 FA	↓[Gly],[trig], [cholestérol] [LDL]et [VLDL], avec ↑ [HDL].	[81]
Cinnamon *Cinnamomum cassia*	Cinnamaldehyde C_9H_8O 	Oil dose: 300 mg/kg/day via gavage for 5 days.	↓ [Glycemia] after 4 hours of treatment. No significant changes in hepatic or renal function markers (ALT, AST, CREA, UREA), confirming safety at the tested dose.	[82]
		Ethanol extracts: 300, 400, and 500 mg/kg/day for 28 days.	↓ [Gly], ↑ TCA cycle enzyme activities. ↓ [AST], [ALT], [ALP], [UREA], [CREAT]. Improved pancreatic architecture and beta-cell regeneration.	[87]

Fenugreek *Trigonella Foenum-Graecum*	Trigonelline $C_7H_7NO_2$ 	Ethanol extract: 1 g/kg/day for 15 days.	↓ [Gly] and body weight loss in rats.	[45]
		Ethanol extract: 100 mg/kg/day for 21 days.	↓[Gly], [Chol], [LDL], [VLDL]; ↑ [HDL], but ↑ [AST], [ALT].	[46]
Aloe vera *Aloe barbadensis*	Acemannan $C_{66}H_{100}NO_{49}$	Gel extract: 400 mg/kg/day for 28 days.	↓[Gly], improved pancreatic and hepatorenal tissue architecture	[88]
		Aqueous extract: 100, 250, 500 mg/kg/day for 10 days.	↓ [Gly], improved hepatic tissue architecture.	[89]
Ginger *Zingiber officinale*	(6)-Gingerol $C_{17}H_{26}O_4$ 	Ethanol extracts: 100, 250, 500 mg/kg/day for 10 days.	↓[Gly]	[90]
		Aqueous extract: 500 mg/kg/day for 7 weeks.	↓ [Gly], ↓ [Chol], ↓ [Trig], ↓ [Urinary proteins] compared to diabetic rats.	[91]
Thyme *Thymus vulgaris*	Thymol $C_{10}H_{14}O$ 	Hydromethanolic and aqueous extracts.	**α-glucosidase**: IC50 = 0.51 ± 0.02 and 0.24 ± 0.09 mg/ml respectively, **α-amylase** : IC50 = 1.56 ± 0.09 mg/ml and ≥ 2.50mg/ml.	[92]

	Carvacrol $C_{10}H_{14}O$ 	Essential oil	α-glucosidase IC50= 4.66 ± 0.42 mg/ ml α-Amylase IC50=37.67 ± 0.12 mg/ ml.	[93]
Wormwood *Artemisia herba-alba*	Dicaffeoylquinic acid $C_{24}H_{25}O12$	Aqueous extract: 400 mg/kg/day for 30 days.	↓ [Glycemia], ↓ [UREA], ↓ [CREAT]. Improved renal tissue and reduced oxidative stress.	[94]
		Ethanolic extract: used is 390 mg/kg/d for 60 days	↓[Gly]	[95]
Eucalyptus *Eucalyptus camaldulensis and globulus*	Gallic acid 	Ethanol extract: 400 mg/kg/day for 21 days.	Weight loss, improved hematological parameters, ↑ antioxidant activity, ↓ [Gly].	[71]
	Chlorogenic acid	The rats were fed a diet containing 10% Eucalyptus camaldulensis leaves for 14 days.	↓[Gly], ↓[Urea], [Crea], [Chol], [LDL] with ↑[HDL], and ↓[AST], [ALT], [Albumin], [Total protein], as well as ↓[Total bilirubin] compared to diabetic rats. Enhances antioxidant activity (AOX).	[72]

				
Bitter orange *Citrus aurantium*	Hesperetin $C_{16}H_{14}O_6$ 	Aqueous extract: 0.5 ml/kg for 45 days.	Weight loss, normoglycemia, ↑insulin sensitivity. ↑ [Trig], indicating adipose tissue lipolysis.	[76]
		Alcoholic extract: used was 300 and 500 mg/kg/day for 21 days.	↓[Glucose], [Cholesterol], [Triglycerides], [LDL] and ↑[HDL] at a dose of 500 mg/kg, showing better effects compared to the 300 mg/kg dose.	[77]
	Naringenin $C_{15}H_{12}O_5$ 			

3. Optimizing antidiabetic treatments with bioactive compound synergies

The interaction between bioactive compounds and antidiabetic drugs (ADDs), as well as their impact on the body, has garnered increasing attention in recent research. These studies highlight their potential to enhance therapeutic strategies for diabetes management, particularly by amplifying hypoglycemic effects and mitigating complications associated with the disease. The synergistic use of bioactive compounds with antidiabetic drugs has shown promising results in improving glycemic control and reducing diabetes-related complications. In this review, we explore the synergistic effects of the 10 medicinal plants listed in Table 03 However, for three of these plants (Citrus aurantium,Eucalyptus, Thymus vulgaris), we did not find studies addressing their synergistic effects with ADDs. Therefore, we focused on three other plants (Oat grains, Pomegranate, Garlic) for which studies on their combination with antidiabetic drugs were available. Table 03 below summarizes the key findings from these studies.

In a study conducted by Sankar et *al* [95], the combination of *sesame oil* with glibenclamide in diabetic patients resulted in a significant reduction in fasting blood glucose (FBG) levels, glycated hemoglobin (HbA1c), total cholesterol, triglycerides, and LDL levels, while increasing HDL cholesterol. Furthermore, this combination enhanced antioxidant defenses, as evidenced by increased activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), as well as elevated levels of vitamin C, vitamin E, β-carotene, and reduced glutathione (GSH). We previously reported that sesame oil exhibited an additive effect with antihypertensive and antidiabetic drugs, simultaneously lowering blood pressure and blood glucose levels in hypertensive and diabetic-hypertensive patients [95]. This combined therapy demonstrated remarkable effects compared to groups treated with monotherapies. The exact mechanism by

which sesame oil improves HbA1c levels remains unclear but may be linked to its antioxidant properties. Additionally, previous studies have shown that diets rich in monounsaturated fatty acids (MUFA) improve glycemic control [96]. Sesame oil, which contains 40% MUFA, may have enhanced its antihyperglycemic effects. Moreover, sesame lignans such as sesamin and episesamin play a crucial role in modulating cholesterol metabolism by inhibiting its synthesis and absorption, as reported in spontaneously hypertensive rats prone to stroke [97]. These compounds, abundantly present in *sesame oil*, may explain the observed improvement in lipid profiles, further strengthening its role as a complementary therapeutic agent in managing diabetes and associated metabolic disorders.

Similarly, Bamosa et *al* [98] investigated the effects of combining *Nigella sativa* seeds with antidiabetic drugs (glibenclamide, metformin, and rosiglitazone) over three months in diabetic patients. A daily dose of 2 g of *Nigella sativa* seeds significantly reduced fasting blood glucose (FBG), 2-hour postprandial glucose (2h PG), and HbA1c without affecting body weight, while also improving insulin sensitivity as evidenced by decreased HOMA2-IR scores. Additionally, research on *Nigella sativa* has highlighted its antidiabetic mechanisms and molecular targets. The active compound thymoquinone plays a pivotal role by modulating key pathways such as AMPK activation, which enhances glucose uptake in peripheral tissues and promotes GLUT-4 translocation to the plasma membrane [99]. Studies have also demonstrated its inhibitory effects on α-amylase and α-glucosidase enzymes, thereby reducing postprandial glucose spikes. Furthermore, *Nigella sativa* reduces oxidative stress and inflammation, two major contributors to insulin resistance, through the upregulation of antioxidant enzymes and suppression of pro-inflammatory cytokines like TNF-α and IL-6 [100]. Interactions between *Nigella sativa* and antidiabetic drugs suggest potential synergistic benefits. For instance, its combination with metformin may amplify glucose-lowering effects by enhancing insulin sensitivity, while reducing metformin's gastrointestinal side effects. Similarly, when combined with glibenclamide, *Nigella sativa* may potentiate insulin secretion through pancreatic β-cell protection and regeneration [101]. These findings underline the therapeutic potential of *Nigella sativa* as an adjunct treatment for diabetes, warranting further investigation into its molecular mechanisms and clinical applications.

In another investigation, Bugudare et *al* [102] assessed the effects of combining *Cinnamomum cassia* with glibenclamide, metformin, or both in diabetic rats. Although no hypoglycemic synergy was observed with the combinations of HAECC + glibenclamide or metformin, HAECC alone at 666.66 mg/kg effectively normalized blood glucose levels, reduced serum cholesterol, and increased HDL levels, exhibiting effects comparable to glibenclamide and metformin. Recent findings by Jianqin Yu et *al* (2024) offer valuable insights into the antidiabetic mechanisms of *Cinnamomum cassia* (CC). Using advanced bioinformatics tools, including TCMSP, DisGeNET, and GeneCards, the study identified 11 active components and 66 potential antidiabetic targets of CC. Molecular docking analyses revealed a high binding affinity of CC's bioactive compounds to key targets such as PPAR-γ and IL-6 receptors. Furthermore, *In vivo* experiments conducted on a T2DM mouse model demonstrated that CC modulates PPAR-γ activity and suppresses IL-6-mediated inflammation, thereby enhancing its antidiabetic effects. These findings underscore the multi-pathway therapeutic potential of CC, highlighting its role in regulating glucose metabolism, improving lipid profiles, and controlling inflammation. Combined with the results of Bugudare et *al* [102], which demonstrated CC’s standalone efficacy in normalizing blood glucose and improving lipid profiles, this evidence strongly supports the integration of CC as a complementary approach in diabetes management.

Huseini et *al* [103] evaluated the effects of adding *Aloe vera* to glyburide or metformin in diabetic patients. The study demonstrated that both combinations significantly reduced fasting blood glucose (FBG), HbA1c, cholesterol, and LDL levels. Notably, no adverse effects were reported, highlighting the potential safety and efficacy of *Aloe vera* as an adjunct therapy. When combined with glyburide or metformin, *Aloe vera*

may amplify glucose-lowering effects through complementary pathways, potentially allowing for dose reductions of these medications. In addition to these clinical findings, *Aloe vera* has shown potential hepatoprotective effects in diabetes. Oral administration of *Aloe vera* extract improved hepatic function in streptozotocin (STZ)-induced diabetes [104]. The bioactive component anthraquinone has been reported to promote glucose tolerance and insulin sensitivity by upregulating insulin receptor substrates (IRS-1), activating phosphoinositide-3-kinase (PI3Ks), and modulating metabolic-related genes [105].

The study conducted by Haritha et *al* [106] evaluated the synergistic effect of combining *fenugreek seed* powder (1 g/kg) with glimepiride or insulin in male diabetic Sprague-Dawley rats over an 8-week period. The combination of *fenugreek* with antidiabetic drugs may enhance their respective mechanisms of action. The pharmacological properties of fenugreek are attributed to its various constituents. Dialyzed fenugreek seed extract has been reported to exert a hypoglycemic effect by stimulating the insulin signaling pathway, leading to the activation of tyrosine phosphorylation of insulin receptor B, insulin receptor substrate 1 (IRS1), and the p85 subunit of PI3-kinase in adipocytes and liver cells, which promotes GLUT4 translocation to the cell surface [86]. Fenugreek may also exert its therapeutic effects through its alkaloids by modulating insulin secretion [107]. Additionally, fenugreek treatment normalized the lipid profile due to its ability to stimulate insulin secretion [108].

The study conducted by Hsan L. Al-Omari et *al* [109] examined the effects of combining crude *Ginger* extract (GCE) with glibenclamide and insulin in diabetic rats. The combination of GCE at 25 mg/kg with glibenclamide resulted in a more pronounced reduction in blood glucose levels compared to glibenclamide alone. Similarly, administering GCE at 50 mg/kg in combination with insulin produced a significant decrease in blood glucose levels, greater than that achieved with insulin alone. At a lower dose of 25 mg/kg, GCE appears to effectively complement the action of glibenclamide, which stimulates insulin secretion. This low-dose combination may enhance glucose uptake in peripheral tissues and optimize the effect of glibenclamide. At a dose of 50 mg/kg, GCE could excessively increase insulin sensitivity, leading to a more intense insulin action in peripheral tissues (muscles, liver, adipose tissues). Such a response might be disproportionate to the administered insulin dose (1.2 IU/kg), thereby increasing the risk of hypoglycemia. Furthermore, another study by Abhilash et *al* [110] reported that combining ginger with glibenclamide could not only enhance the hypoglycemic effect but also improve cellular defenses by increasing the activity of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD). These observations suggest that ginger, through its bioactive properties, exerts a synergistic effect with conventional antidiabetic agents like glibenclamide and insulin. Crude ginger extract could thus improve metabolic responses by increasing insulin sensitivity and promoting better glycemic control. However, the exact mechanism underlying these interactions remains unclear.

The study by Poonam et *al* [111] examined the effects of combining aqueous garlic extract *Allium sativum*, (ASE) with glibenclamide in diabetic rats. The experimental groups received ASE (500 mg/kg) in combination with either a low dose (0.25 mg/kg) or a high dose (0.5 mg/kg) of glibenclamide. The results revealed that both combinations significantly reduced blood glucose levels (54.68% with the low dose and 55.5% with the high dose) and were more effective in promoting weight gain compared to glibenclamide alone. The hypoglycemic effect of garlic is attributed to its sulfur-containing compounds, particularly di(2-propenyl) disulfide and 2-propenyl propyl disulfide, which are thought to stimulate insulin secretion either directly or indirectly. As highlighted by Poonam et *al* [111] , these compounds may also preserve endogenous insulin by preventing its inactivation through interactions with thiol-containing molecules such as cysteine, glutathione, and serum albumins. Additionally, garlic extract has been shown to improve glucose utilization, as it significantly lowered blood glucose levels in glucose-loaded rats. This effect may result from the restoration of delayed insulin responses or the inhibition of intestinal glucose absorption.

ASE exhibited a synergistic effect with glibenclamide, suggesting its potential to reduce the required dose of glibenclamide while enhancing therapeutic efficacy and minimizing side effects. Furthermore, garlic extract was reported to stimulate insulin production, promote pancreatic islet neogenesis, and restore glucose homeostasis in diabetic rats [112]. Histopathological improvements in the pancreas were also observed following garlic treatment, as reported by Masjedi et *al* [113]. These findings emphasize the therapeutic potential of garlic in diabetes management, particularly as an adjunct to conventional antidiabetic drugs like glibenclamide.

Chakraborty et *al* [114] evaluated the combined effects of *Pomegranate* juice (PJ) and tolbutamide (TOL) in diabetic rats. The treatment group received TOL (20 mg/kg) alongside PJ (3 mL/rat), leading to a significant reduction in blood glucose levels and an increase in serum insulin levels. However, this combination also caused an elevation in markers such as AST, ALT, ALP, CK-MB, CK-NAC, LDH, creatinine, and albumin, suggesting potential hepatic or metabolic impacts. The hypoglycemic effect of TOL is well-known and is primarily attributed to its ability to stimulate insulin secretion from pancreatic β-cells. Conversely, the antidiabetic effects of PJ are associated with its strong free radical scavenging properties, offering protection against oxidative stress induced by diabetes. Additionally, PJ has been shown to exhibit agonistic activity on receptor binding and nitric oxide production, further supporting glycemic control [115]. These findings indicate a potential synergistic interaction between TOL and PJ, wherein TOL lowers blood glucose by enhancing insulin secretion, while PJ improves insulin sensitivity and mitigates oxidative stress.

The combined effects of *Artemisia turanica* extract and metformin on diabetic rats were investigated by [116]. Diabetes was induced using streptozotocin (STZ), and the rats were treated with Artemisia turanica extract (70 mg/kg) and metformin (300 mg/kg) for four weeks, starting three days post-STZ injection. This combination therapy significantly reduced serum levels of AST and ALT, indicating improved liver function. It also decreased hepatic malondialdehyde (MDA), a marker of oxidative stress, while enhancing antioxidant defenses, as evidenced by increased total thiol content, superoxide dismutase (SOD) activity, and catalase activity in the liver. Furthermore, the coadministration of metformin and Artemisia turanica extract improved lipid profiles by significantly increasing serum HDL-C and reducing serum LDL-C. Serum cholesterol and triglycerides were lowered by 14% and 26%, respectively. These hypolipidemic effects are consistent with previous findings on other *Artemisia species*, such as *Artemisia vulgaris* and *Artemisia sieberi*, which have been attributed to their bioactive compounds [117]. Phytochemical analysis of Artemisia turanica extract identified tannins, flavonoids, terpenoids, and steroids, which are likely responsible for its lipid-lowering properties. The study highlights the therapeutic potential of *Artemisia turanica* as an adjunctive treatment alongside metformin for improving glycemic control, liver function, and lipid profiles, making it a promising candidate for managing diabetes and its complications.

All the medicinal plants listed in Table 3 contain bioactive compounds with significant therapeutic potential for type 2 diabetes. The main targets of antidiabetic metabolites derived from medicinal plants are illustrated in Figure 1. Bioactive metabolites from natural sources have demonstrated notable efficacy in targeting key pathways and enzymes involved in diabetes management. For instance, the formation of Advanced Glycation End-products (AGEs), a major factor in diabetic complications, can be mitigated by bioactive molecules that inhibit glycation or neutralize reactive carbonyl species [118]. Similarly, various plant-derived compounds, thereby reducing carbohydrate digestion and glucose absorption [119], effectively inhibit the enzymes α-glucosidase and α-amylase, critical in postprandial glucose regulation. Furthermore, aldose reductase, implicated in diabetic neuropathy and retinopathy, represents another significant target for bioactive metabolites, which prevent sorbitol accumulation in the polyol pathway [120]. Additionally, angiotensin-converting enzyme (ACE) inhibitors derived from natural products can

help manage diabetes-induced hypertension by modulating vascular tone. The regulation of Tyrosine Protein Phosphatase 1B (PTP1B), an inhibitor of insulin signaling, through natural inhibitors enhances insulin sensitivity and glucose uptake [121]. Bioactive compounds also exhibit antioxidant activity by reducing ROS formation and lipid peroxidation, protecting cells from oxidative stress-induced damage. Furthermore, metabolites that activate GLUT-4 translocation and AMP-activated protein kinase (AMPK) contribute to improved glucose uptake and metabolic homeostasis.

Table 3: Summarizing medicinal plants combined with antidiabetic drugs.

Plante + ADO	**Experimentation method**	**Type of study**	**Results**	**Reference**
sesame oil+ glibenclamide	Diabetic patients consume 35 g of sesame oil in a salad alongside glibenclamide.	Patients (32 male and 28 female)	⬇ Reduction in blood glucose levels and HbA1c. ⬇ Decrease in total cholesterol, triglycerides, and LDL levels. ⬆ Increase in HDL levels. **Antioxidant improvements:** Enhanced activities of SOD, GPx, and CAT enzymes, along with increased levels of vitamin C, vitamin E, β-carotene, and reduced glutathione (GSH).	[95]
Nigella sativa seeds+ + (glipenclamide, metformin, rosiglitazone)	Randomly divided into three dose groups, capsules containing *Nigella sativa* were orally administered at doses of 1, 2, and 3 g/day for three months to diabetic patients receiving standard treatment.	Patients 94 (43 males and 51 females)	The 2 g/day dose reduced FBG, 2h PG, and HbA1c without changes in body weight, and decreased HOMA2.	[98]
(Cinnamomum Cassia + Glibenclamide) (Cinnamomum Cassia + Metformin). (Cinnamomum Cassia + Glibenclamide + Metformin)	Groupe: Extrait hydroalcoolique de Cinnamomum Cassi (285.71 mg/kg + glibenclamide (1 mg/kg), Group : HAECC (666.66 mg/kg) + glibenclamide (1 mg/kg), Group 9: HAECC (285.71 mg/kg + metformin (300 mg/kg), Group : HAECC (666.66 mg/kg) + metformin (300 mg/kg), Group : HAECC (285.71 mg/kg + glibenclamide (1 mg/kg) and metformin (300 mg/kg), Group : HAECC (666.66 mg/kg) + glibenclamide (1 mg/kg) and metformin (300 mg/kg). HAECC: hydroalcoholic extract of *Cinnamomum cassia*	diabetic rats	**Hypoglycemic Synergy**: No hypoglycemic synergy observed with the combinations of HAECC + glibenclamide or metformin. **Comparison of Treatments**: -The effect of HAECC combined with glibenclamide or metformin is similar to that of the drugs alone. -Glibenclamide shows slightly greater effects compared to HAECC and metformin. **Effects of HAECC 666.66 mg/kg**: -Normalizes blood	[102]

			glucose levels. -Reduces serum cholesterol and increases HDL, with effects comparable to those of glibenclamide and metformin.	
Aloe vera+ glyburide Aloe vera+metformine	Type 2 diabetic patients undergoing daily treatment with -Two tablets of glyburide (5 mg each) and two tablets of metformin (500 mg each). -Group received aloe vera gel (one 300 mg capsule every 12 hours) for two months.	67 patients aged 40 to 60 years	⬇[Gly], [HbA1c], [TC]and [LDL] No adverse effects were reported.	[103]
Fenugreek + Glimepiride Fenugreek + Insulin	- 1 g/kg of fenugreek seed powder combined with Glimepiride was administered to diabetic rats for 8 weeks. -1 g/kg of fenugreek seed powder was administered with insulin treatment	Diabetic male Sprague-Dawley rats	Reduction in [Gly], [TC], [TG], and [LDL], accompanied by an increase in albumin levels, total protein, and body weight observed during the 8th week	[106]
Ginger crude extract (GCE)+ Glibenclamide Ginger crude extract (GCE)+ Insulin	-Glibenclamide (5 mg/kg, orally) was administered, followed by GCE (25, 50, or 100 mg/kg, orally). - An injection of insulin (1.2 IU/kg, intraperitoneally) was then given, followed by another dose of GCE (25, 50, or 100 mg/kg, orally).	Diabetic Male albino rats.	-At a dose of 25 mg/kg of GCE with glibenclamide: a greater reduction in blood glucose levels than with glibenclamide alone. -At a dose of 50 mg/kg of GCE with insulin: a greater reduction in blood glucose levels than with insulin alone.	[109]
Aqueous extract of garlic (*Allium sativum*) + Glibenclamide	Diabetic rats received ASE (500 mg/kg) combined with either a low dose (0.25 mg/kg) or a high dose (0.5 mg/kg) of glibenclamide.	Diabetic rats Wistar	-The combination of glibenclamide with ASE achieved significant blood glucose reductions (54.68% with low dose and 55.5% with high dose) and was more effective in promoting body weight gain.	[111]
Pomegranate juice (PJ)+ tolbutamide (TOL).	-Diabetic rats received the combination of TOL (20mg/kg) and PJ (3mL/rat).	Diabetic adult Wistar albino rats	The combination of TOL and PJ significantly reduced blood glucose levels, increased serum insulin, and elevated markers such as AST, ALT, ALP, CK-MB, CK-NAC, LDH, creatinine, and albumin.	[114]

Artemisia turanica + metformin	Artemisia turanica extract (70 mg/kg) and metformin (300 mg/kg) were orally administered to rats for 4 weeks, starting three days after STZ injection.	Diabetic male Wistar rats	⬇ AST ⬇ ALT ⬇ the liver tissue level of MDA ⬆Liver total thiol content ⬆Liver superoxide dismutase (SOD) ⬆Liver catalase activity	[116]
Oat grains + Metformin	Ten diabetic rats were treated daily with oat grains and metformin (200 mg/kg, orally).	Diabetic male Wistar rats	no significant difference the mean body weight ⬇ fasting blood glucose ⬇blood insulin level ⬇blood HOMA level ⬇ TG ,CT, and LDL ⬆ HDL ⬇ mean blood MDA level normal architecture of the pancreatic tissue The hepatocytes appeared more or less normal in shape (polygonal) and size	[132]

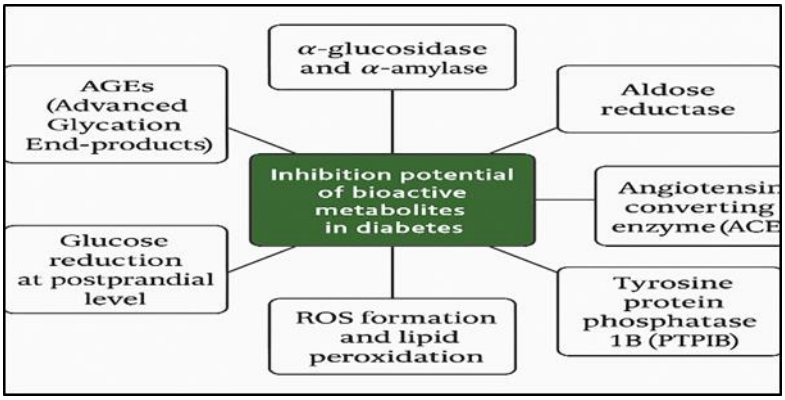


Figure 1: Bioactive Metabolites and Their Role in Diabetes Inhibition.

4. Interest of the MLSD technique in drug interactions

Multiple Ligand Simultaneous Docking (MLSD) is an advanced computational technique used to model and analyze the simultaneous interactions of multiple ligands within the same binding site of a target protein [122]. Unlike traditional docking, which examines the interactions of one ligand at a time, MLSD provides a comprehensive view of competitive, cooperative, and synergistic behaviors between ligands [123] [124]. By exploring competitive and cooperative binding effects, MLSD can identify therapeutic synergies or antagonisms that might remain undetected using conventional approaches [125][126]. This technique plays a crucial role in developing therapeutic combinations by optimizing efficacy while reducing required doses, thereby minimizing side effects [127][128]. Additionally, MLSD aids in predicting potential resistance mechanisms associated with drug combinations, guiding the rational design of multi-target therapeutic strategies. The insights obtained from MLSD are also valuable for understanding how ligands mutually influence their binding affinities, unveiling potential improvements in therapeutic efficacy when phytochemical compounds are combined with conventional treatments [125] [128]. This method accelerates drug discovery by simulating complex interactions in biological systems prior to experimental validation. It serves as an indispensable tool for polypharmacological approaches aimed at maximizing clinical benefits and providing safer, more effective
Treatments [125].

MLSD in Diabetes Research

In our research on the Multiple Ligand Simultaneous Docking (MLSD) technique, we found that this method is still relatively unknown and rarely utilized, with only three articles identified that discuss its application. Two of these studies explore the interaction of a single ligand with two distinct enzymatic targets. For instance, compound 4f, a derivative of 4-thiazolidinone, simultaneously inhibits aldose reductase (AR) and protein tyrosine phosphatase 1B (PTP1B), two key enzymes involved in diabetes complications [129]. Similarly, Gedunin, a natural molecule, demonstrates superior inhibition of
salivary and pancreatic α-amylase compared to acarbose, a reference drug for diabetes treatment [130]. The third study examines the combined effect of two drugs, aspirin (ASP) and pioglitazone (PGL), on the enzyme catalase. This combination significantly enhances catalase activity compared to PGL alone, with ASP increasing the stability and affinity of catalase for PGL, thereby amplifying its catalytic effect [131].
These findings highlight the potential of the MLSD technique to identify complex multi-target interactions, focusing primarily on the interactions between a ligand and multiple enzymatic targets. However, this method does not address specific interactions between phenolic molecules and drugs targeting a single or dual site. The limited use of this approach in the literature nonetheless underscores the need for further research to expand its application and better exploit its advantages in designing novel treatments for complex diseases such as diabetes.

5. General conclusion

The interaction between medicinal plants and antidiabetic pharmaceutical agents can significantly alter their pharmacokinetic and/or pharmacodynamic properties. These interactions are inherently complex due to the presence of multiple bioactive components in plants, which target various sites and exert therapeutic

effects by modulating or correcting specific anomalies. The beneficial effects of medicinal plants in diabetes management have been supported by numerous studies.

In this review, the co-administration of medicinal plants with synthetic drugs is summarized in Tables 2 and 3. While the predominant mechanisms of action of certain molecules or a combination of bioactive compounds have been presented—demonstrating their potential to mimic the actions of synthetic agents without inducing adverse effects—the precise mechanisms of action of these plants remain poorly understood and insufficiently established.

The application of Multiple Ligand Simultaneous Docking (MLSD) is still relatively unknown and underutilized in in silico studies. However, employing this technique is critical to investigating the interactions between natural and synthetic molecules targeting the same site. MLSD can provide valuable insights and hypotheses before progressing to in vitro and in vivo testing, enabling a deeper understanding of the synergistic or competitive dynamics between these compounds.

Ultimately, integrating MLSD into diabetes research could pave the way for more rational design of plant-drug combinations and enhance therapeutic precision in future antidiabetic strategies.

Table 04: Targets and ligands used in molecular docking for diabetes treatment.

Targets	Ligands	Results	References
Aldose reductase and protein tyrosine phosphatase 1B (PTP1B)	Compound 4f derived from 4-thiazolidinone	Inhibits two target enzymes: AR inhibition : IC_{50} = 5,3 µM. PTP1B inhibition : IC_{50} = 12,7 µM.	[128]
α-salivary and pancreatic amylase	Geduniu	$IC_{50} \leq$ Standard acarbose	[129]
Catalase	Aspirine + pioglitazone	↑↑ The catalase activity compared to PGL alone is significantly enhanced, with ASP strengthening the stability and affinity of catalase for PGL, thereby amplifying its catalytic effect.	[130]

6. References

[1] Gupta, A., Chauhan, S.S., Gaur, A.S. et al. Computational screening for investigating the synergistic regulatory potential of drugs and phytochemicals in combination with 2-deoxy-D-glucose against SARS-CoV-2. Struct Chem 33, 2179–2193 (2022). https://doi.org/10.1007/s11224-022-02049-0.

[2] Omer, A. B., Altayb, H. N., Al-Abbasi, F. A., Gupta, G., Ahmed, M. M., Alghamdi, A. M., ... & Kazmi, I. (2023). Acemannan ameliorates STZ-activated diabetes by attenuating high glucose via inhibiting

inflammatory cytokines and apoptosis pathway. International journal of biological macromolecules, 253, 127127.
[3] Yella, S. S. T., Kumar, R. N., Ayyanna, C., Varghese, A. M., Amaravathi, P., & Vangoori, Y. (2019). The combined effect of Trigonella foenum seeds and Coriandrum sativum leaf extracts in alloxan-induced diabetes mellitus wistar albino rats. Bioinformation, 15(10), 716.
[4] Preumont, V., Muhindo, C. T., Reychler, H., Rahelic, D., & Buysschaert, M. (2016). CA-075: Hygiène bucco-dentaire et pertes dentaires dans une cohorte de patients diabétiques de type 1 et de type 2. Diabetes & Metabolism, 42, A55.
[5] Belhadj, M., Arbouche, Z., Brouri, M., Malek, R., Semrouni, M., Zekri, S., ... & Abrouk, S. (2019). BAROMÈTRE Algérie: enquête nationale sur la prise en charge des personnes diabétiques. Médecine des maladies Métaboliques, 13(2), 188-194.
[6] Bahijri, S. M., Jambi, H. A., Al Raddadi, R. M., Ferns, G., & Tuomilehto, J. (2016). The prevalence of diabetes and prediabetes in the adult population of Jeddah, Saudi Arabia-a community-based survey. PloS one, 11(4), e0152559.
[7] Chang, H. Y., Huang, Y. Y., Chung, C. J., & Liu, F. H. (2023). A comparative analysis of complementary therapies use among patients attending diabetic clinics in Taiwan: 2007 vs. 2023. BMC Complementary Medicine and Therapies, 23(1), 455.
[8] Beck, J. G., Chatterjee, J., Laufer, B., Kiran, M. U., Frank, A. O., Neubauer, S., ... & Kessler, H. (2012). Intestinal permeability of cyclic peptides: common key backbone motifs identified. Journal of the American Chemical Society, 134(29), 12125-12133.
[9] Qi, L. W., Chen, C. Y., & Li, P. (2009). Structural characterization and identification of iridoid glycosides, saponins, phenolic acids and flavonoids in Flos Lonicerae Japonicae by a fast liquid chromatography method with diode- array detection and time- of- flight mass spectrometry. Rapid Communications in Mass Spectrometry: An International Journal Devoted to the Rapid Dissemination of Up- to- the- Minute Research in Mass Spectrometry, 23(19), 3227-3242.
[10] Moon, D. O. (2024). Plant-derived flavonoids as AMPK activators: unveiling their potential in type 2 diabetes management through mechanistic insights, docking studies, and pharmacokinetics. Applied Sciences, 14(19), 8607.
[11] DeMarsilis, A., Reddy, N., Boutari, C., Filippaios, A., Sternthal, E., Katsiki, N., & Mantzoros, C. (2022). Pharmacotherapy of type 2 diabetes: An update and future directions. Metabolism, 137, 155332.
[12] Di Magno, L., Di Pastena, F., Bordone, R., Coni, S., & Canettieri, G. (2022). The mechanism of action of biguanides: New answers to a complex question. Cancers, 14(13), 3220.
[13] Walker, R.S.; Linton, A.L. Phenethyldiguanide: A Dangerous Side-Effect. Br. Med. J. 1959, 2,1005–1006.
[14] Bailey, C. J. (2017). Metformin: historical overview. Diabetologia, 60(9), 1566-1576.
[15] Ferrannini, E., Muscelli, E., Frascerra, S., Baldi, S., Mari, A., Heise, T., ... & Woerle, H. J. (2014). Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. The Journal of clinical investigation, 124(2), 499-508.
[16] Krentz, A. J., & Bailey, C. J. (2005). Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs, 65, 385-411.
[17]Viollet, B., Guigas, B., Garcia, N. S., Leclerc, J., Foretz, M., & Andreelli, F. (2012). Cellular and molecular mechanisms of metformin: an overview. Clinical science, 122(6), 253-270.
[18] Handelsman, Y., Bloomgarden, Z. T., Grunberger, G., Umpierrez, G., Zimmerman, R. S., Bailey, T. S., ... & Zangeneh, F. (2015). American Association of Clinical Endocrinologists and American College of Endocrinology–clinical practice guidelines for developing a diabetes mellitus comprehensive care plan–2015—executive summary. Endocrine Practice, 21(4), 413-437.

[19] Benrachadi, L., Saleh, Z. M., & Bouziane, A. (2019). L'impact de la thérapeutique parodontale sur l'équilibre de diabète: revue systématique. La Presse Médicale, 48(1), 4-18.
[20] Darmon, P., Bauduceau, B., Bordier, L., Charbonnel, B., Cosson, E., Detournay, B., ... & Scheen, A. (2019). Prise de position de la Société Francophone du Diabète (SFD) sur la prise en charge médicamenteuse de l'hyperglycémie du patient diabétique de type 2—2019. Med Mal Metab, 13, 711-732.
[21] Sharma, V. K., Barde, A., & Rattan, S. (2021). A short review on synthetic strategies toward glitazone drugs. Synthetic Communications, 51(1), 57-80.
[22] Nolan, C. J., Madiraju, M. S., Delghingaro-Augusto, V., Peyot, M. L., & Prentki, M. (2006). Fatty acid signaling in the β-cell and insulin secretion. Diabetes, 55(Supplement_2), S16-S23.
[23] Chiarelli, F., & Marcovecchio, M. L. (2008). Insulin resistance and obesity in childhood. European journal of endocrinology, 159(Supplement_1), S67-S74.
[24] Colca, J. R., McDonald, W. G., Waldon, D. J., Leone, J. W., Lull, J. M., Bannow, C. A., ... & Mathews, W. R. (2004). Identification of a novel mitochondrial protein ("mitoNEET") cross-linked specifically by a thiazolidinedione photoprobe. American Journal of Physiology-Endocrinology and Metabolism, 286(2), E252-E260.
[25] Harrower, A. D. (1996). Pharmacokinetics of oral antihyperglycaemic agents in patients with renal insufficiency. Clinical pharmacokinetics, 31, 111-119.
[26] Asano, N. (2003). Glycosidase inhibitors: update and perspectives on practical use. Glycobiology, 13(10), 93R-104R.
[25] kameda, y., asano, n., yoshikawa, m., takeuchi, m., yamaguchi, t., matsui, k., ... & fukase, h. (1984). vaholamine, a new α-glucosidase inhibiting aminocyclitol produced by streptomyces hygroscopicus. the journal of antibiotics, 37(11), 1301-1307.
[26] HAS, A. (2013). Stratégie médicamenteuse du contrôle glycémique du diabète de type 2. Epidémiologie et coût du diabète en France. Argumentaire.
[27] Madsbad, S. (2012). Dipeptidyl peptidase-4 (DPP-4) inhibitors are favourable to glucagon-like peptide-1 (GLP-1) agonists: no. European Journal of Internal Medicine, 23(2), 132-136.
[28] Orlandella, R. M., Turbitt, W. J., Gibson, J. T., Boi, S. K., Li, P., Smith Jr, D. L., & Norian, L. A. (2020). The antidiabetic agent acarbose improves anti-PD-1 and rapamycin efficacy in preclinical renal cancer. Cancers, 12(10), 2872.
[29] Obaid, Q. A., Al-Shammari, A. M., & Khudair, K. K. (2022). Glucose deprivation induced by acarbose and oncolytic newcastle disease virus promote metabolic oxidative stress and cell death in a breast cancer model. Frontiers in Molecular Biosciences, 9, 816510.
[30] Drucker, D. J., Habener, J. F., & Holst, J. J. (2017). Discovery, characterization, and clinical development of the glucagon-like peptides. The Journal of clinical investigation, 127(12), 4217-4227.
[31] Drucker, D. J., & Nauck, M. A. (2006). The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet, 368(9548), 1696-1705.
[32] Al-Hariri MT, Yar T, Bamosa AO, El-Bahai MN.Effects of two-months Nigella sativa supplementation on cardiac hemodynamics and adrenergic responsiveness. J Pak Med Assoc. 2009;59:5.
[33] Woo CC, Loo SY, Gee V, Yap CW, Sethi G, et al. Anticancer activity of thymoquinone in breast cancer cells: possible involvement of PPAR- gamma pathway, Biochemical Pharmacology 2011; 82(5):454-457.
[34] Megantara, S., Utami, D., Puspitasari, L., & Mustarichie, R. (2017). Insilico study of thymoquinone as peroxisome proliferator activated receptor gamma agonist in the treatment of type 2 diabetes mellitus. Journal of Pharmaceutical Sciences and Research, 9(9), 1478.
[35] Sene, B., Sarr, F., Diouf, D., Sow, M. S., Traore, D., Kane, A., & Niang, M. (2018). Synthèse des connaissances et quelques acquis de recherche sur le sésame (Sesamum Indicum L.) au Sénégal. International Journal of Biological and Chemical Sciences, 12(3), 1469-1483.

[36] Narasimhan, R., & Mohan, A. (2012). Phytochemical screening of Sesamum indicum seed extract. World journal of pharmacy and pharmaceutical sciences, 1(4), 1298-1308.

[37] Zhang, Y., Liu, F., Lin, Y., Li, L., Chen, M., & Ni, L. (2022). A comprehensive review on distribution, pharmacological properties, and mechanisms of action of sesamin. Journal of Chemistry, 2022(1), 4236525.

[38] Aslam, M., Shabbir, M.A., Pasha, I., Shukat, R., Siddique, U., Manzoor, M.F. and Ayub, S., 2020. Protective effect of sesame (Sesamum indicum) seed oil against hypercholesterolemic in spraguedawley male rats.

[39] Sayeh and A. Hassan, "A comprehensive mechanisticinsight into the dietary and estrogenic lignans, arctigenin andsesamin as potential anticarcinogenic and anticancer agents.Current status, challenges, and future perspectives," CriticalReviews in Food Science and Nutrition, vol. 61, pp. 1–17, 2021.

[40] Hong, L., Yi, W., Liangliang, C., Juncheng, H., Qin, W., & Xiaoxiang, Z. (2013). Hypoglycaemic and hypolipidaemic activities of sesamin from sesame meal and its ability to ameliorate insulin resistance in KK- Ay mice. Journal of the Science of Food and Agriculture, 93(8), 1833-1838.

[41] Nadeem, C. Situ, A. Mahmud et al., "Antioxidant activityof sesame (Sesamum indicum L.) cake extract for the sta-bilization of olein based butter," Journal of the American OilChemists' Society, vol. 91, no. 6, pp. 967–977, 2014.

[42] Neelakantan, N., Narayanan, M., de Souza, R. J., & van Dam, R. M. (2014). Effect of fenugreek (Trigonella foenum-graecum L.) intake on glycemia: a meta-analysis of clinical trials. Nutrition journal, 13, 1-11.

[43] Sarker, D. K., Ray, P., Dutta, A. K., Rouf, R., & Uddin, S. J. (2024). Antidiabetic potential of fenugreek (Trigonella foenum- graecum): A magic herb for diabetes mellitus. Food Science & Nutrition.

[44] Jyothi, D., Koland, M., Priya, S., & James, J. P. (2017). Formulation of herbal capsule containing Trigonella foenum-graecum seed extract for the treatment of diabetes. Journal of Young Pharmacists, 9(3), 352.

[45] Yella, S. S. T., Kumar, R. N., Ayyanna, C., Varghese, A. M., Amaravathi, P., & Vangoori, Y. (2019). The combined effect of Trigonella foenum seeds and Coriandrum sativum leaf extracts in alloxan-induced diabetes mellitus wistar albino rats. Bioinformation, 15(10), 716.

[46] Afifi, N. A., Ramadan, A., Erian, E. Y., Saleh, D. O., Sedik, A. A., Badawi, M., & El Hotaby, W. (2017). Trigonelline attenuates hepatic complications and molecular alterations in high-fat high-fructose diet-induced insulin resistance in rats. Canadian Journal of Physiology and Pharmacology, 95(4), 427-436.

[47] Membrez, M., Migliavacca, E., Christen, S., Yaku, K., Trieu, J., Lee, A. K., ... & Feige, J. N. (2024). Trigonelline is an NAD+ precursor that improves muscle function during ageing and is reduced in human sarcopenia. Nature metabolism, 6(3), 433-447.

[48] Yoo, E. A., Kim, S. D., Lee, W. M., Park, H. J., Kim, S. K., Cho, J. Y., ... & Rhee, M. H. (2008). Evaluation of antioxidant, antinociceptive, and anti- inflammatory activities of ethanol extracts from Aloe saponaria Haw. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 22(10), 1389-1395.

[49] Dick WR, Fletcher EA, Shah SA. Reduction of Fasting Blood Glucose and Hemoglobin A1c Using Oral Aloe Vera: A Meta-Analysis. J Altern Complement Med. 2016 Jun;22(6):450-7. doi: 10.1089/acm.2015.0122. Epub 2016 May 6.

[50] Omer, A. B., Altayb, H. N., Al-Abbasi, F. A., Gupta, G., Ahmed, M. M., Alghamdi, A. M., ... & Kazmi, I. (2023). Acemannan ameliorates STZ-activated diabetes by attenuating high glucose via inhibiting inflammatory cytokines and apoptosis pathway. International journal of biological macromolecules, 253, 127127.

[51] Kiuchi, F., Iwakami, S., Shibuya, M., Hanaoka, F., & Sankawa, U. (1992). Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chemical and Pharmaceutical bulletin, 40(2), 387-391.

[52] Kim, H. W., Murakami, A., Abe, M., Ozawa, Y., Morimitsu, Y., Williams, M. V., & Ohigashi, H. (2005). Suppressive effects of mioga ginger and ginger constituents on reactive oxygen and nitrogen species generation, and the expression of inducible pro-inflammatory genes in macrophages. Antioxidants & redox signaling, 7(11-12), 1621-1629.

[53] Vatté, J., Bourdeau, V., Ferbeyre, G., & Schmitzer, A.R. (2024). Gaining Insight into Mitochondrial Targeting: AUTAC-Biguanide as an Anticancer Agent. Molecules, 29, 3773.

[54] Zhigulin, A. S., Novikova, A. O., & Barygin, O. I. (2024). Mechanisms of NMDA Receptor Inhibition by Biguanide Compounds. Pharmaceuticals, 17(9), 1234.

[55] Keezhipadathil, J. (2019). Evaluation of suspected adverse drug reactions of oral anti-diabetic drugs in a tertiary care hospital for type ii diabetes mellitus. Indian Journal of Pharmacy Practice, 12(2).

[56] Wang, G. S., & Hoyte, C. (2019). Review of biguanide (metformin) toxicity. Journal of intensive care medicine, 34(11-12), 863-876.

[57] Rong, L., Zou, J., Ran, W., Qi, X., Chen, Y., Cui, H., & Guo, J. (2023). Advancements in the treatment of non-alcoholic fatty liver disease (NAFLD). Frontiers in endocrinology, 13, 1087260.

[58] Arner, P., Kulyté, A., Batchelor, K., Laurencikiene, J., Livingston, J., & Rydén, M. (2018). Mapping of biguanide transporters in human fat cells and their impact on lipolysis. Diabetes, Obesity and Metabolism, 20(10), 2416-2425.

[59] Abdel-Aziz, H., Nahrstedt, A., Petereit, F., Windeck, T., Ploch, M., & Verspohl, E. J. (2005). 5-HT3 receptor blocking activity of arylalkanes isolated from the rhizome of Zingiber officinale. Planta medica, 71(07), 609-616.

[60] Machiani, AM., Javanmard, A., Ostadi, A., & Alizadeh, K. (2023). Improvement in Essential Oil Quantity and Quality of Thyme (Thymus vulgaris L.) by Integrative Application of Chitosan Nanoparticles and Arbuscular Mycorrhizal Fungi under Water Stress Conditions. Plants (Basel, Switzerland), 12(7), 1422.

[61] Jain, N., & Choudhary, P. (2022). Phytochemistry, Traditional Uses and Pharmacological Aspect of Thymus vulgaris: A Review. Indian Journal of Pharmaceutical Sciences, 84(6), 1369-1379.

[62] Fidan H, Stefanova G, Kostova I, Stankov S, Damyanova S, Stoyanova A, Zheljazkov VD. Chemical Composition and Antimicrobial Activity of Laurus nobilis L. Essential Oils from Bulgaria. Molecules. 2019. 22;24(4):804.

[63] Lahlou, R. A., Samba, N., Soeiro, P., Alves, G., Gonçalves, A. C., Silva, L. R., ... & Ismael, M. I. (2022). Thymus hirtus Willd. ssp. algeriensis Boiss. and Reut: A Comprehensive Review on Phytochemistry, Bioactivities, and Health-Enhancing Effects. Foods, 11(20), 3195.

[64] Twaij HA, Al-Badr A (1988). Hypoglycaemic activity of Artemisia herba-alba. J Ethnopharmacol, 24 (2-3) : 123 - 126.

[65] Al-Shamaony L, Al Khazraji MS, Twaij HA (1994). Hypoglycemic effects of Artemisia herba-alba . II. Effect of a valuable extract on some blood parameters in diabetic animals. J Ethnopharmacol, 43(3) : 167 – 171

[66] Marrif HI, Ali BH, Hassan KM (1995). Some pharmacological studies on Artemisia herbaalba (Asso.) in rabbits and mice. J Ethnopharmacol, 49(1) : 51 – 55

[67] Taştekin D, Atasever M, Adigüzel G, Keleş M , Taştekin A (2006). Hypoglycaemic effect of Artemisia herba-alba in experimental hyperglycaemic rats. Bull Vet Inst Pulawy, 50 : 235-238.

[68] Huang, Y., Xu, W., Chen, G., Sun, Y., & Zeng, X. (2024). Anti-diabetic effect of di-caffeoylquinic acid is associated with the modulation of gut microbiota and bile acid metabolism.

[69] Piz, M. D. J. J., Campos, V. B., Campos, M. L. G., Gómez, X. S. R., García, S. N. J., Barragán, R. A. M., ... & Solís, M. O. V. (2022). Efecto de infusión de Eucalyptus Camaldulensis Dehn en valores de

glucosa sanguínea en pacientes con diabetes tipo 2: Effect of Eucalyptus Camaldulensis Dehn infusion on blood glucose values in patients with type 2 diabetes. South Florida Journal of Development, 3(2), 2053-2071.

[70] Akinmoladun, A. C., Kazeem, B. S. J., Bello, M., & Olaleye, M. T. (2023). Effect of standardized Eucalyptus globulus leaf extract on brain oxidative stress and aberrant neurochemistry of fructose-streptozotocin-induced diabetic rats. Nigerian Journal of Physiological Sciences, 38(1), 65-72.

[71] Uadia, P. O., Emmanuel, C. O., Oriakhi, K., & Imafidon, K. E. (2024). Anti-diabetic effect of Eucalyptus camaldulensis (Red gum) leaf-supplemented diet in streptozotocin-induced diabetic rats. Tropical Journal of Pharmaceutical Research, 23(2), 315-326.

[72] Precious, O. O., & Uwagboe, A. N. (2024). Anti-inflammatory Evaluation of the anti-diabetic effect of Rauvolfia vomitoria and Citrus aurantium decoction on streptozotocin-induced diabetic Wistar rats.

[73] Opajobi AO, Esume CO, Campbell P, Onyesom I, Osasuyi A. Effects of aqueous extracts of Rauvolfia vomitoria and Citrus aurantium on liver enzymes of streptozotocininduced diabetic and normal rabbits. Cont J Med Res. 2011; 5(1):1-5.

[74] Ebrahimzadeh MA, Nabavi SF, Nabavi SM, Pourmorad F. Nitric oxide radical scavenging potential of some Elburz medicinal plants. Afr J Biotechnol. 2010; 9(32):5212-5217.

[75] Campbell, J. I., Mortensen, A., & Mølgaard, P. (2006). Tissue lipid lowering-effect of a traditional Nigerian anti-diabetic infusion of Rauwolfia vomitoria foilage and Citrus aurantium fruit. Journal of Ethnopharmacology, 104(3), 379-386.

[76] Sharma, M., Fernandes, J., Ahirwar, D., & Jain, R. (2008). Hypoglycemic and hypolipidimic activity of alcoholic extract of citrus aurantium in normal and alloxan-induced diabetic rats. Pharmacologyonline, 3, 161-171.

[77] Alaryani, F. S. (2024). Examining the pancreatic regenerative potential of Nigella sativa in diabetic rats: Evaluation of histological changes and transcription factors pdx-1 and neurog-3 levels. Materials Express, 14(3), 376-384.

[78] AlSuhaymi, N. (2024). Therapeutic Effects of Nigella sativa Oil and Whole Seeds on STZ‐Induced Diabetic Rats: A Biochemical and Immunohistochemical Study. Oxidative Medicine and Cellular Longevity, 2024(1), 5594090.

[79] Huang, Y., Liu, C., Ge, Z., Huang, F., Tang, H., Zhou, Q., ... & Zheng, C. (2023). Influence of different thermal treatment methods on the processing qualities of sesame seeds and cold-pressed oil. Food Chemistry, 404, 134683.

[80] Gurumallu, S. C., AlRamadneh, T. N., Sarjan, H. N., Bhaskar, A., Pereira, C. M. F., & Javaraiah, R. (2022). Synergistic hypoglycemic and hypolipidemic effects of ω-3 and ω-6 fatty acids from Indian flax and sesame seed oils in streptozotocin-induced diabetic rats. Phytomedicine Plus, 2(3), 100284.

[81] Cordero-Pérez, P., Hernández-Cruz, F. E., Garza-Guzmán, D., Moreno-Peña, D. P., Sánchez-Martínez, C., Torres-González, L., ... & Rodríguez-Rodríguez, D. R. (2024). Antidiabetic and Anti-Inflammatory Effect of Cinnamomum cassia Oil in Alloxan-Induced Diabetic Rats. Pharmaceuticals, 17(9), 1135.

[82] Anand, P., Murali, K. Y., Tandon, V., Murthy, P. S., & Chandra, R. (2010). Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chemico-biological interactions, 186(1), 72-81.

[83] Juan Jiang et al. 2017. Cinnamaldehyde induces fat cell-autonomous thermogenesis and metabolic reprogramming. Metabolism 77: 58-64; doi: 10.1016/j.metabol.2017.08.006

[84] Hernández-Cruz, F. E., Cordero-Pérez, P., Moreno-Peña, D. P., Muñoz-Espinosa, L. E., & Concepción, S. M. (2024). Evaluation of the effect of Cinnamomum cassia oil on markers of oxidative stress and its modification in gene expression in a diabetic rat model induced with alloxane. Annals of Hepatology, 29, 101398.

[85] Çelik, R., Mert, H., Comba, B., & Mert, N. (2022). Effects of cinnamaldehyde on glucose-6-phosphate dehydrogenase activity, some biochemical and hematological parameters in diabetic rats. Biomarkers, 27(3), 270-277.
[86] Vijayakumar, K., Rengarajan, R. L., Suganthi, N., Prasanna, B., Velayuthaprabhu, S., Shenbagam, M., & Vijaya Anand, A. (2022). Acute toxicity studies and protective effects of Cinnamon cassia bark extract in streptozotocin-induced diabetic rats. Drug and Chemical Toxicology, 45(5), 2086-2096.
[87] Isirima, J. C. Sokiprim Akoko (2023). Antihyperglycemic and Histological Effect of Aloe vera on Alloxan-Induced Diabetes in Wistar Rats. Sch Int J Tradit Complement Med, 6(8), 120-128.
[88] Hasan, A. K., Jat, R. K., & Khan, A. M. (2022). Effects of aqueous leaves extract of Aloe barbadensis on blood glucose levels of streptozotocin-induced diabetic Wistar rats.
[89] Efejene, I. O., Orororo, O. C., Odeghe, O. B., & Ejevwo, E.(2023). Effect of Ethanolic Extract of Zingiber Officinale Rhizome on Blood Glucose Level in Glucose-induced Hyperglycaemic Wistar Rats.
[90] Al-Amin, Z. M., Thomson, M., Al-Qattan, K. K., Peltonen-Shalaby, R., & Ali, M. (2006). Anti-diabetic and hypolipidaemic properties of ginger (Zingiber officinale) in streptozotocin-induced diabetic rats. British journal of nutrition, 96(4), 660-666.
[91] Dessalegn, E., Bultosa, G., Haki, G. D., & Rupasinghe, H. V. (2019). Evaluation of in vitro antidiabetic potential of Thymus schimperi R. and Thymus vulgaris L. Evaluation, 6, 9-16.
[92] Laftouhi, A., Slimani, M., Elrherabi, A., Bouhrim, M., Mahraz, M. A., Idrissi, A. M., ... & Taleb, M. (2024). Effect of Temperature and Water Stress on the Antioxidant and Antidiabetic Activities of Thymus vulgaris Essential Oil. Tropical Journal of Natural Product Research, 8(1).
[93] Sekiou, O., Boumendjel, M., Taibi, F., Tichati, L., Boumendjel, A., & Messarah, M. (2021). Nephroprotective effect of Artemisia herba alba aqueous extract in alloxan-induced diabetic rats. Journal of traditional and complementary medicine, 11(1), 53-61.
[94] Awad, N. E., Seida, A. A., El-Khayat, Z., Shaffie, N., & Abd El-Aziz, A. M. (2012). Hypoglycemic activity of Artemisia herba-alba (Asso.) used in Egyptian traditional medicine as hypoglycemic remedy. Journal of Applied Pharmaceutical Science, (Issue), 30-39.
[95] Sankar, D., Ali, A., Sambandam, G., & Rao, R. (2011). Sesame oil exhibits synergistic effect with anti-diabetic medication in patients with type 2 diabetes mellitus. Clinical Nutrition, 30(3), 351-358.
[96] Brehm BJ, Lattin BL, Summer SS, Boback JA, Gilchrist GM, Jandacek RJ, et al. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. Diabetes Care 2009;32:215e20.
[97] Ogawa H, Sasagawa S, Murakami T, Yoshizumi H. Sesame lignans modulate cholesterol metabolism in the stroke-prone spontaneously hypertensive rat. Clin Exp Pharmacol Physiol Suppl 1995;22:S310e2.
[98] Bamosa, A. O., Kaatabi, H., Lebdaa, F. M., Elq, A. M., & Al-Sultanb, A. (2010). Effect of Nigella sativa seeds on the glycemic control of patients with type 2 diabetes mellitus. Indian J Physiol Pharmacol, 54(4), 344-54.
[99] Hina, Younus. (2018). Antidiabetic Action of Thymoquinone. 7-17. doi: 10.1007/978-981-10-8800-1_2.
[100] Mahomoodally, M. F., Aumeeruddy, M. Z., Legoabe, L. J., Montesano, D., & Zengin, G. (2022). Nigella sativa L. and its active compound thymoquinone in the clinical management of diabetes: A systematic review. International journal of molecular sciences, 23(20), 12111.
[101] Utomo, F., Jaya, P., & Siregar, U. A. (2023). Pengaruh Penggunaan Kombinasi Habbatussauda (Nigella sativa) dan Glibenclamide pada Kadar Glukosa Darah. Jurnal Kedokteran dan Kesehatan, 19(2), 157-164.
[102] Bugudare, U. S., Divakar, K., Krishnaveni Bai, R., & Ashfaq, M. (2011). Influence of hydroalcoholic extract of Cinnamomum cassia on anti-diabetic effect of glibenclamide, metformin alone and their combination. Pharmacologyonline, 2, 798-807.

[103] Huseini, H. F., Kianbakht, S., Hajiaghaee, R., & Dabaghian, F. H. (2012). Anti-hyperglycemic and anti-hypercholesterolemic effects of Aloe vera leaf gel in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. Planta medica, 78(04), 311-316.
[104] Rajasekaran S, Sriram N, Arulselvan P, Subramanian S, (2007): Effect of Aloe vera leaf gel extract on membrane bound phosphatases and lysosomal hydrolases in rats with streptozotocin diabetes. Pharmazie., 62:221–225.
[105] Mohammed A, Ibrahim MA, Tajuddeen N, Aliyu AB, Isah MB, (2020). Antidiabetic potential of anthraquinones: a review. Phytother Res., 34:486–504.
[106] Haritha, C., Reddy, A. G., Reddy, Y. R., & Anilkumar, B. (2015). Pharmacodynamic interaction of fenugreek, insulin and glimepiride on sero-biochemical parameters in diabetic Sprague-Dawley rats. Veterinary World, 8(5), 656.
[107] Neveen, H. I., Eleneen, A., & Maha, M. S. (2007). Assessment of ddt residues in milk and some dairy products. Zagazig Vet J, 35(4), 27-35.
[108] Yassin, M. and Mwafy, S. (2007) Protective potential of glimepiride and Nerium oleander extract on lipid profile, body growth rate, and renal function in streptozotocin-induced diabetic rats. Turk. J. Biol., 31: 95-102.
[109] Al-Khawaldeh, O. A., Al-Hassan, M. A., & Froelicher, E. S. (2012). Self-efficacy, self-management, and glycemic control in adults with type 2 diabetes mellitus. Journal of Diabetes and its Complications, 26(1), 10-16.
[110] Abhilash, G., Kumar, A., & Naveen, B. (2020). Significant role of ginger extracted compounds for diabetes treatment. International Research Journal of Pharmaceutical and Applied Sciences, 10(2), 19-22.
[111] Poonam, T., Prakash, G. P., & Kumar, L. V. (2013). Influence of Allium sativum extract on the hypoglycemic activity of glibenclamide: an approach to possible herb-drug interaction. Drug metabolism and drug interactions, 28(4), 225-230.
[112] Al- Adsani, A. M., Al- Qattan, K. K., Barhoush, S. A., Abbood, M. S., & Al- Bustan, S. A. (2024). Garlic Extract Promotes Pancreatic Islet Neogenesis Through α- to- β- Cell Transdifferentiation and Normalizes Glucose Homeostasis in Diabetic Rats. Molecular Nutrition & Food Research, 68(19), 2400362.
[113] Masjedi, F., Gol, A., Dabiri, S., & Javadi, A. (2009). Investigating the preventive effect of garlic on blood glucose levels and histopathology of pancreas in streptozotocin-induced diabetic rats. Physiology and Pharmacology, 13(2), 179-190.
[114] Chakraborty, M., Ahmed, M. G., & Bhattacharjee, A. (2017). The potential for interaction of tolbutamide with pomegranate juice against diabetic induced complications in rats. Integrative Medicine Research, 6(4), 354-360.
[115] Katz, S. R., Newman, R. A., & Lansky, E. P. (2007). Punica granatum: heuristic treatment for diabetes mellitus. Journal of medicinal food, 10(2), 213-217.
[116] Yazdi, H. B., Hojati, V., Shiravi, A., Hosseinian, S., & Vaezi, G. (2020). The role of Artemisia turanica extract on renal oxidative and biochemical markers in STZ-induced diabetes in rat. Avicenna Journal of Phytomedicine, 10(5), 504.
[117] El-Tantawy, W. H. (2015). Biochemical effects, hypolipidemic and anti-inflammatory activities of Artemisia vulgaris extract in hypercholesterolemic rats. Journal of clinical biochemistry and nutrition, 57(1), 33-38.
[118] Dar, M. I., Gulya, A., Abass, S., Dev, K., Parveen, R., Ahmad, S., & Qureshi, M. I. (2024). Hallmarks of diabetes mellitus and insights into the therapeutic potential of synergy-based combinations of phytochemicals in reducing oxidative stress-induced diabetic complications. Natural Product Research, 1-15.

[119] Khan, F., Khan, M. V., Kumar, A., & Akhtar, S. (2024). Recent Advances in the Development of Alpha-Glucosidase and Alpha-Amylase Inhibitors in Type 2 Diabetes Management: Insights from In silico to In vitro Studies. Current Drug Targets, 25(12), 782-795.
[120] Upadhyaya, S. R., Magar, L. B., Thapa, R., Joshi, S., Khadayat, K., Marasini, B. P., & Parajuli, N. (2023). Biochemical Analysis and Human Aldose Reductase Inhibition Activity of Selected Medicinal Plants of Nepal. Journal of Chemistry, 2023(1), 9614164.
[121] Liu, Z., Gao, H., Zhao, Z., Huang, M., Wang, S., & Zhan, J. (2023). Status of research on natural protein tyrosine phosphatase 1B inhibitors as potential antidiabetic agents: Update. Biomedicine & Pharmacotherapy, 157, 113990.
[122] Dehghan, G., Rashtbari, S., Yekta, R., & Sheibani, N. (2019). Synergistic inhibition of catalase activity by food colorants sunset yellow and curcumin: An experimental and MLSD simulation approach. Chemico-Biological Interactions, 311, 108746.
[123] Li H, Li C. Multiple ligand simultaneous docking: orchestrated dancing of ligands in binding sites of protein. J Comput Chem. 2010;31: 2014–2022.
[124] Li H, Liu A, Zhao Z, Xu Y, Lin J, Jou D, et al. Fragment-based drug design and drug repositioning using multiple ligand simultaneous docking (MLSD): identifying celecoxib and template compounds as novel inhibitors of signal transducer and activator of transcription 3 (STAT3). J Med Chem. 2011;54: 5592–5596.
[125] Wang, Y., Qian, Y., Fang, Q. et al. Saturated palmitic acid induces myocardial inflammatory injuries through direct binding to TLR4 accessory protein MD2. Nat Commun 8, 13997 (2017). https://doi.org/10.1038/ncomms13997
[126] Devi A, Jain S, Singhal D, Ghosh A, Kumar V, Dwibedi V, et al. Multiple ligand simultaneous docking analysis of epigallocatechin-O-gallate (green tea) and withaferin A (ashwagandha) effects on skin-aging related enzymes. Indian Journal of Pharmaceutical Sciences. 2023;85. doi:10.36468/pharmaceutical-sciences.1171
[127] Srivastav, A. K., Rajput, P. K., Jaiswal, J., Yadav, U. C., & Kumar, U. (2024). In vitro and in silico investigation of glycyrrhizic acid encapsulated zein nanoparticles: a synergistic targeted drug delivery approach for breast cancer. International Journal of Biological Macromolecules, 266, 131368.
[128] Khataee S, Dehghan G, Yekta R, Rashtbari S, Maleki S, Khataee A. The protective effect of natural phenolic compound on the functional and structural responses of inhibited catalase by a common azo food dye. Food Chem Toxicol. 2022;160: 112801.
[129] Ottanà, R., Paoli, P., Cappiello, M., Nguyen, T. N., Adornato, I., Del Corso, A., ... & Maccari, R. (2021).In search for Multi-Target ligands as potential agents for diabetes mellitus and its complications—a structure-activity relationship study on inhibitors of aldose reductase and protein tyrosine phosphatase 1B. Molecules, 26(2), 330.
[130] Mazumdar, S., Marar, T., Patki, J., Devarajan, S., Zambare, V., & Swami, D. (2020). In silico and in vitro analysis reveal multi-target anti-hyperglycaemic properties of gedunin, a limonoid from neem (Azadirachta indica). Clinical Phytoscience, 6, 1-11.
[131] Panahi, Y., Yekta, R., Dehghan, G., Rashtbari, S., Jafari, N. J., & Moosavi-Movahedi, A. A. (2019). Activation of catalase via co-administration of aspirin and pioglitazone: Experimental and MLSD simulation approaches. Biochimie, 156, 100-108.
[132] Ghaly, R., Ismael, H., Khamis, A., Mahmoud, S., El-Gerbed, M. S., & Aborhyem, S. (2022). Efficacy of Avena Sativa on Regulating Some Biochemical Parameters in Type 2 Diabetic Male Albino Rats. Journal of High Institute of Public Health, 52(1), 33-44.