REVIEW PAPER

A Comparative Overview of Natural and Synthetic Anti-Diabetic Compounds

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ABSTRACT

Diabetes mellitus continues to increase all over the world and has been a cause of a huge burden on the health system of the population. They are associated with certain limitations. Which has encouraged the interest in natural compounds over the synthetic compounds. These alternatives are preferred for their multi-targeted actions, improved patient safety, cost effectiveness and their long-standing use in traditional medicine, which support their therapeutic potential. The pharmacology efficacy, safety profile and potential applicability in integrative therapeutic regimens of each natural and synthetic anti-diabetic compounds are comprehensively evaluated in this study. This study evaluates several important natural compounds, containing extract from Rosmarinus officinalis, Zingiber officinale, Trigonella foenum-graecum, Nigella sativa, Elettaria cardamomum, Cinnamomum verum and Bellis perennis. Their potential to lower glycated hemoglobin known as HbA1c is analyzed, including their active chemical constituents and the way they function in the body. Additionally widely used synthetic drugs including insulin, metformin, dipeptidyl peptidase-4 inhibitors (DPP-4), GLP-1 receptor agonists, thiazolidinediones, sulfonylureas, sodium-glucose cotransporter 2 (SGLT-2) inhibitors are evaluated for their efficacy, safety profile, mechanism of action and potential applicability in integrative therapeutic regimens. This review of natural and synthetic anti-diabetic agents indicates the ability for HbA1C reduction, specific targeting on the safety, efficacy and the cost effectiveness. It evaluates the potential of integrative therapy that combines both classes to enhance outcomes and minimizes side effects. Patient-related treatment approaches are also considered in this study. This comparative review emphasizes the need for more research to enhance the anti-diabetic treatment to better combine natural and synthetic approaches into personal and long term treatment plans.

Keywords: Diabetes mellitus, natural compounds, synthetic compounds, HbA1C reduction, herbal remedies, SARS of synthetic based medicines, comparative tables.

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INTRODUCTION

According to the international diabetes federation (IDF) diabetes has become a major global health concern, 463 million adults between 20 and 79 years of age were living with diabetes in 2019, and this figure is expected to increase to 578 million by 2030. During the period approximately 373.9 million adults (7.5% of the global adult population) were affected by impaired glucose tolerance, with nearly half of these individuals being under 50 years of age. The prevalence of diabetes was slightly higher in the men (9.6%) than in the women (9.0%)[1]. The rapid global rise in type 2 diabetes has become a major public health challenge, affecting both individual quality of life and healthcare system worldwide. The growing concern of diabetes mellitus can be linked to several factors, including demographic changes, an aging population, reduced physical activity and unhealthy dietary lifestyles, along with a serious impact on human body, diabetes also create a major economic burden because of increasing the cost of treatment and medicines [2]. The pathophysiology of Type 2 diabetes mellitus (T2DM) involves multiple metabolic disturbance. These include impaired insulin secretion

from pancreatic β-cells, elevated glucagon release from α-cells, and excessive hepatic glucose production. Increased lipolysis, reduced insulin sensitivity in peripheral tissues. Additionally, renal glucose reabsorption is enhanced, and glucose uptake in skeletal muscles, adipose tissue, and liver is compromised. Altered central regulatory mechanism in the brain also contributed to poor glycemic regulation [3]. Even though there have been major improvement in diabetes treatment and new medicines, the overall burden of diabetes mellitus is still increasing. The people or populations are affected by diabetes related health problems were include in disability- adjusted life years (DALYs)[4]. Although lifestyle modification- such as improved diet and increased physical activity, play a crucial role in glycemic control, most individuals with T2DM ultimately require pharmacological intervention for sustained management. Currently, several classes of oral antidiabetic agents are available including sulfonylureas, biguanides, α-glucosidase inhibitors, and peroxisome proliferator-activated receptor gamma (PPARγ) agonists. Alpha-glucosidase inhibitors help in controlling the blood sugar levels by the functioning of slow down the carbohydrate digestion and delaying absorption of glucose in intestine. This helps reduce the rapid rise in blood glucose levels after taking a meals, since these drugs do not directly increased insulin secretion, they usually causes lower risks of hypoglycemia when used alone[5]. PPARγ agonists improves insulin sensitivity in the body. They produce their therapeutic action by increasing the glucose uptake in peripheral tissues and regulating the secretion of adipokines and inflammatory substances. These drugs also also helps in lowering free fatty acid levels in the blood, which helps to reducing in lipotoxicity and provide better pancreatic beta-cell function[6]. synthetic anti-diabetic drugs are productive in the treatment of diabetes mellitus, these drugs are come with some several disadvantages that includes weight gain, risk of hypoglycemia, reduced effectiveness due to inadequate dosing and problems related to drug absorption, drug metabolism and drug bioavailability, some drugs may also causes unwanted side effects that knows as adverse drug reactions, for example, metformin, that are most common anti-diabetic drug used as a first-line treatment in diabetes mellitus and improving insulin sensitivity, it also causes some gastrointestinal problems such as nausea, diarrhea and stomach discomfort, mostly at the starting of the treatment. It is also not recommended for the patient suffering with severe kidney disease, liver disorder and heart disease. Similarly, thiazolidinediones, that act as a PPARγ agonists may causes fluid retention, swelling and increasing the risk of heart failure [7]. There are also some drugs that produces some safety concern, such as pioglitazone has restriction in distribution in several countries because of its possible link with bladder cancer, while rosiglitazone are associated with cardiovascular risks. Despite the availability of many anti-diabetic drugs, maintaining the long term blood glucose control with less or null complications remains major challenge in diabetes treatment[8].

The World Health Organization (WHO) states across 70-90% of the world population, especially in the developing countries were depends on the plant-based traditional treatment or herbal remedies for primary health care. The population were prefers herbal medicines mainly due to its lower cost, easy availability in rural areas as well as urban areas , cultural acceptance and the belief that they are safer and more effective in human body than synthetic medications. Medicinal plants carries a multiple variety of bio active chemical compounds such as alkaloids, glycosides, flavonoids and carotenoids, that helps to provide the potential antidiabetic effects [9]. Herbal medications are generally affordable in cost and also causes the less side effects, many plant-based medicines shows blood glucose lowering effects similar to synthetic drugs like sulfonylureas [10]. Modern anti-diabetic medications can effectively reducing the high blood glucose levels in most patients with type-2 diabetes, a permanent cure is still unavailable. Diabetes treatment should targeted multiple pathways instead only focusing one pathways. Newer treatments such as glucagon-like peptide-1(GLP-1) based therapies were provide some promising results, but their use may be limited because of their high cost and possible side effects [11]. As a results, there is growing interest in natural plant- based therapies as alternative or supportive treatment options. This review aims to compare the natural anti-diabetic compounds and synthetic anti-diabetic compounds based on their mechanism of actions, adverse side effects, HbA1C reduction, safety, effectiveness and also explain their possible combined use for developing safer and more effective treatment strategies [12, 13].

METHODOLOGY

This review was operated by using a structured literature search approach to identify relevant studies

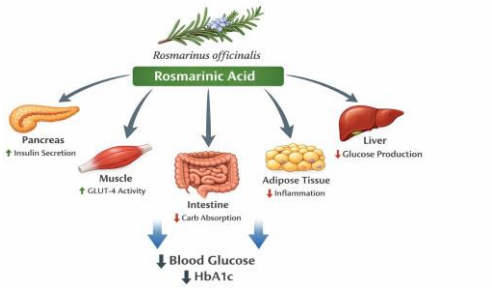
comparing natural and synthetic anti-diabetic compounds used in the treatment of diabetes mellitus, especially in non insulin-dependent (T2DM) diabetes mellitus. Scientific database including PubMed, Google Scholar, Scopus and ScienceDirect were collected for review articles between 2020-2025.

The search strategy included keyword such as "diabetes mellitus, type-2 diabetes, natural anti-diabetic compounds, synthetic anti-diabetic compounds, herbal remedies for management of diabetes mellitus, HbA1c reduction, mechanism of actions, safety profile and integrative therapies of diabetes" were used to refine the search results, Total 150 articles were identified, of which 52 articles were screened after duplicate removal, and 97 studies were finally taken in this review paper.

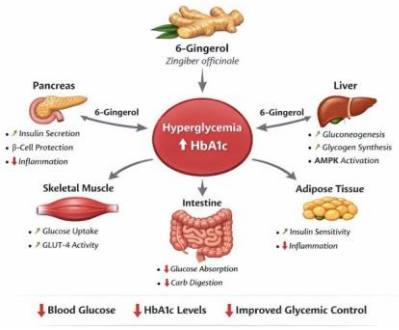
LITERATURE REVIEW

Natural compounds

1) *Rosmarinus officinalis*: *Rosmarinus officinalis* commonly known as rosemary, an aromatic evergreen shrub widely cultivated for both culinary and ornamental purposes. Its therapeutic properties are mainly attributed to bioactive constituents such as monoterpenes, diterpenes, and phenolic compounds including gallic acid, Carnosic acid, and rosmarinic acid, a derivative of caffeic acid, along with its related metabolites such as chlorogenic acid and hydroxydihydrocaffeic acid, plays a central role in its pharmacological activity [14]. Rosmarinic acid (RA) exhibits multiple biological effects including anti-diabetic, antimutagenic, anti-tumor, and anti-proliferative activities. In metabolic regulation, RA enhance glucose uptake and activate AMP-activated protein kinase(AMPK), a key cellular energy sensor involved in maintaining glucose homeostasis and stimulating skeletal muscle glucose absorption. Experimental studies shows that *R. officinalis* extracts reduce blood glucose level in-vivo and activate AMPK in hepatocytes [15]. Experimental and clinical evidence suggests that rosmarinic acid plays a beneficial role in regulating blood glucose levels. Research conducted on the diabetic animal models has demonstrated that administration of rosmarinic acid leads to significant decrease in fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). So, rosmarinic acid therapy was contributed to increase in total hemoglobin and a lowering in elevated HbA1c concentrations, indicating better long- term glycemic control [16].

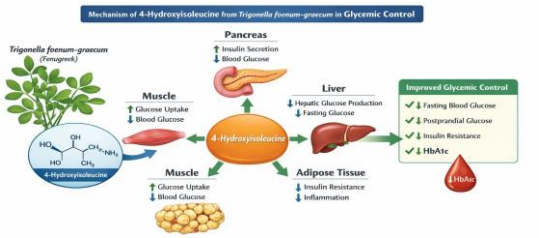


2) *Zingiber officinale*: *Zingiber officinale* (ginger) widely cultivated in Southeast Asia, is globally recognized for its culinary and medicinal applications. Although its anti-diabetic mechanism is not attributed to a single compound, its diverse phytochemical composition contributes to metabolic regulation. Ginger contains lipids (approximately 9%), oleoresins (5-8%), and volatile oils such as sesquiterpenes, zingiberene, geranial, and β-bisabolene. Major bioactive phenolic include gingerols, shogaols, zingerone, and paradols [17, 18]. Gingerol, particularly 6-gingerol, is considered a key active compound. It enhances a intracellular glucose transporter (GLUT4) translocation in skeletal muscle cells, thereby improving glucose uptake. Additionally it increase glycogen synthase- 1 activity and promotes GLUT4 membrane expression. During cooking, gingerol undergoes reverse aldol transformation to form zingerone, which has reduced pungency [19]. Clinical trials demonstrated that supplementation with ginger (3g/day for 7-8 weeks) significantly reduced fasting blood glucose (FBG), HbA1c and insulin resistance makers, supporting its therapeutic potential in diabetes management [18-20].

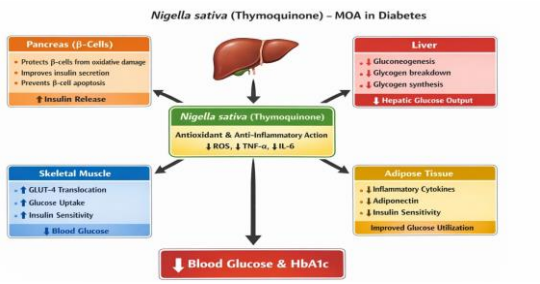


3) *Trigonella foenum-graecum*: *Trigonella foenum-graecum* (fenugreek) has been extensively used in traditional medicine and is supported by substantial scientific evidence for its anti-diabetic properties. Key bioactive components include soluble fiber, saponins, trigonelline, diosgenin, and 4-hydroxyisoleucine, all off which contribute to improved glucose metabolism [21]. Fenugreek has been shown to decrease fasting

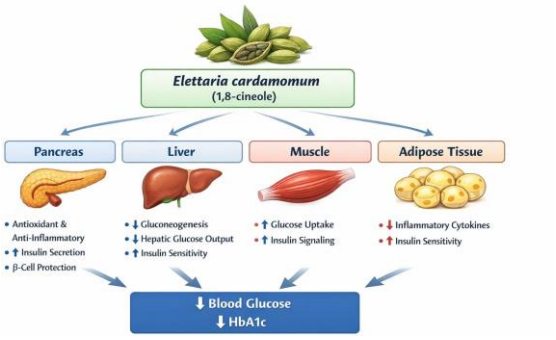
blood glucose (FBG) and enhance glucose tolerance in human studies. Its extract inhibit carbohydrate-digesting enzymes and reduce gastrointestinal glucose absorption, thereby lowering postprandial blood glucose levels. Additionally, fenugreek exerts insulinotropic effects on pancreatic β-cells and promotes peripheral glucose uptake [22]. Clinical trials suggests that fenugreek supplementation is associated with an average reduction of nearly 0.85% in HbA1c levels compared to control groups. However, variation in the dosage, disease severity and methodological limitations have contributed to inconsistent finding across studies [22, 23]



4) *Nigella sativa*: Approximately 50 mL of N. sativa tea in the fasting state reduced HbA1c levels from 7.0% to 5.9%. Furthermore, supplementation with 2 g/day and 3 g/day for 12 weeks resulted in significant decreases in HbA1c. Extended intake of 5 g/day of N. sativa tea for six months also produced marked reductions in HbA1c levels. In addition, oral administration of 4 g of *Nigella sativa* (black seed), a herbaceous plant belonging to the Ranunculaceae family, is native to India, Pakistan, and the Mediterranean region, and is widely cultivated across Arab and other Mediterranean countries. For centuries, it has been traditionally used as a culinary spice, food preservative, and therapeutic agent in various systems of folk medicine throughout Asia and the Middle East [24]. The seeds of N. sativa contain numerous bioactive constituents, including thymoquinone, linoleic acid, oleic acid, palmitic acid, and stearic acid. In this, thymoquinone is considered the major active chemical consituents and contains nearly 14.5% of its volatile oil content [25]. The hypoglycemic activity of N. sativa is depends on thymoquinone, that provide prevention of oxidative damage in pancreatic-beta cells. It may also help to improve the function of enzymes involved in glucose metabolism. Some clinical studies have indicating that regular intake of nigella sativa helped lower fasting blood glucose levels ,with value decreasing from 99.4 ± 3.1 mg/dL to 92.3 ± 4.8 mg/dL [26, 27].

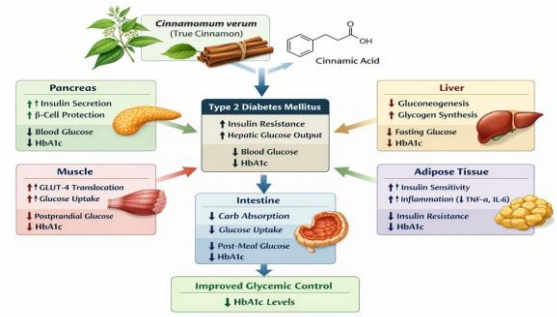


5) *Elettaria cardamomum*: *Elettaria cardamomum*, commonly known as cardamom (elaichi) that often called the queen of species. It is belongs to the ginger family "zingiberaceae. *Elettaria cardamomum* contains a various amount of bioactive chemical constituents such as quercetin, caffeic acid, gallic acid, luteolin and limonene. 1,8-cineole is the major bioactive chemical constituent that plays an a major role in lowering the cholesterol levels, reduces the inflammation, act as an anti-oxidant and supports relaxation of the blood vessels [28]. Major studies proved that 1, 8-cineole also provide the protection against cardiovascular problems by improving the antioxidant function of high density lipoprotein (HDL) and prevent the oxidative damage to lipoproteins. It has shown it has potential to improving the insulin sensitivity, reduces the obesity-related problem, controlling the glucose formation in the liver and protect pancreatic beta cells by reducing the oxidative stress by its therapeutic actions [29]. The collecting data from some research articles shows that cardamom has a wide range of anti-diabetic potential. Any individual with T2DM consuming the regular intake of cardamom daily at the amount of 3g-5g for 8-10 weeks it results in decreasing the HbA1c reduction and reduction in fasting and post-meal blood glucose levels [30, 31].

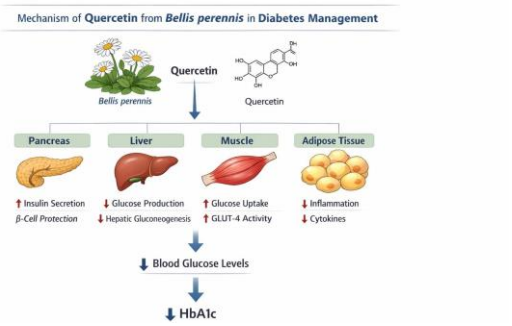


6) *Cinnamomum verum*: *Cinnamomum verum* also called as dal chini, is a traditional herbal medicine that play a major role in the treatment of diabetes mellitus due to their naturally occurring bioactive compounds such as cinnamaldehyde, cinnamic acid and volatile

oils. These bioactive compounds were involves in several metabolic pathways to improving blood glucose levels [32]. Cinnamon enhances GLUT4 translocation in muscle and adipose tissue, stimulates hepatic glycogen synthesis through inhibition of glycogen synthase kinase-3β, and suppresses gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [33, 34]. Cinnamon may help to control the rising of post-meal blood sugar levels by lowering the breakdown of carbohydrate by the help of digestive enzymes known as alpha amylase that inhibits the post-meal blood sugar levels. The findings of research articles shown that regular intake of cinnamon around 1-4 g daily can reduces the HbA1c reduction about 0.83% to 5%, especially in the patients that suffering from type 2 diabetes [32, 35, 36].

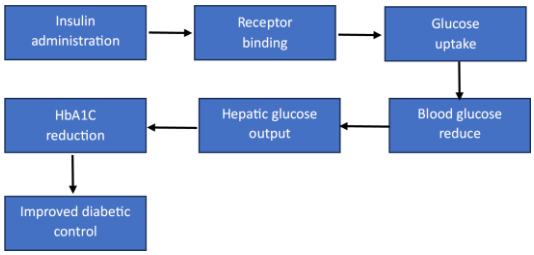


7) *Bellis perennis*: *Bellis perennis* also known as common daisy is a herbal medicinal plant that plays an important role in the management of type-2 diabetes mellitus because it contains a several phytochemical constituents such as gallic acid, abscisic acid, quercetin, caffeic acid and tannic acid, these chemical constituents were helps in lowering the blood glucose levels [37]. This phytochemical plant rich in polyphenols such as rutin, isoquercitrin, quercetin, quercitrin along with flavones such as apigenin-7-glucoside and apigenin [38]. The extract of *Bellis perennis* may improve glucose regulation by stimulating GLUT-4 translocation in skeletal muscle cells that helps in increasing glucose uptake without involvement of insulin [39, 40]. The several experimental studies have indicates that the plant has additional metabolic benefits, its extract helps in lowering the triglyceride levels, slow gastric emptying time, inhibit pancreatic lipase activity and also supports in production of collagen in human dermal fibroblasts. These combined effects highlights that therapeutic potential of *B. perennis* as a natural source of anti- diabetic compounds were supports in the management of diabetes mellitus [41, 42].

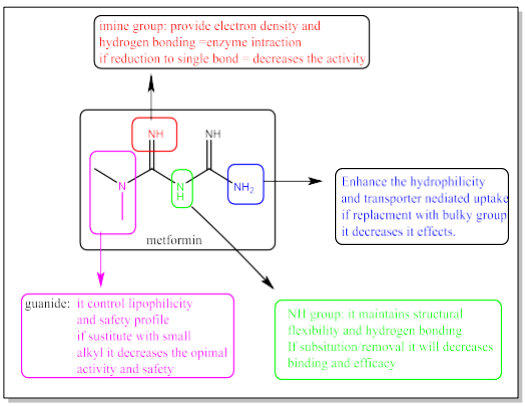


Synthetic compounds

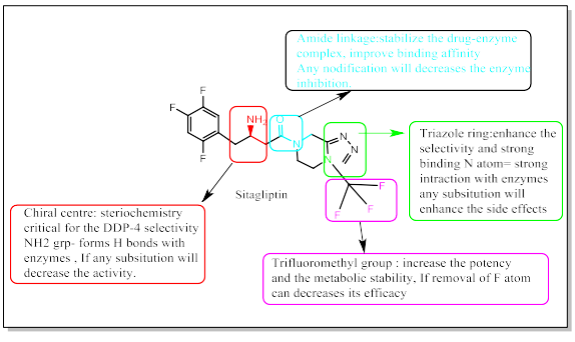
1) Insulin: insulin therapy are the key therapeutic modality of glycemic control in diabetes mellitus. Concentration- dependent metabolic effects of insulin exist, with low low infusion rates insulin closely inhibits the hepatic glucose production by suppressing glycogenolysis and glucogenolysis. Insulin also promotes peripheral glucose uptake, especially in the skeletal muscles and fat by creating glucose transporter activity and intracellular glucose metabolism [43, 44]. It has been clinically determined that in individuals with a fasting plasma glucose level high glycemic response by a high dose of insulin infusion is greater than that of low dose, indicating the dose responsiveness of insulin-mediated glucose regulation [45]. Insulin therapy is an effective treatment, pharmacokinetic constraints are linked to insulin therapy using conventional methods. Normal human insulin has slower onset and longer duration of effect that could lead to postprandial hyperglycemia. The neutron protamine Hagedorn (NPH) insulin exhibits unstable absorption kinetics and patchy basal coverage, and is incapable of its stabilization of 24 hours glycemic controls [41]. The comparative trials indicate that the agents are not always effective in generating great improvements in HbA1c reduction or significant improvement in reduction of hypoglycemic risks compared to normal insulin. In comparison with NPH insulin, the use of long acting basal analouges such as insulin detemir, predict a reduced rate of hypoglycemia. the outcome once daily detemir therapy is usually poor HbA1c reduction about 7.4%, but two doses per day provide better glycemic control, showing similar efficacy to insulin glargine on treat-to-target studies [42, 46].



2) Biguanides (Metformin) : Metformin is the first-line pharmacological option to use in treatment of diabetes mellitus while, the fact that its full-fledged inborn mechanisms have not been completely elucidated, there is a growing body of evidence that suggests that metformin serves an important role in rectifying distorted metabolic signaling pathways apart from lowering glucose [47]. The main anti-hyperglycemic effect of metformin is facilitated by the control of cellular energy homeostasis. It inhibits hepatic gluconeogenesis and reverses the glucagon-induced hepatic signaling, and thus reduces the hepatic glucose production. Metformin suppress mitochondrial respiratory chain complex 1 and induces changes in intracellular cyclic AMP (cAMP) levels and consequent regulation of protein kinase A(PKA) activity to glucagon signaling [48, 49]. The activation of 5-AMP- activated protein kinase(AMPK) is regularly involved in pharmacological effects of metformin, especially in lipid metabolism, it is through that activation of AMPK is not obligatory to the glucose lowering effects of metformin [48, 50]. It has a positive safety record and is broadly accepted clinically, metformin can cause side effects, the worst of the gastrointestinal problems including abdominal discomfort, bloating, diarrhea and weight loss. As clinical evidence metformin typically yield a 1-2 percentages point decreases in glycated hemoglobin (HbA1c), 1.12% average is reported [48, 51].



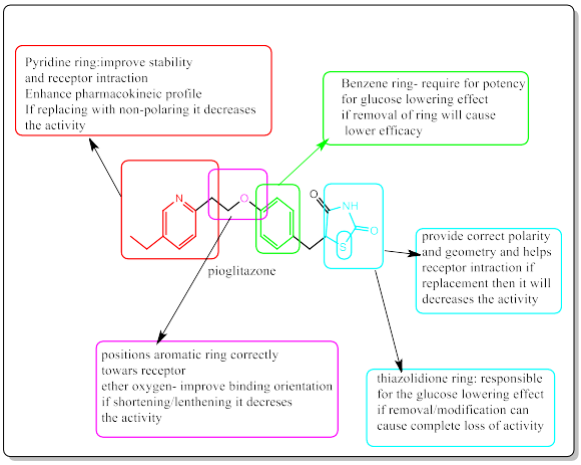
3) Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: DDP-4 inhibitors enhance glycemic regulation, as well as by enhancing the secretion of insulin and the suppression of glucagon released by raising the levels of endogenous glucagon-like peptide-1 (GLP-1). GLP-1 is act as incretin hormone that is released by intestinal L-cells when nutrients are ingested [52]. It controls the postprandial glucose levels by improving insulin level when ingested with glucose making it glucose – dependent, slows gastric emptying, and reduces appetite, and has a low probability of resulting in a hypoglycemia. These act by inhibiting the decomposition of GLP-1 by DDP-4 by these agents, which at therapeutic doses yield about 8090 percent inhibition. The degradation of GLP-1 in the mucosa of the intestine can be prohibited and thereby have an effect on the neural pathways related to the regulation of metabolism [52, 53]. Depending on their reactions with DDP-4 active sites these drugs can be divided into three main classes such as class 1 (include saxagliptin, vildagliptin) establish a covalent bond with the catalytic ser630 residue. Class 2 (includes alogliptin, linagliptin) binds non-covalently. Class 3 (include sitagliptin, anagliptin) are non- covalently bound in an alternative position in the active site without a covalent bond formed. DDDP-4 inhibitors decreases the levels of HbA1c reduction by 0.5-1.0. They are non-hypoglycemic, and linked to a lower chances of hypoglycemia [55-57]. Their safety profile and the lack of the necessity to change the dosage makes them the perfect ones compared to sulfonylureas. They can be used with the insulin therapy to achieve an extra HbA1c lowering of approx. 0.5-0.8% and can even reduce the incidence of hypoglycemic episodes [58, 59].



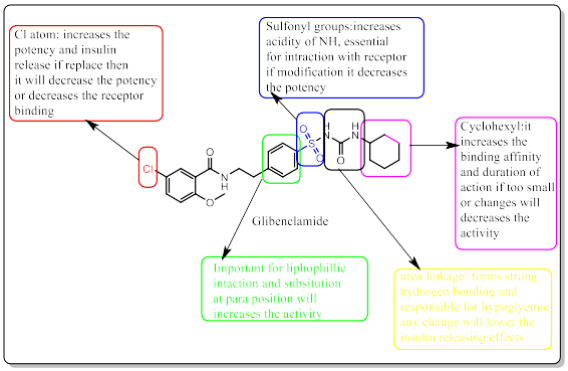
4) GLP-1 Receptor Agonists (GLP-1 RAs): Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), commonly known as incretin mimetics, replicate the physiological actions of endogenous GLP-1 and enhance glycemic regulation following nutrient intake [60]. These are the agents that enhances

the post-prandial glucose levels by promoting glucose dependent insulin secretion and inhibiting glucagon release. Their insulinotropic action is glucose dependent and there was chances of developing hypoglycemia are minimal [61]. Their anti-hyperglycemic effects, GLP-1 Ra's slow gastric emptying, and have a central antipyretic effects, that clinically leads to weight loss. Randomized controlled trials have provide the evidence on effectiveness to reduce their blood glucose levels. These agents have been demonstrated to enhance pancreatic beta cell functions and to stimulate insulin production, prevent cardiovascular and renal damage and might even have beneficial cardiovascular and protective effects [62, 63]. GLP-1 RAs come in long and short acting formulations. Short acting insulin like agents such as liraglutide are applied once or twice daily, but longer lasting ones including albiglutide and dulaglutide are used once in a week. These drugs are stimulate the insulin release by activating GLP-1 receptors on the pancreatic-2 cells and preventing the release of glucagon. They further suppress their gastrointestinal and central nervous system activities leading to the reduction in appetite and slow glucose absorption [64]. The adverse effects most of the time are gastrointestinal disturbances and such adverse effects are less often with long acting formulations [65]. Reduction in glycated hemoglobin (HbA1c) of about 0.4-1.8% has been analyses through several review papers through comparative clinical studies. They cannot make explicit comparisons of one study across another since studies differ in their trail design, patient group and treatment styles [66].

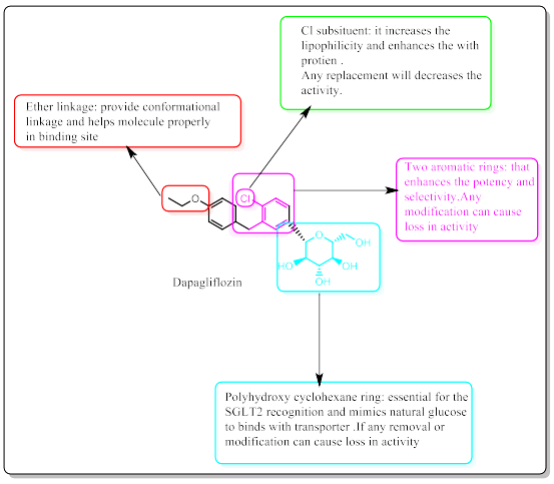
5) Thiazolidinediones (TZDs): Thiazolidinediones are a type of insulin- sensitizing anti-diabetic agents that includes some major drugs of their categories such as rosiglitazone and pioglitazone. The TZDs clinical evidence shows that in type-2 diabetes mellitus patients, treatment with drugs leads to a decrease in plasma glucose and insulin levels in the blood, and lowering in the triglycerides levels [67]. TZDs have their pharmacological effects by activating peroxisomes proliferator activated receptor gamma(PPAR-gamma) , they enhances the insulin sensitivity through enhancement of glucose uptake and by modulating the release of adipokines, inflammatory mediators, the output shows that TZDs is increases the insulin responsiveness of skeletal muscles, liver and adipose tissues [68, 69].these agents promotes the glucose uptake and use in the peripheral tissues, especially skeletal muscles and they also increases the development of insulin-sensitive adipocytes. They do not seems to influence their effects on lipid metabolism with the mass of adipose tissues, but their glucose lowering effects depends on their functionality of adipose tissues to a great extent [70]. TZDs have little negative effects on hepatic glucose production, they positively affects hepatic glucose regulation by increasing adipose tissues and skeletal muscle insulin sensitivity. TZDs has an average HbA1c reduction approx 0.5-1.5%, they can be used with biguanides or sulfonylureas to gain more glycemic control [71, 72]. The improvement in HbA1c levels by the use of TZDs is not usually accompanied by a significant number of hypoglycemic events, which is a frequent problem associated with the use of insulin or sulfonylureas [73].



6) Sulfonylureas: sulfonylureas improve the levels of insulin in circulation by two main mechanism of action, first one is promotion of pancreatic-beta cells to produce insulin and decreased hepatic clearance of insulin. The effects of these agents is achieved by attaching to particular sulfonylurea receptors found on pancreatic-beta cells. The interactions closes the potassium channels that are sensitive to ATP (K ions) and slow down the potassium efflux and membrane depolarization [74, 75]. Depolarization of the membranes then opens the channel of voltage-dependent calcium, which results in the influx of the calcium into the cytoplasm [76]. Calcium level rises in the intracellular compartment triggers the contraction of the elements leading to the exocytosis of the insulin and consequent insulin secretion [77, 78]. The major drug of sulfonylureas categories is glibemclamide should be initiated with 2mg per day and its dose modification should be made according to the glycemic responses. Sulfonylureas reduces the blood glucose levels by about 20% and decreases HbA1c reduction by the average of 1%- 2% [79, 80].



7) Sodium–Glucose Cotransporter 2 (SGLT-2) Inhibitors: sodium glucose cotransporter 2 (SGLT-2) - inhibitors are an a insulin dependent strategy to managing the glycemic control by increasing the urinary glucose excretion. These treatments blocks glucose reabsorption in the proximal renal tubules and increases the glucosuria while reduces the plasma glucose levels [81, 82]. The kidney also play a major role in glucose homeostasis, in which glucose is filtered in the glomeruli and reabsorbed into the blood. Two major transporter systems, like facilitated glucose transporters (GLUTs) and secondary active transporters, sodium through glucose, reabsorption through Na+, glucose transporter system (SGLT) mediate renal glucose reabsorption. SGLT-2 inhibitors are an active agents that specifically inhibits SGLT-2 at the proximal tubule and lowers reabsorption of glucose elevates [83]. The insulin independent mechanism of action is provides therapeutic benefits of this type of classes because it reduces the risk of hypoglycemia. These agents can either be used as monotherapy or be added to other antidiabetic agents. They are effective to a large extent regardless of insulin resistance and can applied to different stages of type-2 diabetes mellitus [84, 85]. The review study and clinical evidence indicating that SGLT-2 inhibitors have been shown to reduces HbA1c average of 0.6-3%, irrespective of background theraphy [86].

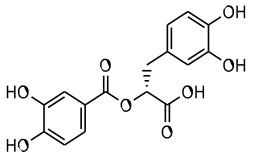
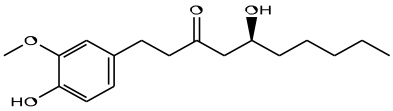
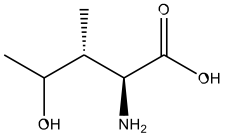
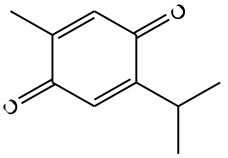


COMPARITIVE ANALYSIS

This section shows a comparative analysis of the chosen natural and synthetic anti-diabetic agents according to their mechanism of actions, the ability to decreases the glycated hemoglobin (HbA1c), and the adverse effects. Table 1 has covered the main natural compounds that have the potential to lower glucose levels, such as *Rosmarinus officinalis* (rosemary), *Trigonella-foenum graecum* (fenugreek), *Zingiber offficinale* (ginger powder), *Nigella sativa* (black seeds), *Elettaria cardomomum* (cardamom), *Cinnamomom verum* (cinnamom), *Bellis perennis.* The comparison was on their bases of mechanism of action, potential side effects and reported HbA1c reduction. Main focuses on the HbA1c reduction results, with HbA1c reduction indicating long-term control of glycemic parameters [87, 88]. Table 2 describes the key categories of anti-diabetic medications, such as insulin, sulfonylureas, metformin, thiazolidinediones, DDP-4 inhibitors, SGLT-2 inhibitors and GLP-1 receptor agonists. A combinations of mechanism of actions, therapeutic benefits and limitations that are known to date are given in each of the classes to enable comparison of them [89, 90]. Table 3 shows the results of both types and compares natural and synthetic compounds in the term of representative examples, the magnitude if the HbA1c reduction, the pharmacodynamic processes, the onset of action, the therapeutic effect, the safety, limitations, availability, cost and administrations [91]. Natural compounds usually have multi-targeted effects in term of mechanism of action, including anti-oxidant effects, anti-inflammatory effects, insulin sensitizing effects and have more systemic advantages. On other hand, synthetic drugs, in turn, operate via specific molecular mechanism for example by inhibiting SGLT2 or by activating GLP-1 receptors and can be easily glycemic controlled [92]. As a safety perspective , natural

compounds are having a few or lesser side effects , but their therapeutic effects usually taking some longer period of time, synthetic anti-diabetic compounds are more likely to have rapid and string glycemic actions but can cause some adverse effects such as hypoglycemia(with insulin and sulfonylureas) and gastrointestinal discomfort[93]. Natural compounds are to be more economical and reachable in accessibility in terms of economic factors. Recently developed drug classes like GLP-1 receptor agonists are relatively costly and have a potential to pose a financial burden on patients [91, 94].

Table 1: comparison of natural anti-diabetic compounds

Agents	Mechanism of action	HbA1c reduction	Possible adverse effect	Chemical structure
Rosmarinus officinalis (rosemary extract)	Exhibits both anti-inflammatory activities and antioxidative, which may facilitate enhanced regulation of glucose homeostatis [15].	Moderate reduction in HbA1c levels. (0.5%)	Potential allergic reaction in individual sensitive rosemary.	 (2R)-2-[(3,4-dihydroxyphenyl)carbonyl]oxy-3-(3,4-dihydroxyphenyl)propanoic ac
Zingiber officinale (ginger)	Enhances insulin responsiveness while attenuating inflammatory processes [19].	Moderate reduction in HbA1c levels. (0.35%)	Gastrointestinal disturbance, such as diarrhea and constipation.	 (5S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one
Trigonella foenum-graecum (Fenugreek)	Lower blood glucose level by inhibiting carbohydrate breakdown and enhancing pancreatic insulin release [21].	Moderate reduction in HbA1c levels. (0.85%)	Gastrointestinal disturbance, such as bloating and diarrhea.	 (2S,3R)-2-amino-4-hydroxy-3-methylpentanoic acid
Nigella sativa (black seeds)	Improve insulin sensitivity, Reduce circulating glucose concentration and exhibit significant antioxidative activity [25, 26].	Significant reduction in HbA1c levels. (1.52%)	Generally well-tolerated, but potential allergic reactions in some individuals.	 2-isopropyl-5-methyl-1,4-benzoquinone

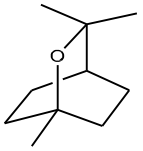
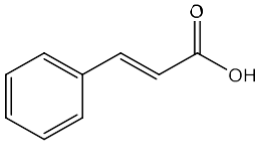
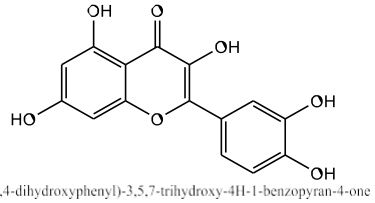
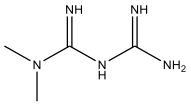
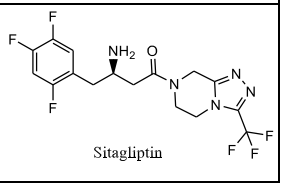
Elettaria cardamomum (cardamom)	Improves insulin sensitivity and reduces oxidative stress [29].	Moderate reduction in HbA1c levels. (0.4%)	Generally well-tolerated but potential interaction with certain medication.	 Eucalyptol
Cinnamomum verum (cinnamon)	Improve insulin sensitivity and reduces inflammation [35].	Moderate reduction in HbA1c levels. (0.83%)	Potential drug interaction with anticoagulants .	 (E)-3-phenylprop-2-enoic acid
Bellis perennis (daisy)	Provide antioxidant and anti-inflammatory activities, which may support improved regulation of glucose metabolism [39, 95].	Limited direct clinical evidence regarding the HbA1c level reduction.	Individual sensitive to daisies may experience potential allergic.	 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one

Table 2: Comparison of synthetic anti-diabetic compound

Agents	**Mechanism of action**	**HbA1c reduction**	**advantages**	**limitations**	**Chemical structure**
insulin	Directly reduces blood glucose levels my helping cells to absorb more glucose[46], [96].	1.5-2.5%	Suitable for type-1 and severe type-2 diabetes mellitus.	Risk of hypoglycemia , weight gain and require injection.	Not applicable due to complex protein structure . It is a peptide hormone consist of 51 amino acids arranged in A chain and B chains linked by disulfide bonds.
Biguanides (metformin)	Lowering the hepatic glucose production, enhancing the insulin sensitivity[49] , [51].	1.0-2.0%	First line treatment and cost effective.	May cause gastrointestinal disturbances and carries a potential risk of lactic acidosis.	 metformin
Dipeptidyl peptidase-4 (DPP-4) inhibitors.	Prevent the breakdown of GLP-1 receptor, enhancing the	0.5-1.0%	Associated with a minimal risk of hypoglycemi	Costly and moderate efficacy.	 Sitagliptin

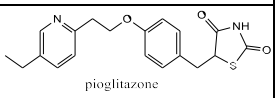
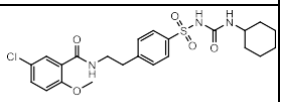
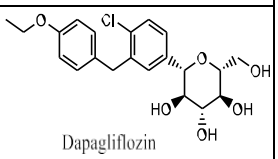
	insulin release[52].		a and well tolerability.		
GLP-1 receptor agonists	Act similarly to GLP-1 by promoting insulin and delay gastric emptying time[58].	0.3-1.9%	Weight loss and supports cardiovascular health.	Administered via injection and may be risk of nausea and pancreatitis.	_____
Thiazolidinediones	Increase insulin sensitivity in adipose tissue[69], [71].	0.5-1.5%	Enhances overall lipid parameters by helping to regulate cholesterol and triglyceride levels.	Weight gain, fluid retention and risk of heart failure.	 pioglitazone
Sulfonylureas	Stimulate insulin secretion from pancreatic β-cells[76].	1.0-2.0%	Rapid glucose lowering effect.	Risk of hypoglycemia and potential weight gain.	 Glibenclamide
Sodium-glucose cotransporter 2(SGLT-2) inhibitors	Facilitates the elimination of excess glucose from the body by increasing its removal through urine[97].	0.6-0.9%	Provides protective effects for both the cardiovascular systems and kidney function.	May increase the risk of genitourinary infections and dehydration.	 Dapagliflozin

Table 3: Comparison of natural vs synthetic compounds.

Factors	Natural compounds	Synthetic compounds
Samples	*Nigella sativa, Trigonella foenum-graecum, cinnamon, Rosmarinus officinalis, Zingiber officinale, bellis perennis*.	Metformin, sulfonylureas, GLP-1 agonists, insulin, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones.
HbA1c reduction	0.5-1.5%	0.5-2.8%
Mechanism of action	Broad and holistic: it helps the body to respond better to insulin, lower oxidative damage, and supports the recovery and growth of pancreatic β-cells.	Targeted: it works through specific pathways such as activating AMPK, blocking SGLT-2 activity, and stimulating GLP-1 receptors.
Onset of action	Its benefits slowly, with noticeable changes appearing over several weeks to a few months.	Produce quick and noticeable results, often seen within a few days to a few weeks.
Ease of administration	Can be taken by mouth or included as part of the daily diet	Supplied in standardized dosage forms such as tablets, capsules or injections. Taken as prescribed medicinal preparations rather than through dietary sources.

Efficacy	Beneficial for individuals with mild to moderate diabetes and can be used alongside other treatments as supportive therapy.	More superior for severe cases of diabetes, with established options available as first- line therapy.
Safety profile	Low risk of side effects, minimal risk of hypoglycemia.	Higher risk of side effects including hypoglycemia, weight gain and gastrointestinal issue.
Additional benefits	Provide antioxidant and anti-inflammatory support, contributing to better overall metabolic balance and health.	Cardiovascular protection(for example, with SGLT-2 inhibitors and GLP-1 receptors agonists) while delivering precise control of blood glucose levels.
Limitations	Challenges include ensuring consistent dosing, variations in the amount of active ingredients and a lack of extensive large-scale clinical studies.	Newer medication can be costly, may carry particular adverse effects and required close monitoring.
Accessibility and cost	Cost-effective and easily accessible, particularly in low income region.	Relatively costly, particularly the new drug categories such as SGLT-2 inhibitors and GLP-1 agonists.

Potential for integrative therapy

The study of this review indicates that both natural and synthetic anti-diabetic agents suggest significant potential for an integrative therapeutic approach in the management of Type-2 diabetes mellitus (T2DM). Since diabetes involves multiple pathological pathways including insulin resistance, impaired insulin secretion, oxidative stress, chronic inflammation, and altered glucose metabolism. A combination of therapies targeting different mechanism may provide excellent outcomes. Natural compounds such as thymoquinone from *Nigella sativa*, gingerols from *Zingiber officinale*, trigonelline from *Trigonella foenum-graceum*, cinnamaldehyde from *Cinnamomum verum*, and rosmarinic acid from *Rosmarinus officinalis* produce insulin-sensitizing, glucose lowering effect, anti- inflammatory and anti-oxidant. These properties may complement the targeted actions of synthetic drugs such as metformin, SGLT-2 inhibitors, GLP-1 receptor agonist and insulin. As per the case study, metformin primarily reduces hepatic glucose production through AMPK-related pathways, while cinnamon and fenugreek may enhance peripheral glucose uptake and reduces postprandial hyperglycemia. Similarly, antioxidant-rich herbal compounds may help reduces oxidative stress and inflammation, potentially lowering the long term diabetic complications. Integrative therapy have some several advantages such as , its improved glycemic control through multi-targeted mechanism, reduced the dosage requirement of synthetic medication, low risk of adverse drug reactions, better management of diabetic complications. However, challenges remain regarding herb-drug interactions, standardization of herbal formulations, dosage optimization, and lack of large-scale clinical trials. So further clinical validation is required before widespread adoption of integrative treatment strategies.

Future perspectives

The future of diabetes management is expected to move towards strongly to more personalized, multi-targeted and safer therapeutic approaches. While synthetic medications were remains necessary for rapid glycemic control, natural medications provide promising supportive benefits due to their broad spectrum pharmacological actions. Future studies to be aimed at processing the large scale clinical studies to determine the long term effectiveness and safety profile of natural compounds either it used as single therapy or as a combinations with conventional synthetic medications. The another major concern is that herbal formulations are not standard because there are differences in the source of plants, methods of extracting compounds and its concentration in therapeutic effects. Thus, the standardization of the formulations and the quality of the drugs and dosage is still necessary. The new drug delivery methods including nano-technology based carriers, encapsulation, and targeted delivery system can enhances the bioavailabilty, stability. Overall, the future of diabetes treatment is likely to involve evidence-based integration of natural and synthetic therapies, which may provide more effective, affordable, and patient-centered approaches for long-term diabetes management.

CONCLUSION

This review highlights the effectiveness and safety of both synthetic and natural anti-diabetic therapies. Several natural substance, including nigella sativa,

Elettaria cardamomum, Cinnamomum cassia, Trigonella foenum- graecum, Rosmarinus officinale and extract of *Bellis perennis*, have demonstrated encouraging results in controlling blood glucose levels and supporting overall metabolic health . However, more detailed research is still require to clearly understand how these compounds work and to established appropriate and safe dosage ranges. At same time, synthetic treatments such as biguanides, sulfonylureas, and insulin remain well established and effectiveness in managing the blood glucose levels. These medications are promising advantages, they might not suit all the patients and may also present undesirable side effects. An integrated treatment methods that combines both natural and synthetic anti-diabetic agents can be a more balanced and efficient solution that can be used to manage the disease like diabetes mellitus, such integration therapy can results in contributing to a superior glycemic regulation and decreases the negative effects and improves the overall quality of the life of the patients dealing with type 2 diabetes mellitus. In future, the research can be estimated to determining the most useful combinations of natural and synthetic agents and an improved understanding of its mechanism of action. There is also a point of view to prepared individuals treatment plans that based on individuals patients profiles. Clinical trials on the large scale is also important in order to established long term safety and therapeutic efficacy of such combinations therapies. The implementation of a more integrated and patient centered-approach can eventually results in better diabetic mellitus management and health outcomes.

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Use of artificial intelligence (AI)-assisted technology
The authors declare that they have not used artificial intelligence (AI) tools for writing and editing the manuscript, and no images were manipulated using AI.

Ethics Approval and Consent to Participate
None

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