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The Impact of *Zingiber officinale*, *Cinnamomum*, and *Aloe barbadensis* on Glycemic Regulation in Type 2 Diabetes: A Systematic Review.

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ABSTRACT

Background & Purpose:

Type 2 Diabetes Mellitus (T2DM) is a global health challenge, with increasing prevalence and significant complications that impact the quality of life. Despite the availability of synthetic drugs, many patients seek alternative treatments, including natural products, to manage their condition. Various herbal plants, such as ginger, cinnamon, and Aloe vera, have shown potential in regulating blood glucose and improving insulin sensitivity. Purpose: The aim of this review is to explore the current progress of natural products in the management of T2DM, examining both their potential and limitations. Investigations into the natural ways of managing T2DM have led many to explore the benefits of various plants and their derived compounds. However, extensive research is still needed to confirm their efficacy and safety.

Recent Findings:

Several studies have highlighted the promising effects of ginger, cinnamon, and Aloe vera in blood glucose control. The current progress of these natural products used in Type II Diabetes mellitus, contain bioactive compounds that influence metabolic pathways such as insulin signaling, glucose absorption, and oxidative stress regulation. However, evidence remains inconclusive for many natural products, and further studies are needed to confirm their efficacy and safety. Additionally, some herbal products may interact with other medications, highlighting the need for strict research methodologies and quality control. In the current work, we discussed the findings about the impact of selected herbal medicinal plants and their active compounds on individuals diagnosed with T2DM.

Summary:

Ginger, cinnamon, and aloe vera show promising therapeutic effects for the management of Type 2 Diabetes Mellitus.

Keywords:

Natural herbal medicine, natural treatments, blood glucose regulation, insulin sensitivity, type 2 diabetes, and alternative therapy

INTRODUCTION

Type 2 Diabetes Mellitus (*T2DM*) is a global health challenge, with increasing prevalence and significant complications that impact the quality of life, that still affects populations around the world. Despite the availability of synthetic drugs, many patients seek alternative treatments, including natural products, to manage their condition [1]. While conventional medications such as metformin, sulfonylureas, and insulin are the cornerstone of diabetes treatment, they often come with side effects, including gastrointestinal issues, weight gain, and risk of hypoglycemia. These limitations, along with the rising cost of synthetic drugs and the growing prevalence of drug resistance, have led to an increasing interest in herbal therapies. Many herbal products, such as ginger, cinnamon, and Aloe vera, have shown potential in regulating blood glucose levels and improving insulin sensitivity. However, despite these promising effects, there is a lack of comprehensive research validating their long-term efficacy and safety [2, 3].

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Diabetes mellitus is a worldwide health problem, a term referring to a group of metabolic disorders accompanied by hyperglycemia; an increase in blood glucose levels. This dysfunction is related to multiple reasons: either the deterioration in insulin hormone secretion, the cell receptors do not properly respond to insulin or even both[1].

Uncontrolled diabetes cause seious health problems that may lead to death if not trated.It can lead to eye complications, including glaucoma, cataracts, and diabetic retinopathy. Foot neuropathy, foot ulcers, and in later stages, gangrene, which could lead to foot amputation is recorded also . Patients also suffer from compromised immune defence and become more susceptible to several bacterial and fungal infections. Heart diseases are commonly associated with diabetes and manfest as reduced blood supply to the heart muscle, increased risk of atherosclerosis, elevated blood pressure, development of coronary artery disease that ends with cardiac arrest. (accumulation of ketone bodies in the blood) can lead to kidney damage. Nephropathy is a common complication of diabetes and occurs when blood glucose levels are elevated leading to accumulation of keton bodies(Ketoacidosis)that could lead to the damage of small blood vessels and nephrons , over the time leads to impaired kidneys' ability to filter waste and excess fluids from the blood, accumulation of waste products, fluid retention, and an increased risk of high blood pressure. If untreated, diabetic nephropathy can progress to chronic kidney disease (CKD) and eventually end-stage renal disease (ESRD), requiring dialysis or kidney transplantation. [4].

Diabetes Millites is divided into two primary classifications: type I and type II. Type II diabetes constitutes a majority, over 90%, of individuals diagnosed with diabetes [5]. Another classification was done according to the American Diabetes Association, where type I diabetes is when the absolute deficiency in insulin secretion is the main characteristic of this type [6].

Methods:

This review was based on a comprehensive literature search conducted in PubMed, Google Scholar, ScienceDirect, MDPI, and Frontiers to identify relevant studies published between January 2000 and January 2026 The included literature was identified and reviewed based on defined search strategies, criteria, and research questions. Following the literature search, the full texts were carefully examined to determine the eligibility for inclusion in this review. Conference abstracts, editorials, and studies with unavailable or incomplete data were excluded. Several online databases (http://mpns.kew.org/mpns- portal/, http://www.theplantlist.org/, or http://www.Plants of theworldonline.org) were used to validate and standardize the Latin names of the plant species.

When searching the literature, the following terms were used as keywords: “Drug–herb interactions”, “Gut Microbiota and Diabetes”, “Ginger and Gut Microbiota” “cinnamon and Gut Microbiota” “Aloe vera and Gut Microbiota”, “cinnamon and hypoglycemic drugs”, “ginger and anticoagulant”,” signaling pathways and diabetes”,” signaling molecules and T2-DM” from PubMed. “herbal medicine,” “medicinal plants,” “traditional medicine,” “metabolic disease,” “metabolic syndrome,” “diabetes,” “ginger and type-II diabetes,” , ”aloe vera and type -II diabetes,” “Cinnamon and Type-II diabetes,” “Type-II diabetes millets,” Type two DM complications,” “Signaling pathways in Diabetes,” and “ Type-II diabetes and gut microbiota.”, ”Medicinal plants and clinical trials and diabetes” from ScienceDirect and “Gut Microbiota and Diabetes” “Ginger and Gut Microbiota” from Google Scholar.

TypeI Diabetes (TID):

Type I diabetes mellitus (TIDM) is recognized as a chronic auto-immune disorder in which the pancreatic islet β-cells are destructed, resulting in insulin deficiency [7, 8] Many genetic factors have been reported to contribute significantly to the progression of T1DM, including mutations in the HLA (human leukocyte antigen) genes, particularly the HLA-DR3 and HLA-DR4 alleles, which are strongly associated with an increased risk of developing autoimmune diabetes. Other genetic factors include variations in the INS gene, which encodes insulin, and the PTPN22 gene, which regulates immune system function. These genetic variations play a role in the autoimmune destruction of insulin-producing beta cells in the pancreas [7]. Anti-pancreatic islet cell antibodies, anti-glutamate decarboxylase (GAD) antibodies, anti-insulin antibodies, anti-tyrosine phosphatase antibodies, and anti-zinc transporter 8 antibodies were demonstrated as immunological markers of T1DM [9]

The treatment of this TIDM is mainly dependent on insulin therapy (through subcutaneous injection of insulin), non-insulin treatments like the administration of Injectable or oral glucose-lowering drugs like Pramlintide that is dependent upon the naturally occurring beta-cell peptide amylin [10] or surgical treatment (Pancreas and Islet Transplantation) [11].

Type II Diabetes(TIID):

While type I diabetes is when the insulin deficiency is the main cause. Type II Diabetes is related to either insulin resistance(IR) or β-cell dysfunction. It is a multifactorial disorder that occurs due to a complex interplay between environmental and/or genetic risk factors [12]. Importantly, a number of signaling pathways substantially control the advancement of core pathological changes in *T2DM*M There is a notable links between signaling pathways and *T2DM*M pathogenesis and therapy [13]. Environmental risk factors include lifestyles, Diet, inflammatory factors, adipocytokines, hepatocyte factors, and environmental endocrine disruptors [14]. Several reports indicated that metabolic stress induces the progression of multiple cellular events that ultimately leads to IR and β cell dysfunction. Inspite of the biological differences between the different peripheral metabolic tissues/organs, they show notable resemblance. These cellular events include low inflammation state, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, lipotoxicity damage, cell death, and so on, whose interaction could cause inflammatory attack, protein turbulence, reactive oxygen species (ROS) accumulation, ATP deficiency,and ceramide overload, accelerating the pathogenesis of IR and β cell dysfunction[15&16].

Insulin Sensitivity:

TIIDM is featured with two main factors; IR and subsequent β cell dysfunction, which are the results of the feedback loops between disordered insulin secretion and insulin action. Insulin resistance(IR) , defined as the impairment of insulin sensitivity and it is a predictor of *T2DM*M and describes the failure of target organs/tissues to respond to insulin stimulation[17]. Many studies have reported that numerous factors including obesity, overnutrition, physical inactivity, gut microbiota disturbance, and family history of TIIDM may induce IR[18]. Insulin is the only peptide hormone that is mainly responsiple for lowering blood glucose by acting on specific target organs and/or tissues, including hypothalamus, liver, adipose tissue, and skeletal muscle. The hypothalamus regulates appetite, and the signaling pathways triggered by insulin, as well as leptin, play key roles in conserving energy consumption , glucose homeostasis and insulin sensitivity in peripheral tissues [19]. Upon insulin stimulation, diverse physiological responses in peripheral tissues takes place, including increased glycogenesis and de novo lipogenesis (DNL) but decreased gluconeogenesis in the liver enhanced glucose uptake in the skeletal muscle and adipose tissue, suppressed lipolysis in the adipose tissue, and so on. Dysregulation of these responses, at least a part of them, is therefore to be the major consequence of IR[20]. In addition, a decrease in circulating adiponectin, an insulin-sensitizing, anti-inflammatory, anti atherosclerotic, and hepato-protective factor secreated by adipocytes; has been found to promote hepatic and muscular IR[21].

B-cell Dysfunction:

Under normal conditions, β cells are inactive in secreting insulin during fasting period, and postprandial transient hyperglycemia stimulates β cells to release insulin, thereby increasing the blood insulin levels to answer for the demands of lowering blood glucose. Generally, β cells are capable of producing sufficient insulin to compensate for IR and maintaining euglycemia. However, chronic exposure to excess circulating nutrients, along with the consequent changed epigenetic factors, could induce a toxic state in the pancreatic islet, resulting in β cell dysfunction and compensatory failure followed by insulin deficiency, eventually causing hyperglycemia and *T2DM*M[22].

Mitochondia:

Mitochondria serve as the primary place of glucose metabolism and ATP production in cells. Mitochondrial dysfunction, is highly implicated in TIIDM progression; where is a defect in mitochondrial dynamics and thus cellular bioenergetics as elevated glucose levels stimulate mitochondria to enhance ROS production[46]. Under normal conditions, mitochondria depends on its powerful plasticity of dynamic structures to maintain ROS and ATP imbalances. These balance is compromised under pathological states, advancing IR, β cell dysfunction and

*T2DM*M[23] Additional pathological changes may be also intimately associated with IR. For example, compositional and functional alterations in gut microbiota have been observed in patients with IR and metabolic dysfunction, which may modulate cellular metabolism and energy homeostasis through homeostatic and pathogenic microbiota-host interactions. The balance of gut microbiome vs. alterations in the gut microbiome is important for normal physiological processes.The intestinal composition of microorganisms was found to interfere with host metabolism and affects abnormal blood glucose regulation. Gut microbiota was found in several pathways involved in both healthy and disease states. It includes amino acids synthesis, production of short-chain fatty acids (SCFA), absorption of nutrients, prevention of colonization with pathological bacteria, influence on the composition of bile acid, and production of several pattern recognition molecules[24,25].

The gastrointestinal tract has a complex and distinct population of microorganisms that constitute the gut microbiota. The change in gut microbial composition leads to dysbiosis that induces inflammation which is regarded as main sign of altered gut homeostasis in patients with diabetes. Also, the bidirectional relation between diabetes and gut microbiota is related to inflammation[26]. Dysbiosis is mainly observed in chronic inflammation , autoimmune diseases and metabolic disorders. Sustantial evidence indicated that the mucus layer and epithelial cell junctions that comprise the intestinal barrier can be impaired by microbial dysbiosis, leading to increased intestinal permeability. As a result the leakage of bacteria or products of bacteria takes place and initiates a cascade of chronic inflammation, that is ongoing, and a state of low-grade inflammation, that is noted in diabetes [27].

Gut dysbiosis is found to affect the production of SCFA, altering the bile acid profile and the endocannabinoid system, causing a reduction in GLP-1, GLP-2 (glucagon-like-peptide 1,2) and PYY (peptide YY),that impaired gut barrier and initiates a cascade of events that lead impaired insulin sensitivity, increased inflammation, more oxidative stress, increased steatosis, and increased fat mass which ultimately, influences the epigenetic control of the genes involved in inflammation and insulin resistance in TIIDM. Persistant oxidative stress and low-grade inflammation,due to gut dysbiosis, pancreatic beta cell death rate and insulin resistance become increased [28,29].

SIGNALING PATHWAYS IN *T2DM*M

Sevral important signaling pathways are involved in IR and/or β cell dysfunction, including PI3K/AKT, AMPK, MAPK pathways among others. These pathways interact together through inward and backward loops regulating various processes regarding insulin action and production, as well as other pathophysiological modules controlling glucose metabolism. Extensive research have stated that dysregulations of these pathways in the corresponding cells and tissues is observed in patients with TIIDM, IR, and obesity.

PI3K/AKT pathway:

PI3k/AKT is main signalling molecule that is recruited upon insulin release from β cell.It is the main effector protein to act in response to insulin action in the liver ,adipose tissue and skeletal muscles. PI3k/AKT pathway is regarded as the primary response pathway effector pathway in response to insulin action on liver, adipose tissue and skeletal muscle. Firstly, binding of insulin to its extracellular receptor activates.Activation of PI3K/AKT by insulin , although similar, the final activation outcome is different across tissues leading to different biological actions.In the liver, activation of PI3k/AKT lead to decreased hepatic glucose production (HGP), icreased lipid biosynthesis and glycogen synthesis[30,31].

Moreover, AKT2 activation in the adipose tissue can promote DNL via the mechanisms similar to those in the liver and suppress the lipolysis through multiple downstream mechanisms. These mechanisms involve the suppression of cAMP-dependent protein kinase A (PKA) activity and the regulation of lipolytic regulatory proteins, such as mTORC1, S6K1, protein phosphatase-1 (PPI) protein phosphatase-2A (PP2A), and interferon regulatory factor-4 (IRF4) [32]. It is to conclude that activation of down stream pathways of AKT grant the prepheral action of insulin in terms of reducing blood glucose, preserving insulin sensitivity and contributing to glucose homeostasis.It is noticed that the PI3K/AKT pathway has a protective role on insulin sensitivity, as a result it is mainly inactived in insulin-resistant tissues leading to disruption of insulin metabolic pathway in those tissues [33] .On the other hand, several defects related to IR and T-II DM contribute to PI3K/AKT deactivation.This includesmutation of the pathway itself, dysregulation of some regulator proteins or other

signaling pathways, lipid accumulation oralteration, reduced circulating adiponectin, and enhanced inflammation state. In *T2DM*M, these factors together with the impaired AKT pathway, control IR progression and thus systemic glucose state in a complicated way. Alterations of both the upstream and downstream components in the PI3K/AKT pathway itself have been found to aggravate peripheral IR. While in the adipose tissue and skeletal muscle, enhanced glucose uptake is a shared outcome of insulin-induced AKT2 activation, which is mainly related to an increase in the density of glucose transporter 4 (GLUT4) in the plasma membrane [34].

AMPK pathway:

AMPK plays a critical role in response to cellular energy status , hence , it can be activated canonically via increasing AMP and/or ADP levels and noncanonically through other stimulations related to lysosomes,mitochondria, Ca2+/calmodulin-dependent protein kinase kinase 2 (CaMKK2) and TGFβ-activated kinase1 (TAK1). These diverse activation mechanisms allow AMP to monitor availability of glucose, glycogen, fattay acids , Ca2+, leptin and adiponectin , the lysosomal and nuclear DNA damage as well as enhancement by diverse drugs [35,36]. It was proven that activation of AMPK pathway and its subsequent up and down stream molecules induces a remarkable effect on peripheral insulin actions, glucose uptake, nutrient intake, lipid metabolism, inflammation, insulin secretion, and thus systematic homeostasis of glucose and lipids.Activated AMPK elcit its action through stimulation of catabolic pathways of ATP and increase energy consumption via phosphorylation and inactivation of anabolic protein pathways. AMPK pathway in cellular metabolism and functions are prone to endow it with an incredible significance in the peripheral insulin action, glucose uptake, nutrient intake, lipid metabolism, inflammation, insulin secretion, and thus systematic homeostasis of glucose and lipids, warranting the vigorous attention of its therapeutic potential in the area of *T2DM* [37].

MAPK pathway

MAPK pathway is activated by Multiple stimuli, such as hormones, growth factors, and TGFβ-related agents via a dedicated three-tiered protein kinase cascade that is comprised of a MAPK kinase kinase (MAPKKK), a MAPK kinase (MAPKK), and the MAPK [38]. Activated MAPK pathways adopt a specific phosphorylation of transcriptional factors that are capable of connecting extracellular stimuli to cellular events such as proliferation, inflammation, differentiation and apoptosis. Accumulating evidence suggests that MAPK pathways are altered in several metabolic tissues during T2DM progression and play significant roles in peripheral IR and β cell fate. The MAPK signaling pathways contain three major subclasses which are ; the extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun N-terminal kinases (JNKs), and p38 family[39]. It was found that ERK1/2, JNKs, and p38s pathways are all basically activated in the liver of both mice and humans with metabolic stress, and contribute to impaired hepatic insulin sensitivity and glucose metabolism, exacerbating the progression of T2DM. Hepatic ERK1/2 activities have been found to be increased in both genetic and diet-induced obesity mouse modelstriggering overall IR and impaired glucose homeostasis, while obese mice with decreased hepatic ERK1/2 showed better systemic insulin and glucose tolerance[40].

The activation of ERK1/2 is implicated in some biological functions and cellular processes that exacerbate insulin resistance including phosphorylation of IRS proteins, the connection between the (Conjugated Bile Acids) CBA stimulation and impaired hepatic glucose metabolism. the negative effect of hepatocyte-derived fibrinogen-related protein1 (HFREP1) in hepatic insulin sensitivity, the positive feedback between macrophage-secreted cytokine and hepatocytes IR and the gluconeogenic response of FGF21 stimulation on the liver [41].

Meanwhile, In the pancreas, the activity of ERK1/2 is upregulated by hyperglycemia thereby promoting (glucose stimulated insulin secretion) GSIS and survival of pancreatic islets during T2DM progression. In β cells , ERK1/2 activation was found to be sensitive to glucose and (Glucagon Like Peptide-1) GLP-1 action and upregulates insulin regulating transcription genes by controlling the formation of transcriptional complex composed of (nuclear factor of activated T cells) NFAT and its partners [42].

ERK1/2 also is involved in insulin granules release as several reports indicated that ERK1 is fundamental in activating genes involved in β cell survival such as MSK1 (mitogen- and stress- activated kinase 1) and CREB(cAMP-responsive element-binding protein).Meanwhile, other MAPK pathways may have differen

effects on β cells biology, such as that the suppression of p38 and JNK is vital for metformin to enhance the expression of pancreatic sinaling molecules that is involved in glycerol influx and insulin secretion of β cells in T2DM[43].Hence, more studies are needed to uncover the role of MAPK pathway on the pancrease, Also, the prolonged activation of MAPK/ERK signal transduction in hypothalamus as an antidiabetic effect as targeting MAPK signalling in T-IIDM may potentiate scope of antidiabetic interventions [44].

GLUT :

GLUT(glucose transporter) is a carrier protein that takes a major part in transfer of molecules through cell membrane.It has four different types with different biological functions that depends on the substrate, distribution, location and mechanism of action [45]. GLUT-4 is usually found in skeletal muscle and adipose tissue. Insulin-induced glucose transport within adipose and muscular tissues by activating GLUT4 enhanced glucose uptake. In case of insulin resistance, the ability of insulin to translocate GLUT4 become compromised leading to its accumulation.Hence, the IR state involves a disorder in GLUT4 traffic [46].Also, impaired insulin-stimulated GLUT4 translocation in these tissues underlies insulin resistance, which is a major risk factor for type 2 diabetes and other metabolic diseases. As a result of its role in controlling glucose uptake by peripheral tissues relying on insulin status , it may represent a good target for T-II DM drug discovery. Numerous naturally occurring products have the ability to target GLUT4 activation, so they may be applied due to their safety [47]. On the other hand , GLUT2 is another transporter protein that is vital for gut integrity as it preserves the gut barrier via keeping tight junctions in the intestinal epithelial cells.Bile acids along with short chain fatty acids and endo-cannabenoidome system cooperate together to maintain healthy barrier.As a result , food intake, lipids, blood glucose, insulin resistance, inflammation, and hepatic steatosis will be decreased [48].

Mounting details demonstrate that changes in the human genome, dietary habits, or a reduction in daily physical activity are not alone responsible for the rise in obesity and type 2 diabetes. The quality of diet is considered a key factor in the prevalence of *T2DM*, especially diets that contain higher percentages of glucose or trans-fat intake. In contrast, a diet that contains higher fiber percentages, like cereals, and poly-unsaturated fat, like peanut butter, lowers the risk of diabetes[49]. On the same mannar, Diets composed of carbohydrates and amino acids is fermented into short chain fatty acids (SCFAs), an important factor in gut integrity that influences signaling pathways in intestinal gluconeogenesis, gut wall integrity, GLP-1 (Glucagon-like peptide 1) secretion, beta cell function, and insulin secretion [50].

In addition, other factors like alpha-amylase enzyme, which is a glycoside hydrolase enzyme, are mainly secreted by salivary glands. Its main role is the digestion of macromolecules such as starch. It was found that diabetic patients have higher levels of alpha-amylase than non-diabetic patients. Diminishing glucose elevation levels is one of the therapeutic strategies for managing type 2 diabetes. This can be maintained by the inhibition of such enzymes responsible for carbohydrate break-down as α-amylase and α-glucosidase that lead to the decrement of glucose uptake into the blood, hence reducing postprandial blood glucose elevations. Many studies demonstrated that natural extracts can inhibit α-amylase [51].

According to The World Health Organization, obesity is the excessive fat accumulation in the body resulting from unbalanced energy intake in diet and energy dissipation, which is a health risk. Obesity can be diagnosed via the measurement of Body mass index (BMI), which is calculated as body weight (kg)/height $(m)^2$. Being overweight is considered to be a BMI of 25–29.9 kg/m^2, and obesity is a BMI of ≥30 kg/m2 52] Obesity is associated with serious physiological changes that disrupt normal metabolism.These includes, brown adipose tissue (BAT) dysfunction; which, contributes to insulin resistance and hyperlipidemia[53]. Also, Inflammation within the adipose tissue elevates the pro-inflammatory cytokines levels, leading to metabolic inflammation, which in turn provokes B-cell dysfunction in the pancreas, leading to dysfunction of adipose tissue[54]. The decrement in adiponectin levels along with the increase in cortisol levels also affects IR[55]. Adipogenesis dysfunction, impairment in the pathways associated with the differentiation and proliferation of precursor cells into adipose cells, affects its ability to store excess fats, leading to the accumulation of ectopic fat and finally insulin resistance[56].

Despite the global warning against smoking behavior of people around the world, the number of smokers still increases. In addition, nicotine utilization can affect the normal function of beta cells and induce their death program, hence causing *T2DM* disorder [57]. On the other hand, for alcohol consumption, some studies reported

that heavy consumption would promote obesity development and liver dysfunction that could lead to *T2DM* [58] While other studies declared that moderate alcohol consumption may have a positive effect in increasing insulin sensitivity, increasing adiponectin levels and hence decrease the inflammatory effects[59]. Lower-grade inflammation was found to be a key factor in the development of type 2 diabetes. White blood cell (WBC), C-reactive protein (CRP), interleukin (IL)-6 plasminogen activator inhibitor-1, and other mediators were reported to activate the inflammation [60] Some reports showed the relationship between unbalanced glucose levels and insulin resistance with CRP and WBC, especially CRP that is considered a biomarker when related to insulin resistance than WBC [61]. In addition, Adipocytokines are cytokines secreted from adipocytes of adipose tissues and contribute to the development of metabolic disorders and low-grade inflammation mediated by obesity [62]. Adipokines include the following: Leptin is one of the adipokines that normally can either block lipogenesis or induce lipolysis, affecting the levels of intracellular lipids in the liver and beta-cells of the pancreas and hence increasing insulin sensitivity [63]. TNF-α (Tumor Necrosis Factor-alpha) is a pro-inflammatory cytokine that plays a critical role in the development of insulin resistance and the progression of Type 2 Diabetes Mellitus (*T2DM*M). It is secreted by various immune cells, including adipocytes and macrophages, and is known to interfere with insulin signaling pathways. TNF-α can inhibit the phosphorylation of insulin receptor substrates, leading to reduced insulin receptor activity and impaired glucose uptake by cells. Elevated levels of TNF-α are commonly observed in individuals with obesity and *T2DM*, contributing to chronic low-grade inflammation, which further exacerbates insulin resistance and glucose metabolism dysfunction. Adiponectin inhibition can interfere with the autophosphorylation of tyrosine- residue and insulin receptor substrate-1, which is important in the progression of the intracellular signal of the hormone [64,65]. Adipsin is an adipocytokine that is normally catalyzed by complement factor C3a and has the role of stimulating insulin production by beta-cells. It was found that adipsin levels are decreased in *T2DM*M patients [66].

Some studies reported that a multifunctional glycoprotein that is specifically secreted from human hepatocytes called Fetuin-A is related to metabolic disorders such as *T2DM* as they declared that *T2DM* and insulin resistance are characterized by the high percentage of fetuin-A. The main mechanism of fetuin-A to induce *T2DM* is mainly by inhibiting the autophosphorylation of tyrosine kinase and insulin receptor substrate-1, then causing the induction of lower-grade inflammation. [67]. In addition, the environmental endocrine disrupters, also called environmental estrogen, are chemicals that interfere with the hormonal system and lead to metabolism disturbance, causing pancreatic beta cell dysfunction and, hence, diabetes [68]. One of these endocrine disrupters is Bisphenol A [BPA, 2, 2-bis(4-hydroxyphenyl)propane]. It is an organic chemical compound that is consumed in many manufacturing processes, such as epoxy resins lining food and beverage containers, baby bottles, dental sealants, and fillings, and in many other products, BPA tends to cause adverse human health effects by causing beta- cell dysfunction(by hyperstimulation of insulin secretion by binding to a membrane estrogenic receptor), thyroid hormone unbalance, liver function impairment and obesity development. High exposure to these metabolic disrupters threatens human health.[69].

Gestational diabetes mellitus (GDM) is a type of diabetes related to pregnancy, most frequently diagnosed in the middle of the last trimester, that was not overt diabetes before gestation. In addition, diabetes can be a result of other specific factors such as a single genetic mutation in an autosomal dominant gene (monogenic diabetes) (as neonatal diabetes and maturity-onset diabetes of the young), Exocrine pancreatic disorders (such as cystic fibrosis and pancreatitis), and diabetes stimulated by drugs- or chemicals (such as the utilization of glucocorticoid steroids during HIV/AIDS treatment, which are used to manage inflammation and immune response, can contribute to insulin resistance and the development of Type 2 Diabetes Mellitus (*T2DM*). At the same time, our main topic is going to be diabetes type 2[70].

The management strategies for Type two diabetes mellitus(T2DM):

Conventional management of Type two Diabetes typically involves the use of synthetic medications, such as metformin, sulfonylureas, and insulin. Metformin is often the first-line treatment, which helps reduce glucose production in the liver and improves insulin sensitivity. Metformin is also available either once or twice- daily

dosage according to its release, either extended or immediate [71]. The Second generation of sulfonylureas, including (glyburide, glipizide, glimepiride, and gliclazide) are considered powerful glycemic control compounds that can be utilized by patients either as a monotherapy or in combination with other diabetic medications. Sulfonylureas stimulate insulin release from the pancreas, while insulin therapy is used when other medications are not effective. Others like biguanides (reduces hepatic glucose production), peroxisome proliferator-activated receptor-γ (PPARγ) agonists (boosts the action of insulin); α-glucosidase inhibitors (interferes with absorption of glucose in the gut)[70]. This class of treatment is costless but includes some medications that have a high risk of hypoglycemia, except for some newer agents. Its main action is to enhance glucose-independent insulin secretion by beta-cells directly [72]. In addition, thiazolidinediones, such as Pioglitazone and rosiglitazone, have a potent effect on T2DM in lowering glucose levels without any risk for hypoglycemia but also have an increasing effect on body weight. This class of medications acts by improving insulin sensitivity by increasing the response of β-cells toward the glucose level [73]. Glp-1 receptor agonists like exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide , are potent therapies in controlling blood glucose levels without the risk of hypoglycemia, also have an effect in decreasing body weight besides lowering proteinuria for renal disease patients [74]. Other medication strategies involve DPP4 (Dipeptidyl peptidase-4 inhibitors), SGLT2 (Sodium-Glucose transport protein 2 inhibitors), insulins, α-glucosidase inhibitors, dopaminergic antagonists, bile acid sequestrants, meglitinides, and amylinomimetics. The management of hyperglycemia in individuals with diabetes is of utmost importance in mitigating the likelihood of developing microvascular and macrovascular complications [75]. Referencing the glycemic index (GI), which is the measurement of the elevating levels of glucose in response to utilizing a carbohydrate diet that contains also glucose, comparing this elevation by utilizing a standard amount of glucose. As the GI decreased, the complications of diabetes also decreased [76].Furthermore, diabetes type 2 is leading to compromised functionality in the processes of glucose, lipid, and protein metabolism. [7, 8]. However, these treatments are associated with various side effects, which is why many patients turn to alternative therapies, including herbal products like ginger, cinnamon, and Aloe vera.

Overview of Medicinal Plants and Their Anti-Diabetic Properties:

Numerous novel therapeutic interventions have been implemented in an attempt to regulate blood glucose levels within the normal range, with the ultimate goal of mitigating the potential consequences associated with this enduring medical condition. Nevertheless, it is worth noting that oral antidiabetic drugs may occasionally be linked to adverse effects that result in the cessation of drug usage. Medicinal plants or plant-based medicine have been used widely as a cost-effective source for the treatment and/or modulation of diabetes and its complications. Many of the developing countries depend primarily on plant-based medicine to treat people with diabetes along with other disease conditions. Spices and natural compounds have been widely recognized for their inherent anti-inflammatory, antioxidant, and antidiabetic attributes over an extended period [77]. Several pharmaceutical companies rely mainly on drugs that are structurally derived from natural compounds isolated from traditional medicinal plants. For example, the anti-hyperglycemic drug called metformin, currently used to treat diabetes, can be traced back to the traditional use of Galega officinalis to treat diabetes [78]. The most common medicinal plants with hypoglycemic activities, that improve the immune system and manage blood sugar levels in humans include *Allium sativum* (garlic), *Momordica charantia* (Bitter Melon), *Hibiscus sabdariffa* L. (Roselle Plant), *Zingiber officinale Rosc* (Ginger), cinnamon, and *Aloe vera*. Given that many medicinal plants are easily accessible, cheap, and useful for managing diabetes, many developing countries and a few wealthy countries use medicinal plants to meet their healthcare needs [79].

In this study, we provide the findings about the impact of supplementation of natural herbs such as ginger, cinnamon, and Aloe Vera on individuals diagnosed with type 2 diabetes. Providing a concise overview, recent research has unveiled their promise as a therapy option for type 2 diabetes mellitus.

Herbal plants: for the treatment of *T2DM*M:

Ginger:

Ginger is a dietary natural herb that possesses numerous beneficial properties. In this study, we provide the findings about the impact of ginger supplementation on individuals diagnosed with type 2 diabetes. [80]. Ginger (*Zingiber officinale*) has been utilized as a form of herbal medicine for the treatment of many maladies

across different regions of the world during ancient times. Ginger, a spice that has few adverse effects and is deemed safe by the Food and Drug Administration, is regarded as non-toxic. Ginger has been shown to possess qualities that may be advantageous in the prevention and treatment of cancer, thrombosis, inflammation, arthritis, dyslipidemia, and pain. Additionally, ginger has demonstrated potential advantages for individuals with diabetes. The functionality of ginger can be attributed to its composition of bioactive substances, specifically gingerols and their related dehydration products (shogaols), as well as volatile oils containing sesquiterpenes (e.g., beta-bisabolene and (-)-zingiberene) and monoterpenes (primarily geranial and neral) [75]. Furthermore, it has been shown in phytochemical studies that the primary components of ginger include gingerol, shogaol, zingerone, and paradol [5].

Numerous research has demonstrated the anti-diabetic properties of ginger. In general, the impact of ginger on blood glucose levels, lipid profiles, and oxidative stress [81]. The physiological processes responsible for these actions are closely linked to the secretion and effects of insulin, as well as the enhancement of glucose and fat metabolism. [82]. Numerous researches have demonstrated the hypolipidemic action of ginger, as well as the inhibitory impact of ginger pretreatment on induced hyperglycemia and hypoinsulinemia. Furthermore, several empirical investigations have demonstrated the anti-diabetic, hypo-lipidemic, and anti-oxidative characteristics of ginger, hence highlighting its efficacy in safeguarding against and managing metabolic illnesses [83]. Ginger has been found to have an impact on various markers in individuals with type 2 diabetes, including fasting blood sugar levels, hemoglobin A1c levels, apolipoprotein B levels, apolipoprotein A-I levels, and malondialdehyde levels[5].

Antihyperglycemic Effects of ginger

Several researches have been conducted to investigate the effectiveness of ginger in regulating hyperglycemia. According to a study, the administration of a singular dose of ginger juice effectively inhibited the occurrence of acute hyperglycemia induced by 5-hydroxytryptamine (5-HT), indicating the potential involvement of 5-HT receptors in the regulation of glycemic control. During the oral glucose tolerance test, the administration of ginger resulted in a notable reduction in the area under the curve of plasma glucose levels and an elevation in the area under the curve for insulin in rats with streptozotocin-induced diabetes. The administration of ginger over an extended period has shown significant effects on blood glucose levels, as well as notable reductions in serum triglyceride and total cholesterol levels. Additionally, ginger supplementation led to higher insulin levels and effectively avoided the loss of body weight, as well as weight loss in the liver and kidneys, in animal models with type 1 diabetes [80].

Additional research has demonstrated that the use of ginger powder (at a dosage of 200 mg/kg) effectively mitigated symptoms associated with metabolic syndrome. These symptoms encompassed a reduction in blood glucose and total cholesterol levels, as well as an elevation in overall antioxidant capacity[84]. In an animal model of type 2 diabetes caused by a combination of a high-fat diet and STZ, ginger treatment resulted in improved glucose tolerance and increased serum insulin levels in diabetic rats[85]. In addition, the primary pungent constituent found in ginger, known as [6]-gingerol (at a dosage of 100 mg/kg bw), exhibited a notable reduction in fasting blood glucose levels and an enhancement in glucose tolerance among db/db type 2 diabetic mice. Moreover, it led to a decrease in plasma triglyceride, total cholesterol, free fatty acid, low-density lipoprotein, and plasma insulin concentrations[81]. In the clinical investigation, diabetic patients were administered a divided dose of 3 g of dry ginger powder daily for a duration of 30 days. The results of the study revealed a noteworthy decrease in blood glucose levels, as well as reductions in triglyceride, total cholesterol, LDL cholesterol, and VLDL cholesterol levels[85].

Mode of Action of Ginger on Glycaemic Control:

Ginger effect on the enzymes in Carbohydrate Metabolism.

The primary enzymes responsible for regulating carbohydrate metabolism in hyperglycemia and type 2 diabetes are α-amylase and α-glucosidase. The study observed a correlation between the inhibitory activity of ginger on these two enzymes and the phenolic concentrations of gingerol and shogaol in the extracts. However, the results indicated only a minimal inhibitory effect on α-glucosidase, while no inhibitory effect was observed on α-

amylase. Additional in vivo investigations have demonstrated that the administration of ginger resulted in a considerable rise in the activities of pancreatic lipase, amylase, trypsin, and chymotrypsin [86]. Also, It has been shown that ginger reduces cellular oxidation and scavenges superoxide anion and hydroxyl radicals[83].

Ginger effect on insulin release

Diabetes mellitus is distinguished by impairments in the secretion of insulin and the responsiveness to insulin. In the experimental rat model of type 1 diabetes produced by STZ, it was shown that the decrease in blood glucose levels was concomitant with a fall in insulin concentration. There is evidence to suggest that ginger can regulate the secretion of insulin. The research demonstrated that the administration of ginger extract increased plasma insulin levels while simultaneously reducing blood glucose levels[87]. According to a study conducted by Li *et al*. (2012a), ginger plays a significant role in facilitating the clearance of glucose in insulin-responsive peripheral tissues, hence contributing to the maintenance of blood glucose homeostasis[88]. According to Huang *et al*. (2019), a study conducted by Huang and colleagues demonstrated that the consumption of dietary ginger resulted in a significant improvement in HbA1c levels from the initial measurement to the subsequent follow-up. This finding suggests that ginger, as a natural remedy, may have a prolonged effect on regulating glucose levels in individuals diagnosed with type 2 diabetes [88.89].

Ginger effect on the lipid profiles.

A prevalent characteristic observed in individuals with obesity and diabetes is compromised glucose metabolism in response to insulin stimulation. The association between insulin resistance in peripheral tissues and increased levels of circulating lipids and deposition of lipids in tissues has been widely recognized. According to Daily *et al*. (2015), the findings from the mechanistic studies indicated that an excess of free fatty acid and fatty acid oxidation had an inhibitory effect on the transport of glucose into peripheral tissues. This inhibition occurs at the initial phase of glucose metabolism, which is the rate-limiting step[87]. Multiple studies have provided evidence of the notable lipid-lowering benefits of ginger, leading to an increase in insulin sensitivity. According to a study conducted by Andallu *et al*. (2003), the first clinical studies demonstrated that ginger exhibited positive effects on the lipid profile of individuals with diabetes[90]. According to Salih and his collegues in 2023, there have been reports suggesting that ginger may possess the ability to reduce lipid peroxidation and subsequently lower the levels of malondialdehyde (MDA)[91]. This action is believed to be mediated by the modulation of enzymatic blood levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). The antioxidant activity of ginger has been associated with its ability to reduce lipid peroxidation. This can be ascribed to the presence of several phenolic compounds in ginger, which exhibit inhibitory effects on lipid peroxidation and help retain the antioxidant components. Furthermore, several studies had demonstrated that the administration of ginger supplements resulted in a decrease in the levels of fasting blood sugar (FBS), glycated hemoglobin (HbA1c), apolipoprotein B (Apo B), Apo B/Apo A-I ratio, and malondialdehyde (MDA), while simultaneously increasing the level of apolipoprotein A-I (Apo A-I) in individuals diagnosed with type 2 diabetes[92].

Effect of ginger on some key organs:

Ginger has shown prominent protective effects on diabetic liver, kidney, and neural system complications. Ginger's effects on the body are primarily driven by its bioactive compounds, gingerols and shogaols. These compounds were proven to possess potent anti-inflammatory and antioxidant properties.It interacts with various organ systems to provide therapeutic benefits, most notably in the digestive, cardiovascular, and respiratory systems[88,93,94].

Ginger effect on liver

Research findings have indicated that the administration of hepatic ginger at a dosage of 400 mg/kg resulted in a significant reduction in both triglyceride and cholesterol levels inside the liver. The results of molecular investigations demonstrated an elevation in the expression of liver mRNA and protein levels of the low-density lipoprotein (LDL) receptor, whereas the protein expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase was observed to be downregulated. The mechanistic data indicated that the impact of ginger on lipid homeostasis can be attributed, at least in part, to a reduction in cholesterol biosynthesis and an increase in the hepatic uptake of circulating LDL cholesterol. Additionally, the administration of ginger resulted in the

inhibition of gene and protein expression related to hepatic inflammation indicators, specifically TNFα and IL-6, as well as a reduction in NF-κB activity[93,88].

Ginger effect on kidney

It was observed that the administration of an ethanolic ginger extract resulted in a decrease in blood glucose levels and a restoration of several components such as total carbohydrates, pyruvate, glycogen, and total protein in kidney tissue[94].

Ginger effect on central nervous system

The findings of a research investigation conducted on streptozotocin-induced diabetic rats showed that ethanolic ginger extract exhibited neuroprotective properties through the facilitation of brain antioxidative defense systems and the suppression of malondialdehyde (MDA) levels. A study conducted a notable decline in the activities of antioxidant marker enzymes, namely superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), in diabetic rats. However, upon oral administration of ginger, these decreased activities were found to be enhanced. Consequently, this led to a reduction in the levels of glutathione and malondialdehyde in the cerebral cortex, cerebellum, hippocampus, and hypothalamus of the rats[95,87].

Mechanism of Action of Ginger:

Ginger (*Zingiber officinale*) has long been recognized for its medicinal properties, including its potential to manage Type 2 Diabetes Mellitus (*T2DM*). The beneficial effects of ginger in diabetes are attributed to its bioactive compounds, such as gingerol, shogaol, zingerone, and paradol, as well as its volatile oils, which influence multiple biological mechanisms involved in glucose metabolism, insulin sensitivity, and overall metabolic regulation[96].

Improvement of Insulin Sensitivity: Ginger has been shown to enhance insulin sensitivity in peripheral tissues, which is crucial in managing Type 2 Diabetes. Insulin resistance, a key feature of *T2DM*, impairs the ability of cells to respond to insulin effectively. By improving insulin receptor function and signaling, ginger facilitates better glucose uptake into cells, thereby reducing blood glucose levels. This effect is particularly beneficial for individuals with *T2DM* who have impaired insulin response[97].

Regulation of Blood Glucose Levels: Ginger helps regulate blood glucose levels by influencing various metabolic pathways. It has been demonstrated to lower fasting blood glucose and improve glucose tolerance, particularly in animal models and clinical studies. The active compounds in ginger may promote glucose utilization and enhance insulin secretion from pancreatic β-cells, which helps maintain blood glucose homeostasis. Ginger has also shown potential in reducing postprandial (after-meal) blood glucose levels, thereby preventing harmful glucose spikes[98].

Inhibition of Carbohydrate-Hydrolyzing Enzymes: One of the mechanisms by which ginger exerts its anti-diabetic effects is through the inhibition of carbohydrate-digesting enzymes, such as α-amylase and α-glucosidase. These enzymes are responsible for breaking down complex carbohydrates into glucose in the digestive system. By inhibiting these enzymes, ginger slows the absorption of glucose, which helps prevent rapid increases in blood sugar levels after meals, contributing to better blood glucose control[99].

Antioxidant and Anti-inflammatory Effects: Chronic oxidative stress and inflammation play a significant role in the development and progression of Type 2 Diabetes. Ginger possesses potent antioxidant properties that help reduce oxidative stress by neutralizing harmful free radicals. Additionally, ginger's anti-inflammatory compounds, such as gingerols, help reduce the levels of pro-inflammatory cytokines like TNF-α and IL-6, which are typically elevated in individuals with *T2DM*. By reducing oxidative stress and inflammation, ginger helps protect pancreatic β-cells from damage, supports insulin function, and contributes to better glucose metabolism[100].

Impact on Lipid Profile: Dyslipidemia, which involves elevated cholesterol and triglyceride levels, is commonly associated with Type 2 Diabetes. Ginger has been shown to improve lipid profiles by lowering total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol levels. This effect not only

improves the metabolic health of individuals with diabetes but also reduces the risk of cardiovascular complications, which are common in *T2DM* patients[101].

Reduction in Hepatic Glucose Production: Ginger may also have an impact on reducing hepatic (liver) glucose production. In *T2DM*, the liver tends to overproduce glucose due to dysregulated gluconeogenesis. Ginger's bioactive compounds help modulate liver function, decreasing excessive glucose production and preventing hyperglycemia. This regulation helps maintain balanced blood sugar levels[102].

Pancreatic β-Cell Protection: Ginger has protective effects on the pancreatic β-cells, which are responsible for producing insulin. Research suggests that ginger may reduce β-cell apoptosis (cell death) caused by oxidative stress and inflammation, promoting the survival and function of these cells. By protecting β-cells, ginger supports sustained insulin production, helping manage blood glucose levels more effectively[103].

Modulation of Gut Microbiota: Recent studies suggest that ginger may influence gut microbiota composition. Gut health is increasingly recognized as an important factor in glucose metabolism and insulin sensitivity. By promoting a healthy balance of gut bacteria, ginger may improve glucose absorption, regulate insulin signaling, and contribute to better blood glucose control in individuals with Type 2 Diabetes[104].

In conclusion, ginger's mechanisms of action for managing Type 2 Diabetes Mellitus include improving insulin sensitivity, regulating blood glucose levels, inhibiting carbohydrate-digesting enzymes, providing antioxidant and anti-inflammatory effects, improving lipid profiles, reducing hepatic glucose production, and protecting pancreatic β-cells. These multifaceted actions make ginger a promising natural therapy for managing *T2DM*. However, further clinical studies are needed to confirm its full therapeutic potential and optimize its use in diabetes management[82].

Ginger-Drug (Anticoagulant) interaction:

Several reports stated that the excessive or concurrent use of ginger (*Zingiber officinale*) and anticoagulants (e.g., warfarin, dabigatran, or rivaroxaban) may significantly increase the risk of bleeding as ginger is strong P-glycoprotein (P-gp) inhibitor and has been reported to significantly reduce the P-gp-mediated efflux of anticoagulant drugs and impair platelet aggregation and inhibit P-glycoprotein, which can raise drug concentrations[105,106].

It is known that Warfarin possess narrow therapeutic window and numerous interactions complicate its safe management, necessitating ongoing monitoring to prevent serious complications from inadequate or excessive anticoagulation. This is due to that warfarin affects the metabolism of medicinal plants through CYP450 enzymes, and while interactions are rare, caution is advised for older adults and those with a history of gastrointestinal bleeding, liver or kidney disease, or bleeding disorders. Also, oral anticoagulants (like warfarin) are derived from coumarin, which inhibits the synthesis of vitamin K and prevents the formation of blood clots. Verma *et al*. showed that 5 g of ginger in two divided doses consumed with a fatty meal significantly inhibited platelet aggregation in healthy males[107,108].

Cinnamon:

Cinnamon is well known as a spice and is purported to have an anti-diabetic effect. There are two main types of cinnamon, Ceylon cinnamon (C.zeylanicum) and Chinese cinnamon (C.aromaticum), both of which have received the most research. The chemical content of cinnamon species was found to be different from each other.While the Chinese cinnamon contain 85–90% cinnamaldehyde, this ratio is 65–70% in the Ceylon cinnamon. Moreover, this ratio varies according to the quality of the cinnamon. Studies have shown that ground cinnamon is more effective than its extract. It has been reported in clinical studies that Chinese cinnamon is more effective than Ceylon cinnamon. Also, chinese cinnamon contains more coumarin than other types of cinnamon[109], which poses a health concern.

Mode of action of cinnamon:

Cinnamon, a well-known spice, has been found to exhibit significant anti-diabetic properties, particularly in managing blood glucose levels in individuals with Type 2 Diabetes Mellitus (*T2DM*). The mechanisms by which cinnamon exerts its effects involve multiple biological pathways, including enzyme inhibition, modulation of insulin sensitivity, and antioxidant properties[110].

Inhibition of Carbohydrate-Hydrolyzing Enzymes: Cinnamon has been shown to inhibit the activity of enzymes like α-glucosidase and α-amylase. These enzymes are responsible for breaking down complex carbohydrates into glucose in the digestive system. By inhibiting these enzymes, cinnamon slows the absorption of glucose into the bloodstream, reducing postprandial (after-meal) blood glucose spikes. This mechanism helps in controlling blood sugar levels after eating[111].

Enhancement of Insulin Sensitivity: One of the key features of Type 2 Diabetes is insulin resistance, where the body's cells become less responsive to insulin, resulting in elevated blood glucose levels. Cinnamon helps improve insulin sensitivity by increasing the efficiency of insulin receptors on cell surfaces. This enhancement allows the body to use insulin more effectively, aiding in better glucose uptake by the cells, thus lowering blood glucose levels[112].

Activation of Insulin Signaling Pathways: Cinnamon has been found to activate key insulin signaling pathways, which improve glucose uptake in tissues such as muscle and fat. The active compounds in cinnamon, such as cinnamaldehyde, are believed to influence cellular pathways that regulate glucose metabolism, including the activation of the PI3K/Akt pathway, which plays a crucial role in insulin signaling and glucose transport[113].

Reduction in Oxidative Stress: Chronic oxidative stress is a major factor contributing to insulin resistance and the progression of Type 2 Diabetes. Cinnamon contains potent antioxidants, including polyphenols and flavonoids, which neutralize harmful free radicals in the body. By reducing oxidative stress, cinnamon helps protect insulin-producing pancreatic β-cells from damage and supports better overall metabolic function[114].

Modulation of Lipid Profile: Cinnamon also has beneficial effects on lipid metabolism, which is often dysregulated in individuals with *T2DM*. It has been shown to reduce levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides while increasing high-density lipoprotein (HDL) cholesterol. These changes help improve lipid profiles and reduce the risk of cardiovascular complications, which are common in people with diabetes[115].

Anti-inflammatory Effects: Inflammation is a key contributor to insulin resistance. Cinnamon has anti-inflammatory properties that help reduce the levels of pro-inflammatory cytokines such as TNF-α and interleukins. By reducing systemic inflammation, cinnamon contributes to the alleviation of insulin resistance and improves the body's ability to regulate blood sugar levels[116].

Impact on Gut Microbiota:

Recent studies suggest that Cinnamon may be considered a promising, natural adjuvant in Type 2 Diabetes (T2D) management. There is evidence that cinnamon and its bioactive compounds, such as cinnamaldehyde, gallic acid, eugenol, and beta caryophyllene, have been associated with antihyperglycaemic, anti-lipidemic, and antioxidant effects. Cinnamon extract was reported to mimic insulin and improve cellular glucose uptake. Furthermore, A proanthocyanidin (Cinnamtannin B1) extracted from the stem of Ceylon cinnamon facilitates the activation of β-subunit phosphorylation in various insulin receptors including adipocytes. It was reported that cinnamon extract (CE) has the ability to enhance the insulin receptor (IR)-β (which is stimulated by insulin) in skeletal muscles of rats fed with chow diet. Moreover, it was also revealed that utilization of glucose in rats fed high fructose diet (HFD) improved due to CE. Also , due to Cinnamon's high polyphenol content, it helps lower inflammation and oxidative stress. By acting as a prebiotic, it strengthens the gut barrier and reduces intestinal inflammation. This prevents pro-inflammatory toxins from "leaking" into the bloodstream—a key driver of insulin resistance. Ultimately, these changes stabilize glucose and lipid metabolism, leading to better overall metabolic health[ ]. Studies indicated that the intake of 1–3 grams of cinnamon daily over several weeks can significantly lower fasting plasma glucose, HbA1c, and lipid levels. In conclusion, When combined with a known probiotics, cinnamon extract can form a symbiotic effect, further improving antioxidant capacity and glycemic indices [114-117].

Cinnamon clinical studies

A study conducted by Shihabudeen *et al*. examined the ability of cinnamon extract to inhibit the enzyme α-glucosidase, which helps regulate postprandial blood glucose levels, in sucrose and maltose-loaded STZ-

induced diabetic rats. The cinnamon methanol extract was prepared using the Soxhlet extraction method, and both healthy male albino Wistar rats and STZ-induced diabetic rats were used for testing. In vitro experiments were conducted to assess the inhibitory effects of cinnamon extract on yeast α-glucosidase and rat intestinal α-glucosidase. Studies conducted in vitro showed that cinnamon extract had a dose-dependent inhibitory effect on both yeast and mammalian a-glucosidase, with an $\mathbf{IC_{50}}$ value of 5.83 g/ml(yeast) and 670 g/ml (mammalian). In rats with diabetes induced by streptozotocin (STZ), the study demonstrated that cinnamon bark extract effectively inhibits the enzyme α-glucosidase, leading to a reduction in postprandial hyperglycemia. This inhibition of α-glucosidase helps prevent the rapid increase in blood glucose levels after meals by slowing the breakdown of carbohydrates, thus helping to manage blood sugar spikes. Cinnamon extract has the potential to be a nutraceutical treatment for postprandial hyperglycemia; however, particular inhibitors from the crude extract have to be separated, characterized, and employed therapeutically[118].

In a study conducted by Kang *et al*. on the carbohydrate hydrolyzing enzyme inhibition of cinnamon proanthocyanidins (PACs), Five grams of cinnamon bark powder were extracted for two hours at room temperature in 100 mL of acetone solution (CAE) (acetone: water: hydrochloric acid, 70:29.9:0.01) and for thirty minutes at 90 °C in 100 mL of deionized water (CWE). LH-20 was used to purify the PACs from CAE (CAE-PAC) so they could be further examined. By using the 4-Dimethylaminocinnamaldehyde (DMAC) test to measure PAC content, it was found that CAE-PAC, CAE, and CWE had respective PAC concentrations of 795, 177, and 123 mg/g. It was discovered that CAE and CWE each contained 152 and 134 mg/g of total phenols, respectively. The inhibitory effect against rat -glucosidase was assessed after all extracts were adjusted to the same PAC content (180, 90, 45, and 20g). Rat

glucosidase inhibitory activity was low in the CAEPAC fraction, with CAE having the greatest inhibitory a ctivity.There were more specific maltase and sucrase inhibitory activity in CAE than CWE.In light of the fact th at CAE inhibits carbohydrate hydrolyzing enzymes, the results point to the fact that the observed bioactivity is n ot PAC dependent and that it has a stronger anti-hyperglycemic potential than CWE[119].

Another study by Beejmohun *et al*., the acute effects of a particular hydro-alcoholic extract (CCE) of Ceylon cinnamon on the breakdown of carbohydrates and the lowering of post-meal blood sugar levels were examined. Preclinical tests included in vivo starch tolerance and in vitro enzymatic assays in rats, followed by a clinical trial in 18 healthy males and females that was randomized, double-blind, placebo-controlled, and cross-over. The volunteers took 1g of Ceylon cinnamon hydro-alcoholic extract (CCE) before eating a meal, and the in vitro results showed that CCE inhibited pancreatic alpha-amylase activity by $\mathbf{IC_{50}}$ of 25 g . In rats, an in vivo study using a dosage of 12.5 mg/kg body weight of CCE showed an immediate, dose-dependent reduction in the glycemic response to starch. In humans, a 1g dose of CCE significantly lowered the glycemic curve[120].

36 adults between the ages of 35 and 77 were randomly assigned to one of two equal groups (n=18) in a randomized control experiment by Rachid *et al*. to investigate the influence of aqueous cinnamon extract on postprandial glycemia levels in patients with type 2 diabetes. For the oral glucose tolerance test, one group simply consumed glucose solution, while the other group consumed glucose solution along with cinnamon aqueous extract (6 g/100 mL). The cinnamon extract had little to no impact on the postprandial glycemia levels in patients with type 2 diabetes mellitus because the differences between the groups in the tests were small[121].

44 patients with type 2 diabetes were divided into two equal groups (n=22) in a double-blind, randomized, placebo-controlled clinical trial study by Talaei *et al*. to determine the effects of daily intake of three grams of cinnamon on the glycemic indicator, advanced glycation end products, and antioxidant status in patients with type 2 diabetes over the course of eight weeks. Of these 44 patients, only 39 patients completed the study. Cinnamon supplementation exhibited no noticeable impact on glycemic and inflammatory indicators in type 2 diabetic patients[122].

For three months, 160 people between the ages of 18 and 80 were divided into two equal groups (n=80) and given either 3 grams of cinnamon or a placebo in addition to their oral diabetic medications. Lira Neto *et al*. conducted this study to determine the effectiveness of cinnamon as an adjuvant treatment in reducing glycemic levels in people with type 2 diabetes. The results showed very little decrease in the glycemic measures in the cinnamon group[123].140 patients were divided into four groups in a triple-blind, placebo-controlled, randomized clinical trial by Zare *et al*. to examine the impact of cinnamon supplementation on anthropometric,

glycemic, and lipid outcomes of patients with DM type II based on their baseline BMI. The cinnamon groups (BMI 27) and the placebo groups (BMI 27) each received capsules of cinnamon or placebo (500 mg). Consequently, cinnamon may enhance anthropometric measurements, glycemic indices, and lipid profiles in type II diabetes patients, particularly in those with higher BMIs[124].

In a randomized, triple-blinded clinical research, cinnamon and caucasian whortleberry (Vaccinium arctostaphylos L.) were evaluated for their impact on body mass index (BMI), lipid profile, and blood glucose control in people with type 2 diabetes (T2DM). There aren't many variations between before and after taking the supplements since 105 participants were divided into three groups and given either placebo, cinnamon, or whortleberry supplements (1 g/day) for 90 days[125].

In conclusion, cinnamon works through multiple mechanisms to help manage Type 2 Diabetes Mellitus. Its ability to inhibit carbohydrate-digesting enzymes, enhance insulin sensitivity, reduce oxidative stress, improve lipid profiles, and exhibit anti-inflammatory effects makes it a promising natural remedy in the management of T2DM. However, further clinical studies are needed to fully understand its potential and optimize its therapeutic use. Cinnamon does not significantly affect people with type 2 diabetes, according to the results of all research trials, but it is, however, advised to take the medication with cinnamon, they concluded. However, cinnamon studies suggested that cinnamon may improve insulin sensitivity and blood sugar control[126].

Cinnamon-Drug Interaction:

Cinnamon is a medicinal plant which is used as a dietary supplement for a wide range of diseases. Also,multiple preclinical and clinical studies have examined efficacy of cinnamon in these medical conditions. Diabetes mellitus is the most popular investigated indication for cinnamon. Co-administration of cinnamon with antidiabetic drugs and/or insulin can potentiate the blood glucose-lowering effects, which escalate the risk of hypoglycemia. Cinnamon has been shown in vitro to increase glucose uptake, glycogen synthesis and insulin sensitivity. Also, cinnamon supplementation significantly reduced serum levels of FPG, insulin, HOMA-IR, and HbA1c in T2DM patients For FPG and HbA1c, this reduction was the strongest in T2DM participants.Despite conflicting results, many studies showed improvement in glycemic control in patients with diabetes and pre-diabetes taking cinnamon supplementation [127,128].However, clinical data are conflicting. Some small studies have reported that cinnamon reduced fasting blood glucose levels and/or glycosylated hemoglobin (HbA1c) in patients with type 2 diabetes, whereas others have not. Recent trials and animal studies indicated that prolonged consumption of cinnamon promoted satiety and diminished mean food consumption, which contributed to lower FPG and 2-h post-prandial blood glucose levels [129]. It is stated that this potential effect of cinnamon on FPG concentration is due to the increasing the levels of PI3-kinase and phosphorylated intracellular protein IRS-1, and therefore stimulating the activity of insulin receptors, and increasing cellular glucose uptake [130]. This mechanism is responsible for a dose-dependent reduction in serum insulin levels by cinnamon intake, Furthermore, the bioactive ingredients of cinnamon prepreations may have different results on glycemic control, as it is not clear whether both the extract and powder of cinnamon are equally effective [131]. it is suggested that the ability of cinnamon to lower FPG in T2D patients may be due to its polyphenol compounds' potential to enhance insulin signaling and then potentiate insulin-regulated glucose utilization. if antidiabetic agents are used concomitantly with cinnamon. Patients should be advised on the potential signs and symptoms of hypoglycemia (e.g., headache, dizziness, drowsiness, nervousness, confusion, tremor, hunger, weakness, perspiration, palpitation, and tachycardia)[132].

Aloe Vera

Aloe vera is a delectable plant that belongs to the Liliaceae family, which comprises around 420 species. *Aloe barbadensis Miller*, the predominant species, is commonly referred to as A. vera. *Aloe vera* doesn't have a single "active ingredient" that is responsible for its many benefits. Instead, it contains a complex mix of over 75 potentially active components working together to produce its effects. Some of the key bioactive compounds in

aloe vera include Polysaccharides[133]. These sugars, like acemannan, are believed to have anti-inflammatory and immune-boosting properties. Anthraquinones: These compounds, found mostly in the aloe latex (layer beneath the rind), have laxative effects but should be limited due to potential side effects. Vitamins, minerals, and enzymes: *Aloe vera* is a rich source of various vitamins (including A, C, and E) and minerals that contribute to its overall health benefits[134]. The specific combination of these components and their interaction is thought to be responsible for the various properties aloe vera is known for, such as wound healing, soothing skin irritation, and potentially aiding blood sugar control **(Figure 1)**[135].

Mode of action of aloe vera

Aloe vera, known for its numerous health benefits, has demonstrated promising effects in the management of Type 2 Diabetes Mellitus (T2DM). The therapeutic effects of Aloe vera in diabetes are attributed to its bioactive compounds, including polysaccharides (e.g., acemannan), anthraquinones, vitamins, and minerals. These compounds influence various physiological mechanisms that help regulate blood glucose levels and improve overall metabolic health[136].

Improvement of Insulin Sensitivity: Aloe vera has been shown to enhance insulin sensitivity, which is a key factor in the management of Type 2 Diabetes. Insulin resistance, where the body's cells become less responsive to insulin, is a hallmark of T2DM. *Aloe vera*'s active compounds help improve the responsiveness of cells to insulin, allowing better glucose uptake and reducing blood sugar levels. This insulin-sensitizing effect is particularly important for people with T2DM, who often face challenges in utilizing insulin effectively[137].

Regulation of Blood Glucose Levels: Aloe vera plays a direct role in lowering blood glucose levels. It has been found to reduce fasting blood glucose and postprandial glucose levels by enhancing glucose utilization in peripheral tissues. Some studies have suggested that *Aloe vera* may promote the secretion of insulin from the pancreas, thereby increasing insulin availability to the body. Moreover, its polysaccharide content, such as acemannan, may support better glucose metabolism and reduce the need for excessive insulin production[138].

Modulation of Hepatic Glucose Production: Aloe vera has been shown to influence hepatic (liver) glucose production. In individuals with T2DM, the liver often produces excessive glucose through a process called gluconeogenesis. Aloe vera helps regulate this process by enhancing the liver's glucose uptake and storage, which in turn helps balance blood glucose levels. This action may prevent hyperglycemia (elevated blood glucose) by limiting the liver's overproduction of glucose [139].

Anti-inflammatory Effects: Chronic inflammation is a significant contributor to insulin resistance and the progression of Type 2 Diabetes. Aloe vera has potent anti-inflammatory properties, which help reduce levels of pro-inflammatory cytokines, such as TNF-α and IL-6, that are elevated in people with diabetes. By mitigating inflammation, Aloe vera aids in improving insulin sensitivity and reducing the risk of complications associated with T2DM[140].

Antioxidant Activity: Oxidative stress is another critical factor that exacerbates insulin resistance and leads to complications in T2DM. Aloe vera is rich in antioxidants, such as flavonoids, vitamins (e.g., Vitamin C and Vitamin E), and polyphenols, which neutralize free radicals in the body. By reducing oxidative stress, Aloe vera helps protect β-cells in the pancreas (which produce insulin), enhances insulin function, and supports overall cellular health, preventing the damage caused by high glucose levels[141].

Lipid Profile Improvement: Diabetes often leads to dyslipidemia, characterized by elevated cholesterol and triglyceride levels. Aloe vera has demonstrated the ability to improve lipid profiles by reducing total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides while increasing high-density lipoprotein (HDL) cholesterol. This effect not only contributes to better blood sugar management but also helps reduce the cardiovascular risks associated with Type 2 Diabetes[142].

Pancreatic Beta-Cell Protection: *Aloe vera* has shown protective effects on pancreatic β-cells. These cells are responsible for insulin production, and their dysfunction is a central issue in T2DM. Aloe vera's bioactive compounds may help protect β-cells from damage caused by oxidative stress and inflammation, thereby improving insulin secretion and glucose homeostasis. Studies have indicated that *Aloe vera* supplementation may reduce β-cell apoptosis (cell death) and support their functional integrity[143].

Gut Microbiota Modulation:

Recent research suggests that *Aloe vera* may influence gut microbiota composition, which plays a critical role in glucose metabolism. It was reported that Aloe vera (specifically gel and Aloin) showed potential in Type 2 Diabetes (T2DM) management by improving glycaemic control, reducing inflammation, and favorably modulating gut microbiota. It was observed that It Aloe vera treatment increases SCFA (short chain fatty acids) -producing bacteria and beneficial flora (e.g., *Bacteroides*) leading to reduced dysbiosis and enhanced insulin sensitivity. Studies have indicated that Aloe vera can reduce fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol, and triglycerides. Also, active components like acemannan and aloin, as well as fermented aloe beverages showed a potential decrease in inflammatory markers (TNF-, IL-6) enhancing insulin sensitivity. It could be concluded that Aloe vera may acts as a prebiotic through increasing beneficial bacteria and reducing proinflammatory bacteria, which helps manage microbial dysbiosis associated with diabetes[144,145].

***Aloe vera* clinical studies**

Multiple studies have shown that A. vera may lower blood glucose levels by safeguarding pancreatic cells and/or enhancing insulin sensitivity. In this review, we focused on the impact of A. vera and its active constituents, which are significant in type 2 diabetes mellitus.

Devaraj *et al*. Performed a randomized, double-blind, placebo-controlled trial involving 45 patients with prediabetes to investigate the hypoglycemic effects and safety of two aloe products: UP780, a chromone-enriched aloe vera gel fillet powder, and AC952, an aloe vera gel fillet powder standardized to 10% polysaccharide devoid of chromone. Patients were administered either 500-mg pills of UP780, AC952, or a placebo twice daily for eight weeks. Baseline and eight-week measurements of fasting blood glucose and urine glucose concentrations were obtained. Substantial reductions ($p < 0.05$) were observed in HbA1c, fructosamine, insulin, and urinary F2-isoprostanes (an indicator of oxidative stress) in the UP780 cohort, whereas AC952 treatment correlated with significantly lowered levels of glucose, fructosamine, and total and LDL cholesterol (actual data not explained)[145].

Govindarajan *et al*.examined the antidiabetic properties of the *Aloe vera* carbohydrate fraction (AVCF) on glucose metabolism in streptozotocin-induced diabetic rats. The findings demonstrated that AVCF substantially lowered fasting blood glucose levels and elevated insulin secretion, signifying improved pancreatic function. Moreover, AVCF therapy enhanced glycogen production in the liver while concurrently reducing gluconeogenesis rates, indicating a beneficial alteration in glucose metabolism[140]. Histological examination of pancreatic tissues demonstrated protective benefits against diabetes-induced damage, hence reinforcing the efficiency of AVCF. Another recent study documented the oral administration of A. vera extract (AL300 and AL500 mg twice daily) to prediabetic individuals over 8 weeks. Following 4 weeks of treatment, fasting blood glucose levels are markedly decreased with AL300 alone, while HbA1C, total cholesterol, and LDL cholesterol levels are dramatically diminished with AL500 supplementation after 8 weeks[137, 141].

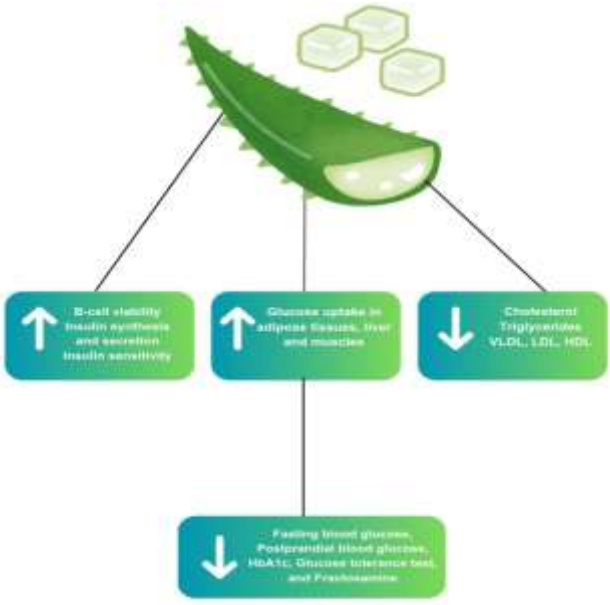

Figure 1. The favorable effects of A. vera on high blood sugar levels and high cholesterol levels VLDL: Very Low-Density Lipoprotein - LDL: Low-Density Lipoprotein - HDL: High-Density Lipoprotein. (created by Biorender.com)

In a study conducted by Choudhary *et al*., ninety male patients in the age group of 35–65 years were selected for this investigation and categorized into three groups. Two groups were administered Aloe vera gel powder at dosages of 100 mg and 200 mg for three months, whilst the control group got no treatment. Following this, both treatment groups continued supplementation along with nutritional counseling for an additional three months. The findings showed a significant reduction in FBG levels of 11.4% and 15.4%, respectively, and postprandial glucose levels of 18.5% and 27.8%. Total Cholesterol was reduced by 8.6% and 10.1%, Triglycerides by 9.6% and 12.2%, LDL-C (low-density lipoproteins) by 12.8% and 14.6%, VLDL (very-low density lipoproteins) by 9.6% and 12.2%, and an increase in HDL-C (high-density lipoproteins) by 7.3% and 9.4% was observed. Total cholesterol to HDL-C ratio reduced from 5.6 to 4.8 and 6.1 to 5.0, respectively, and LDL-C to HDL-C ratio decreased from 3.7 to 3.0 and 4.1 to 3.1[146].

Another investigation indicated that the intake of a high molecular weight fraction of A. vera, comprising less than 10 ppm of barbaloin and polysaccharide (MW: 1000 kDa), along with glycoprotein verectin (MW: 29 kDa) for 12 weeks (2 tablespoons thrice daily), may reduce serum triglyceride levels without impacting cholesterol levels, and showed no signs of renal or hepatic toxicity[147].

Two trials examined the impact of polyherbal formulations containing A. vera alongside conventional medications on diabetic individuals with unmanaged dyslipidemia. The intervention group exhibited significant improvements in serum triglycerides, total cholesterol, LDL, and HbA1c levels, with the tested substance effectively reducing serum lipids in diabetics with uncontrolled dyslipidemia as an adjunct therapy[148,149] .

Choi *et al*. investigated the metabolic effects of the aloe vera gel QDM complex in obese prediabetic or early-diabetic patients over 8 weeks. The supplementation of A. vera QDM complex considerably reduced body weight, body fat mass, fasting blood glucose, and insulin levels by the conclusion of the experiment[150]

A randomized double-blind placebo-controlled clinical trial indicated that 300 mg of Aloe gel capsules administered for 2 months to 30 hyperlipidemic type 2 diabetics significantly decreased fasting blood glucose (FBG), hemoglobin A1c (HbA1c), total cholesterol (TC), and low-density lipoprotein (LDL) levels, with no notable impact on liver or kidney function tests, suggesting its safety as an antihyperglycemic and anti-hypercholesterolemic agent[151].

A further trial yielded conflicting results, revealing that administering 300 mg of A. vera extract to insulin-dependent diabetics resistant to oral hypoglycaemic medications for two months resulted in a notable reduction in fasting blood glucose (FBG) and HbA1c levels while exerting no meaningful impact on the lipid profile. The absence of response in this trial may be ascribed to chronic hyperglycemia in patients, which might induce oxidative stress, or to the suboptimal dosage of A. vera[152]. A pilot study conducted over 8 weeks on two aloe products (UP780 and AC952) in patients with prediabetes/metabolic syndrome indicated that AC952 led to significant decreases in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), alongside reductions in blood glucose levels, HbA1C levels, and enhancements in insulin sensitivity. Nonetheless, it was determined to be ineffective in reducing triglyceride levels and elevating HDL-C levels in the serum[153]. The variances in the therapeutic efficacy of various A. vera preparations may be ascribed to multiple factors, including discrepancies among studies regarding the standardization of the A. vera production process, dosing frequency, duration of treatment, laboratory testing units, and the racial demographics of the selected patients. This variance affects the interpretation of clinical results[154].

***Aloe vera*-Drug Interactions:**

Many literature reviews reported the ability of Aloe vera (*Aloe barbadensis miller*) to alleviate the chronic hyperglycemia and perturbed lipid profile accompanied with DM, that leads to cardiovascular complications in the disease. It is known that *Aloe* contain valuable components and compounds, mainly including anthraquinone, naphthone, polysaccharides, proteins and enzymes, organic acids, and carbohydrates (e.g., mannan, galactose-rich polysaccharides), and galacturonic acid. Among these chemical components, anthraquinone is the main active component found in aloe latex, which includes aloin A, aloin B (isoaloin),

aloin emodin, rhein, aloin and aloin saponin I, II, III, IV. In addition to water, aloe polysaccharide (AP) is the main component of aloe gel, and the most common (AP) is glucose-mannose polysaccharide (155,158,160). Several studies report potential interactions between aloe vera and antidiabetic drugs. Of note is its interaction with glibenclamide, a sulphonylurea which exerts its antidiabetic potential by inhibiting ATP sensitive potassium channels in pancreatic β cells, resulting in cell membrane depolarization and subsequent insulin release. The combination of aloe vera and antidiabetics has generally been shown to have an additive effect. For instance, aloe has been shown to produce a greater anti-hyperglycaemic effect, when compared to the sole therapy with glibenclamide, pioglitazone or repaglinide [156,157].

Yet, it is reported that, among the Aloe ingredients, some ingredients such as aloe emodin, rhein, quercetin and aloe gel have been reported to have the effect of improving constipation. Also,using aloe vera with other laxatives can intensify this effect, causing excessive diarrhea, abdominal pain, and potential potassium depletion. This Laxative effect may result in depletion medications time in the digestive system, decreasing the effectiveness of other oral medications (such as metformin)[158].Patients with DM-II are advised to be cautious as interaction between oral hypoglycemic drugs and *Aloe vera* was reported [159). Also, a possible interaction of *Aloe vera* and drugs that may alter electrolyte balance, such as thiazide diuretics and corticosteroids. Risk for hypokalemia-related arrhythmia suggests a potential interaction with cardiac glycosides [160,161].

In conclusion, clinical studies indicate the potential advantages of Aloe vera in enhancing different metabolic parameters in persons with type 2 diabetes. Although these findings are encouraging, additional rigorously designed trials are necessary to validate these effects and to determine the most effective therapy strategy. Nonetheless, these trials underscore the significance of investigating natural products as an adjunctive approach for managing this complicated disease.

The three natural products used in the management of diabetes were summarized in the table **(Table 1).**

Plant name	**Scientific name**	**The most active ingredients**	**Possible effects on Diabetes (Biochemical pathways)**	**advantages**	**disadvantages**	**Refreneces**

1. Ginger	***Zingiber officinale***	Gingerols, shogaol, zingerone, and paradol	Ginger shows promise in managing type 2 diabetes, and researchers believe it works through several mechanisms: 1. Enzyme Inhibition: Gingerol, the main bioactive component in ginger, may inhibit enzymes like alpha-amylase and alpha-glucosidase. These enzymes break down carbohydrates in the small intestine, leading to a rise in blood sugar levels. Inhibiting them can help slow down sugar absorption. 2. Improved Insulin Action: Ginger may enhance insulin sensitivity, allowing cells to utilize glucose more efficiently. This can potentially lower blood sugar levels. Increased Insulin Secretion: Some studies suggest ginger might stimulate the pancreas to release more insulin, further aiding blood sugar control. 3. Reduced Inflammation: Chronic inflammation is linked to insulin resistance in type 2 diabetes. Ginger's anti-inflammatory properties might help improve insulin sensitivity. Glycogen Synthesis: Ginger may promote the liver's ability to store glucose as glycogen, another way to regulate blood sugar levels.	**Can be used as** anti-diabetic, hypo-lipidemic, and anti-oxidative characteristics of ginger, hence highlighting its efficacy in safeguarding against and managing metabolic illnesses.	The optimal dosage of ginger for blood sugar control is still being determined. Additionally, consistent daily intake is likely necessary for any potential benefits. Ginger can interact with certain medications, particularly blood thinners and blood pressure medications. It's crucial to consult a doctor before using ginger if you're already taking medications. In large amounts, ginger can cause mild side effects like heartburn, diarrhea, and stomach upset. Ginger should not be used as a substitute for prescribed medications for type 2 diabetes.	**[80—109]**

2. Cinnamon	***Cinnamomum verum*.**	The most active ingredient in cinnamon is called cinnamaldehyde.	It seems to offer several potential mechanisms for improving blood sugar control in type 2 diabetes, As: 1. Enhanced Insulin Sensitivity: Cinnamaldehyde may mimic insulin's action by increasing the number of insulin receptors on cells. This allows cells to take up glucose more efficiently from the bloodstream, leading to lower blood sugar levels. 2. Improved Insulin Signaling: Studies suggest cinnamon may activate certain pathways involved in insulin signaling, making the body's existing insulin work more effectively. This could further enhance glucose uptake into cells. Enzyme Inhibition: Similar to ginger, cinnamon might inhibit enzymes like alpha-amylase, which break down carbohydrates in the small intestine. This can slow down sugar absorption and prevent post-meal blood sugar spikes. Glucose 3. Metabolism Regulation: Cinnamon may influence how the body processes glucose in the liver. Studies suggest it can promote glycogen synthesis, where excess glucose is stored as glycogen for later use. This helps regulate blood sugar by preventing too much glucose from circulating freely. 4. Antioxidant Activity: Cinnamon possesses antioxidant properties that may help combat oxidative stress, a factor contributing to insulin resistance in type 2 diabetes. By reducing oxidative stress, Cinnamon: Studies suggest cinnamon may improve insulin sensitivity and blood sugar control cinnamon might indirectly improve insulin sensitivity.	high doses or certain types of cinnamon (like cassia cinnamon) can be high in coumarin, a blood-thinning compound that might interact with medications. Consulting a doctor before using cinnamon for diabetes management is crucial. Cinnamon should not replace prescribed medications for type 2 diabetes**.**	**[110-132]**

3. Aloe Vera	***Aloe vera***, (L.) Burm.f.	Include Polysaccharides: These sugars, like acemannan, are believed to have anti-inflammatory and immune-boosting properties. Anthraquinones: These compounds, found mostly in the aloe latex (layer beneath the rind), have laxative effects but should be limited due to potential side effects.Vitamins, minerals, and enzymes: Aloe vera is a rich source of various vitamins (including A, C, and E) and minerals that contribute to its overall health benefits.	Aloe vera contains over 75 potentially active components, making it difficult to pinpoint a single "active ingredient" for blood sugar control's likely the combination of these components working together contributes to any effects on blood sugar. • It's believed that the combined action of these compounds, including polysaccharides, vitamins, minerals, and anthraquinones (in limited amounts), contributes to its overall effects. • Some studies suggest aloe vera may enhance insulin sensitivity, allowing cells to utilize glucose more efficiently. This could be due to polysaccharides like acemannan influencing insulin signaling pathways. • Studies have observed aloe vera consumption leading to reduced blood sugar levels in diabetic animal models. The exact reasons are still under investigation, but it might involve influencing glucose metabolism or mimicking insulin's action to a limited extent. • Aloe vera possesses antioxidant properties that may help combat oxidative stress, a factor contributing to insulin resistance. By reducing oxidative stress, aloe vera might indirectly improve insulin sensitivity.	The current evidence for aloe vera's effectiveness in managing type 2 diabetes is inconclusive. More high-quality research, particularly well-designed human trials, is needed to confirm its benefits and determine optimal dosages. Due to the presence of anthraquinones (laxatives) in the aloe latex, it's important to avoid aloe latex for diabetes management and focus on aloe vera gel, which is generally considered safe for most people in moderation. Aloe vera should not replace prescribed medications for type 2 diabetes.	**[133-161]**

Other natural products may be promising.

Fiber-rich options like guar gum, psyllium, and oat bran may help regulate blood sugar by slowing down carbohydrate absorption in the gut. Specific plant compounds are under investigation for their potential blood sugar benefit, such as Berberine, which is an alkaloid found in some plants like Berberis vulgar that might help in the management of blood sugar levels. In addition, some studies are ongoing into the potential benefits of various antioxidants for type 2 diabetes management [70].

Conclusion

An integrative strategy that blends traditional medical treatments with complementary and alternative medicine (CAM) therapies is necessary for the thorough management of type 2 diabetic mellitus (*T2DM*M). Although traditional therapies like medication and lifestyle changes are still essential, CAM provides extra advantages in terms of glycaemic management, affordability, and cultural compatibility. Herbal plants therapies have demonstrated encouraging findings in the management of type 2 diabetes and the enhancement of patient outcomes. Notwithstanding the possible advantages, issues like quality control, standardization, and the dangers of herbal remedies call for cautious regulation and patient education. Healthcare systems can manage type 2 diabetes more holistically and patient-centered by combining complementary and alternative medicine (CAM) with traditional medical techniques. This would ultimately improve health-related quality of life and lessen the prevalence of diabetes worldwide.This review explores some herbal plants with potential benefits for type 2 diabetes, emphasizing the need for responsible use and ongoing research. It was found that some plants such as ginger, cinnamon and aloe vera play a significant role in the regulation of blood sugar, thus helping in the management of type 2 diabetes and its complications.

Compliance with Ethical Standards

Conflict of competing interest The authors declare that they have no financial or non-financial competing interests that are directly or indirectly related to the work submitted for publication.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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