THE ANTIOXIDANT MECHANISM IN THE PREVENTION OF TYPE 2 DIABETES AND ITS COMPLICATIONS: A NARRATIVE REVIEW

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Abstract:

Type 2 diabetes mellitus (T2DM) is considered a chronic metabolic disease in which oxidative stress plays a vital part in the pathogenesis of diabetes. Essentially, hyperglycemia instigates the auto-oxidation of glucose to free radicals. The free radicals overwhelm endogenous antioxidant defense in macrovascular and microvascular dysfunctions. The antioxidants (such as vitamin C and α-lipoic acid) effectively reduce diabetic complications; they are used to treat and decrease the complication of diabetes mellitus. Supplementations with antioxidants and medicinal plants that possess antioxidant activity have been investigated for hypoglycemic effects. This review article sums up the role and mechanism of antioxidants in the prevention of T2DM and its complications.

***Keywords*:** Antioxidant, Prediabetes, Diabetes, Prevention

Introduction

Diabetes mellitus (DM) is a chronic disease due to either insulin deficiency or insulin resistance (1). Internationally, more than 190 million people from different age groups are affected by DM; it is one of the leading causes of mutilation and death worldwide (2). In the pancreas, beta cells in the islets of Langerhans secret insulin hormone, which is essential in regulating carbohydrate metabolism. Almost in all tissues, insulin facilitates glucose transport into cells, decreasing the glucose level in circulating blood. Insulin secretion is linked with amplified glucose levels (3). Various studies have already established that this link is directly associated with intracellular enzymes and stimulates the transcription of glucokinase, phosphofructokinase, pyruvate kinase, and fructose-2,6 biphosphatase (4, 5). Based on some previous experimental and clinical studies, it is known that oxidative stress plays a central task in the pathogenesis of diabetes (6). Oxidative stress, a state characterized by an imbalance of the generation of free radicals against the body's ability to neutralize them, might add to the development of insulin resistance and the elimination of beta cells in the pancreas. In diabetes, oxidation of glucose, glycation of proteins, and subsequent breakdown of the glycated protein produce free radicals. Excessive amounts of free radicals and a corresponding drop in antioxidant enzymes cause enzyme inactivation, cell damage, and lipid peroxidation (7). This article focuses on the mechanism of antioxidants in preventing type 2 diabetes mellitus (T2DM) and its complications.

Method

Search strategy

A detailed literature search on papers published over the last five years (2018–2023) was conducted. However, a few previous important articles were also picked to make this review more informative.

Study selection

The following criteria were used to select the studies:

a. Papers pertaining to the mechanism of antioxidants, i.e., how antioxidants work against diabetes

b. Case reports, review papers, letters to the editor, and conference proceedings were included.

Data extraction

The main focuses were: how antioxidant can be found, how antioxidant works, and how antioxidant fights against T2DM and its complications. The above-mentioned information was collected from the selected articles.

Discussion

In this review, we were mainly focusing on type 2 diabetes mellitus (T2DM), which is also known as non-insulin-dependent diabetes mellitus (NIDDM) (8). Several processes inhibit insulin production by pancreatic beta cells and impede insulin action during insulin resistance (9). In T2DM, numerous genetic defects as well as certain environmental factors, are accountable for beta cell flaws and peripheral tissue insulin resistance. There are multiple factors behind T2DM (10). Obesity, ethnic origin, age, and family history of diabetes contribute the most to its development (11). Even though a solid genetic predilection has been recognized, genotype only establishes the circumstances for the individual to be more or less prone to ecological effects with lifestyle factors (12). T2DM develops when insulin secretion or activities do not work (13). Insulin resistance signifies suppressing muscle, liver, and adipose tissue metabolic reactions to insulin operation (14). Following insulin binding to its specific receptor, there is a failure in the signaling pathways. Chronic insulin resistance leads to hyperglycemia. Then the beta cells could not produce sufficient insulin in response to the metabolic demand caused by insulin resistance and T2DM. All T2DM patients have some insufficiency in the ability of beta cells to produce insulin (15).

Oxidative stress in type 2 diabetes and related complications

Free radicals are molecules or atoms with one or more unpaired electrons (16). The free radicals encourage damage to cells by passing the unpaired electron through, ensuing in the oxidation of cell components and molecules (17). Free radicals are usually very unstable and very much reactive. There are three types of free radicals: reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive chlorine species (RCS). Free radicals have been proven to alter gene expression and initiate cell death which causes many diseases, including T2DM (18). Oxidative stress is the condition in which the free radicals in the body outnumber the antioxidant resistance (19). Oxidation is a chemical reaction to relocate electrons from a substance to an oxidizing agent (20). To date, good experimental and clinical evidence point to the amplified ROS in diabetes and the development of diabetes is strongly connected to oxidative stress.

a. Oxidative stress can be caused by elevated ROS and/or RNS, which include:

b. Charged species (for example: hydroxyl radical and superoxide)

Uncharged species (for example: peroxide of hydrogen and singlet oxygen) (21)

High-glucose-generated ROS is directly linked to higher glucose and other metabolic derangements essential for the progression of diabetic complications. The auto-oxidation of glucose may be a reasonable contributing factor to oxidative stress in T2DM (22). A few studies have shown that augmented extra- and intracellular glucose levels result in oxidative stress, equally in vivo and clinical diabetic setting research (23).

Once insulin resistance is present, a small amount of ROS that leaks out of the mitochondria can result in oxidative stress, a contributing cause of T2DM. The basic steps that lead to diabetes are complex because hyperglycemia may also be induced by a link between high oxidative stress and high blood sugar (24).

Lipid peroxidation, as well as protein oxidation, typically can be calculated as oxidative stress biomarkers. In most cases, oxidative stress in diabetes is supplied by various mechanisms, including glycated protein formation, excessive oxygen radical formation commencing the auto-oxidation of glucose, and antioxidant enzyme glycation, which edge the capacity of antioxidants to detoxify the free radicals (25). Overall, the overexpression in conjunction with the commencement of mitochondrial inner membrane's uncoupling enzymes (UCPs) has been recommended to boost superoxide creation under diabetic circumstances (26).

In T2DM, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is essential for ROS generation. NADPH oxidase is found in the plasma membranes of various kinds of renal cells, including mesangial, endothelial, proximal tubular, fibroblast, and vascular smooth muscle cells (27). The development of NADPH oxidase-dependent ROS oxidation is essential for hyperglycemia to induce oxidative stress. NADPH oxidase exacerbates oxidative stress and ultimately contributes to diabetes complications. Free fatty acid (FFA) levels are raised by beta cell failure caused by prolonged high hyperglycemia (28).

Oxidative stress decreases insulin secretion and damages the mitochondria. Oxidative exposure from beta cell preparations to hydrogen peroxide (H_2O_2) can enhance the output of protein cycline-reliant kinase inhibitor 1 (p21) and diminish insulin mRNA, cytosolic adenosine triphosphate ATP, and calcium variation in the cytosol and mitochondria (29).

Many vascular cell types have the ability to produce ROS under hyperglycemic conditions. Hyperglycemia in diabetes increases the level of ROS, which causes T2DM problems (30). Nevertheless, further research is needed to determine the precise processes through which oxidative stress might result in diabetes issues (31). In Figure 1, the mechanism is described in brief.

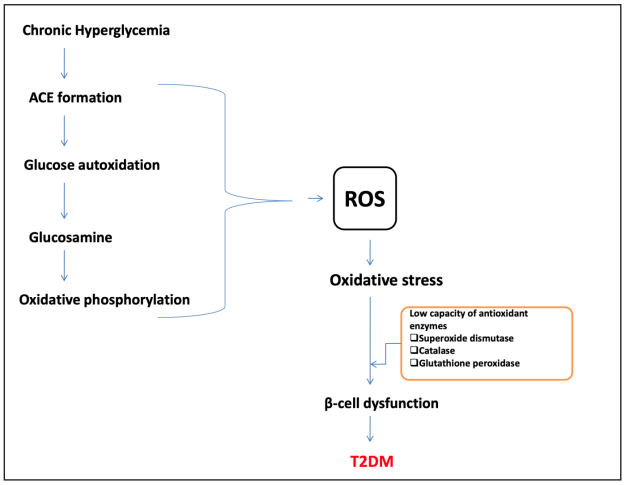

Figure 1: Oxidative stress mechanism towards T2DM.

T2DM is strongly associated with both microvascular and macrovascular complications. Microvascular complications of diabetes are long-term complications that affect small blood vessels. The microvascular complications include retinopathy, nephropathy, and neuropathy.

The genesis and evolution of diabetic retinopathy are closely reliant on oxidative stress. The production of reactive oxygen species (ROS) generates quite a few pathological changes, including activation of the polyol pathway (POP) (32), protein kinase C (PKC) (33), advanced glycation end products (AGEs) as well as hexosamine pathway (34). The oxidative stress can further deteriorate the retinal blood vessels and induce inflammation, aggravating the retinal damage. Another mechanism is via the starting of redox-sensitive NF-kB. NF-kB is a significant monitor of antioxidant enzymes (34). Excessive ROS damages mitochondria, and mitochondrial ROS contribute to metabolic disorders by blocking glyceraldehyde 3-phosphate dehydrogenase. ROS buildup causes damage to mitochondrial DNA (mtDNA) and mitochondrial function, which increases cell death in the cells that support the retina, such as the retinal pigment epithelium (RPE) (35). RPE is crucial in sustaining the retina's health and function, and its damage can lead to retinal degeneration.

Diabetic nephropathy (DN) is also a microvascular complication and the most common and severe complication of T2DM. The first sign of DN is typically microalbuminuria. It usually evolves to explicit albuminuria, which points to more severe renal dysfunction in T2DM patients (36). In DN, excessive quantities of ROS affect the activation of mitogen-activated protein kinases, protein kinase C, and other cytokines and transcription factors, leading to a rise in extracellular matrix (ECM) gene expression and the progression of fibrosis and final-stage renal disease. In addition, ROS can negatively affect kidney cells, such as podocytes and tubular cells, which are essential for normal kidney function (37).

Oxidative stress affects nerve cells via numerous molecular signaling mechanisms in diabetic neuropathy. It causes harmful metabolites and excessive NADPH. These conditions cause intracellular redox stress, cell alterations, and ROS overproduction. Schwann cells, myelinated axons, and dorsal root ganglia sensory neurons perish, disrupting the peripheral nervous system. Mitochondrial energy deficiency also damages axons by impairing their transit (38). Several studies have reported the role of oxidative stress in the initiation and progression of diabetic neuropathy. One recent study reported a decrease in the level of oxidative markers after alpha-lipoic acid management (39). Alpha-lipoic acid is a sulfur-containing antioxidant involved in mitochondrial energy generation and is responsible for scavenging ROS (40). In the study, some vascular stiffness parameters are linked to oxidative damage markers for lipids and proteins. Another study showed that increased oxidative stress markers were associated with the severity of diabetic neuropathy (41). Similarly, another study found that diabetic patients with neuropathy had higher oxidative stress levels than those without neuropathy (42). Table 1 summarizes the key points on how antioxidant works against T2DM and its complications.

Table 1: Antioxidant mechanisms against T2DM and complications

Complications	Mechanisms to *Prevent*	References
T2DM	- Antioxidants work by neutralizing free radicals, preventing cell damage, and reducing oxidative stress - Antioxidants scavenge free radicals by donating an electron to the unstable molecule and stabilizing it - Antioxidants also prevent the formation of free radicals by inhibiting the enzymes responsible for their production - Antioxidants improve insulin sensitivity, which helps cells to take up glucose more efficiently, reducing blood sugar levels - Antioxidants also reduce inflammation, which is linked to insulin resistance and T2DM	37, 38

Table 1: Antioxidant mechanisms against T2DM and complications (continued)

Complications	Mechanisms to *Prevent*	References
Diabetic retinopathy	- High blood glucose levels lead to oxidative stress in the retina - Antioxidants scavenge free radicals and protect against oxidative stress - Antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase mainly protect against oxidative stress - Antioxidants prevent damage to retinal cells and blood vessels. It could reduce the risk of developing diabetic retinopathy or slow its progression	39, 40
Diabetic nephropathy	- Diabetes causes an increase in reactive oxygen species (ROS) production, leading to oxidative stress and damage in the kidneys - Antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, are essential for scavenging ROS and maintaining redox balance in the kidneys - Various antioxidant compounds, such as vitamins C and E, flavonoids, and carotenoids, can also act as ROS scavengers and protect against oxidative damage - Nrf2 is a transcription factor that regulates the expression of antioxidant enzymes and other cytoprotective genes - Activating the Nrf2 signaling pathway can enhance the antioxidant defense system in the kidneys - In addition to direct ROS scavenging, some antioxidants may also modulate intracellular signaling pathways involved in diabetic nephropathy	42

Table 1: Antioxidant mechanisms against T2DM and complications (continued)

Complications	Mechanisms to *Prevent*	References
Diabetic neuropathy	-Diabetes causes an increase in reactive oxygen species (ROS) production, leading to oxidative stress and damage in the nerves Antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, scavenge ROS and maintain redox balance in the nerves. -Various antioxidant compounds, such as vitamins C and E, flavonoids, and carotenoids, act as ROS scavengers and protect against oxidative damage -Activating the Nrf2 signaling pathway can enhance the antioxidant defense system in the nerves -In addition to direct ROS scavenging, some antioxidants may modulate intracellular signaling pathways involved in diabetic neuropathy	43

Antioxidants

Controlling diabetes-related hyperglycemia is fundamental for arresting the development and progression of diabetes and its complications. Antioxidants are compounds that inhibit oxidation; they may prevent and sometimes delay some types of cell damage. Antioxidants are a natural method of defending cells against attack by ROS (43). Our body circulates a range of nutrients for their antioxidant properties in addition to developing antioxidant enzymes. Antioxidants terminate the chain reactions that involve free radicals by removing free radical intermediates, inhibiting other oxidation reactions, and oxidizing themselves (44).

Antioxidants are found in many foods, especially fruits and vegetables. In recent times, medicinal research has focused on antioxidant therapy in managing several diseases, most notably diabetes (45). Many experimental studies and clinical trials have recommended antioxidants' efficacy in alleviating diabetes complications. The therapeutic plan may use synthetic antioxidants, natural antioxidants, and drugs combined with antioxidants. Medicinal plants with antioxidant action are generally well-accepted for treating T2DM (46).

Generally, antioxidants can be categorized into two types: non-enzymatic and enzymatic (47). Non-enzymatic antioxidants disrupt free radical chain reactions. It includes vitamin C, vitamin E, carotenoids, and polyphenols (48). Enzymatic antioxidants break down as well as eliminate free radicals. These antioxidant enzymes reduce dangerous oxidative products by changing them into hydrogen peroxide, which turns into water. Enzymatic antioxidants must be produced in our bodies because they cannot be supplemented orally (49). It is known that superoxide dismutase (SOD), glutathione peroxidase (GPx), along with catalase is the essential enzymatic antioxidants (50).

Antioxidant therapy protects the beta cell from oxidative stress, which inhibits apoptosis and conserves the beta cells' role (51). Data from previous studies showed that antioxidants decreased diabetic-related complications as well as even reinstated insulin sensitivity; some epidemiological studies have discovered a strong connection between dietary antioxidant intake and fortification against diabetes (52).

In nature, lipophilic antioxidant exists as tocopherol and tocotrienol, both in vitamin E, which protect the cell against oxidative damage (53). Vitamin E has been proven to play an essential role in alleviating hyperglycemia. Antioxidant therapy with vitamin E has been run to control and prevent diabetic complications. In the animal model, vitamin E supplementation decreases the hepatic lipid peroxide level in streptozotocin-induced diabetes. Dietary vitamins and the administration of vitamin E have been linked to glucose absorption (54). The level of glucose severely decreased, and the oral glucose tolerance test (OGGT) improved in diabetic conditions by supplementation of vitamin E. Vitamin E has also been found to control hyperglycemia as well as furthermore to lower the HbA1c by inhibiting the sequence of oxidative stress in diabetic rats. The plasma glucose level was lessened by raising the glucose metabolism in peripheral tissues. However, the mechanism by which antioxidants reduce the glucose level has yet to be understood (55).

Vitamin C is the aqueous antioxidant for scavenging free radicals. Vitamin C is essential to convert vitamin E free radicals to vitamin E as a cofactor obligatory for human hydroxylation reaction (56). The most significant function of vitamin C is vital chain-breaking antioxidants in the aqueous phase. Vitamin C offers steadiness to the cell membrane. It was found that lowered levels of ascorbic acid (vitamin C) and SOD were observed in the diabetic subject while put side by side with the non-diabetic human. Some previous research stated that diabetes might result in reduced plasma vitamin C and vitamin E due to amplified oxidative stress (57). Vitamin C lessens erythrocyte sorbitol levels, as well as microalbuminuria, and plays a principal role in ameliorating insulin resistance in diabetic patients because of its antioxidant function (58).

Polyphenols are naturally established in plant-based meals, and these molecules come in a broad range of complex forms. These chemicals are found in fruits, vegetables, grains, and coffee and are introduced into the human diet (59). Polyphenols are reducing agents. Along with other dietary reducing agents, such as vitamins E and C, polyphenols protect the body's tissues from oxidative stress and related diseases (60). Previous research found that polyphenols might influence glycemia and T2DM by promoting glucose uptake in tissues, consequently improving insulin sensitivity. Several animal models and a limited number of human studies have revealed that polyphenols reduce hyperglycemia and, most importantly, improve insulin secretion and insulin sensitivity (61, 62). By reducing postprandial glucose, influencing insulin signaling pathways and modifying glucose transport, a second method may protect insulin-producing pancreatic cells from damage (63). In addition to this potential mechanism, the following is also possible: a decrease in glucose absorption inside the intestinal wall, stimulation of insulin secretion, inhibition of carbohydrates digestion, modulation of glucose release from the liver, activation of insulin receptors and glucose uptake in insulin-sensitive tissues, modulation of intracellular signaling pathways, and gene expression (64, 65).

Alpha-lipoic acid is measured as a vital potent antioxidant. It is also known as thioctic acid or 1, 2-dithiolane-3-pentanoic acid (66). Alpha-lipoic acid reduces cellular injuries set off by free radicals. Those unstable and highly reactive molecules are derivatives of similarly normal and frazzled cell action (67). Alpha-lipoic acid can reinstate endogenous antioxidants such as glutathione, vitamin C, and vitamin E. It is competent in many pathological circumstances, such as diabetes mellitus, cardiovascular disease, and liver disease.

It has been reported that alpha-lipoic acid aids in glucose metabolism in T2DM patients by activating threonine kinases and tyrosine in the target cells. Due to these mechanisms, it instigates glucose uptake and glycogenesis (68). Many in vitro studies suggested that alpha-lipoic acid increases the translocation of GLUT1 plus GLUT4 to the plasma membrane of adipocytes and skeletal muscle cells. This is directly associated with the improved activity of proteins of the insulin signaling pathway. According to other research, alpha-lipoic acid is competent for ageing reactive oxygen species formed during lipid peroxidation. Moreover, it does guard the cell structure against harm. The constant supplementations of alpha-lipoic acid in diabetic rats were connected with reduced hyperglycemia and diabetic nephropathy (69).

Selenium is found in many foods naturally and is considered a vital trace element. It subsists in organic as well as inorganic forms (70). Selenomethionine, as well as selenocysteine, are organic forms. On the other hand, selenate, along with selenite, is found in inorganic forms. Mostly the inorganic selenite is found in the soil worldwide (71). Derived from previous experimental as well as clinical studies, selenium is utilized to avoid many diseases due to its antioxidant activity. Selenium supplementation in small doses has a beneficial effect on glucose metabolism. It

copies insulin-like trials in the trial animal model (72). Some previous research showed that selenium supplementation activates the essential protein accountable for insulin signal cascade. It is found that the inorganic sodium selenate and sodium selenite are involved in the insulin signaling cascade by the mechanism of kinases (73). In some previous studies on animal models, selenate has been shown to excite glucose uptake and affect the phosphorylation of insulin receptors and, most importantly, insulin receptor substrate 1.

Vitamin E, vitamin C, polyphenols, alpha-lipoic acid, and selenium are regularly used antioxidants in managing DM. These days, antioxidant-based formulations are being developed or formulated for treating various diseases, including diabetes. Table 2 summarizes the efficacy of non-enzymatic antioxidants in diabetes.

Table 2: Non-enzymatic antioxidant mechanism of managing T2DM

Antioxidants	Mechanism/Efficacy in Managing T2DM	Author(s)
Vitamin E	-decreases the hepatic lipid peroxide level -positively linked with glucose absorption (glucose↓OGTT ↓HbA1c ↓)	(66) (67)
Vitamin C	-key chain-breaking antioxidants in the aqueous phase - converts Vitamin E free radicals to Vitamin E -offers steadiness to the cell membrane	(66)(67) (68)
Polyphenols	-decreases hyperglycemia -improves acute insulin secretion and insulin sensitivity. -affects insulin signaling pathways -protects against damage to insulin-secreting pancreatic β-cells.	(72)
Alpha-lipoic acid	-reduces cellular injuries set off by free radicals -starts to reinstate endogenous antioxidants such as glutathione, Vitamin C, and Vitamin E. -boosts the translocation of GLUT1 as well as GLUT4 associated with improved activity of proteins of insulin signaling pathway	(67)
Selenium	-imitates insulin-like actions -activates the essential protein accountable for insulin signal cascade	(69)

Superoxide dismutases (SODs) are metallo-enzymes found in eukaryotes and a few prokaryotes. They are localized in the cytosol in addition to the mitochondrial intermembrane, the mitochondrial matrix and inner membrane, and the extracellular compartment. Since their discovery, their role as an effective antioxidant defense has been firmly recognized. SOD catalyzes the exchange of the superoxide anion free radical ($\bullet O_2^-$) to hydrogen peroxide (H_2O_2) and molecular oxygen O_2. (74). SOD is an antioxidant enzyme that plays an essential job in protecting the body against oxidative stress, which is associated with the development of a lot of chronic diseases, including T2DM (75). SOD protects against DM by scavenging superoxide radicals, a type of ROS. Superoxide radicals are produced during glucose metabolism and additional nutrients in the body (76). SOD converts superoxide radicals into hydrogen peroxide, which is less toxic and can be further detoxified by other enzymes such as catalase and glutathione peroxidase. By lessening superoxide radical levels, SOD protects beta cells from oxidative stress, protecting their function and survival. SOD also improves insulin sensitivity, hence decreasing the incidence of insulin resistance and T2DM (77).

Glutathione peroxidase (GPx) is an antioxidant enzyme in the cytoplasm and mitochondria (78). GPx catalyzes the reduction of hydrogen peroxide (H_2O_2) as well as a variety of organic hydroperoxides (R-O-O-H) to water and the related stable alcohols (R-OH) through glutathione as the reducing

reagent (79). It works by inhibiting the formation of free radicals and defends the cells from oxidative damage. GPx protects against T2DM by detoxifying hydrogen peroxide and other lipid peroxides, which are a type of ROS. GPx uses glutathione (GSH) as a cofactor to convert hydrogen peroxide into water and lipid peroxides into less toxic molecules (80).

Catalase protects against T2DM by detoxifying hydrogen peroxide, a type of ROS. Catalase converts hydrogen peroxide into water and oxygen, thereby reducing the levels of ROS in the body (81). Catalase also improves insulin sensitivity, lowering the likelihood of insulin resistance and type 2 diabetes (82). Catalase has been proven to have anti-inflammatory possessions in addition to its antioxidant action. Chronic inflammation is an added reason that helps the development of T2DM. By reducing inflammation, catalase helps to protect against diabetes and its complications (83).

Chronic inflammation is an additional factor that adds to the chance of development of T2DM. By reducing inflammation, SOD, CAT and GPx help to protect against diabetes and its complications. Increasing SOD, CAT and GPx levels or enhancing their activity may be a latent therapeutic strategy for preventing and treating T2DM (84).

Several studies have explored the effects of medicinal plants on antioxidant enzymes such as SOD, CAT, and GPx in diabetic animal models. The results of these studies have been mixed, with some showing an increase in enzyme activity and others showing a decrease. For example, the effects of *Bixa orellana* on streptozotocin-induced diabetic rats significantly increased in SOD and GPx activity, while CAT activity remained unchanged (85).

A similar pattern was observed in the supplementation of *Berberis vulgaris* on streptozotocin-induced diabetic rats (86). The study found that treatment with *Berberis vulgaris* significantly increased SOD and CAT activity, while GPx activity remained unchanged. In contrast, a study investigating the effects of the *Ocimum sanctum* on a diabetic model observed a significantly decreased SOD and CAT activity, while GPx activity remained unchanged (87). The treatment by *Diospyros kaki* significantly increased the SOD and GPx activity; however, CAT activity did not differ in value in streptozotocin-induced diabetic rats (88).

Another study examined the consequence of *Ginkgo biloba* extract on antioxidant enzyme action in rats' brains, showing hypoxia (89). The results showed that *Ginkgo biloba* extract increased the activity of SOD, CAT as well as GPx, and reduced lipid peroxidation in T2DM. Some studies investigated the effect of green tea polyphenols on oxidative stress and antioxidant enzymes in the brains of rats exposed to okadaic acid. The results showed that green tea polyphenols increased the activity of SOD and GPx, reducing lipid peroxidation and protein oxidation in T2DM. The effect of *Aloe vera* gel on oxidative stress and antioxidant enzymes in the liver and kidneys of rats exposed to fipronil, a pesticide, was also examined (90). The results showed that *Aloe vera* gel increased the activity of SOD and GPx, and also reduced lipid peroxidation and inflammation. The effect of garlic on oxidative stress and antioxidant enzymes in rats treated with cisplatin, a chemotherapy drug, is also essential to discuss. Some studies showed that garlic increased the activity of SOD and GPx, and also reduced lipid peroxidation and DNA damage.

These studies provide evidence for the potential of medicinal plants to modulate antioxidant enzyme activity and protect against oxidative stress. However, further research is needed to fully explore the mechanisms of action as well as the therapeutic potential of these medicinal plants.

Overall, antioxidant enzymes in diabetic animal models act a crucial function in protecting the body against oxidative stress (91). Medicinal plants' supplementation effects appear to vary and depend on the specific plant used. Some plants may increase the activity of all three enzymes, thereby enhancing the body's antioxidant defence system (92). While others may decrease the activity of one or more enzymes, reflecting the protective effect against T2DM. Overall, the research on the effects of medicinal plants on SOD, CAT, and GPx is vital because it helps to understand the mechanisms by which these plants exert their therapeutic effects (93). By modulating the activities of these antioxidant enzymes, medicinal plants may be able to prevent or treat various diseases associated with oxidative stress, including T2DM (94).

Medicinal plants antioxidants and diabetic complications

Nowadays, half of the accessible drugs are derived from plants. Studies with medicinal plants have shown potential effects, countering the complications of T2DM. Recently some plants have shown beneficial effects not only on renal dysfunction in diabetes mellitus but also on renal toxicities caused by a few drugs. Due to the side effects of modern synthetic drugs and growing contraindications to their usage, attention is rising in the exercise of the use of medicinal plants (95). Present pre-clinical studies have verified that many have beneficial effects on some procedures in experimental animals. Alteration of risk factors in diabetes has an extraordinary impact on morbidity and mortality in diabetic patients. Since hyperglycemia leads to increased oxidative stress and activation of the polyol pathway, which may be the reason for inflammation and renal damage, several plant extracts with hypoglycemic properties and protective activities against diabetes complications have been familiar. Metformin is a biguanide hypoglycemic compound from a herbal source such as *Galega officinalis*. Some other herbal medicines, such as curcumin from *Curcuma longa*, and glycosides from *Stelechocarpus cauliflorous* have also been shown to prevent diabetes complications (96).

Certain plants have active components such as flavonoids, xanthones, polysaccharides, and peptides that reduce blood pressure or enhance renal and cardiovascular functions,

frequently found in diabetes patients. Antioxidants included in cereals, fruits, and vegetables are known to protect against diabetic problems. However, no proof that consuming just one antioxidant, like vitamin E or C, may prevent these issues (97). While healthy natural fruits and vegetables appear to function as components of intricate networks, no single antioxidant can effectively work as a whole.

New future through natural antioxidants

T2DM treatment with no side effects is still a challenge in the 21st century for researchers (98). In treating diabetes mellitus, herbal drugs attract great attention because of their efficiency, fewer side effects, and low cost, so various plants are used as herbal treatments. According to the World Health Organization (WHO), approximately 80% of the worldwide population depends on traditional medicines because of poverty and lack of opportunity (99). The phytoconstituents may manipulate metabolic activities, directly affecting the body's glucose level. Dietary antioxidants can oppose diabetic complications; a potential therapeutic approach can be found in natural antioxidants. Through Figure 2, the entire process is described concisely.

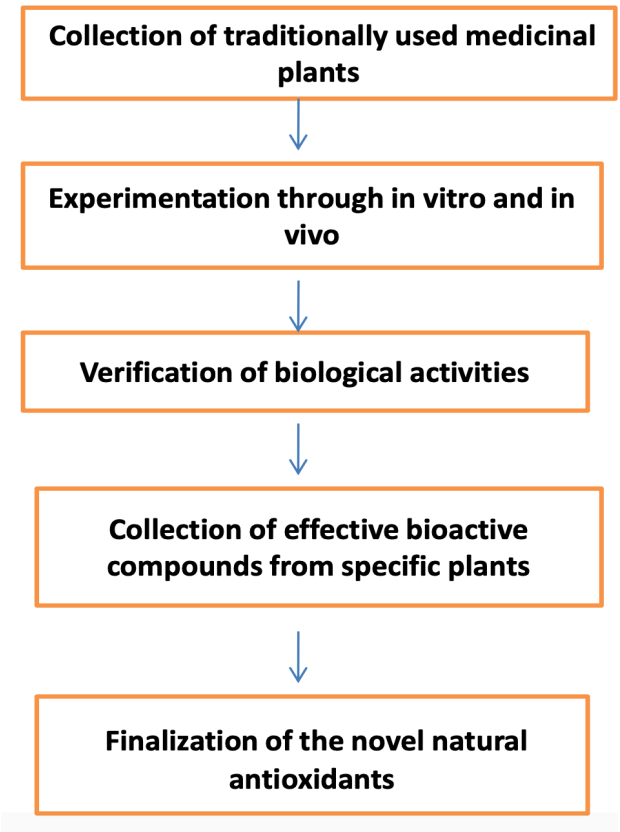

Figure 2: New approaches through natural products.

Conclusion

In conclusion, we emphasized in this review the roles of oxidative stress in T2DM and antioxidants' function in improving the disruptions caused by free radicals in T2DM. Antioxidant-based experimental research has been carried out over two past decades to find new drugs. Among the antioxidants, diet-derivative antioxidants provide hope in the prevention as well as management of diabetes.

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Conflict of interest

The authors declare no competing interests while conducting this study.

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