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Review Article

The Role of Medicinal Plants in Diabetes Mellitus and Oxidative Stress: A Review

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ABSTRACT

Diabetes mellitus is an endocrinology disorder of great global concern. It results from an irregularity in the secretion or action of insulin. It is a metabolic condition characterized by chronic hyperglycemia. Oxidative stress plays a critical role in the pathophysiology of some diseases such as diabetes, aging, cancer, cardiovascular disease, as well as liver and lung diseases. Oxidative stress occurs due to an imbalance between radical generation and radical scavenging. One of the main mechanisms for the development of diabetes complications is via oxidative stress. Oxidative stress is a main upstream occurrence for diabetes complications as well as the development of insulin resistivity. Medicinal plants can be useful in the treatment of numerous diseases and some of their healthful effects are due to their antioxidant activity. Their antihyperglycemic effect is very much linked to their antioxidant potential. This review summarized the antidiabetic potential of some medicinal plants in animal models. There is a continuous need to explore the medicinal capability of herbal products with antioxidant effects in the management of diabetes mellitus.

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Introduction

The prevalence of diabetes mellitus is skyrocketing across the globe (1). This chronic disorder has a lot of severe complications due to its alteration in most metabolic pathways (2). Complications arising from this metabolic disorder have resulted in significant mortality and morbidity (3, 4). Although there are different studies to explicate the molecular mechanisms underlying the etiology of diabetes complications, but their exact pathophysiology is not clearly understood (5). However, one of the key mechanisms involved in the generation of diabetes complications is via oxidative stress (5). This develops when the rate of free radical production surpasses the antioxidant defense systems, hence, resulting in the dangerous effects of free radicals (6). These free radicals are significant physiological components responsible for attaining biological homeostasis, but when their production surpasses the body's antioxidant capacity, oxidative stress occurs (7). Oxidative stress is a main upstream occurrence for diabetes complications as well as the development of insulin resistivity (8, 9).

The practice of traditional medicine is a mainstay in developing countries especially in Africa, hence, there is a continuous need to discover and utilize herbs with medicinal potential in the treatment and management of diseases (10-12). Medicinal plants can be useful in the treatment of numerous diseases due to their various pharmacological actions including antioxidant activities (13-15). This review discusses the pathophysiological processes involved in diabetes, oxidative stress, the implication of antioxidants in diabetes management, and medicinal plants with such activities in animal models.

Diabetes Mellitus

Diabetes mellitus originates from the Greek word 'Diabetes' meaning 'siphon' which implies 'to pass through' and the Latin word 'mellitus' meaning 'sweet' (16). It is an endocrinology disorder resulting from an irregularity in the secretion or action of insulin (17, 18). It is a metabolic condition characterized by chronic hyperglycemia (19). Diabetes mellitus could be classified as type 1, type 2, gestational diabetes, neonatal diabetes and so on (16). The two main classifications of diabetes mellitus are type 1 diabetes mellitus (T1DM) which is also known as insulin-dependent diabetes mellitus (IDDM) and type 2 diabetes mellitus (T2DM) which is known as non-insulin-dependent diabetes mellitus (NIDDM) (20). The acute clinical symptoms of diabetes mellitus are those linked to hyperglycemia which exceeds the renal threshold to result in excessive urination known as polyuria, excessive thirst, dehydration, electrolyte imbalances, and metabolic decompensation, in extreme states known as diabetic ketoacidosis and non-ketotic hyperosmolar coma (21).

Epidemiology

Applying the science of epidemiology to the study of diabetes mellitus has provided important information about this disease such as the incidence and prevalence, mortality and morbidity, and natural history (22). The global prevalence of diabetes mellitus has continued to increase greatly (23, 24). As at 2011, it was estimated that 366 million people were diagnosed with diabetes mellitus in which T2DM consisted of about 90% of the cases. In 2017, an estimate of 462 million people was affected by T2DM, which accounted for about 6.28% of the global population. A similar global prevalence was reported in 2019, which is expected to grow by 2045 to about 700 million (25-27). The total number of people being diagnosed with diabetes mellitus is increasing globally with about 80% of the people with diabetes mellitus in low and middle-income countries (27). Various studies evaluating data trends within Africa indicates an increase in the prevalence of diabetes mellitus in both rural and urban settings, and affecting both gender equally (2, 27-29). In a 2021 report by the International Diabetes Federation (IDF), 537 million adult people have diabetes and have foretold to rise to 643 million in 2030 and 783 by 2045, with 24 million of them within the Africa region by the same year (30). The prevalence of diabetes within the Nigerian adult population (20-79 years) is 3.7% as at 2021 (30).

Although, T2DM is commonly diagnosed in adults, its prevalence has increased in the pediatric age group over the past two decades (31). Based on the population studied, T2DM now represents 8-45% of all new cases of diabetes reported among children and adolescents (32). The prevalence of T2DM in the pediatric population is greater in girls than boys (32); similarly, it is greater in women than men (33). The onset of T2DM in children is between 12-16 years which happens to coincide with the stage of puberty, when insulin resistance begins to develop physiologically (34). In this physiologic state, T2DM develops only if inadequate pancreatic beta-cell function is associated with other risk factors such as obesity (35). Currently, a lot of people (1 in 3 adults) with diabetes are undiagnosed (30). Since pharmacological intervention can reduce the complications of diabetes mellitus, there is an urgent need to detect this disease while it is in early stage (36, 37).

Pathophysiology

The islet of Langerhans situated in the pancreas is made up of two endocrine cells which are the insulin-secreting beta cell and the glucagon-secreting alpha cells (38). These cells continually change their level of hormone secretion in relation to the glucose environment. An imbalance between insulin and glucagon makes the glucose level become inappropriately distorted (39). In diabetes mellitus, there is either absence of insulin or there is an impaired action of insulin which results in hyperglycemia (18, 40).

After a meal, there is an increase in the blood glucose level which stimulates insulin secretion

(41). On the other hand, in fasting conditions, the brain uses up the stored up glucose and this is independent on insulin (42). Insulin inhibits the secretion of glucagon, lowers the concentration of serum fatty acids and causes a decline in glucose production in the liver. When there is insufficient insulin or insulin resistance, there is reduced uptake of glucose by the tissues which leads to extracellular hyperglycemia and intracellular hypoglycemia (43). The intracellular hypoglycemia brings about glucogenesis and gluconeogenesis which leads to the breakdown of fats (44). This is responsible for diabetic ketoacidosis, and also leads to a decrease in protein synthesis and gamma globulins. The extracellular hyperglycemia can lead to a state of hyperglycemic coma and osmotic diuresis (45).

Types of Diabetes Mellitus

T1DM, T2DM, and gestational diabetes mellitus are the main types of diabetes mellitus (18). T1DM is the most common metabolic disease found in children and it can be regarded as an autoimmune disease (21). The prevalence of this metabolic disease varies by age, ethnicity, race and geographic location. T1DM is known as IDDM and it is characterized by the destruction of the pancreatic beta cells secondary to an autoimmune process (46, 47). This eventually leads to a total destruction of beta cells and decreased level or absence of insulin. Several markers of immune destruction of the pancreatic beta cells are present at the time of diagnosis in most individuals and these markers include islet cell antibodies (ICAs), glutamic acid decarboxylase (GAD65), tyrosine phosphatases IA-2 and IA-2b, ZnT8 (zinc transporter 8), and insulin auto-antibodies (IAAs) (47). T1DM is made up of several diseases of the pancreatic beta cells which lead to total insulin deficiency (48). This is due to the autoimmune destruction of the pancreatic beta cells. Most patients with T1DM with no evidence of beta cell autoimmunity have underlying defects in secretion of insulin mostly from inherited abnormality in pancreatic beta cell glucose sensing or from other acquired or genetic diseases (21, 49).

T2DM is known as NIDM. One of the characteristics of this type of diabetes is insulin resistance in peripheral tissues such as the liver and muscles with progressive failure of the beta cells of the pancreas (35). This is usually manifested with defective secretion of insulin in response to glucose stimulus. T2DM is the more common type of diabetes and obesity is a great risk factor for developing this metabolic disease as most individuals with this type of diabetes have intra-abdominal fat (35, 50).

Gestational diabetes mellitus is a form of diabetes in which pregnant women without previous diagnosis of diabetes develops with hyperglycemia (51). It resembles T2DM. This type of diabetes may resolve immediately after delivery or may eventually precede T2DM (52). However, about 60% of the affected women may develop diabetes later in life (53). Gestational diabetes can be treated but it requires careful supervision during pregnancy (54).

Chronic Complications of Diabetes Mellitus

Majority of the forms of diabetes increase the risk of long-term complications. These usually develop after many years but may be the first symptom in those who have been undiagnosed at that time. The major long-term complications of diabetes mellitus are related to damage of the blood vessels. Diabetes mellitus doubles the risk of cardiovascular disease and most deaths in people with diabetes mellitus are as a result of coronary artery disease (55). Other macrovascular diseases linked with diabetes mellitus include stroke, and peripheral artery disease (56).

Other chronic complications of diabetes mellitus are as a result of damage to small blood vessels which include those of the eyes, kidneys, and nerves. Damage to the eyes is known as diabetic retinopathy and it is caused by damage to the blood vessels in the retina of the eye (57). Diabetic retinopathy can lead to gradual loss of vision and eventually, blindness. Also, there is an increase in the risk of developing glaucoma, cataracts, and other eye disorders in diabetes. Diabetic nephropathy is another complication from diabetes mellitus (58). It causes tissue scarring, urine protein loss, and eventually chronic renal disease. Diabetic neuropathy (nerve damage) is another common diabetic complication (59, 60). Symptoms of diabetes neuropathy include numbness, tingling, sudomotor dysfunction, pain, and altered pain sensation, with possible dermal damage. A negative correlation between diabetes and cognitive function has been established (61).

Oxidative Stress

Oxidative stress can be described as a state of imbalance between the production of reactive oxygen species and the biological system's ability to repair the resulting damage or to detoxify the reactive intermediates (62). Numerous researches have established that the major agent in the induction of many diseases such as degenerative or chronic diseases is oxidative stress (62, 63). Oxidative stress has been linked to the induction of disease conditions like ischemic heart disease, atherosclerosis, cancer, immunosuppression, ageing and even diabetes mellitus (63).

Alterations in the normal redox condition of cells can cause harmful effects via the production of free radicals and peroxidase (62). The resultant effect is damage to various cell components such as DNA, protein and lipids. These reactive oxygen species (ROS) includes hydrogen peroxide, hydroxyl anion and superoxide anion. Oxidative stress is thus responsible for disrupting the physiologic mechanisms of cellular signaling (62, 63). Free radicals are molecules with one or more single pair of electron that can easily react with constituents such as proteins, nucleic acid, and lipids (63, 64). The reactive molecule comprises ROS and reactive nitrogen species which are derived from oxygen and nitrogen, respectively. These reactive particles are produced in the cell membrane, mitochondria, peroxisome, lysosome, endoplasmic reticulum, cytoplasm and nucleus. The continuous generation of the reactive species is associated with hyperglycemia (65).

Diabetes and Oxidative Stress: The Link

Some experimental studies have shown that overproduction of free radicals and defect of antioxidants protection is greatly involved in the pathogenesis of diabetes (65, 66). The exact mechanism behind the prooxidant-antioxidant imbalance in diabetes mellitus is increased in the formation of advanced glycation end products (AGEs), auto-oxidation of glucose, polyol pathway, hexosamine pathway, and mitochondrial respiratory chain. The enzymatic source of free radical generation includes xanthine oxidase, nitric oxide synthase and NADPH oxidase (64-66).

The Role of Medicinal Plants in the Management of Diabetes

The practice of traditional medicine is a mainstay in developing countries especially in Africa, hence, there is a continuous need to discover and utilize herbs with medicinal potential in the treatment and management of diseases (10, 12). Medicinal plants can be useful in the treatment of numerous diseases due to their various pharmacological actions including antidiabetic and antioxidant activities (13, 67, 68). Plants contain various parts that are effective in the treatment of diseases and serves as important sources of drugs (13, 69, 70). Some plants have been reported to show hypoglycemic activity and this is due to their phytochemical constituents (71, 72). Some of these phytochemicals reported to be responsible for the hypoglycemic activity of these plants include flavonoids, alkaloids, polysaccharides, sterol, phenolics, peptides and triterpenoid (72).

Some medicinal plants are useful in the management of diabetes because they possess some antioxidant activities (72). Natural substances like fruits and vegetables, in comparison to synthetic antioxidants are more effective in the management of diabetes and can decline the risk of diabetes mellitus (73, 74). Although synthetic antioxidants can be useful in the management of diabetes mellitus, their use is limited due to their toxic effects (75). Hence, the use of some medicinal plants with antioxidant potential to prevent diabetes mellitus complications is beneficial (76).

Selected Plants Reported to Have Antidiabetic Activity in Animal Models

Spondias Mombin (Hog Plum)

S. mombin (as known as yellow mombin or hog plum) is a flowering plant in the family of Anacardiaceae, and is native to the tropical Americas, including the West Indies. It is well known for its medicinal exploits. In a recent study where the antidiabetic and antihyperlipidemic activities of methanolic extract of leaves of *S. mombin* (MESM) in streptozotocin-induced diabetic rats were evaluated, following 28 days treatment of the diabetic rats with varying doses of MESM (125, 250, and 500 mg/kg), it was observed that MESM reduced blood glucose level and reversed the declined plasma insulin level of the diabetic induced rats (77). In other previous studies, the antidiabetic activity of methanol and aqueous leaf extract of *S. mombin* Linn (Anacardiaceae) have also been reported (71, 78).

Allium Sativum (Garlic)

The anti-diabetogenic impact of garlic use alone and in combination with black cumin on diabetic rat model was carried out and the findings concluded that both plant extracts can be useful as anti-diabetogenic agents in diet (79). In another study, the antidiabetic effects of the ethanolic extracts from *A. sativum* were determined in both normal and streptozotocin-induced diabetic rats. The ethanolic extract of the plant was administered for 2 weeks and there was an increased serum insulin in diabetic rats, but not in normal ones (80). It has also been revealed that oral administration of ethanolic extract, juice, and oil of ripe bulb of *A. sativum* reduced the blood glucose in streptozotocin-induced diabetic rats by stimulating the secretion of insulin from pancreas cells. Daily oral administration of 100 mg/kg of garlic extract significantly reduced plasma glucose levels by increasing the plasma insulin levels (81).

Mangifera Indica (Mango)

M. indica has been reported to possess antioxidant activities with therapeutic phytochemicals (82, 83). The hypoglycemic effect of *M. indica* popularly referred to as mango has been evaluated on the leaf part of the plant and it has been shown to be a potential antidiabetic agent (84, 85). In one study conducted during the treatment of diabetic rats with mango peel powder (MPP), there was an increase in the antioxidant property and the lipid peroxidation in the liver, plasma, and kidney reduced. In addition, the glomerular filtration rate (GFR) and the micro albuminuria level improved with treatment with MPP (86).

Acacia Arabica (Babool)

A. arabica is a plant common in the region of North Africa. In a study that was conducted to evaluate the anti-diabetic potential of the *A. arabica* plant, doses of 100 and 200 mg/kg of *A. arabica* bark extract were administered orally to streptozotocin-induced diabetic rats for 3 weeks and after administration, there was an increase in serum insulin, with a reduction in the high serum glucose and insulin resistance (87). The acacia plant contains phytochemicals like polyphenols, tannins, and flavonoids such as quercetin (88). The phytochemicals present is responsible for the anti-diabetogenic effect of the plant. The extract of *A. arabica* helps to improve plasma glucose levels, metabolic disorders in lipid metabolism, and oxidative stress in streptocotozin-induced diabetic rats (87).

Achyranthes Aspera (Chaff-flower)

A. aspera is a well-distributed plant in the tropical world. It is a species of plant in the family of Amaranthaceae. It is an erect, many-branched, spreading, and quadrangular herb that lives several years. The plant and its parts (root, seeds, leaves, flowers, and fruits) have been used for several medicinal purposes. The ethanolic extract of *A. aspera* leaves (1000 mg/kg) when used in streptozotocin-induced diabetic rats greatly decreased the blood glucose level. This could be due to the inhibition of glucose absorption from the intestine or due to an increase in glucose transport from the blood (89). The plant is reported to contain phytochemicals like tanins, terpenoids, steroids, glycoside, flavanoid, carbohydrate and alkaloid (90).

Mimosa Pudica (Sensitive Plant)

M. pudica plant is indigenous to areas like Africa, Europe and Asia. In a study conducted on the seeds ethanolic extract and extract fractions, it was observed that *M. pudica* seed extract significantly increased the level of serum insulin in Wistar rats. It also caused a reduction in the level of thiobarbituric acid reactive substance (TBARS) and caused an increase in the hepatic glutathione and catalase levels (91).

Aloe Barbadensis (Aloe Vera)

Aloe vera is commonly traditional used plant. The ethanol extract of the fresh leaf gel administered to streptozotocin-induced diabetic rats significantly decreased hyperglycemia (92). The aqueous extract of the leaves of *Aloe vera* at a dose of 500 mg/kg body weight of mice was also shown to have a significant hypoglycemic effect (93).

Momordica Charantia (Bitter Melon)

Numerous studies have reported the blood glucose lowering potential of *M. charantia* in diabetic conditions, hence, it is used traditionally (94). The possible mode of antidiabetic actions include its antihyperglycemic effect, suppression of certain gluconeogenic enzymes, preservation of pancreatic islet beta cells, amongst others (95-98). Both the antidiabetic and antioxidant activities of *M. charantia* have been shown, and the plant is suggested to be a potentially new source for the management of diabetes (98).

Conclusion

The use of medicinal plants in the management of diabetes mellitus is increasing. Medicinal plants can be useful in the treatment of numerous diseases and this is largely due to their antioxidant activity. Their antihyperglycemic effect is very much linked to their antioxidant potential. Continuous experimentation and standardization of these plants with antidiabetic and antioxidant activities especially in humans should be performed.

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Conflict of Interest

None declared.

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