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Review Article

Unearthing the Modulatory Operations of Phytochemicals: A Reliable Framework for Therapeutic Approaches

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ABSTRACT

Phytochemicals in no small measure confer active roles in human survival as well as in the prevention of various diseases by their effortless ability to combat oxidative stress known to shorten life expectancy in humans. A number of these factors are well known to predispose an individual to ageing, senescence, microvascular and macrovascular diabetic complications, cardiovascular and neurological disorders. The incidence of cancer amelioration in this regard cannot be discountenanced. A vast array of identified factors that are deep rooted in the cause of diseases implicated in oxidative stress are but not limited to chemical and environmental contaminants in air, food and water while several lifestyle modifications including lack of exercise, smoking and dietary preferences are key factors implicated in disease developments. While we review the extant roles of fruits, vegetables, grains and seed oils as safe for consumption, owing to their astonishing medicinal attributes to counteract the menace of free oxidants in cells, the emphasis on plant-based diets especially the ones that contains phenolic acids and flavonoids with strong antioxidant capabilities cannot be more emphasized. Many of these therapeutic roles are possible by the excess mopping of reactive oxygen in the body thereby protecting cells from damage. The wondrous effects of these antioxidants in cells can be implied to reduce the risk of cardiovascular and neurological diseases such as diabetes mellitus, obesity, hypertension, arterosclerosis, Alzheimer's and long-term cancer.

Keywords: Cardiovascular, Flavonoids, Neurological disorders, Oxidative stress, Phenolic acids, Phytochemicals.

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INTRODUCTION

Phytochemicals usually referred to as plant bioactive components have proven their mettle in the area of therapeutic approaches and in instances where adequate medicinal capabilities are mostly needed. They may be called plant secondary metabolites, and they have been given much reverence in the attenuation of cardiovascular diseases namely type II diabetes mellitus, hypertension, obesity and lots more. Thus, their active participation and action on insulin signaling pathways via stimulation cannot be overemphasized.[1]

From ancient times till date, phytochemicals have being the raw materials for the production and manufacture of oral anti diabetic agents and are employed locally as crude agents in ameliorating various disease conditions.[1,2] A small fraction of the widely estimated species of plants on earth are only utilized by humans and statistics have shown that, of this little proportion of medicinal plants elucidated, polyphenols and flavonoids happens to be the most widely employed phytochemicals owing to their impeccable antioxidant and anti-hyperglycaemic properties.[2] Several bioactive compounds such as carotenoids, polyphenols, vitamins, omega-3-fatty acids, organic acids, nucleosides and nucleotides as well as the phytosterols have demonstrated significant impeccable therapeutic tendencies in the areas of mediating debilitating health challenges.[3] As a form of curiosity, the analysis and characterization of these phytochemicals should be of major interest and as such, day to day attempts have been undertaken to proffer sensitive and selective methods to analyze for pure characterization of bioactive compounds.[3,4] In food consumption, a good number of nutritional constituents take their role in a similar fashion as bioactive compounds dispensing their medicinal properties outside the basic nutritive value of food.[4] A comprehensive evaluation of these phytochemicals basically in health and disease are currently in progress. Besides their effects on health, they appear to have physiological, behavioral and immunological attributes.[5] Currently, more and more

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phytochemicals (bioactive compounds) are still being discovered in everyday research as thirst for new discoveries and innovations suffice. Various diversity in chemical structure and biological function of these compounds have been outlined among which are the carotenoids, flavonoids, carnitine, choline, Co-enzyme Q, phytosterols, glucosinolates and polyphenols.[5,6] Vitamins and minerals should not be categorized as out of the box because they have been found to exhibit transient pharmacological attributes and as such they should be grouped as bioactive compounds.

Virtually, all phytochemicals (bioactive compounds) take properties ranging from antioxidant, anti-carcinogenic, anti-microbial to anti-inflammatory properties.[6] In this regard, many epidemic reports suggest their role in coronary artery diseases. Flavonoids being a family of the phenolics is almost ubiquitous in all plants in varying degrees and much of their presence in plants are in those of cereals, legumes, nuts, olive oil, tea, fruits and vegetables.[6] Their antioxidant properties and effects on cardiovascular diseases cannot be undermined due to their immeasurable medicinal properties.[6] In conclusion, bioactive compounds or molecules portend great abilities with influence on energy intake, while reducing inflammatory agents, arresting oxidation and preventing metabolic disorders.[7] In the aspect of diseases such as cancer, cardiovascular diseases, Alzheimer's, diabetes, cataracts and in Advanced Glycated End products (AGEs), research has shown that bioactive compounds have great prospects in ameliorating the effects of these diseases in humans.[7] Asides being a member of antioxidant family, they are also known to modulate metabolic processes, inhibit receptor activities, repress or activate the presence of enzymes and either induce or inhibit gene expression.[7] Table 1 below highlights the occurrence and medicinal values of some of these bioactive compounds.

Bioactive Compounds from Diabetes Mellitus and Alzheimer's Disease Perspective

Type II diabetes mellitus is a metabolic disease condition characterized by consistent high blood glucose level and due to the reduced number of glucose transporters specific for the uptake of glucose, glucose becomes intolerant to the cells.[8] Alzheimer's disease is a progressive neurological condition associated with poor or declining cognitive ability and behavioral function.[8] In account of the common attributes associated with both conditions, preventive and therapeutic approaches must be extensively employed. Considering the therapeutic approaches to mitigate the effects of diabetes mellitus and Alzheimer's, bioactive compounds must be acknowledged. [8,9]

Many of the bioactive compounds found in the polyphenols, vitamins and carotenoids have been widely employed in mitigating these conditions owing to their antioxidant and anti-inflammatory properties.[9] More revelations on bioactive compounds about their role in reducing blood glucose, enhancing insulin sensitivity, decreasing insulin resistance and inhibition of amyloid plaques have continued to emerge.[9] Epidemiological evidences continue to unfold the incidences of diabetes neuropathy and increased risk of Alzheimer's Disease (AD).[9,10]

Long term complications of diabetes neuropathy in a patient have shown to likely predispose an individual to Alzheimer's disease. AD has continued to dominate major discussions in neurochemistry and nervous system owing to many factors relating to neurons and how they affect cognitive ability both in learning and in memory. A person's brain is subsequently impaired and the ability to learn, communicate and carry out daily activities becomes dysfunctional.[10] Statistics have shown that in an average population of Africans, AD is a factor. With the occurrences and socio-economic factors in the current world, it is therefore expedient to develop a safer, effective and less cost-effective approach to tackle the incidences and symptoms of Alzheimer's disease.[10] Current knowledge admits that no respite is available yet in the treatment of AD or its progression even as the adverse effects of anti-diabetic drugs continue to linger.[11]

Bringing to the fore, the biochemical correlation between Type II diabetes mellitus and AD, it may be possible to establish a common therapeutic agent in the treatment of both conditions. A study conducted on some African population opined that natural bioactive compounds may prove to be the common promising therapeutic agent to be employed owing to their negligible side effects, readily availability and potency.[11,12] As the ever increasing role of bioactive compounds in antioxidant capacity, anti-inflammatory and anti-metastatic effect continues to take centre stage, more of their mechanisms in cell culture and animal models needs to be studied.[12] Figure 1 as indicated depicts the event of insulin signaling alteration in diabetes mellitus as well as its contribution to Alzheimer's disease disordered physiological processes.

Phytochemical Actions on Insulin Signaling Pathways

Phytochemicals often referred to as plants bioactive components have proven their mettle in the area of therapeutic approaches and in instances where adequate medicinal capabilities are mostly needed. They may be called plant secondary metabolites, and they have been given much reverence in the management of type II diabetes mellitus. Thus, their active participation and action on insulin signaling pathways via stimulation cannot be overemphasized (As enunciated in Figure 2).[14]

From ancient times till date, plants bioactive components have been the raw materials for the production and manufacture of oral anti diabetic agents and are employed locally as crude agents in ameliorating various disease conditions.[16] A small fraction of the widely estimated species of plants on earth are only utilized by humans and statistics have shown that, of this little proportion of medicinal plants elucidated, polyphenols and flavonoids happens

Table 1: Bioactive compounds, their occurrence in foods and health promoting properties.

Bioactive compounds	Presence in foods	Health benefits
Flavonoids, flavones and luteolin.	Broccoli, green pepper, parsley, oregano, carrots and rosemary.	Inhibits metastasis.
Apigenin	Many fruits and vegetables, parsley, celery and celeriac.	Metastasis inhibition.
Tangeritin	Citrus peels.	Binds cholesterol, free radical scavenging ability and cancer cells inhibition.
Quercetin	Fruits and vegetables especially onions, apples.	Maintains cardiovascular homeostasis.
Kaempferol	Apples, grapes, tomatoes, green tea, potatoes, onions, broccoli, Brussels sprouts, lettuce, cucumbers, green bean.	Inhibition of cancerous cells and production of free radical scavengers.
Myricetin	Vegetables, fruits, nuts, berries, tea and red wine.	Inhibition of inflammation, protein glycation suppressant and prevention of lipidaemia.
Galangin	Propolis.	Fights bacteria, production of antioxidants, binds carcinogens and prevents inflammation.
Hesperidin	Citrus fruits.	Prevents oxidative processes, binds carcinogens, boost lipid content in blood and cardiovascular homesostasis.
Naringenin	Grapefruits, oranges and tomatoes.	Prevention of oxidative processes, prevention of inflammation and immunological modulator.
Genistein	Soybeans, legumes and chick peas.	Prevention of oxidation and presence of oestrogen-like properties (phyto-oestrogen)
Diadzein	Soybeans and soy products like tofu.	Antioxidative property and presence of oestrogen-like property (phyto-oestrogen).
Glycitein	Soy products	Prevention of oxidation and presence of oestrogen mimetic property.
Pyridoxal	Meats, whole grain products, vegetables, nuts and bananas.	Prevention of coronary heart disease and cancer cells inhibition.
Niacin	Liver, chicken, beef, fish, cereal, peanuts, legumes, avocados, tomatoes, leafy vegetables.	Prevention of cardiovascular diseases.
Riboflavin	Milk, cheese, leafy vegetables, liver, kidneys, legumes, yeast, mushrooms and almonds.	Antioxidation and migrane suppressant.
Nicotinamide	Meat, fish, nuts, mushrooms and vegetables.	Inhibits inflammation and anxiety arrester.
Ascorbic acid	Citrus fruits, tomatoes, tomato juice, potatoes, red and green peppers, kiwifruit, broccoli, strawberries, Brussels sprouts.	Prevention of oxidation, binds carcinogens and lowering cardiovascular risks.

to be the most widely employed phytochemicals owing to their impeccable antioxidant and anti-hyperglycaemic properties.[16,17]

The impeccable roles of these polyphenols and flavonoids majorly in carbohydrate metabolism and glucose homeostasis have been very much exploited in various research and experimental models both *in vitro* and *in vivo* and in clinical research.[18] Numerous are the functions and effects of these bioactive components in plants, some of which are made possible through insulin signaling pathways or by GLUT 4 translocation in cell membrane as shown in Table 2.

The blood glucose lowering effects of polyphenols and flavonoids are greatly attributed to carbohydrate uptake lowering in the intestine by suppressing the carbohydrate intestinal enzymes such as α-amylase and α-glucosidase consequently leading to accelerated β-cell function and insulin action, initiating insulin release and antioxidant as well as anti-inflammatory modulation.[19] The effects of these bioactive components on genetic modulation and expression including their molecular mechanisms on how they potentiate anti-diabetic properties are currently in progress both in intensive research and experimental.[19] In polyphenolic phytochemicals, gene expressions implicated in the incidences of type II diabetes mellitus may be stimulated and these genes function in controlling the movement of glucose to the cell, insulin release and its activity, anti-oxidative effects,

inflammatory processes, metabolism of lipids and many other heat related processes.[20]

A large number of plant bioactive compounds have been studied in experimental animals to reveal gene expression data, insulin signaling pathways as well as GLUT 4 translocation in many target tissues, an addendum to emphasize the impeccable role of some plant bioactive components in targeting insulin signaling and GLUT 4 translocation in glucose uptake regulation.[21] For example, resveratrol has been found to trigger Activated Protein Kinase B (AKT) also known as protein kinase B as well as VEGF in Streptozotocin (STZ)-induced experimental model in the cardiac muscle of rats compared to non-diabetic rats as well as to accelerate GLUT 4 expression in muscle of STZ-induced diabetic rats through PI3K-AKT pathways.[21] More revelations in experimental research had demonstrated that in diseased state reduced GLUT 4 are seen as shown in Figure 2.[21]

Phytochemicals and Their Actions on Glucose Homeostasis

The impeccable roles of these polyphenols and flavonoids majorly in carbohydrate metabolism and glucose homeostasis have been very much exploited in various research and experimental models both *in vitro* and *in vivo* and in clinical research.[22] Numerous are the functions and effects of these bioactive components in plants, some of which are made possible through insulin signaling pathways or by GLUT 4 translocation in cell membrane. In addition, it was also adduced that the two phytochemicals are capable of inhibiting the activity of glucokinase and stimulating glucose-6-phosphatase in the liver to consequently accelerate beta cell function in the pancreas to further release insulin.[22] In this vein, it was also revealed that phytochemicals that belong to the group of tannins such as the gallotannins has role in increasing mRNA expression of GLUT 4 as well as PI3K leukotriene cells.[22] As in the case of 3β-taraxerol, a bioactive compound which is a tri-terpenoid present in *magnifera indica* takes its role as a PI3K dependent dual activator of glucose transport via GLUT 4 trans-membrane movement.[22]

Resveratrol (Polyphenol)

Resveratrol, a bioactive compound of the polyphenolic class, has wide occurrence in grape skins, seeds and red wines with incredible antioxidant and anti-inflammatory benefits. Among its human friendly characteristics are in the maintenance of mental homeostasis and improved mitochondrial function.[23] As it has been reported in cell and animal studies, resveratrol is reputable to have a relieving effect on type II diabetes mellitus prognosis. Resveratrol, being a potent regulator of SIRT 1, an NAD^+ dependent deacetylase has a crucial role in regulating many agents that influences T2DM as it is specific to the activation of SIRT 1.[23] These activities were largely dependent on normal activation of SIRT 1 known to upregulate the activity of key genes needed for pancreatic beta cell functioning.

Additionally, hyperglycaemia suppression and improvement of insulin sensitivity via the activation of SIRT 1 takes centre stage among the crucial roles of resveratrol.[24] In recent times, many research models demonstrated that resveratrol improved T2DM prognosis by regulating the action of mitochondrial biogenesis, lipid metabolism and beta cell via the activation of SIRT 1.

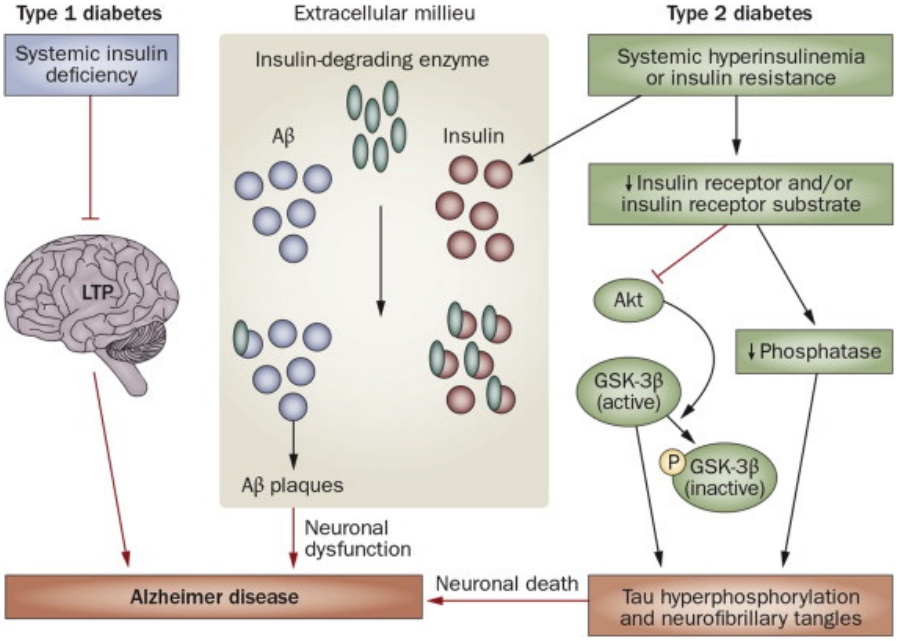

Figure 1: Altered insulin signaling in diabetes mellitus and contribution to Alzheimer's disease pathophysiology.[13]

A decrease in insulin receptor signaling leads to inhibition of Akt and dephosphorylation (activation) of Glycogen Synthase Kinase-3 beta (GSK-3-beta) and results in tau hyperphosphorylation.

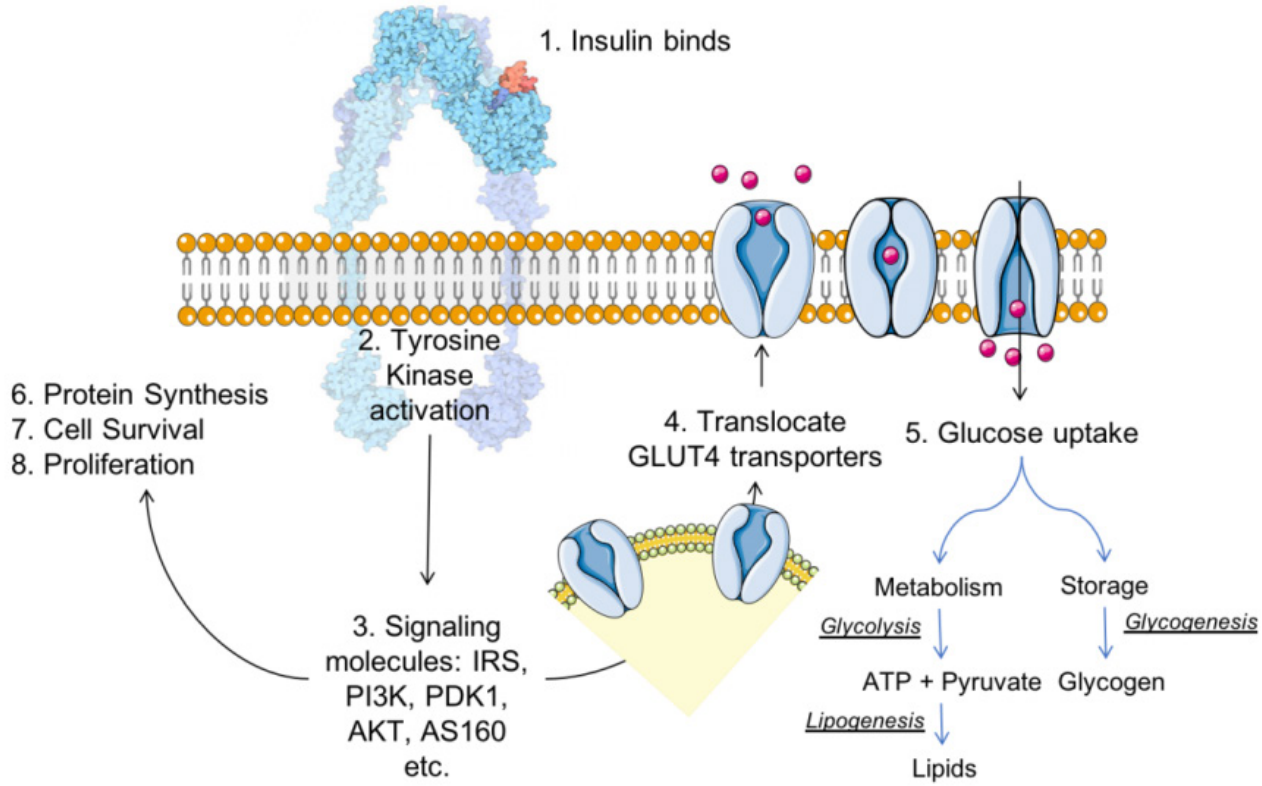

Figure 2: Insulin signaling cascade for insulin function.[15]

Insulin coloured red, insulin receptor coloured blue. Insulin receptor complex formation results in signaling cascade for insulin function.

A positive association between resveratrol and Manganese Superoxide Dismutase (Mn-SOD) has been established. Mn-SOD, a household name in the family of antioxidant enzymes and free radical scavengers in the mitochondria arrest tissue damage and protects the integrity of membrane. An impairment or distortion in the production of this enzyme will lead to increased ROS production and inducement of tissue damage.[24] In recent diabetes study, resveratrol was shown to mediate various histopathological anomaly and improved mitochondrial biogenesis in the kidney of lipid laden mice through an effective collaboration with Mn-SOD enzyme production by resveratrol.[25] Moreover, recent studies further elucidated that resveratrol was confirmed to attenuate pancreas cell loss and improved glucose tolerance in diabetic mice.[25]

In addition, resveratrol has also been credited for its role in increasing glucose uptake in cells via enhanced GLUT 4 translocation. This is made possible by the active regulation of AMP-activated Protein Kinase (AMPK) and Akt/iNOS signaling pathway.[25]

Quercetin (Flavonoid)

Quercetin belongs to a class of flavonoids, and it is found in a wide array of foods including red onions, broccoli, tea and apples.[26] With its exhilarating antioxidant, anti-inflammatory and anti-cancer benefits, quercetin has been labeled to mediate the pathology of T2DM and its complications at any level. In relation to resveratrol, quercetin also stimulate glucose uptake by high re-uptake mechanism in translocating GLUT 4.[26]

In a related development, as quercetin activates AMPK in the liver, the inhibition of Glucose -6-Phosphatase (G6Pase) must take effect thereby suppressing glucose production in the hepatic cells. More reports continue to emerge in the preservation of β cell function and modulation of glucose homeostasis by quercetin as well as its prevention of hydrogen peroxide-induced oxidative destruction in the mitochondria.[26] The ability of quercetin to exert these functions are dependent on its ability to actively phosphorylate Extracellular signal-Regulated Kinase 1 and 2 (ERK1/2) indicating that ERK 1/2 activation is necessary in the action of quercetin. The alignment between SIRT 1 and quercetin also takes prominence when upregulation of SIRT 1 activity was made possible by quercetin to improve glucose metabolism and lipid metabolism as well as evidenced in ameliorating oxidative injury in streptozotocin-induced diabetic rats owing to quercetin influence on Akt signaling pathway.[27] Much has been reported on quercetin on vascular effect in spite of the numerous data highlighting vascular complications as a prominent manifestation causing high mortality and morbidity in diabetic patients. As a remedy to this assertion, quercetin administration was proven to attenuate the progression of diabetes-induced hypertension and also quash diabetes -induced vasoconstriction by its vasodilatation effects and also by prevailing on blood vessels.[27]

Table 2: Reported antidiabetic effects of phytochemicals on insulin signaling pathways accelerating glucose transporter isoform 4 (GLUT 4).

Phytochemicals	Plants	Effects on insulin signaling pathways accelerating GLUT 4
Resveratrol	In almost all plants	Stimulates AKT as well as VEGF and it is also involved in GLUT 4 expression as evidenced in muscle of STZ- induced rats via PI3K-AKT pathways.
Gallotannins	Capparis moon	accelerates GLUT 4 as well as PI3K mRNA expression in the L6 cells.
3β-taraxerol	Magnifera indica	It is involved in glucose transporter activation via the transient displacement of GLUT 4 effected by PI3K.
Astragalus polysaccharide	Astragalusmembranaceus	Maintains the up-regulation and down-regulation of insulin-stimulated PKB-Ser473 phosphorylation and GLUT 4 displacement.
Cyanidin-3-O-β-glucoside	Protocatechuicacid and most plants.	Maintains insulin mimetic property and promotes GLUT 4 displacement as well as adiponectin secretion.
Diadzein	Glycine max	AMPK activation and GLUT 4 translocation Acceleration of glucose homeostasis.
Iridoid, catalpol, specioside	Kigelia pinnata	Activation of GLUT 4 transfer to cell membrane.
Gallic acid	Myriophyllum spicatum	Depresses hyperglycaemia as well as stimulation of glucose uptake via the segmentation of GLUT 4 to the plasma membrane.

Genistein

Isoflavone class of bioactive compound is rich in genistein, and it occurs in a variety of plants among which are the chickpeas, soybeans and fava beans. Several compounds largely present in genistein have been adjudged to prevent and mediate type II diabetes mellitus and Alzheimer's disease owing to their potency and effectiveness in common research.[28] It is no longer surprising that an impaired beta cell function will ultimately lead to decreased insulin production and ultimately rise in blood glucose. Therefore, a comprehensive analysis on genistein is crucial in the management of diabetes mellitus.[28]

According to Goh and Cooper (2018) genistein upon administration trigger the production of insulin through the activation of cAMP/PKA-dependent ERK1/2 signaling pathway.[29] In an animal experiment, diabetes type II mellitus induction by streptozotocin decreased pancreatic insulin, followed by the distruption in cell and tissue structure. However, the treatment segment of the experiment by genistein supplement gradually repaired the pancreas for beta cell mass production and marked reduction in apoptosis. Subsequently, more of genistein effects were seen in ameliorating the damages occasioned by streptozotocin administration and improvement in glucose tolerance.[29] According to a diabetes research conducted on mice with the aim of evaluating the anti-hyperglycaemic effects of genistein, it was reported that genistein upon administration significantly lowered HbAIc levels and markedly reduce blood glucose.[29,30] Moreover, the insulin/glucagon ratio was also observed to be transiently improved in the treatment group in comparison to the control group.[30] In furtherance to other features observed on genistein supplements, the effects of genistein on lipid metabolism and carbohydrate metabolism were also evaluated. It was shown that genistein as a potential therapeutic agent reduced the levels of plasma triglycerides, free fatty acids and total cholesterol while also improving the HDL-cholesterol. These observations may not be unconnected to the prevailing power of genistein on liver glucokinase activity and inhibition of liver fatty acid synthase, prompt regulation of beta oxidation as well as glucose-6-phosphatase activities.[31] Therefore, it may not be a misnomer to conclude that genistein exerts incredible anti-hyperglycaemic effects in the prognosis and treatment of diabetes mellitus.

Epigallocatechin-3-Gallate (EGCG)

Epigallocatechin-3-Gallate (EGCG) is widely distributed in plants of diverse origin most especially in green tea and it belongs to the class of polyphenols.[32] Recently, research conducted on green tea enumerated the medicinal benefits inherent in it and this has been largely ascribed to the abundance of EGCG presence. Epigallocatechin-3-Gallate (EGCG) exerts significant antioxidant benefits and as a result of this, it is now widely used as conventional ingredient in making fruit wines and herbal products.[32] The generation of cytokines and attendant production of inducible Nitric Oxide Synthase (iNOS) involved in angiogenesis and enhancement of inflammatory responses with the cell is characteristic of Type II Diabetes Mellitus (T2DM).[33] However, EGCG was reported to protect cells against pro-inflammatory cytokines generation and that it could have

been able to dispense the protection by forcibly suppressing the expression of iNOS which is a driver of inflammation and apoptotic cells in the muscle via the blockage of NF-κB pathway and as such, EGCG may promulgate its enhanced pancreatic beta cell function.[33]

However, the antioxidant capabilities of EGCG may need to be investigated further as it has been reported in some quarters that EGCG is a pro-oxidant, inducing oxidative stress through formation of Reactive Oxygen Species (ROS) by inhibiting the antioxidant system.[34] Similarly, EGCG was found to trigger hydrogen peroxide production and also stimulating Fe^{2+} dependent formation of toxic radicals leading to inducement of apoptosis and decreased cell viability in beta cell function.[34] Conversely, an animal research study has shown EGCG to be effective in the prevention and development of type II diabetes mellitus alongside its complications although, this assertion was found to be inconsistent with subsequent study. In a diabetic mice model, EGCG administration demonstrated improvement in insulin secretion and oral glucose tolerance test in dose-specific proportions.[34] This exhibition suggests that EGCG may have a positive effect on the pancreas. Moreover, further analysis of the study, indicated that carbohydrate metabolism enzymes such as glucokinase were markedly expressed and a reverse suppression of mRNA PEPCK, glucose-6-phosphatase and fatty acid synthase were not left out.[35] More of the staggering antioxidant and anti-inflammatory potentials of EGCG were evident in decreased malondialdehyde amounts in diabetic mice to mitigate the effect of lipid peroxidation, increased cell survival and also preventing DNA damage.[35]

Conversely, the pro-oxidant nature of EGCG cannot be overly dismissive as it portends great challenges and also gives room to doubt its credibility in consumption owing to its oxidative stress characteristics.[35] According to reliable sources, the severity of pro-oxidant nature of EGCG may vary depending on the cellular environment, erythrocyte count or metal ions and the cell line characteristics in biological systems.[36] Thus, many investigations must be carried out to unravel the actual cause of this negativity. The varying degrees of pro-oxidant secretion induced by EGCG may vary in different pathophysiological conditions.[36]

Hesperidin

Hesperidin, a flavonoid glycoside, is distributed widely in citrus fruits such as lemons and oranges. In recent times, evidences from both *in vitro* and *in vivo* models highlighted the importance of hesperidin in the prognosis and treatment of type II diabetes mellitus alongside its complications more importantly, in its antioxidant, anti-inflammatory and anti-depressant qualities.[37] Hesperidin was found to be protective against oxidative stress occasioned by IL-1β in diabetic rats thereby potentiating the function of pancreatic cells and rekindling the hope of insulin secretion.[37] STZ-induced diabetic rats in conjunction with High Fat Diet (HFD) treatment on administration of hesperidin mediate hyperglycaemia majorly by facilitating the peripheral uptake and utilization of glucose which may not be unconnected to the modulation of GLUT 4 mRNA expression.

Hesperidin also decreased the levels of HbA1c, increase insulin secretion, boost vitamin C and Vitamin E availability in HFD/STZ-induced diabetic rats.[38] These exhibitions were suggested to be largely due to the ability of hesperidin to suppress oxidative stress and pro-inflammatory cytokines.[38] Moreover, the effect of hesperidin on the retina has also been studied as it was able to mediate retina dysfunction by reducing the folding thickness and concomitant increase in retina blood flow owing to its antioxidant and anti-inflammatory properties. This could also be affiliated to its staggering role in the suppression of Advanced Glycation End products (AGEs) and also elevation of the aldose reductase.[38] The neuronal effect of hesperidin demonstrated its role in mediating diabetic neuropathy, a pathological course in diabetes complications by combating neuropathic pain and efficient nerve conduction intensity by fighting free radicals or inhibiting their production.[39]

Anthocyanins

In addition to the class of bioactive compounds, flavonoids are the anthocyanins. They take their pride in influencing the various colours of fruits and vegetables as well as in flowers from blue, red to purple colours.[40] They join the group of compounds having antioxidant benefits making them a reliable alternative to combat type II diabetes mellitus. It was shown that anthocyanins could activate PI3K/Akt and ERK1/2 signaling in cells thereby shielding cells against destructive hydrogen peroxide radicals.[41] More of its antioxidant capabilities were reported in diabetic mice where it suppresses hydrogen peroxide radicals by the activation of transcription factor Nrf2 (Nuclear factor-erythroid factor-2-related factor) a critical transcription factor that regulates the expression of over 1000 genes in the cell under normal and stressed conditions.[41]

Moreover, in hepatic cells, anthocyanins were reported to have prevented insulin resistance owing to its ability to activate PIP3/Akt pathways.[42] Effects of anthocyanins on glucose modulation, glucose tolerance and insulin levels were shown on STZ-induced diabetic rats on injection of anthocyanins. Anthocyanins were able to increase blood glucose levels, improve glucose tolerance and accelerate insulin secretion levels.[42] It decreased haemoglobin glycation by releasing iron from haemoglobin and efficiently transporting oxygen in blood.[42] In recent times, it was also reported that anthocyanins from purple corn were able to increase insulin secretion and facilitate glucose uptake as well as enhancing the action of Free Fatty Acid Receptor-1 (FFAR1) with glucokinase. All these effects were largely due to its ability to regulate GLUT 4 transporter and activate the phosphorylation of insulin receptor.[42]

Carotenoids

A common subset of carotenoids are the lycopenes and they take their sources from tomatoes and pink grape fruits and it belongs to the family of carotenoid.[43] The red colour of tomatoes and grape fruits are due to the presence of lycopene. In contrast to other bioactive compounds reporting numerous data on anti-diabetic properties, lycopene may not be that vast in anti-diabetic qualities but much is known in respect to its antioxidant benefits.[43] Diabetic endothelial dysfunction according to some sources was also shown to be rescued in this regards.[43,44] In recent times, more reports emerged on the role of lycopenes on the kidney. In the aspect of diabetic nephropathy as one of the chronic complications of diabetes mellitus, lycopene protected the kidneys in significant amounts from diabetes mellitus owing to its capacity to stimulate the synthesis of antioxidant enzymes and also stimulating Akt phosphorylation alongside modulating connective tissue growth factor.[44] Moreover, the amelioration of kidney function by lycopene was attributed to its ability to interrupt the AGE-RAGE axis.[44] A more correlation of lycopene and cognitive function was tested in diabetes mice where it was revealed that it prevented cognitive impairment and cholinergic dysfunction by accelerating the rate of acetylcholinesterase synthesis and also declining the rate of Nitric Oxide (NO) and TNF-α production.[44]

Phytochemicals and Their Actions on Cardiovascular Diseases

A more fundamental approach of phytochemicals has been established in the area of cardiovascular diseases ranging from heart attack, stroke, hypertension, atherosclerosis and coronary artery diseases. A more distinctive epidemiological perspective is premised on a diet established on dietary cholesterol.[45] Cholesterol lowering agents such as Sitosterols and mixed solutions of soy sterols have been extensively studied in this regard by considerably lowering cholesterol by approximately 10%.[45] This is made possible by the extant inhibition of cholesterol absorption in the epithelium and through the intestinal lumen. These exciting cholesterol inhibition mechanisms by sitosterols have been attributed to its co-crystallization and precipitation ability in which an ingestion of 1g of β-sitosterol was reported to inhibit the absorption of cholesterol by 40% in a diet containing about 400 mg of cholesterol. Another possible mechanism earlier reported also showed that a significant reduction in plasma cholesterol level could be ascribed to an astronomical increase in LDL receptor activity. [45,46]

Newer technologies and advanced discovery had demonstrated that sitostanol a 5-α saturated sitosterol derivative has great prospect in the reduction of cholesterol absorption in the intestinal lumen more often than sitosterol. More convincing evidential reports have added that sitostanol and in conjunction with cafestol, a terpene present in coffee have a potential ability to inhibit HMG-CoA reductase - a committed enzyme in cholesterol biosynthetic pathway.[46] However, more substantial evidence needs to be reported in rice bran oil as to whether it possesses the capacity to reduce cholesterol levels in humans.[46]

Flavonoids on the other hand present majorly in vegetables, fruits and seeds are majorly categorized as flavonoids, flavones, cathechins, flavanones and anthocyanins. They possess wide dominance in onions, soy, tea and wine.[47] Much of these flavonoids are present as quercetin glucoside in onions and fruits and quercetin rutinoside in vegetables.[47] A considerable level of flavonoid consumption has been directly associated with reduced coronary heart disease and hypertension where a study being undertaken in Finland has reported that, for example, a 0 to 19.0 mg/dL of flavonoid consumption was ascribed to a mortality/morbidity rate of 18.5 per 1000 persons- years in reference to coronary artery disease.[47] However, it should be clearly admissible to point out that a few flavonoids may exert toxic effects ranging from gastro-intestinal disturbances, allergy and hypersensitivity induction to short term dermatological occurrences especially in the event of excessive consumptions.[48] More convincing research is recommended on the major classes of flavonoids to differentiate their structure, potency and would be side effects. A nexus between flavonoids and hypertension is premised on the evidential documentation that flavonoids exhibit antioxidant properties and as a result demonstrates incredible ability to inhibit LDL oxidation in cells.[48] As an addendum, phenolic compounds inhibit oxidation of LDL in humans as seen in red wine. More resounding evidential capabilities of flavonoids are also seen in the inhibition of platelet aggregation and adhesion which could be an alternative mechanism to the attenuation of coronary artery disease by flavonoids.[48,49] Some distinctive mechanistic reactions by which phytochemicals attenuate cardiovascular disease related to oxidative stress have been elucidated some of which are; direct free radical scavenging ability, chelation of pro-oxidant metal ions, attenuation of lipid peroxidation by the generation of antioxidants and HDL activity preservation.[49] Furthermore, inhibition of cellular enzymes implicated in cell-mediated oxidation of LDL particles such as phospholipase A2, cyclo-oxygenase and lipo-oxygenase are extant efficiencies of phytochemicals.[49]

CONCLUSION

Bioactive components in plants have paved the way for the advancement and the wide prominence of folk medicine owing to their sensational promising curative tendencies. The use of traditional medicine or medicinal plants in Africa and beyond has taken centre stage where the usage and search for herbal cures as preventive approach to diabetes mellitus and other debilitating diseases is now globally acclaimed.[49] Folk medicine now provides the only alternative route or curative way to manage metabolic diseases or disorders rather than the preventive approach in the

developing countries for common ailments and it's been used based on testable observations usually as anti-hyperglycaemic, anti-diabetic and anti-hyperlipidaemic remedies due to the effectiveness and its composition in particular plant compound or extracts.[49] The easy accessibility and affordability of these medicinal plants as direct therapeutic agents has paved way for the attractiveness of plants compared to modern medicine.[49]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IRS: Insulin receptor substrate; **PI3K:** Phospho-inositol-3-kinase; **AKT:** Activated protein kinase B; **PDK1:** Phosphoinositol-dependent kinase-1; **AS160:** Akt substrate of 160 kDa; **VEGF:** Vascular endothelial growth factor; **STZ:** Streptozotocin; **PI3K:** Phosphoinositide 3-kinase; **AMPK:** 5' Adenosine Monophosphate-Activated Prot.

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