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Medicinally Important Phytochemicals: An Untapped Research Avenue

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Review Article

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ABSTRACT

The past decade has witnessed a tremendous resurgence in the interest and use of medicinal plants. The beneficial medicinal effects of plant materials typically result from the combinations of secondary products present in them known as phytochemicals. Phytochemicals are biologically active, naturally occurring chemical compounds found in fruits, vegetables, grains, nuts, tea and seeds that promote human health and prevent diseases. The therapeutic effects of these medicinal plants can justifiably be attributed to, among others, the phytochemicals in them especially the flavonoids, alkaloids, sterols, terpenoids, phenolic acids, stilbenes, lignans, tannins and saponins. The abundance of scientific evidence indicates that such bioactive compounds have biological properties such as antioxidant activity, antimicrobial effect, modulation of detoxification enzymes, stimulation of the immune system, decrease of platelet aggregation and modulation of hormone metabolism and anticancer property. This paper avails a review of medicinally important plant-derived compounds that can be used in design of more efficacious therapeutic agents against many communicable and non-communicable diseases.

INTRODUCTION

In recent years, herbal prescriptions have received considerable attention as an alternative way to compensate for perceived deficiencies in orthodox pharmacotherapy worldwide [1]. Despite a lack of medical evidence to support their therapeutic efficacy and toxicological effects, the use of herbal medicine has increased considerably [1]. According to World Health Organization (WHO), up to 80% of the world's population in underdeveloped and developing countries relies on traditional medicine practices for their primary health care needs [2]. Traditional medicines have been accorded greater acceptance in Africa because of the unavailability, unwanted side effects and high costs associated with orthodox medicines, inadequate health facilities and healthcare professionals, coupled with inadequate training of health workers [3]. The therapeutic effects of these medicinal plants can justifiably be attributed to, among others, the phytochemicals in them especially the flavonoids, alkaloids, sterols, terpenoids, phenolic acids, stilbenes, lignans, tannins and saponins.

Phytochemicals are biologically active, naturally occurring chemical compounds found in plants, which protect plant cells from environmental hazards such as pollution, stress, drought, UV exposure and pathogenic attack [4]. These compounds are known as secondary plant metabolites and provide health benefits to humans. They are thought to act as synergistic agents, allowing nutrients to be used more efficiently by the body. Some of the beneficial roles of phytochemicals are low toxicity, low cost, easy availability and their biological properties such as antioxidant activities, antimicrobial effects, modulation of detoxification enzymes, stimulation of the immune system, decrease of platelet aggregation and modulation of hormone metabolism and antineoplastic properties [5].

Phytochemicals are not essential nutrients and are not required by the human body for sustaining life, but have important properties to prevent or to fight some common diseases [6]. Because of this property; many studies have been undertaken to

reveal the health benefits of phytochemicals. In this review, we provide an overview of the role of phytochemical compounds present in medicinal herbs in relation to disease management and human health.

Phenolic Compounds

Phenolic compounds are phytochemicals that have one or more aromatic rings with at least one hydroxyl group. In plants, they play a protective role by minimizing the effect of aggression by predators, parasites and also protect plants from ultraviolet radiation. Phenolics and tepernoids are ubiquitous in fruits, cereals, legumes and vegetables. Plant phenolics include flavonoids, phenolic acids, stilbenes, lignans and tannins [7].

A. Flavonoids

Flavonoids are low molecular weight polyphenolic antioxidants naturally present in fruits, vegetables, and beverages such wine and astea [8]. Flavonoids are believed to have various therapeutic values. Flavonoids have been reported to have antihyperglycemic effect [9]. Genistein **(Figure 1)**, an isoflavone is combined with cisplatin, a cytostatic drug to induce apoptosis of BxPC-3 pancreatic carcinoma cells and also reduce proliferation [10]. Nuclear factor *k*B activation and overexpression reduces the efficacy of chemotherapeutics through inhibition of apoptosis [11]. Genistein down-regulates NF-*k*B and causes a decrease in expression of anti-apoptotic proteins BclXl and Bcl-2 in xenografts of pancreatic carcinoma cells [12,13]. Genistein and 5-fluorouicil act synergistically to induce p21, Bax and p53 expression in colon cancer HT-29 cells [14]. Genistein and arsenic trioxide combination activates caspase-3 and increases cytochrome-c release thus increases apoptosis in human leukemia cells [15]. These two compounds also work synergistically to stimulate apoptosis and reduce cell viability of hepatocellular carcinoma cell lines [16]. Genistein suppresses glucose uptake in hormone-dependent and hormone-independent breast cancer lines and induces overexpression of glucose-regulated protein 78 involved in cell viability [17-19]. A combination of cisplatin and quercetin have a pro-apoptotic effect on human leukemia and laryngeal carcinoma cells [20]. Cyanidin-o-galactoside **(Figure 2)**, cyanidin-3-o-rutinoside **(Figure 3),** procyanidin B5 **(Figure 4)** and robinetinidol-(4-α-8) catechin-(6,4-α) robinetinol are members of the flavonoid group and their derivatives and are believed to inhibit cell proliferation and have free radical scavenging activity [8].

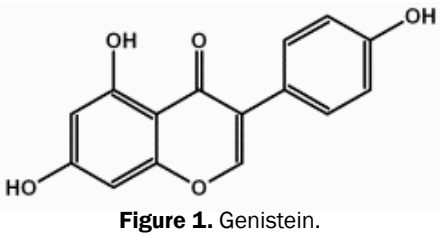

Figure 1. Genistein.

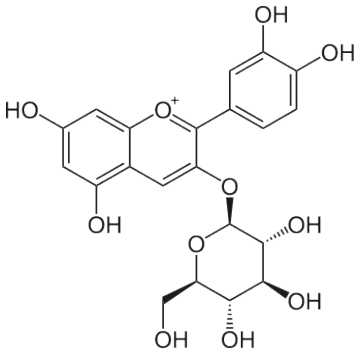

Figure 2. Cyanidin-o-galactoside.

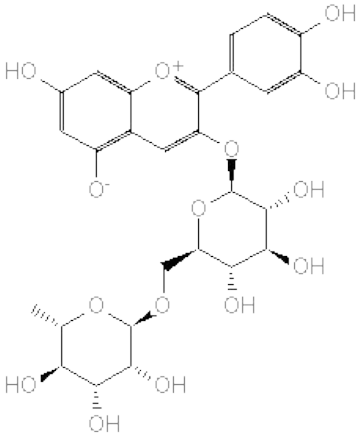

Figure 3. Cyanidin-3-o-rutinoside.

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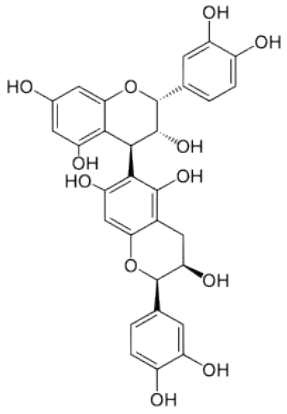

Figure 4. Procyanidin B5.

Flavonoids are known to improve cardiac function, decrease anginas and lowers cholesterol levels. These compounds act by regulation of inflammation mediators [21]. Flavonoids have also been shown to reduce production of pathogenic thrombosis in mice models [22]. A supplement of sea buckthorn which contains high amounts of flavonoids has been shown to restore cardiac function and improve blood circulation in patients with coronary heart disease. Flavonoids have been used in the treatment of chronic cardiac insufficiency and hypertension as they block the activation of necrosis factor kappa-B [23]. Flavonoids like flavone C-glycoside **(Figure 5)**, kakonein **(Figure 6)** and caesalpin P improves the function of pancreatic islet cells and have diabetic activity [24]. Quercetin has been shown to induce apoptosis in mouse pre-adipocytes and to inhibit adipogenesis [25]. The polyhydroxylated flavonol, myricetin **(Figure 7)**, enhances lipogenesis and glucose uptake in the adipocytes and flavanoid, myricetin has demonstrated insulinomimetic properties [26]. This compound, however, has no effect on insulin receptor auto-phosphorylation. Epicatechin **(Figure 8)** and its active principles have demonstrated that they facilitate insulin release *in vitro* through conversion of pro-insulin to insulin [27]. It has been shown that the flavonoid and flavonoid glycosides cause pancreatic beta cell regranulation and have been used in clinical treatment of diabetes due to improved sensitivity of insulin [28].

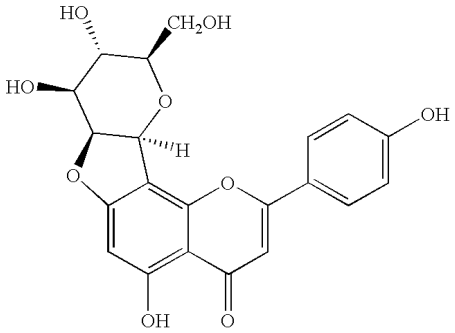

Figure 5. Flavone C-glycoside.

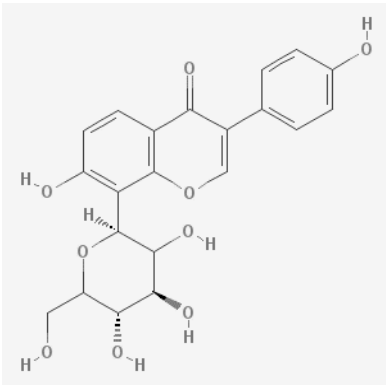

Figure 6. Kakonein.

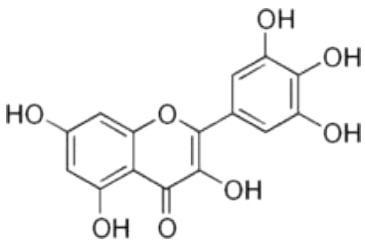

Figure 7. Myricetin.

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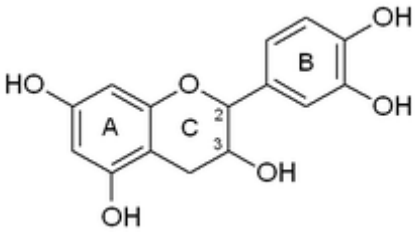

Figure 8. Epicatechin.

Anthocyanins are known to inhibit formation of free radicals thus protecting cardiomyocytes after ischemic episodes [29]. Anthocyanins have vasolidating and antiaggregative activities and also lower levels of oxidized LDL [30]. These compounds are also reported to lower the level of nitric oxide by inhibiting the activity of nitric oxide synthase [31]. Anthocyanins have anti-inflammatory activity as they inhibit cyclooxygenase enzyme. These flavonoids inhibit the expression of VCAM molecules thus inhibiting reaction and adhesion of endothelial cells with leucocytes. These compounds are also believed to decrease the levels of interferon necrosis factor-gamma, interleukin-2 and tumor necrosis factor-alpha and inhibition of mast cell degranulation [32,33]. Proanthocyanins and anthocyanins have antibacterial properties and inhibit adhesion of bacteria to the mucous membrane of the urinary tract [34].

Studies have shown that anthocyanins have protective activity towards paracetamol-induced hepatotoxicity and hepatocytes of hepatitis A and B patients [35,36]. They lower prostaglandin levels by inhibiting COX-2 thus act as anti-inflammatory agents in inflammated connective tissue and joints and activate type II collagen synthesis [37]. Proanthocyanins are believed to alleviate clinical symptoms of pancreatitis like nausea, abdominal pain and vomiting and to slow the pathological changes that take place [38]. These compounds inhibit sensitivity of intestinal cells to insulin and inhibits α-glucosidase enzyme in the intestinal lumen thus lowering sugar levels [39]. Studies have shown that anthocyanins inhibit p53 and e-myc proapoptotic genes activity and induce the expression of Bcl-2 antiapoptotic gene [40]. Proanthocyanins and anthocyanins inhibit the activity of enzymes that induce apoptosis thus confer protective effect on cardiomyocytes after ischemic injury [[41]. Anthocyanins have been used in treatment of Epstein-Barr virus induced lymphoma, pulmonary carcinomas, gastric adenocarcinoma and ovarian carcinoma [42,43].

B. Phenolic acids

Phenolic acids are aromatic secondary plant metabolites widely spread in plants. Phenolic acids that occur naturally can divided into two main categories; cinnammic acid derivatives like ferulic acid **(Figure 9)** and caffeic acid **(Figure10);** and benzoic acid derivatives. Ferulic acid, a phenolic acid is known to have a wide range of therapeutic effect against diseases like diabetes, cancer, neurodegenerative, cardiovascular and inflammatory diseases. These therapeutic effects are believed to be attributed partly to the antioxidant activity of this phenolic acid [44]. Ferulic acid prevents lipid peroxidation and scavenges superoxide free ion radical. The structural characteristics of phenolic acids help them confer the antioxidant properties. These compounds have a phenolic nucleus and an unsaturated side chain that can form a resonance stabilized phenoxy group. Reactive radicals collide with these compounds gaining a hydrogen atom and forming a phenoxy radical [45]. Phenolic acids and their ester derivatives reduce the level of inflammatory mediators like tumor necrosis factor-alpha, prostaglandin E2 [46]. Ferulic acid also lowers the expression and inhibits function of iNOS in cells that are activated by bacterial endotoxin liposaccharide [47]. Ferulic acid derivatives have been reported to suppress the activity of cyclooxygenase-2 promoter activity in human colon cancer DLD-1 cells through the β-galactosidase reporter gene assay system [48]. Ferulic acid hydrophobic esters are reported to enhance inhibition activity of iNOS protein expression of interferon-γ/lipopolysaccharide activated RAW 264.7 cells [49].

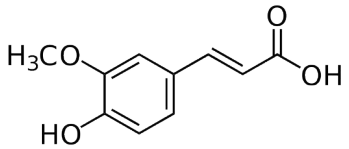

Figure 9. Ferulic acid.

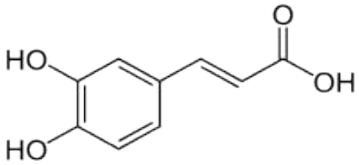

Figure 10. Caffeic acid.

Diabetes, an endocrine disorder is characterized by hyperglycemia leading to oxidative stress due to the over production of free radicals. Phenolic acids reduce the toxicity of streptozotocin by neutralizing the free radicals produced in the pancreas by streptozotocin [50]. The decrease in toxicity and oxidative stress in the pancreatic cells help beta cells to proliferate and secrete more insulin. Increased insulin secretion leads to decrease in glucose levels due to increased glucose utilization by extra hepatic tissues. Phenolic acids are also reported to protect proteins, DNA and lipids from oxidative stress thus exerting anticancer properties

[51]. These compounds also act on pathways that regulate induction to apoptosis, response to oxidative stress and regulation of proliferation. Phenolic acids have been reported to inhibit occurrence of pulmonary cancers in mice, inhibit mutagenesis and decrease urinary N-nitrosoproline levels in humans. Phenolic compounds restore normal homeostasis by inducing apoptosis in cancer cells [52]. Phenolic acids absorb UV radiation forming a stable phenoxyl radical radiation thus terminating free radical chain reactions. These compounds preserve the physiological integrity of cells by scavenging deleterious radicals and chain reactions and suppress radiation-induced oxidative reactions [50].

Phenolic acids are believed to provide protection against polyunsaturated fatty acids (PUFA) and alcohol induced toxicity and also enables the body to overcome deleterious effects of PUFA and alcohol [51]. Phenolic acids preserve the integrity of cells exposed to alcohol stress by quenching the lipid peroxidative chain and scavenging free radicals. The mechanism of action is believed to be by abstraction of H^+ by hydroperoxyl and hydroxyl radicals from a free phenolic substrate to form a phenoxyl radical which then forms products that are excreted in bile [51]. Alzheimer's, a neurodegenerative disease is characterized by free radical-mediated oxidative stress in brain cells. This oxidative stress mainly caused by reactive nitrogen species and reactive oxygen species can lead to neuronal dysfunction, RNA and DNA oxidation and lipid peroxidation. Phenolic acids are reported to prevent oxidative modification of proteins by reducing the chances of oxidative attack on them [51]. Nicotine causes oxidative cellular injury by increasing lipid peroxidation. This is believed to be a major cause of several smoking-related diseases. Phenolic acids increase the endogenous antioxidant defense system, reverses the damage caused by nicotine and protects cells from oxidative damage [50]. These compounds protect the membrane by quenching the free radicals, improve the antioxidant status and inhibit the leakage of marker enzymes into circulation.

C. Stilbenes

Stilbenes are a family of secondary metabolites derived phenylpropanoid pathway that consist a trans-ethene double bond substituted with a phenyl on both carbon atoms of the double bond. Stilbenes are believed to have anticancer properties. The mechanism of action of these compounds is inhibition of the cellular events associated with tumor initiation, promotion and progression. These compounds induces quinone reductase enzyme that plays a role in detoxifying carcinogens thus acts as an anti-mutagen [48]. Stilbenes have anti-inflammatory activities as they inhibit the arachidonic acid pathway leading to the formation of prostaglandins that activate carcinogenesis and stimulate cancer cell growth by inhibiting the hydroperoxidase activity of cyclooxygenase [49]. Stilbenes slow the progression of carcinogenesis in a dose dependent manner thus inhibits the development of preneoplastic lesions. Stilbenes are reported to inhibit DNA synthesis and duplication and lymphocyte proliferation during immunosuppressive therapies [50]. Resveratrol **(Figure 11)** and ellagic acid are also known to induce apoptosis and have antiproliferative activity on human leukemia cells. Curcumin **(Figure 12)** and resveratrol synergistically inhibits growth of p53-negative and p53-positive human colon cancer cells [48].

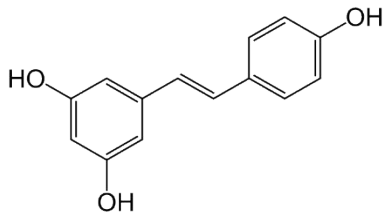

Figure 11. Resveratrol.

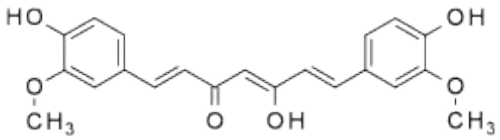

Figure 12. Curcumin.

D. Lignans

Lignans are plant polyphenolic compounds derived from phenylalanine through dimerization of substituted cinnamic acid **(Figure 13)** alcohols. Lignans are known to reduce cell proliferation in colon cancer cells and to exhibit anticancer effects in *in vitro* models. These compounds inhibit of metastatic secondary tumors and decrease levels of colon cancer markers in rat models [51]. Lignans are also reported to suppress the receptor binding of platelet activating factor and inhibit the replication of human immunodeficiency virus at the integration stage. These compounds are also known to inhibit tumor necrosis factor-alpha from lipopolysaccharide-triggered murine microphage [51].

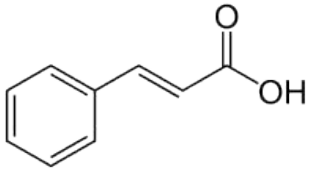

Figure 13. Cinnamic acid.

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E. Tannins

Tannins are polyphenols that are obtained from various parts of different plants belonging to multiple species. It is found in abundance in the tree bark, wood, fruit, fruit pod, leaves and roots and also in plant gall. Tannins can be classified into two broad groups – hydrolysable tannins and condensed tannins. The tannin epigallo-catechin-3-gallate **(Figure 14)** is reported to exhibits anti-diabetic activity [52]. In clinical terms, all forms of tannins may participate in the management of glucose level in blood. Tannin has been shown to stimulate the receptor cells to utilize carbohydrate. Ellagic acid **(Figure 15)** and quercetin act synergistically to reduce viability, proliferation and trigger apoptosis of MOLT-4 human leukemia cells [53]. Ellagic acid and resveratrol are known to effectively inhibit skin tumorgenesis in mice [54].

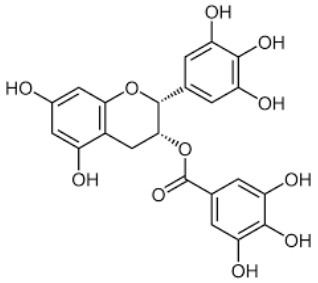

Figure 14. Epigallo-catechin-3-gallate.

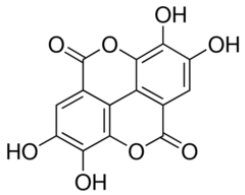

Figure 15. Ellagic acid.

Terpenoids

Terpenoids are compounds synthesized from five carbon isoprene units mainly isopentenyl pyrophosphate and its isomer dimethylallyl pyrophosphate by terpene synthases. Terpenoids have antioxidant properties and also interact with most regulatory proteins. Plant extracts have been used both traditionally and in modern medicine in the treatment of cancer and inflammatory diseases. Terpenes are used as inhibitors of NF-*k*B in modern medicine [55]. NF-kB system is a cytoplasmic sensor that responds to various internal and external signals like genotoxic stress and hypoxia as well as disturbances in the immune system. NF-kB also plays a major role in the development of cellular resistance against apoptosis and anti-apoptotic signaling. Most terpenes in plants occur as terpene derivatives (terpenoids). Sesquiterpenoids are the main tepernes and are known to have NF-kB signaling inhibitory effect while triterpenoids and diterpenoids are also believed to have several potent inhibitors of NF-kB signaling system [56]. Aucubin **(Figure 16),** a monoterpenoid that occurs in plants as a glycoside derivative prevents the nuclear translocation of P65 subunit of NF-kB complex in stimulated mast cells and also inhibits the degradation of IkBa protein [56]. Previous studies also show that aucubin and linalool **(Figure 17)** has antitumor activity plays a protective role against hepatotoxicity and as it has anti-inflammatory activity. Limonene **(Figure 18)** and its derivative perillyl alcohol are believed to have inhibitory effect on pancreatic and mammary tumors [57]. These two compounds are also known to inhibit proliferation and metastasis of gastric cancer. α-Pinene **(Figure 19)**, a terpene extracted from confer trees is known to inhibit translocation of NF-kB or p65 protein into nuclei of LPS-stimulated THP-1 cells [58]. Helenalin A **(Figure 20)**, a sesquiterpene inhibits DNA binding of NF-kB and the transcription of NF-kB-dependent genes by alkylating the p65 subunits of NF-kB complex [56,57]. Artemisinin **(Figure 21),** a lactone extracted from *Artemisia annua* is mainly used as an anti-malarial drug but it is also used as an antifungal, anticancer, immunosuppressive and antiangiogenesis properties [57,58].

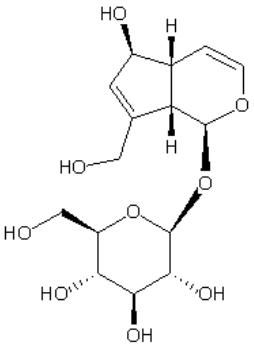

Figure 16. Aucubin.

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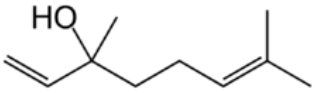

Figure 17. linalool.

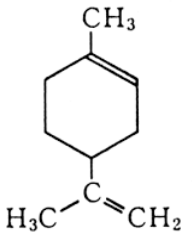

Figure 18. Limonene.

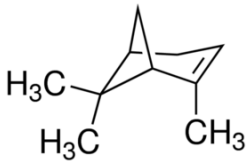

Figure 19. α-Pinene.

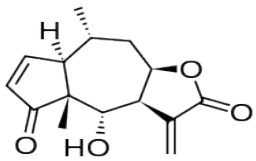

Figure 20. Helenalin A.

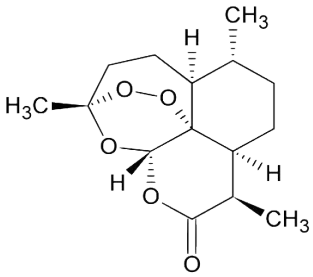

Figure 21. Artemisinin.

Terpenoids also improve the skin tone, increases the concentration of antioxidants in wounds, and restore inflammed tissues by increasing blood supply [59,60]. Terpenoids also improve lung function [61]. The leaves and seeds of *S. spectabilis* are used in the treatment of diabetes due to the presence phytochemicals including terpenoids [62]. Terpenoids have shown to reduce diastolic blood pressure and lower the sugar level in blood in hypertensive and diabetic patients respectively [62]. The anthraquionone **(Figure 22)** in the plant extracts of *Polygonum multiflorum* have been used in the management of peripheral neuropathy, a complication associated with diabetes mellitus [63].

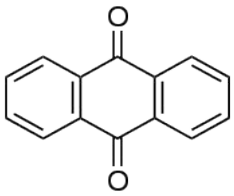

Figure 22. Anthraquionone.

Alkaloids

Alkaloids are phytochemicals that contain nitrogen and are derived from various amino acids. Alkaloids are known to have blood glucose lowering activity. Alkaloids tetrandine **(Figure 23)** and berberine **(Figure 24)** have been reported to demonstrate antioxidant activity responsible for various biological activities associated with this plant including antidiabetic activity [57]. Alkaloid fractions have shown hypoglycemic potential in mice [54]. The alkaloids l-ephedrine **(Figure 25)** of *Ephedra distachya* herbs have shown hypoglycemic effect in diabetic mice due to restoration and regeneration of atrophied pancreatic islets that induces the

secretion of insulin [55]. Alkaloids with therapeutic effects mainly act by affecting chemical transmitters of the nervous system like dopamine, γ-aminobutyric acid, acetylcholine and serotonin. Alkaloids are also known to be anti-arrythmic effects, antihypertensive effects, anticancer and antimalarial activity [64-70].

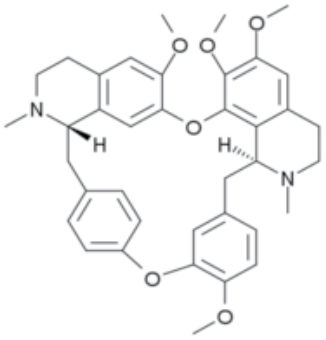

Figure 23. Tetrandine.

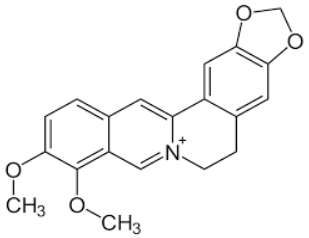

Figure 24. Berberine.

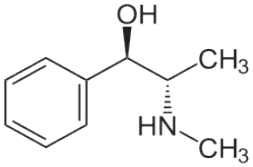

Figure 25. l-ephedrine.

Alkaloids are believed to have neuro-protective, cholinergic and antioxidant activities in Alzheimer's disease [71]. These compounds have memory and cognitive-enhancing activities on Alzheimer's patients. The therapeutic effect of these compounds is believed to be by restricting oxidative stress and inflammatory reactions, enhancing cholinergic transmission, elevating estrogen and other neurotropic agents and preventing β-amyloid toxicity- formation [71]. These compounds inhibit acetylcholinesterase enzyme. Inhibition of this enzyme enhances acetylcholine activity which is one of the main strategies in the management of Alzheimer's disease. Tetramethylpyrazine **(Figure 26)**, an amide alkaloid and is known to elicit hypotensive effects by inhibiting platelet aggregation and vasoconstriction [72]. This alkaloid is also believed to cause inotropic and chronotropic responses on isolated atria. Tetramethylpyrazine is used in the treatment of occlusive cerebral arteriolar diseases due to its vasodilatory effects. Alkaloids have also been reported to have antimicrobial, cytotoxic and trypanocidal activity. These compounds act by intercalating DNA thus impairing replication and transcription causing frame-shift mutations [72]. Alkaloids are also believed to elicit antimicrobial and trypanocidal activity by inhibition of protein biosynthesis and by interaction with neuroreceptors [73].

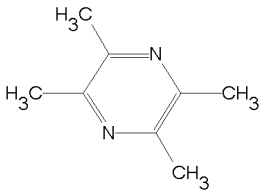

Figure 26. Tetramethylpyrazine.

Saponins

Saponins are plant compounds that occur either as steroid alkaloids, glycosides of triterpenoids or steroids. These phytochemicals are known to have hypocholesterolaemic, immunostimulant, hypoglycemic effect and anticarcinogenic properties [74]. The hypoglycemic effect of saponins is believed to due to stimulation of pancreatic β-cells, inhibition of glucose transport across the brush border cells of the small intestines and suppression of transfer of glucose from the stomach to the small intestines. Saponins are also reported to inhibit gastric emptying in a dose dependent manner [75]. Saponins lower cholesterol level by forming large micelles that are then excreted in bile. These compounds are said to lower serum levels of low density lipoproteins-cholesterol and decrease absorption of cholesterol in the intestines [76].

Saponins are believed to act as adjuvants in enhancing antibody production and in the stimulation of cell mediated immune system. These compounds are reported to interact with antigen-presenting cells and induce interferon and interleukin production thus mediating immunostimulant effects [72]. Saponins inhibit tumor cell growth by apoptosis in leukemia cell line and by cell cycle arrest in breast cancer cell line [69]. They also exert antiproliferative active to prostate carcinoma cells by inducing apoptosis and cell cycle arrest at G1 phase. Saponins induce apoptosis by stimulation of cytochrome c-caspase pathway. The structure of the sugar portion in saponins influences the tumor specificity of cytotoxic action.

Saponins are believed to lower the risk of cancer and other chronic diseases. These compounds are effective for both hormone dependent and non-hormone dependent cancer [77]. Saponins are also believed to antifungal and hypocholesterolemic effects. These effects are believed to be due to combination with bile acids to form micellar aggregates. Saponins prevent hyperlipemia and liver injury induced by lipid peroxidation [78]. The mechanism of action of these compounds in this case is through inhibition of lipid peroxide peroxidation and inhibition of lipid peroxide production. Saponins are also believed to inhibit HIV infection *in vitro in* addition to having antitumor properties. This effect can be attributed to the prevention effect of HIV-induced cell fusion but have no direct effect on reverse transcriptase activity of the virus[79]. Saponins have been reported to have superoxide scavenging effect on oxygen radicals that are implicated in the development and initiation of several diseases [80]. This pro-oxidative activity makes saponins to act as hydrogen abstractor leading to initial reaction of lipid oxidation.

Cardiac Glycosides

Cardiac glycosides are plant secondary metabolites that have a glycoside unit and act on the contractile action of the cardiac muscle. These compounds have been used traditionally for the treatment of cardiac arrhythmias and congestive heart failure as they increase contractile force [81]. Digitalis is the most commonly used cardiac glycoside both traditionally and in modern medicine. This glycoside contains two glycosides; digitoxin **(Figure 27)** and digoxin **(Figure 28)** whose structures differ only by an extra hydroxyl group on digoxin. Cardiac glycosides act by inhibition of Na^+, K^+-ATPase resulting to decreased intracellular K^+ ions and increased intracellular Ca^{2+} and Na^+ ions [82]. Digitalis directly inhibits proliferation of androgen dependent and androgen independent prostate cancer cell lines by initiating apoptosis and increasing intracellular Ca^{2+} [83]. Studies shows inhibition of cell growth in androgen dependent prostate cancer cells by ouabain **(Figure 29)** [83]. Oleandrin **(Figure 30)** and bufalin **(Figure 31)** have apoptotic effect on normal leukocytes [84].

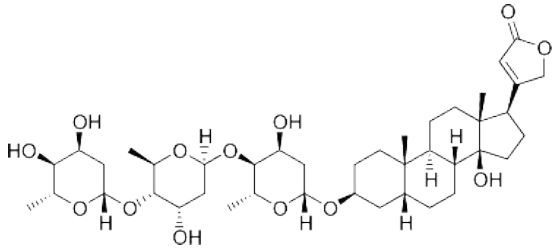

Figure 27. Digitoxin.

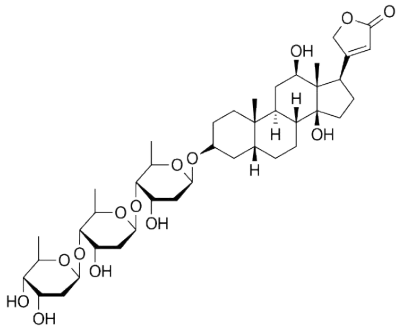

Figure 28. Digoxin.

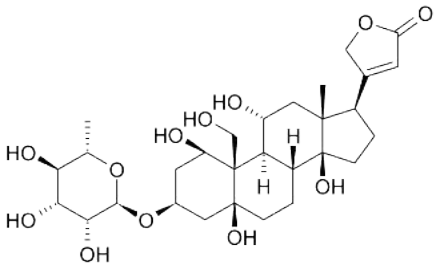

Figure 29. Ouabain.

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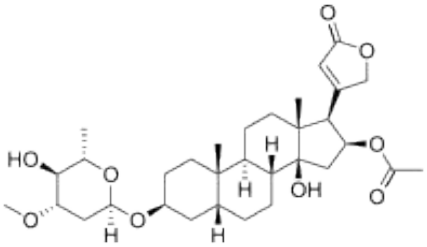

Figure 30. Oleandrin.

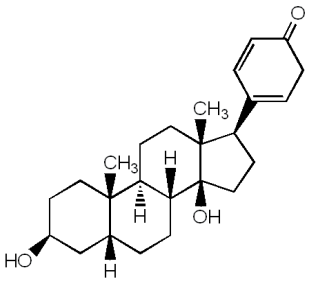

Figure 31. Bufalin.

Cardiac glycosides have been reported to inhibit the four genes that are overexpressed in prostate cancer cells including the inhibitors of apoptosis inhibitor survivin and transcription factors [85]. Digitoxin suppresses hypersecretion of IL8, a protein implicated in lung inflammation thus inhibiting activation of the NF-B signaling pathway in cystic fibrosis [85]. These compounds have been reported to exert cytotoxic effects in both cell lines derived in advanced cancer and normal prostate epithelial cells. Oleandrin, a glycoside derived from oleander, induces apoptosis by sustaining $Ca2^{+}$ increase that precedes release of cytochrome c from mitochondrion and caspase activation. Oleandrin is also reported to cause cell arrest at G2-M phase of the cell cycle in a dose dependent manner [86]. Oleandrin ability to inhibit cell growth and tumor cell proliferation is believed to be due to inhibition of the up-regulation of pERK and pAkt formation [86].

Sterols

Phytosterols are subgroup of steroids that have structures and functions similar to cholesterol. Phytosterols in plants act as substrates for the synthesis of secondary metabolites, regulate permeability and fluidity of cell membranes and also act as biogenic precursors of growth factors [87]. Phytosterols occurs either as sterols or stanols; the saturated forms of sterols. Absorption of stanols in the intestines is lower than that of sterols resulting to lower concentrations in blood serum. Phytosterols inhibit absorption of cholesterol in the intestines. Phytosterols and cholesterol require Niemann-Pick C1-like protein for their entry in the intestine cells. Cholesterol is esterified in the enterocytes by acetyl-coenzyme A acetyltransferase-2 enzyme and are packed into chylomicrons and transported to the lymphatic system. ABC transporters pump phytosterols and non-esterified cholesterols back to the intestinal lumen. This process lowers the amount of cholesterol assimilated in the system [88]. Clinical studies have shown that phytosterol intake leads to up to 15% reduction of LDL-cholesterol [89,90]. Intake of plant stanols reduces both plant sterol and cholesterol concentrations in the serum [91]. Genetic differences in sterol metabolism and amount of phytosterols determines the effectiveness of cholesterol lowering by phytosterol supplements. Apolipoprotein E-4 homozygote persons taking supplements with phytosterols have increased cholesterol absorption capacity and thus show significant LDL-cholesterol reduction than their counterparts [92].

β-Sitosterol **(Figure 32)** is the main phytosterol in plants and it is also found in human serum together with its glycoside at lower concentrations. β-sitosterol and β-sitosterol glycoside have been reported to reduce incidences of inflammatory diseases and carcinogen-induced cancer [93,94]. These compounds are also believed to have insulin releasing effect, anti-complement and antipyretic activity [94-96]. β-sitosterol and its glycoside together have immune modulating activities on non-infectious conditions like rheumatoid arthritis and allergies and chronic infectious diseases like tuberculosis and Human Papilloma Virus [97]. A mixture of the two with higher concentrations of β-sitosterol is reported to influence the proliferation of T-lymphocytes after these cells are activated by mitogens *in vitro*. However, these phytosterols are shown to increase the proliferation of TH1-type helper cells while inhibiting TH2-type helper cells. They also inhibit the secretion of IL-4 but increases the secretion of IFN-g and IL-2 [97]. This specificity towards certain T-helper cells implies that this mixture have significant modulatory and regulatory activities in conditions where enhancement of TH1-helper cell is important for the clearance of pathogens. The mixture is also reported to increase the lytic ability of natural killer cells to cancer cell lines *in vitro* [98]. β-sitosterol and its glycoside have anti-inflammatory activity as they inhibit both tumor necrosis factor alpha and interleukin-6 in a dose dependent manner.

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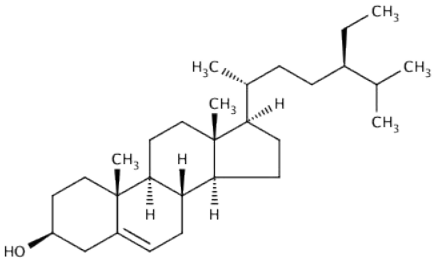

Figure 32. β-sitosterol.

CONCLUSION

More than 80% of the world population solely relies on medicinal plants for their primary health care needs. Some of these herbs are proven to provide symptomatic relief and assist in the prevention of the secondary complication of the diseases, while others are reported to help in regeneration of abnormal cells and in overcoming disease causing pathogens. Moreover, these natural substances are readily available, cheap and do not result in adverse side effects usually associated with synthetic drugs. Most of the side effects caused by phytotherapy methods of disease management are not as severe as those caused by conventional methods. The therapeutic effects of these medicinal plants can justifiably be attributed to, among others, the phytochemicals in them especially the flavonoids, alkaloids, sterols, terpenoids, phenolic acids, stilbenes, lignans, tannins and saponins. They cover a wide range of therapeutic indications with a great diversity of chemical structures. Therefore, these phytochemicals provide qualified lead for the development of new drug entities in drug design and discovery.

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