Toxicological Significance of Bioactive Compounds of Plant Origin

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ABSTRACT

Aim/Background: The evaluation of toxicological significance of medicinal plants is necessary prior to their use for drug development or for the purpose of improving the therapeutic efficacy of existing therapies. Regrettably, there is little information on the toxicity profiles of the chemical constituents of commonly used medicinal plants. Meanwhile, available information on the toxicity concerns of the use of medicinal plants are often taken for granted and ignored. Materials and Methods: The information and data used in this review report were sourced from scientific databases such as Google Scholar, PubMed, SpringerLink, Medline, ScienceDirect, and Mendeley. Results: The noxious chemical compounds in plants may be neurotoxic, mutagenic or cytotoxic. They may disrupt metabolic processes in living organisms and adversely affect the skin and the mucosal tissues, etc. It is noteworthy that the beneficial as well as the toxicological outcomes following the use of plant materials depends on the chemical nature of their constituent bioactive compounds. Conclusion: Plants, especially those used for ethnomedicinal purposes, contain significant amounts of noxious bioactive compounds, which may elicit adverse health effects on both humans and other animals. The isolation and purification of plant bioactive compounds for toxicological evaluation prior to their usage in the development of pharmaceutical formulations is recommended. Key words: Bioactive compounds, Cytotoxins, Neurotoxins, Plant, Toxicological significance.

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INTRODUCTION

Plants possess complexities of biosynthetic pathways and a vast array of bioactive compounds known as secondary metabolites. The major attributes of these secondary metabolites are specific carbon skeleton structures. Generally, these vast arrays of low molecular mass bioactive compounds are essential for the protection of the plants against pathological conditions, and to ameliorate or cure diseases in living organisms including humans. However, noxious bioactive compounds may elicit toxic actions in the form of multi-organ damage and failure in animals or humans that may in certain conditions, lead to death, even when consumed in small amounts.

There are restrictions on the general acceptability and incorporation of plants of medicinal significance into orthodox medicine practices due to inability to provide precise descriptions of their biochemical constituents, actual dosage and toxicological profiles, which are required to guarantee their safety use. Regrettably, there is little information on the toxicity profiles of the chemical constituents of commonly used medicinal plants. Accordingly, the evaluation of toxicological significance of medicinal plants is necessary prior to their use for drug development or for the purpose of improving the therapeutic efficacy of already existing therapies. Some pernicious bioactive compounds synthesized by plants include the cyanogenic glycosides, lectins, gossypol, veratridines, myristicin, chlorogenic acid, goitrogens, β-N-oxalyl-L-a,β-diaminopropionic acid (an amino acid known to be toxic to the nerves), protease and amylase inhibitors, etc. These noxious botanical chemical compounds have been reported to be neurotoxic, mutagenic, and cytotoxic, disrupt metabolic processes in living organisms, and adversely affect the skin as well as the mucosal tissues. Meanwhile, available information on the toxicity concerns of the use of medicinal plants are often taken for granted and ignored.

Plants are composed of bioactive compounds that repel, deter and poison animals as well as prevent microbial growth and development. These bioactive compounds are either constitutive or their biosynthesis may be induced by stressful situations such as drought, microbial invasion, cellular injuries etc. However, herbivores have over time acquired different enzymatic processes by which toxic bioactive compounds are rendered non-toxic, deactivated and egested. Microorganisms present in the intestine or rumen of herbivorous animals are also involved in the detoxification of toxic bioactive compounds. This review paper reported the toxicological significance of bioactive compounds biosynthesized by plants.

METHODS

Information and data acquisition

The information and data used in this review report were sourced from scientific databases such as Google Scholar, PubMed, Springer Link, Medline, Science Direct, and Mendeley. Keywords such as ‘plant toxins’, ‘bioactive compounds’, ‘toxic bioactive compounds’, ‘herb toxicity’, ‘plant secondary metabolites’ and ‘toxic bioactive compounds’ were used to collate relevant articles. Scholarly publications from 1972-2019 were retrieved from these scientific search engines giving rise to 122 references that were cited in this report.

Biosynthesis of plant bioactive compounds

The phenylpropanoids biosynthetic pathway is the major route by which bioactive compounds accumulate in plants. The core of this biosynthetic pathway is the shikimate pathway. The phenylpropanoids biosynthetic pathway leads to the generation of molecules referred to as plant secondary metabolites, owing to the fact that they were observed as components that do not exhibit any vital function in plants, although recently, the crucial functions of these molecules in plants have been extensively revised and ascertained. Nevertheless, primary metabolism is often erroneously regarded to be more significant to the survival of the plant than secondary metabolism. Plant primary metabolism includes photosynthesis and other related processes and compounds such as sugars, lipid and amino acids metabolisms and...
respiration. Photosynthesis generates carbohydrates that give rise to carbon skeletons necessary for nitrogen assimilation, which eventually results to the biosynthesis of amino acids as well as other related bioactive compounds. The biosynthesis of secondary metabolites is linked to the metabolism of primary metabolites because many products of primary metabolism are the activators of the phenylpropanoids pathway of secondary metabolites (Figure 1).14,17

**General classifications and mode of actions of toxic bioactive compounds**

Toxic bioactive compounds are categorized into four major classes based on their oral toxicity using rat models. These classes include Ia, Ib, II and III. The class Ia is extremely poisonous (≤ 5 mg/kg body weight); Class Ib is highly poisonous (5–50 mg/kg body weight); Class II is moderately poisonous (50–500 mg/kg body weight); Class III is slightly poisonous (≥ 500 mg/kg body weight).19,20

The most toxic bioactive compounds in plants are the neurotoxins, which disrupt the functions of the nervous system. The next most toxic are the cytotoxins and metabolic toxins, which are deleterious to the heart, muscles, liver, and kidneys, as well as reproductive and respiratory processes.13

**Neurotoxins**

Neurotoxins cause disruption in the ion channels of neuronal cells of Na⁺, K⁺, and Ca²⁺ channels by permanent induction or inhibition of these ion channels. This leads to the blockage of neuronal signal transduction, as well as the interruption of the actions of the central nervous system (CNS) and neuromuscular signaling, and thereby halt the functions of the smooth and striated muscles of the lungs, skeleton and heart.19,21-23 The ion pump of Na⁺/K⁺-ATPase activity, which is essential for the sustenance of ion gradient between the interior and exterior sides of neuronal membranes required for the performance of transport and transudational processes, are compromised by the actions of neurotoxins. For instance, the cardiac glycosides strongly inhibit the ion pump of Na⁺/K⁺-ATPase activity, and therefore are placed in the group of Class Ia toxins.13 Certain neuroactive compounds in plants can induce the expression of neuroreceptors, and thereby act as agonists, whereas some other bioactive compounds impede and block the actions of neuroreceptors (antagonists). The expression and impediment of neuroreceptors leads to the state of over excitement, delusion and disruption of the central nervous system, which can eventually lead to a prolonged period of unconsciousness in mammals at lower doses. Relatively high doses of neurotoxins cause the interruption of the functions of the cardiopulmonary system and eventual death of the organism.13,19 The major bioactive compounds that have been reported to be neurotoxic are the alkaloids. The neurotoxic actions of the alkaloids were linked to their structural similarities with endogenous neurotransmitters, namely; adrenaline, dopamine, serotonin, acetylcholine, noradrenaline, GABA or glutamate.19,22

**Cellular respiration inhibition**

Plant bioactive compounds stored in the vacuoles, referred to as cyanogenic glycosides, generate hydrogen cyanide (HCN), which inhibits cellular respiration required for ATP biosynthesis in the mitochondria. In the mitochondrial respiratory chain, cyanate ion (CN⁻) attaches itself to the iron moiety of the terminal cytochrome oxidase component of the respiratory chain.19,22 HCN is liberated when the cyanogenic glycosides in the vacuoles come in contact with cytosolic enzymes and is hydrolyzed by enzymes such as β-glucosidase and nitrilase. Upon the hydrolysis of cyanogenic glycosides, toxic HCN is liberated (Figure 2).15 Other inhibitors of mitochondrial ATP generation include the rotenoids, certain alkaloids, diterpenes and tricyclic terpenes.20

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**Figure 1:** The metabolism of plant primary and secondary metabolites, showing the various biosynthetic pathways of bioactive compounds.14
Cytotoxins

Certain bioactive compounds disrupt the normal functions of cells by targeting biomembranes, which are responsible for the regulation of inflow and outflow of cellular metabolites and ions. The integrity and fluidity of cell membranes can be disrupted by steroidal and triterpenoid saponins. These bioactive compounds also target cellular enzymes and proteins, as well as DNA/RNA and related processes. Some toxic plant compounds also interfere with protein synthesis in the ribosomes. These plant toxins bind to cell membranes using their β-chain (haptoomer), while the α-chain (effectomer) migrates into the cytoplasm by endocytosis and inhibits protein synthesis. Bioactive compounds with exocyclic methylene group (-CH₂), sulphydryl group (-SH), or reactive double or triple bonds form covalent bonds with proteins, and thus interfere with the three-dimensional structure and functions of proteins.

DNA and RNA alkylation and intercalation

Bioactive compounds damage DNA and RNA by intercalation and alkylation reactions. Intercalating secondary metabolites initiates DNA stabilization, thereby blocking the replication of DNA, which eventually leads to frame shift mutation that causes cell death or malformations, as well as promoting cancerous outcomes. The β-carboline, alkaloids, atroquines, berberine, furanocoumarins, sanguinarine, emetine are examples of intercalating compounds. Alkylating bioactive compounds, such as pyrrolizidine alkaloids, paquilloside, cycasine, furanocoumarins, aristolochic acids and others with epoxide or aldehyde groups have been reported to cause extensive modification of DNA bases in a covalent manner. DNA and RNA alkylation and intercalation reactions may induce mutation, cancer, abortion or birth defects in pregnant individuals.

Skin and mucosal tissues damage

The diterpenes, also known as phorbol esters, are endogenous signaling compounds of structural similarity with diacylglycerol. Certain plant bioactive compounds including the diterpenes stimulate the enzyme protein kinase C. Upon contact with the skin, mucosal tissue, or the eyes, diterpenes provoke painful inflammation, accompanied by ulcers as well as blister formation.

Some phytochemicals, such as the furanocoumarins, infiltrate the skin and intercalate dermal cells. Furanocoumarins alkylate the DNA, damage cells and initiate intense blister formation as well as necrosis. Some of these compounds are converted to their active forms in order to elicit their toxic effects. For instance, the glycoside ranunculin in plant vacuoles decomposes into the active form, protoanemonin following plant tissue injury. Protoanemonin alkylates proteins and DNA, as well as causing skin irritation and mucosal tissue inflammation. The plant bioactive compound, tuliposide A, is also known to elicit toxic effects following the conversion to its active toxic form tulipalin A.

Adverse health effects of plant bioactive compounds

Bioactive compounds synthesized by plants do not only elicit beneficial effects on living organisms including humans, some of these compounds also elicit toxic effects depending on their chemical nature. However, more emphasis is given to their medicinal effects than the toxic actions they exhibit.

Alkaloids

Alkaloids are cyclo-organic low molecular weight bioactive compounds made up of negatively charged nitrogen atoms. Alkaloid toxicity may occur following the intake of food contaminated with alkaloid-rich plants. Basically, the intoxication of this plant metabolite is dependent on the quantity consumed as well as the sensitivity of the target organism. The major classes of alkaloids reported to elicit toxic effects include the steroidal alkaloids, tropane alkaloids, pyrrolizidine alkaloids, quinolizidine alkaloids and piperidine alkaloids.

Steroidal alkaloids

Steroidal alkaloids have been observed to be very harmful to mammals. Cyclopamine, a steroidal alkaloid, found in Veratrum californicum (Liliaceae) has been reported to induce teratogenic effects leading to craniofacial birth disorders and cyclops in lambs that graze on this plant. The combination of the glycoalkaloids, choaconine and solanine, present in the following plants of the Solanaceae family: Solanum nigrum (nightshades), S. lycopersicum (tomato), Capsicum annuum (pepper), S. tuberosum (potato), S. melongena (eggplant), Petunia spp. (petunia) have been reported to escalate steroidal alkaloids toxicity by synergistic actions. Solanine has been reported to induce neurological and gastrointestinal defects by deactivation of acetyl cholinesterase action and obstruction of cerebral transport.

Tropane alkaloids

Plant families rich in tropane alkaloids such as the Solanaceae, Brassicaceae, Erythroxylaceae, Convulvulaceae, and Euphorbiaceae, which are used extensively for folkloric and medicinal purposes, have been linked to photosensitivity, impaired vision, constipation, reduction in the moisture content of the mucous membrane of the upper digestive tract and respiratory tract. Tropane alkaloids which exhibit these toxic effects include atropine, scopolamine and hyoscyamine. These plants containing tropane alkaloids are present in various families of the Solanaceae, Euphorbiaceae, Erythroxylaceae, Brassicaceae and Convulvulaceae. Tropane alkaloids toxicity usually occurs following the consumption of Datura (a genus of nine plant species and a member of the Solanaceae family, rich in hyoscyamine and scopolamine).

Pyrrolizidine alkaloids

Plants that belong to the Fabaceae, Asteraceae and Boraginaceae families contain pyrrolizidine alkaloids. This class of alkaloid has been reported to cause acute and chronic liver toxicity. Pyrrolizidine alkaloids also provoke acute toxicity such as diarrhea, purging, nausea, stomach ache and edema in humans and animals. Carcinogenicity and genotoxicity have been reported as the major toxicity indices of the pyrrolizidine alkaloids. According to Cushman et al. among the 350 plants screened for pyrrolizidine alkaloids, half were observed to be hepatotoxic, whereas other toxic actions include carcinogenicity.
Quinolizidine alkaloids
Certain quinolizidine alkaloids, such as the lupin alkaloids, cause acute toxicity in humans following the consumption of lupin beans that were not debittered. Some symptoms of quinolizidine alkaloids toxicity include impaired vision, confusion, drying of the mouth and redness of the face.

Piperidine alkaloids
Acute toxicity of the piperidine alkaloids in neonates results in musculoskeletal deformities. Symptoms of acute toxicity of these alkaloids in animal models include weakness of the muscles, constant excretion of urine and faeces, muscle fasciculation, rapid heartbeat, ataxia, loss of consciousness and death due to respiratory arrest. Anabaseine, ammodendrine, γ-coniceine, N-acetylhystrine, coniines are some piperidine alkaloids that have been reported to elicit teratogenic effects, and are present in the following toxic plants: *Nicotiana tabacum*, *Conium maculatum*, *N. glauca*, some *Lupinus* spp. and *Laburnum* spp. (Figure 3).

Tannins
Tannins are bitter polyphenolic bioactive compounds, which are soluble in water and adhere to and precipitate proteins, alkaloids, etc. Both hydrolyzable and condensed tannins are toxic. The basic molecular configurations of hydrolyzable and condensed tannins are represented in Figure 4.

Hydrolyzable tannins
Hydrolyzable tannin poisoning in animal models, especially ruminants, has been reported. Animal models fed with leguminous plants rich in tannins such as *Terminalia oblongata*, *Clidemia hirta* as well as oak species (*Quercus* spp.) suffered from severe acute toxicity. The toxic outcomes associated with hydrolyzable tannins include hemorrhagic gastroenteritis, liver necrosis, and renal dysfunction as well as proximal tubular necrosis. Continuous consumption of plants containing about 20% hydrolyzable tannins has been reported to be associated with high morbidity and mortality in animals. The water soluble ellagitanin punicalagin is toxic to both the liver and kidneys of cattle.

Condensed tannins
Condensed tannins such as the proanthocyanidins have been reported to provoke systemic toxicity in animals and humans. Proanthocyanidins toxicity has been linked to impaired protein and carbohydrate digestion. The consumption of *Acacia* spp. and other legumes has been observed to cause increased mortality of animals and the possibility of these plant species to contain large amounts of proanthocyanidins and low protein levels have been reported. Condensed tannins exhibit toxic actions on the digestive tract mucosa, which impairs the absorption rate of nutrients. High proanthocyanidins levels in foods lead to a reduction in the absorption rate of essential amino acids, especially lysine and methionine. Low level of methionine in the body is associated with high susceptibility to cyanogenic glycosides poisoning. Methionine plays a major role in cyanide detoxification by the methylation of cyanate to thiocyanate.

Saponins
Some groups of saponins are typically characterized as a family of glycosides with both hydrophilic and hydrophobic groups, and are thus amphipathic bioactive compounds. The diverse sugar moieties that may be associated with these compounds are attached to sapogenin-steroid alkaloids, steroids or triterpenes, which are responsible for the various structural orientations of the saponins and the basis for their classification.
The pore formation effects of saponins on membranes have been extensively reported. Saponins induce erythrocyte membranes lysis. Saponins cause the hemolysis of erythrocytes, via the affinity of the aglycone moiety of saponins for the membrane sterols (cholesterol), which leads to the formation of insoluble complexes. The glycosides concentration needed for membrane penetration is lower for membranes that are rich in cholesterol than those containing little or no cholesterol. Human erythrocyte membranes that were subjected to saponins treatment were observed to have 40 – 50 Å diameter pores in comparison with 80 Å generated pores in artificial membranes. The membrane pores developed following saponin treatment were observed to last longer in comparison with the reversible pores generated by other compounds (e.g. vitamin A). The pores formed in the membranes containing saponins were permanently penetrable by large substances such as ferritin.

The triterpenoid and steroid saponins, which are composed of one sugar unit and referred to as monodesmoside saponins, elicit greater hemolytic effect in comparison with their counterparts that are made up of two sugar units (bidesmoside saponins), although with exceptions. Certain saponins have been reported to hinder active mucosal transport, facilitate the movement of molecules which are not normally allowed to enter the cell and mitigate the transmural potential difference. The acidic triterpenes, together with branched tetrasaccharide moieties, were observed to be among the compounds responsible in the reduction of the transmural potential difference.

Saponins have been reported to retard the rate of protein digestion by forming complexes with protein. For instance, endogenous saponins obstruct the hydrolysis of soybeans proteins by chymotrypsin. Free bovine serum albumin was observed to be much more digestible than the complex formed between bovine serum albumin and soybeans saponins. Casein and Quillaja saponins give rise to high molecular weight complexes at high temperatures (78°C).

Plants such as Pueraria thunbergiana, Phellodendron cortex, fenugreek, Aralia cortex and Calendula officinalis have been reported to elicit hypoglycemic actions due to their saponin contents. Endogenous saponins have been reported to elevate the levels of plasma insulin in Wistar rats by stimulation of the β-cells. The triterpenoid saponin glycoside and oleandric acid impede the transportation of glucose from the stomach to the small intestine. Momordin Ic, a saponin, also obstructed gastric emptying in a concentration-dependent manner. Saponins have also been reported to block the pancreatic lipase action, thereby retarded dietary fat absorption.

Saponins are deleterious to the reproductive systems of animal models. The antizygotic, anti-implantation and abortifacient actions of saponins have been reported. Saponins isolated from Guttierrezia spp. and Agave lecheguilla induce abortion as well as cause death in animal models subjected to 2-3 mg/kg body weight of saponins. Saponins isolated from crude extracts of Costus speciosus, Phytolacca dodendra and Gleditischia horrid induce infertility in mice. Also, 3β, 16β, 17α-tri-hydroxy-cholest-5-en-22-one16-O-(2-O-4-methoxybenzoyl-β-D-xylpyranosyl)-(1→3)-(2-O-acetyl-α-L-arabinopyranoside) (or OSW-1), a steroidal saponin, from Ornithogalum saundersiae inhibited the synthesis of estrogen at 9 mg/kg, elongated dioestrus period and deactivated the genes involved in steroidogenesis. The spermicidal effect in comparison with their counterparts that are made up of two sugar units (bidesmoside saponins), although with exceptions. Certain saponins have been reported to hinder active mucosal transport, facilitate the movement of molecules which are not normally allowed to enter the cell and mitigate the transmural potential difference. The acidic triterpenes, together with branched tetrasaccharide moieties, were observed to be among the compounds responsible in the reduction of the transmural potential difference.

Flavonoids are phenolic compounds of low molecular weight, and include the flavonols, flavan-3-ols, anthocyanins, flavones, flavonanes and isoflavones. The flavan-3-ols, flavonanes and the precursor chalcones are some of the known toxic flavonoids.

Flavan3-ols
Hemolytic anemia and thrombocytopenia have been observed in patients administered with cyanidanol. Cyanidanol is the chemotherapeutic name of catechin, a flavan-3-ol. Hematological values normalized upon the stoppage of the administration of this drug. Platelet and red blood cell antibodies were also observed to be present in four and three patients respectively out of the five patients administered cyanidanol. The levels of red blood cell antibodies in the patients were dependent on the dosage of cyanidanol administered.

Chalcones
The shrub Piper methysticum (popularly called Kava) was reported to be toxic to the liver and provokes hepatic injury and failure. P. methysticum was previously used in Switzerland and Germany as a mood enhancer and anxiolytic. However, the use of this plant as a herbal cure was banned following its toxic effects on the liver. P. methysticum is composed of lactone derivatives (kavatones) and the kavachalcones e.g. flavokavain C (Figure 6). The chalcones are precursors for the biosynthesis of flavonoids.

Glycosides
These are glycosylated compounds with the aglycone moieties composed of vitamins, terpenoids, alkaloids, polyphenols, steroids, antibiotics and others attached to uralonic acid or monosaccharide or oligosaccharide. The biological actions of the glycosides are attributed to their glycosidic
residue.\textsuperscript{69} The common toxic classes of the glycosides include the cardiac glycosides, diterpenoid glycosides, cyanogenic glycosides, anthraquinone glycosides.

**Cardiac glycosides**
Cardiac glycosides are known to cause hyperkalemia, a condition that leads to higher than normal level of potassium ions in the blood.\textsuperscript{70} The cardiac glycoside derivatives digitalis and strophanthus e.g. ouabain inhibits the Na\(^+\)/K\(^+\)-ATPase activity of biomembranes.\textsuperscript{71,72}

**Diterpenoid glycosides**
The intake of diterpenoid glycosides is associated with centrilobular hepatic necrosis, as well as renal proximal tubule necrosis in both humans and animals.\textsuperscript{12} Diterpenoid glycosides have also been linked with the obstruction of oxidative phosphorylation in the mitochondria by impeding the adenine nucleoside carrier.\textsuperscript{12}

**Cyanogenic glycosides**
The cyanogenic glycosides, which occur in more than 2,650 plant species, are \(\beta\)-linked glycosides of \(\alpha\)-hydroxynitriles.\textsuperscript{10} Upon consumption of plants containing this class of glycosides, hydrogen cyanide is liberated into circulation and impedes the effective use of oxygen in the peripheral tissues as a result of inhibition of cytochrome oxidase activity in the mitochondrial electron transport chain. Other deleterious effects associated with cyanide intake include permanent paralysis, angular stomatitis and destruction of the optic nerves, tropical ataxic neuropathy, goiter, and congenital hypothyroidism in infants, sensorineural hearing loss and sensory gait ataxia.\textsuperscript{12} Cyanogenic glycosides occur among the *Prunus* spp. (Rosaceae family) such as *P. persica* (peach), *P. dulcis* (almond), *P. cerasus* (cherry), *P. domestica* (plum), *P. armeniaca* (apricot), as well as *Manihot esculenta* Crantz (cassava), *Phaseolus lunatus* (lima beans), *Sorghum bicolor* (Sorghum) and *Bambusa vulgaris* (bamboo shoots).\textsuperscript{10,41,73} Examples of some cyanogenic glycosides that occur in the edible parts of plants include linamarin and lotaustralin found in both *M. esculenta* and *P. lunatus*. Others include amygdalin, dhurrin and taxiphyllin from *P. dulcis*, *S. bicolor* and *B. vulgaris* respectively (Figure 7).\textsuperscript{10}

**Anthraquinone glycosides**
Constant intake of drugs composed of anthraquinone glycosides can lead to rhabdomyolysis, kidney and liver failure as well as loss of electrolyte and fluid.\textsuperscript{74,75}

**Terpenoids**
The terpenoids originate from five carbon isoprene units, which are grouped together in various combinations in order to produce different combinations of terpene derivatives, generally known as the isoprenoids. The majority of the terpenoids occur in the glycosidic form instead of none or low polar terpene aglycone form.\textsuperscript{12,76} Terpenoids are comprised of the other groups of bioactive compounds in different plant categories.\textsuperscript{12} The diterpenes, sesquiterpenes, triterpenes are some of the common classes of toxic terpenoids.

**Diterpenes**
The diterpene atractyloside occurs in many plants and is used extensively in ethnomedicine. Toxicological evaluation showed that diterpenes...
cause proximal tubule necrosis in humans, engendering kidney failure and death.\textsuperscript{77} Atractylloside was reported to suppress adenine nucleoside carrier in isolated mitochondria, and thereby inhibits oxidative phosphorylation and elicits abnormal changes in the metabolism of carbohydrates as well as hepatic and renal damage.\textsuperscript{78} Other toxic health effects associated with the use of plant products containing diterpene include gastrointestinal hemorrhage, hepatic necrosis etc.\textsuperscript{79}

The compound daphnetoxin is a daphnane-type orthoester diterpene, present mostly in plants that belong to the Thymelaeaceae family. Daphnetoxin isolated from \textit{Gnidia burchellii} and \textit{G. polypechala} cause emphysema and diarrhea in ruminants.\textsuperscript{80} Daphnetoxin has been reported to enhance proton leakage in the inner mitochondrial membrane, stimulate mitochondrial permeability transition pore, and suppress ATP synthase activity, as well as inhibiting the mitochondrial respiratory chain.\textsuperscript{81} Daphnetoxin also caused deleterious effects on the kidneys, central nervous system and circulatory system.\textsuperscript{78}

The pentacyclic diterpenes gibberellic acid or gibberellins A3, GA3 and GA (Figure 8) are toxic to mammals by eliciting major hazardous effects on the lung, breast, liver and kidney.\textsuperscript{82} The carcinogenicity index of gibberellic acid using animal models has been ascertained.\textsuperscript{83} Gibberellic acid was reported by Ozmen \textit{et al.}\textsuperscript{84} to disrupt sexual differentiation in mice. Additionally, the pentacyclic diterpene initiated oxidative stress in adult rats, which was caused by generation of overwhelming levels of free radicals, accompanied by the destructions of kidney, spleen, heart, liver, stomach cells.\textsuperscript{85,86} Gibberellic acid has also been reported to be neurotoxic, caused elevated malondialdehyde levels, mitigated catalase antioxidant effects of certain enzymes of the cerebrum and cerebellum such as catalase, glutathione peroxidase and superoxide dismutase, decreased glutathione and ascorbic acid levels, caused uncontrolled growth of external granular layer, as well as decreased the level of cerebellum purkinje cells in rats.\textsuperscript{87}

## Sesquiterpenes

The furanosesquiterpenoids from the following plants, namely; \textit{Athanasia trifurcate}, \textit{Lasiospermum bipinnatum}, \textit{Nidorella foetida} and \textit{A. minuta} (Asteraceae family) elicited harmful effects on the liver and stimulated photo-sensitivity.\textsuperscript{80,88} Accordingly, the sesquiterpene lactones present in \textit{Geigeria ornativa} of the Asteraceae family were noted to be responsible for the syndrome called “vermeersiekte” in sheep, since these animals developed this disease following the consumption of \textit{G. ornativa}.\textsuperscript{89,90}

## Triterpenes

The tetranortriterpenes from \textit{Melia azedarach} (Meliaceae) have been reported to be toxic to both humans and animals. Some of the symptoms of tetranortriterpenes toxicity are diarrhea, respiratory disorder, vomiting etc. in both animals and humans.\textsuperscript{80}

## Coumarins

The coumarins occur in various plant sources as benzo[\textit{a}]pyrene derivatives (Figure 9).\textsuperscript{91} The coumarins initiate lung tumors and liver cancer in mice and rats respectively. The toxic effects of the coumarins have been attributed to the ability of rodents to metabolize coumarin to the toxic unstable compound, 3, 4-coumarin epoxide.\textsuperscript{92} Although the coumarins are hepatotoxic, they are often detoxified when metabolized to a low toxic hydroxylated derivative known as 7-hydroxycoumarin.\textsuperscript{93} The mutagenicity and carcinogenicity of the furanocoumarins have been demonstrated by their capacities to alkylate and intercalate DNA. Furanocoumarins isolated from the Apiaceae family possess skin penetrating capabilities, and when absorbed into the skin, intercalate dermal cells. Furthermore, upon exposure of the skin to sunlight, these compounds alkylate DNA leading to cell death and the formation of blisters.\textsuperscript{13} Coumatetrayl has been reported to cause hemoptysis with an elevation of the international normalized ratio (INR > 9.5) as well as partial thromboplastin time (PTT = 83 sec).\textsuperscript{12,14} According to Binks and Davies,\textsuperscript{95} coumarins inhibit the post-translational carboxylation of various blood clotting factors.

## Phenolic compounds

Phenolic compounds are composed of lignin as ester groups. These compounds occur as constituents of alcohol insoluble fractions, or are attached to glycosides in alcohol soluble fractions following extraction.\textsuperscript{96} Some natural phenolic compounds are carcinogenic and mutagenic. However, the toxic actions of phenolics can be mitigated, since these compounds are rapidly metabolized in adults.\textsuperscript{97} The dihydrobenzylchalcone phenolic compound chamuvaritin, from \textit{Uvaria chamae}, has been reported to initiate mutation in \textit{Salmonella typhimurium} strains TA98 and TA100 by stimulation of hepatic microsomal enzyme. This metabolic stimulation was essential for the expression of chamusvaritin mutagenic activity in \textit{S. typhimurium}, and the mutation was induced in a concentration dependent manner.\textsuperscript{97,98} The possible mutagenic and carcinogenic actions of chamusvaritin have been attributed to its heterocyclic and hydrophobic nature. The capability of chamusvaritin to cause tumor formation in animals was linked to the initiation of frame shift mutation in \textit{S. typhimurium} TA98 strain.\textsuperscript{97,98}

![Atractyloside](image1.png)

![Daphnetoxin](image2.png)

![Gibberellic acid](image3.png)

**Figure 8:** Some terpenoids.
The yellow polyphenolic compound gossypol from *Gossypium* spp. of cotton seeds, is known to penetrate the cells and inhibit the actions of protein kinase C as well as various dehydrogenase enzymes. Gossypols induce infertility in males and have been used in China as a male oral contraceptive. Gossypol was reported by Botha and Penrith to cause diarrhea, shortness of breath, unthriftiness and loss of appetite, and eventually death in pigs after 13 months. Postmortem assessment of the pigs that died without preliminary signs and symptoms presented cardiomyopathy, extreme hepatosis, centrilobular necrosis, as well as hemorrhage which might have affected the lobule. *In vitro* analysis of human erythrocytes showed that gossypol induced the death of human erythrocytes and thereby promoted hemolytic anemia.

The naphthoquinone compound, plumbagin, from genera: *Plumbago, Drosera, Nepenthes* as well as that isolated from various African herbs: *Diospyros canaliculata* and *D. crassiflora* have been reported to cause toxic actions in rat and mouse models. For instance, the genotoxicity and mutagenicity of plumbagin has been reported. In mouse models, plumbagin was observed to cause elevation in the levels of acid phosphatase and serum phosphate, as well as increased leucocyte counts. This compound was also toxic to the liver and reproductive system of mice as a result of DNA damage. Reports showed that the coumarin compound phytoalexin scopoletin exhibited systemic toxicity in animal models. The compound has been identified in *Scopolia carniolica* Solanaceae, *Viburnum prunifolium* Adoxaceae, *Artemisia scoparia* Asteraceae, *Convolvulus tricolor* Convulvulaceae, *Garcinia brevipedicellata* Clusiaceae, *Macaranga barteri* Euphorbiaceae, *Scaphophthalam thommeri* Sterculiaceae, *Torilis radiate* Apiaceae, *Pentas longiflora* Rubiaceae, *Tachiadenus longiflorus* Gentianaceae and *A. afra* Asteraceae. Scoopletin stimulates testicular failure at the sperm maintenance level and decreases citric acid and fructose levels of guinea pigs’ male reproductive organs. The identification of scopoletin, as well as other coumarins in cassava suggested that scrotal dermatitis, nerve deafness, endemic goiter, ataxia, glossitis, cretinism, tropical neuropathy accompanied by optic atrophy, stomatitis and psychological disorder, which were considered to be caused by the cyanogenic glycosides were also caused by the presence of scopoletin in food products such as garri, flour, etc. This is due to the fact that most of the cyanide in cassava was lost during cassava processing, whereas the scopoletin levels in cassava was not altered during processing. Phenol, which is the major component of the phenolics, is a neurotoxin that can possibly lead to instant death by impeding neural transmission system when present in the bloodstream. Phenol is also harmful to the skin, eyes, as well the respiratory tract. Hydroquinone has also been reported to be toxic. The rotenoids found in certain legumes obstruct cellular respiration by inhibiting the mitochondrial respiratory chain. The cucurbitacins are cytotoxins that inhibit cell division as well as hinder vesicle transport along microtubules. The molecular configurations of some phenolic compounds are represented in Figure 10.

**CONCLUSION**

Some deleterious actions of toxic compounds from plant were summarized in this review. It is noteworthy that the beneficial as well as the toxicological outcomes following the use of plant materials depend on the chemical nature of their constituent bioactive compounds. Plants, especially those used for ethnomedicinal purposes, contain significant amounts of noxious bioactive compounds, which may possibly elicit adverse health effects on both humans and animals. However, the
presence of noxious bioactive compounds in medicinal plants are reduced to minimal levels or completely eliminated following the processing of the herbal materials prior consumption. Nevertheless, the isolation and purification of plant bioactive compounds for toxicological evaluation prior to their usage in the development of pharmaceutical formulations is recommended. In as much as vast arrays of plants are used for the treatment of various diseases, the toxicological significance of such plants should be adequately considered before usage.

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Authors’ Contributions

FOO/PCC conceived and designed the scope of the report. FOO/PCC/CMC contributed in writing the paper. FOO/PCC/revised and edited the manuscript draft. FOO/PCC/CMC authors were the resource persons who provided all the necessary materials for writing the manuscript. All authors have read and approved the manuscript in the present form and gave the permission to submit the manuscript for publication.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ABBREVIATIONS


REFERENCES

Ohiagu, et al.: Toxicological Significance of Bioactive Compounds


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PICTORIAL ABSTRACT

SUMMARY

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• The presence of noxious bioactive compounds in medicinal plants are reduced to minimal levels or completely eliminated following the processing of the herbal materials prior consumption.

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• The toxicological significance of medicinal plants should be adequately considered before usage.