



Research Journal of  
**Phytochemistry**

ISSN 1819-3471



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## Bioactive Principles from Medicinal Plants

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### ABSTRACT

Plants are widely used in many indigenous systems of medicine for therapeutic purposes and are increasingly becoming popular in modern society as alternatives to synthetic medicines. Bioactive principles are derived from the products of plant primary metabolites, which are associated with the process of photosynthesis. The present review highlighted the chemical diversity and medicinal potentials of bioactive principles as well inherent toxicity concerns associated with the use of these plant products, which are of relevance to the clinician, pharmacist or toxicologist. Plant materials are composed of vast array of bioactive principles of which their isolation, identification and characterization for analytical evaluation requires expertise with cutting edge analytical protocols and instrumentations. Bioactive principles are responsible for the therapeutic activities of medicinal plants and provide unlimited opportunities for new drug leads because of their unmatched availability and chemical diversity. For the most part, the beneficial or toxic outcomes of standardized plant extracts depend on the chemical peculiarities of the containing bioactive principles.

**Key words:** Bioactive principles, bioassay, herb extraction, herb medicinal value, herb toxicity

### INTRODUCTION

Plants are widely used in many indigenous systems of medicine for therapeutic purposes and are increasingly becoming popular in modern society as alternatives to synthetic medicines. Herbal medicine, also called botanical medicine or phytomedicine is generally cheaper, accessible or readily available and more culturally acceptable to many because of the belief that they cause less side effects than some synthetic drugs (Carlson, 2002; Dey and De, 2015). Recent research efforts in drug discovery from medicinal plants involve a multifaceted approach that combines botanical, phytochemical, biological and molecular techniques (Balunas and Kinghorn, 2005). Bioactive principles are responsible for the therapeutic activities of medicinal plants such as hypoglycemic, anti-diabetic, anti-oxidant, anti-microbial, anti-inflammatory, anti-carcinogenic, anti-malarial, anti-cholinergic, anti-leprosy activities etc. (Negi *et al.*, 2011). For instance, arrays of bioactive principles from diverse anti-diabetic plants have been exhaustively described elsewhere (Marles and Farnsworth, 1995; Chikezie *et al.*, 2015). Thus, pure compounds or standardized extracts from medicinal plants provide unlimited opportunities for new drug leads because of the unmatched availability and chemical diversity of bioactive principles from the plant kingdom (Ramawat *et al.*, 2009; Sasidharan *et al.*, 2011). In same manner of chemical diversity, most effective poisonous agents to humans and animals have their origin from various classes of

chemical substances from plants. Some notable noxious compounds from plants are the cyanogenic glycosides (Aregheore and Agunbiade, 1991; FSANZ., 2004), myristicin (Lee *et al.*, 2005), phytohaemagglutinins or lectin (Tadele, 2015), neurotoxic amino acids e.g.,  $\beta$ -N-Oxalyl-L- $\alpha$ ,  $\beta$ -diaminopropionic acid (ODAP) (Rao *et al.*, 1964; Akande *et al.*, 2010), protease inhibitors, chlorogenic acid, amylase inhibitors, gossypol, goitrogens (Akande *et al.*, 2010; Tadele, 2015), veratridines (Schep *et al.*, 2006) etc.

The renewed interest in natural products research, in recent years, has led to the development of new drugs, such as the anti-cancer chemotherapies- paclitaxel (Taxol) from the Pacific Northwest, *Taxus brevifolia* Nutt. and the analogue, docetaxel, Vinca alkaloids vinblastine and vincristine, isolated from the Madagascar periwinkle, *Catharanthus roseus* (L.) G. Don., etoposide and teniposide, isolated from roots of *Podophyllum* species; in addition to other drugs derived from natural products, which account for over 40% of new registered drugs (Gueritte and Fahy, 2005; Fadeyi *et al.*, 2013; <http://www.eolss.net/Sample-Chapters/C03/E6-79-04.pdf>). Furthermore, earlier survey showed that about 70-80% of Asian and African populations rely on herbal remedies for their primary health care needs (Chikezie *et al.*, 2015; Neergheen-Bhujun, 2013); *Artemisia annua* gave mankind artemisinin; the current WHO recommended anti-malarial agent (WHO, 2001). The earliest anti-malarial agent-quinine was obtained from *Cinchona officinalis* bark that dates back to 1638 (Zhang and Moller, 2000; Abdel-Azim *et al.*, 2011). Aside the therapeutic usefulness of bioactive principles, plants extracts are used as agrochemicals, flavor and fragrance ingredients, food additives and pesticides (Ramawat *et al.*, 2009; Rahimi *et al.*, 2012). Many databases are available to describe the complete pharmacophore analysis of active principles possessing anti-diabetic, anti-microbial, anti-cancerous and anti-oxidant properties from medicinal plants (Pitchai *et al.*, 2010). The present review highlighted the chemical diversity and medicinal potentials of bioactive principles as well inherent toxicity concerns associated with the use of these plant products, which are of relevance to the clinician, pharmacist or toxicologist.

**Evidence acquisition:** Scientific search engines such as PubMed, Pubget, Medline, EMBASE, Mendeley, Google Scholar, ScienceDirect and SpringerLink were used to retrieve online publications from 1962-2015. Keywords such as 'bioassay', 'bioactive principles', 'herb extraction', 'herb toxicity', 'herb medicinal value' and 'phytomedicine' were used to collate relevant articles. The results were then cross-referenced to generate a total number of 204 references cited in this review.

**Selection of plant species:** A review of literatures involving research on medicinal plants suggests that scientist follow more or less the same general strategy to investigate plant materials for their pharmacological properties (Kingham and Balandrin, 1993; Heinrich *et al.*, 2004). Plant species and plant part collected randomly are investigated using available phytochemical methods. However, a more targeted approach is often preferred to random selection (Kingham and Balandrin, 1993; Harborne, 1998; Heinrich *et al.*, 2004). Plant materials to be investigated are selected on the basis of some specific traditional uses; the so-called ethno-botanical bio-prospecting approach. Plant extracts used for traditional remedies for certain diseases are more likely to contain biologically active principles of medicinal interest (Fabricant and Farnsworth, 2001; Carlson, 2002; Heinrich *et al.*, 2004). Alternatively, the plant can be selected based on chemo-taxonomical data. In the chemo-taxonomical approach, pre-knowledge that a particular group of plants contain certain classes of natural products may be used to predict that taxonomically related plant may contain structurally similar biomolecules (Heinrich *et al.*, 2004). Plant species may be

selected based on field observations. For instance, plant species that thrive in hostile environment replete with bacteria, fungi or virus synthesize defensive natural products against these pathogens, which may also exhibit bactericidal, fungicidal or virucidal activity in human system.

Another approach known as information driven approach utilizes a combination of ethno-botanical, chemo-taxonomic and random approaches together with a database that contain all relevant information concerning a particular plant species (Pitchai *et al.*, 2010). The database is used to prioritize which plant should be extracted and screened for biological activity. This approach is favored by large organization, particularly, pharmacological companies, interested in screening thousands of samples for bioactivity; since it reduces cost by avoidable repetitions of encountering common or already known drugs.

**Collection and identification of plant material:** The whole plant or a particular plant part can be collected depending on where the metabolites of interest, if they are known, are accumulated and stored. Hence aerial (e.g., leaf, stem, flowering tops, fruit, seed and bark) and underground (e.g., tuber, bulb and root) parts can be collected separately. Collection of plant materials can be influenced by factors such as the age of the plant and environmental conditions (e.g., temperature, rainfall, sunlight, soil characteristics and altitude) (Harborne, 1998). Therefore, it is important to take these factors into consideration for the purpose of ensuring reproducible profile of plant metabolites (Sarker *et al.*, 2006). The plant from which the bioactive principles are to be collected must be correctly identified. A plant taxonomist or a botanist should be involved in the detailed authentication of the plant. Any feature related to the collection, such as the name of the plant, identity of the plant part collected, place and date of collection the plant should be recorded as voucher deposit in the herbarium for future references.

**Drying and grinding of plant material:** Once the plant material has been collected, a common practice involves drying the samples on trays at ambient room temperature with adequate ventilation. Dry conditions are essential to prevent the formation of artifacts as a result of microbial fermentation and subsequent degradation of the plant metabolites. Furthermore, plant materials are cut or sliced into small pieces to facilitate homogenous drying and prevented from direct sunlight impact to minimize undesirable chemical reactions of plant metabolites resulting to the formation of artifacts (Sarker *et al.*, 2006). Oven drying facilitate faster drying rate and minimize hydrolysis or related reactions in the plant material. Dried samples are usually kept in sealed containers in a dry and cool place. Prolong storage should be discouraged to avoid decomposition of plant metabolites.

After the drying process, plant materials are ground into fine powder to give a more homogenous sample with increased surface area. Mechanical grinders such as hammer and cutting mills are employed to shred the plant material into various particle sizes. Potential draw-back of the grinding procedure is that samples rich in fats and volatile oils may clog up the sieves, which generates heat during the process that may degrade thermo-labile metabolites.

**Extraction of plant materials:** For scientific evaluations of medicinal plants, extraction of bioactive principles from the plant material is crucial in order to obtain the desired chemical components from the plant materials for separation and characterization. Analytical extraction ensures that potential active constituents are not lost, distorted or destroyed during the preparation of the extract from plant samples. Plant materials are commonly extracted by means of liquid solvents in what is known as the solid-liquid solvent extraction. A typical solid-liquid

solvent extraction process for plant materials involve drying and grinding of the plant material, choosing a suitable extraction solvent and extraction procedure (Jones and Kingborn, 2005).

The choice of the extraction solvent depends mainly on the polarity and solubility of the bioactive principle of interest. Although water is generally used in many traditional herbal extraction protocols, organic solvents of varying polarities are often exploited to obtain bioactive principles of varying polarities and solubilities. The choice of extraction procedure depends on the nature of the source material and the compound to be isolated. Conventional solvent extraction procedures applicable to plant natural products include, but not limited to the use of maceration, heating under reflux, sonification, percolation, soxhlet extraction, steam distillation and sequential solvent extraction. Contemporary extraction techniques include ultrasound, solid-phase micro-extraction, supercritical-fluid extraction, pressurized-liquid extraction, microwave-assisted extraction, solid-phase extraction and surfactant mediated techniques (Vinatoru *et al.*, 1997; Sasidharan *et al.*, 2011; Chua, 2013; Azmir *et al.*, 2013). The efficiencies of conventional and contemporary extraction methods mostly depend on the critical input parameters; understanding the nature of plant matrix; chemistry of bioactive principles and scientific expertise (Azmir *et al.*, 2013). The polarity of commonly used extraction solvents and chemical profiles of the extracts are summarized in Table 1.

The recent development of cost-effective, sustainable and well-controlled application of tissue culture technology such as *in vitro* regeneration and genetic transformation/enhancement of medicinal plants serve to boost the selective mass production of bioactive principles (Kutchan, 1995; Zhou and Wu, 2006; Rahimi *et al.*, 2012). The technology is an advantage in that it provides continuous, reliable source of plant pharmaceuticals and a platform for large scale plant tissue culture from which bioactive principles could be harvested.

**Isolation, identification and characterization of bioactive principles:** Plant materials are composed of vast array of bioactive principles of which their isolation, identification and characterization for analytical evaluation requires expertise with cutting edge analytical protocols and instrumentations. For instance, frequently encountered isolation techniques involve the use of Thin-layer Chromatography (TLC), column chromatography, flash chromatography, Sephadex chromatography and High Performance Liquid Chromatography (HPLC) (Roeder, 1995; Kwag *et al.*, 2003; Sasidharan *et al.*, 2011; Jayeola *et al.*, 2011; Ouedraogo *et al.*, 2012; Karayil *et al.*, 2014; Nwanna *et al.*, 2014). In addition, non-chromatographic techniques such as

Table 1: Polarity of extraction solvents and chemical profiles of extracts

Polarity	Solvent	Chemical profile of extract	References
Low	n-Hexane	Fatty acids, wax and terpenoids	Ayaffor <i>et al.</i> (1994)
	Chloroform	Fatty acids, wax and terpenoids	Perrett <i>et al.</i> (1995), Cowan (1999), Bruneton (1999)
Medium	Dichloromethane	Less polar and polar flavonoids, tannins and terpenoids	Bruneton (1999), Scalbert <i>et al.</i> (2005), Sasidharan <i>et al.</i> (2011)
	Ethylacetate	Less polar and polar flavonoids, tannins and terpenoids	Bruneton (1999), Scalbert <i>et al.</i> (2005)
	Acetone	Less polar and polar flavonoids, tannins, terpenoids and glycosides	Eloff (1998), Bruneton (1999) Scalbert <i>et al.</i> (2005)
High	Ethanol	Polar flavonoids, tannins and glycoside (saponins)	Cowan (1999), Bruneton (1999)
	Methanol	Carbohydrates, lectin, amino acids, polypeptides, phenolic acids, phenylpropanoids, polar flavonoids, glycosides and alkaloids	Bruneton (1999), Scalbert <i>et al.</i> (2005)
	Water	Carbohydrates, lectin, amino acids, polypeptides, phenolic acids, phenylpropanoids, polar flavonoids, glycosides and alkaloids	Kaul <i>et al.</i> (1985), Jones and Kinghorn (2005)
	Aqueous acid or base	Alkaloids	Bruneton (1999)

immunoassay, which use monoclonal antibodies (MAbs), phytochemical screening assay (Sasidharan *et al.*, 2011; Savithramma *et al.*, 2011; Belonwu *et al.*, 2014), have equally been very rewarding. Separated bioactive fractions may further be subjected to identification and characterization protocols using the Fourier Transform Infrared Spectroscopy (FTIR) and Gas Chromatography-Mass Spectrometry (GC-MS) (Eberhardt *et al.*, 2007; Hazra *et al.*, 2007; Eneji *et al.*, 2011; Kiruthika and Sornaraj, 2011; Sasidharan *et al.*, 2011).

Chemical screening or metabolite profiling protocols of herbal extracts using hyphenated techniques, particularly, the LC/UV, LC/MS and LC/NMR serve to distinguish between novel and already known bioactive principles in the course of search for new lead compounds from medicinal plants. Furthermore, spectroscopic techniques such as UV/VIS and IR spectrophotometry, carbon and proton NMR, MS and x-ray diffraction are applied for elucidation of structural conformations of bioactive principles (Ashnagar *et al.*, 2007; Ejele *et al.*, 2012; Ejele *et al.*, 2014; Karayil *et al.*, 2014; <http://www.eolss.net/Sample-Chapters/C03/E6-79-04.pdf>). Also, chemical techniques involving hydrolysis, formation of derivatives and hydration reaction coupled with structural modifications of bioactive principles are applied to establish structure/function relationship (<http://www.eolss.net/Sample-Chapters/C03/E6-79-04.pdf>).

**Biological and pharmacological screening:** Biological activity of plant extracts are often demonstrated using *in vitro* and *in vivo* bioassay methods (Marles and Farnsworth, 1995; Kwag *et al.*, 2003; Kinghorn *et al.*, 2011; van de Venter *et al.*, 2008; Crawford *et al.*, 2011; Karakas *et al.*, 2012). The combinations of vast arrays of plant compounds make it virtually experimentally unattainable to isolate bioactive principles to obtain absolute purity. Therefore, in order to elucidate the therapeutic activity as well as toxicity of bioactive principles, bioassay-guided approach involving biological and pharmacological targets are used during purification and fractionation steps. The *in vivo* bioassay methods involve the use of microorganisms, whole invertebrate and vertebrate animals, whereas *in vitro* procedures employ isolated subcellular systems such as enzymes and receptors as well as animal or human cell culture (Kwag *et al.*, 2003; Eldeen and van Staden, 2007; Crawford *et al.*, 2011; Attard and Pacioni, 2012; <http://www.eolss.net/Sample-Chapters/C03/E6-79-04.pdf>).

**Bioactive principles of medicinal and toxicological significance:** Bioactive principles, also referred as plant secondary metabolites, are derived from the products of plant primary metabolites, which are associated with the process of photosynthesis viz.; carbohydrates, amino acids and simple lipids (Fig. 1).

Although bioactive principles are generally not involved in growth and metabolism of plants, they play critical roles in the survival of plants by their functions in the defense of the plant against pathogenic organisms and predatory herbivores (Bernhoft, 2010; Ingebrigtsen, 2010). Additionally, bioactive principles may serve as vehicle for the elimination of nitrogenous waste products and sustenance of plants in situation of drought (Enneking and Wink, 2000; Thipyapong *et al.*, 2004; Tadele, 2015; Belonwu *et al.*, 2014). Also, plant secondary metabolites are referred to as the active principle of plants because they exert diverse range of pharmacological effects in mammalian systems. An overview of plant metabolic pathways (Fig. 1 and 2) showed that bioactive principles are synthesized by two major pathways: the shikimic acid or aromatic amino acid and mevalonic acid pathways (Ramawat *et al.*, 2009).

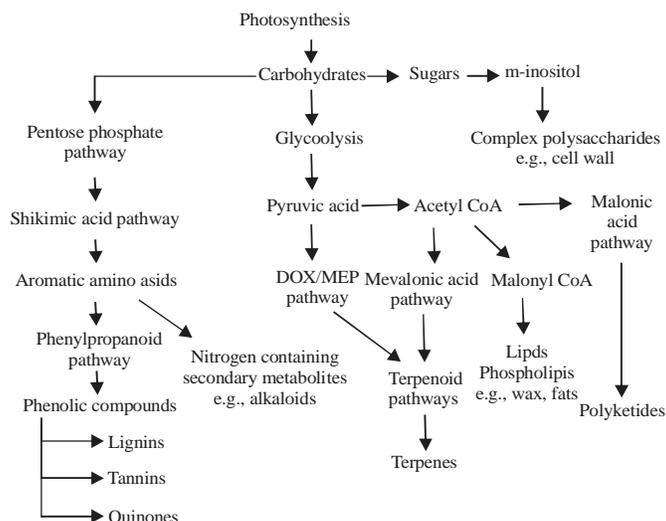


Fig. 1: Biosynthetic pathways leading to synthesis of secondary metabolites (Ramawat *et al.*, 2009); DOX (1-deoxy-D-xylulose); MEP (methylerythriol-4-phosphate)

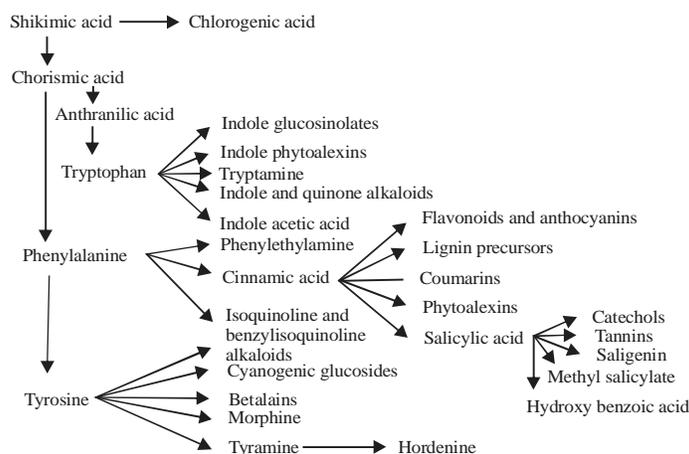


Fig. 2: Shikimic acid pathway leading to the biosynthesis of diverse bioactive principles (Ramawat *et al.*, 2009)

**Alkaloids:** They are diverse low-molecular-weight, cyclic organic compounds containing nitrogen in a negative oxidation state. Alkaloids belong to the broad category of alkaline secondary metabolites that constitute the pharmacologically bioactive principles that are predominant, but not exclusively present, in flowering plants (Kutchan, 1995; Pelletier, 1983). Alkaloids are synthesized from decarboxylation of amino acids to produce amines, which react with amine oxides to form aldehydes. The Mannich-type condensation of the aldehydes and amine groups yield characteristic heterocyclic rings of alkaloids. Furthermore, the chemical nature of their nitrogen ring serves as basis for the sub-classification of alkaloids: for instance, glycoalkaloids is the aglycone moiety that is glycosylated with a carbohydrate (Tadele, 2015). However, few alkaloids occur as glycosides of sugar such as glucose, rhamnose and galactose, whereas some weak basic

alkaloids (nicotine) occur freely in nature and others as amides (piperine) and esters (atropine, cocaine) of organic acids (Ramawat, 2007; Ramawat *et al.*, 2009). Chemo-taxonomical survey showed that alkaloids are widely distributed in higher plants belonging to Apocyanaceae, Ranunculaceae, Papaveraceae, Solanaceae and Rutaceae in Africa as well as in lower plants, insects, marine organisms and microorganisms (Kutchan, 1995; Ramawat *et al.*, 2009; Kuete, 2014). Alkaloids are pharmacologically active compounds in that they affect the central nervous system, reduce appetite and act as diuretic (Yadav *et al.*, 2014). Moreover, recent review showed that certain alkaloids are medicinally applied as local anesthetic (Kuete, 2014), stimulants-{caffeine, nicotine, theobromine, methylated derivatives of xanthine, methylated uric acids such as theacrine, methyllicberine and liberine (Ramawat *et al.*, 2009)}, psychedelics, analgesics-{morphine (Ojewole, 2006; Pan *et al.*, 2011), codeine (Kutchan, 1995), N-methyl-N-deethylaconitine (Nyirimigabo *et al.*, 2015)}, bactericidal-{piperidine (Jouvenaz *et al.*, 1972), harmandiamines A-C (Maneerat *et al.*, 2012)}, anti-cancer drugs-{camptothecin, vinblastine, vincristine (Parekh *et al.*, 2009; Ramawat *et al.*, 2009)}, anti-hypertensive agents-{serpentine (Newman *et al.*, 2003; Lesney, 2004; Gupta *et al.*, 2005; Gurib-Fakim, 2006)}, cholinomimetics-{aceclidine (Kuete, 2014)}, spasmolysis agents-(Capasso *et al.*, 1997), vasodilators-{rutaecarpine (Chiou *et al.*, 1994)}, anti-arrhythmia, anti-asthma (Kuete, 2014), anti-malarials {quinine and artemisinin (Ramawat *et al.*, 2009)} etc.

Reports have showed that the exposure or ingestion of certain plant alkaloids could provoke harmful outcomes. Insects and herbivores are often repulsed by the potential toxicity and bitter taste of alkaloids. For instance, lupin alkaloids are feeding deterrents and lethal to certain species of insects, especially aphids (Berlandier, 1996). Also, quinolizidine alkaloids toxicity to insects and vertebrates is attributable to the interactions of sparteine or lupanine (alkaloids) with N-acetylcholine receptors (nAChR) (sparteine or lupanine activates nAChR), Na<sup>+</sup>/K<sup>+</sup>- channels and interference with protein biosynthesis (Enneking and Wink, 2000). The anti-nutrients attributes of alkaloids are in connection with their actions in the central nervous system, which disrupt or cause inappropriate transmission of electrochemical signals. Specifically, massive intake of tropane alkaloids elicits rapid heartbeat, paralysis and in fatal case, leads to death. Likewise, high dose of tryptamine alkaloids cause staggering gait and death (Gemedé and Ratta, 2014). Strychnine alkaloids are used as rat poison (Ramawat *et al.*, 2009). The molecular configurations of some common alkaloids are shown in Fig. 3.

**Flavonoids:** The bioflavonoid are collections of low molecular weight phenolic groups of phytochemicals that include the anthocyanins (e.g., cyanidin, pelargonidin, petunidin), the flavonols (quercetin, kaempferol), flavones (luteolin, apigenin), flavanones (myricetin, naringin, hesperetin, naringenin), flavan-3-ols (catechin, epicatechin, galocatechin) and, although sometimes classified separately, the isoflavones (genistein, daidzein) (Lila, 2004). Flavonoids are widely distributed in the plant kingdom and have been reported to exhibit strong antioxidant activity (Saija *et al.*, 1995; Heijnen *et al.*, 2001; Havsteen, 2002; Galati and O'Brien, 2004; Lila, 2004) and there appeared to be a structure/activity relationship in the capability of flavonoids to scavenge peroxynitrite (Heijnen *et al.*, 2001; Lila, 2004). Phenylalanine is the precursor for the biosynthesis of flavonoids via the flavone synthase pathway (Fig. 4). Flavonoids are plant pigments and for the most part, are responsible for display marvelous colours of flower petals and the emission of brilliant fluorescence when green plant cells are excited by UV light (Harborne and Williams, 2000;

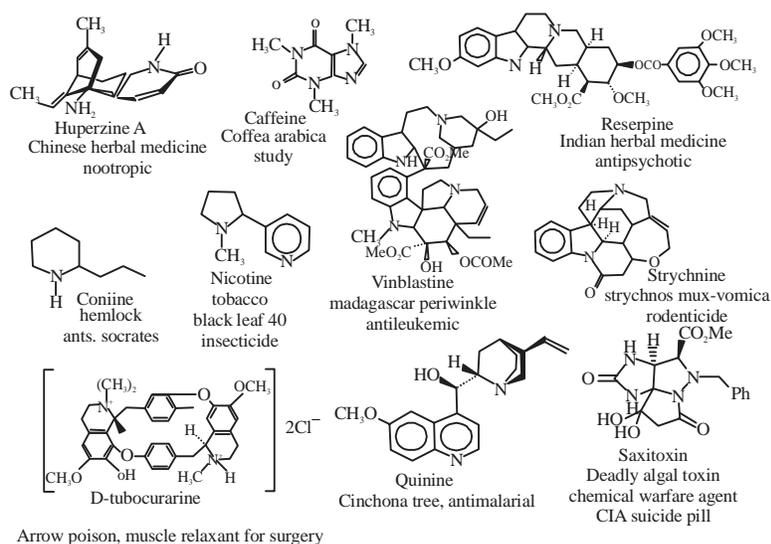


Fig. 3: Molecular structures of some common alkaloids (www.drug-alcohol.com)

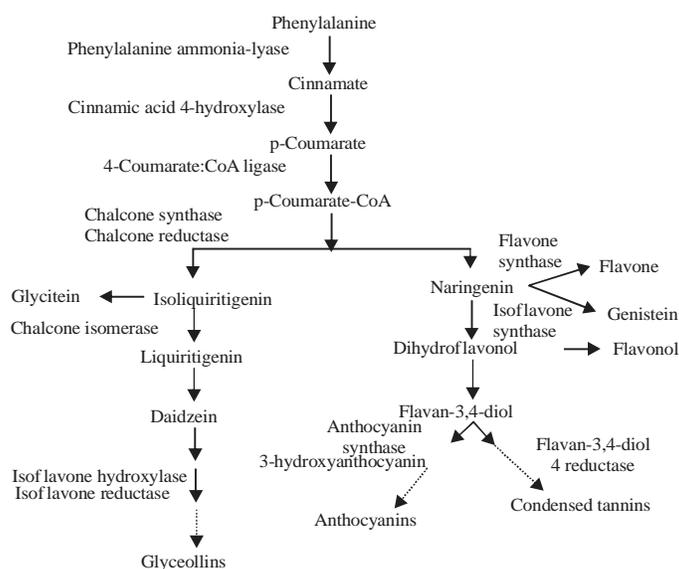


Fig. 4: Pathway leading to the biosynthesis of diverse bioactive principles from phenylalanine (Ramawat *et al.*, 2009)

Havsteen, 2002). Base on their peculiarities and distribution in plant kingdom, flavonoids are used by botanists for taxonomical classification of plants (Havsteen, 2002).

The basic structural configuration of flavonoid compounds is the 2-phenyl-benzo[*a*]pyrane or flavane nucleus, which consists of two benzene rings (A and B) linked through a heterocyclic pyrane ring (C) (Fig. 5) (Brown, 1980). Common flavonoids including: quercetin 7-O-(6-trans caffeoyl)- $\beta$ -glucopyranosyl-(1-3)- $\alpha$ -rhamnopyranoside-3-O- $\beta$ -glucopyranoside, kaempferol 7-O-(6-trans-caffeoyl)- $\beta$ -glucopyranosyl-(1-3)- $\alpha$ -rhamnopyranoside-3-O- $\beta$ -glucopyranoside and kaempferol 7-O-(6-

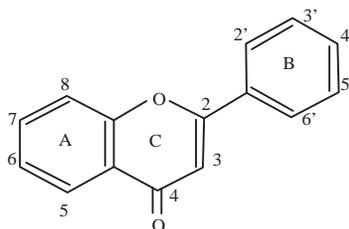


Fig. 5: The skeleton structure of a class of flavonoids (the flavones)

trans-p-coumaroyl)- $\beta$ -glucopyranosyl-(1-3)- $\alpha$ -rhamnopyranoside-3-O- $\beta$ -glucopyranoside, that have been isolated from Chinese herbal medicine, the tubers and roots of *Aconitum* (Ranunculaceae) and *Aconitum napellus* are particularly rich in  $\beta$ -3, 4-dihydroxyphenethyl  $\beta$ -glucopyranoside (Nyirimigabo *et al.*, 2015).

Flavonoids are classified based on their biosynthetic origin. For instance, chalcones, flavanones, flavan-3-ols and flavan-3, 4-diols, are intermediates, whereas anthocyanidins, proanthocyanidins, flavones and flavonols are end products of the biosynthetic pathways (Cushnie and Lamb, 2005). Additionally, the isoflavones and related isoflavonoids are other two classes of flavonoid in which the 2-phenyl side chain of flavanone isomerizes at the 3 position (Harborne, 1998; Cushnie and Lamb, 2005).

Some medicinal benefits attributable to the presence of flavonoids in diets include prevention oxidative cell damage (antioxidant and free radical scavengers), anti-inflammatory and anti-carcinogenic effects (Galati and O'Brien, 2004). Flavonoids have been noted to act as bactericidal to several strains of bacteria, inhibit important viral enzymes, such as reverse transcriptase and protease and kill certain pathogenic protozoans (Enneking and Wink, 2000; Havsteen, 2002; Cushnie and Lamb, 2005). *In vitro* studies have revealed that quercetin inhibits DNA gyrase, whereas sophoraflavone G and (-)-epigallocatechin gallate impede cytoplasmic membrane function and licochalcones A and C inhibit energy metabolism (Cushnie and Lamb, 2005) in susceptible bacteria. Furthermore, two flavones from *Artemisia giraldi*, identified as 6, 7, 4-trihydroxy-3, 5-dimethoxyflavone and 5, 5-dihydroxy-8, 2, 4-trimethoxyflavone, together with 5, 7, 4-trihydroxy-3, 5-dimethoxyflavone have been reported to exhibit anti-microbial activity against *Aspergillus flavus*, which causes invasive disease in immunosuppressed individuals (Cushnie and Lamb, 2005). Phytoestrogens are weakly estrogenic isoflavones and lignans that bind to estrogen receptors, which function both as antioxidants and protective agents against cardiovascular disease in man (Adlercreutz, 2010).

Flavonoids extracted from *Morus indica* caused up-regulation of hepatic superoxide dismutase (SOD) activity, reduction of hepatic malondialdehyde (MDA) content, down-regulation of hepatic CYP2E1 expression and increase of glucose transporter 4 (GLUT-4) expressions in skeletal muscle of experimental rats, which were indications that *M. indica* flavonoids may ameliorate hyperlipidemia and hyperglycemia engendered by high fat diet (Ma *et al.*, 2012). Likewise, flavonoids - hesperidin, boswellic acid, ellagic acid, quercetin, rutin and naringenin improved hyperlipidemia and hyperglycemia by partly regulating fatty acid and cholesterol metabolism and affecting gene expression of glucose-regulating enzymes in diabetic animals (Jung *et al.*, 2006; Jadhav and Puchchakayala, 2012). Flavonoids prevent tumorigenesis by inhibiting DNA topoisomerase II activity and p53 down-regulation and thereby elicit tumor cell apoptosis (Galati and O'Brien, 2004). Due to the proven ability of flavonoids to inhibit specific enzymes, to

simulate some hormone secretions and neurotransmitters and to scavenge free radicals, pure flavonoids are used to treat many common diseases (Havsteen, 2002; Prescott *et al.*, 1999; Cushnie and Lamb, 2005). Polymethoxylated flavones are known for their anti-cancer (Silalahi, 2002), anti-inflammatory (Lin *et al.*, 2003) and neuro-protective (Datla *et al.*, 2001) properties. Flavonoids from *Theobroma cacao* caused dose-dependent reduction of interleukin (IL)-2Ra (CD25) expression in activated lymphoid cell line, which suggests the potentials of the use flavonoids in counteracting immune system hyperactivity such as chronic autoimmune inflammatory disease (Ramiro *et al.*, 2005).

Although chemo-preventive activity of flavonoids have been demonstrated using animal *in vivo* experiments, there are claims that dietary flavonoid/phenolic consumption or exposures may provoke toxic flavonoid–drug interactions, liver failure, contact dermatitis, hemolytic anaemias and estrogenic-related toxicity outcomes such as male reproductive health and breast cancer (Enneking and Wink, 2000; Galati and O'Brien, 2004).

**Anthocyanins:** The anthocyanins are the most important and widespread group of colouring matters in plants. These intensely coloured water soluble pigments are responsible for almost all the colours of petals, leaves and fruits of plants. Anthocyanins are basically composed of the aromatic rings of the cyanidin, from which several derivatives are generated by divergent insertions and positioning of substituents such as hydroxyl, methyl or glycosyl groups (Fig. 6a-f). Also, the molecular features of anthocyanins such as position, number and type of substitutions on the cyaniding backbone dictates the level to which anthocyanins exert their bioactive properties as well as the intracellular localization of the pigments (Lazze *et al.*, 2003; Lila, 2004).

Anthocyanins are antioxidants (Fig. 6) (Busic *et al.*, 2008; Aqil *et al.*, 2006; Imaga, 2013; Milugo *et al.*, 2013). According to Del Bas *et al.* (2005), grape seed procyanidins arrest atherogenesis, induce liver CYP7A1 and small heterodimer partner (SHP) expression in healthy rats. SHP positively regulates glucose-stimulated insulin secretion in  $\beta$ -cells and restores glucose sensitivity (Rolo and Palmeira, 2006). A compendium of the biomedical properties of anthocyanins in promoting human health and well-being have been confirmed and exhaustively described using

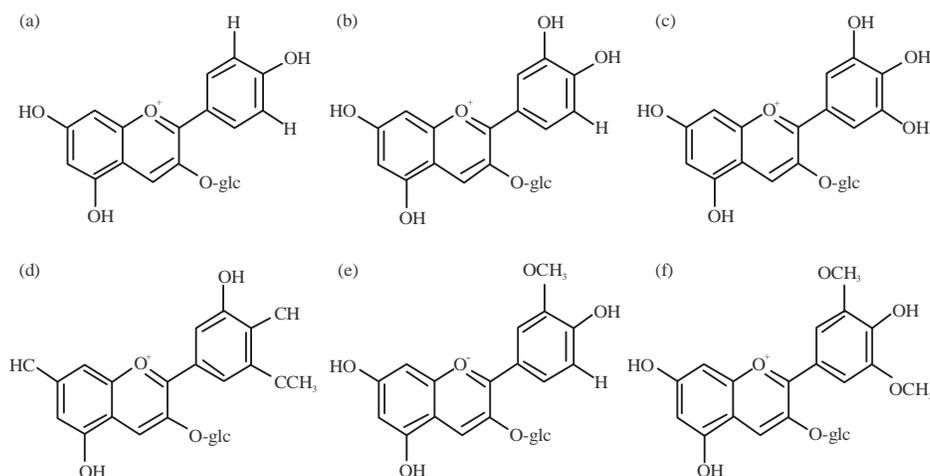


Fig. 6(a-f): Molecular structures of some common anthocyanins (a) Pelargonidin (b) Cyanidin (c) Delphinidin (d) Petunidin (e) Peonidin and (f) Malvidin

*in vivo* and *in vitro* experimental models (Lila, 2004; Ghosh and Konishi, 2007). For instance, antioxidant property and anti-influenza viral activity of polymeric procyanidins from Chinese quince (*Pseudocydonia sinensis* Schneid.), hydroxycinnamic derivatives mainly composed of 3-caffeoylquinic acid and 5-caffeoylquinic acid and polymeric procyanidins from quince (*Cydonia oblonga* Mill.) and 5-caffeoylquinic acid and monomeric and oligomeric procyanidins from apple (*Malus domestica* Mill.) fruits have been confirmed *in vitro* (Hamazu et al., 2005).

**Saponins:** Saponins are a family of amphipathic glycosides in which the varied number sugar moieties are bound to a 'sapogenin-steroid alkaloids, steroids or triterpene resulting to structural varieties of saponins, which serves as basis for their classification (Walsh, 2003; Prabhakar and Dobie, 2008; Bernhoft, 2010). Soybean, lupins and several other legumes are rich sources of triterpene saponins (Enneking and Wink, 2000).

Dietary saponins reduce protein digestibility probably by formation of sparingly digestible saponin-protein complexes and obstruct the absorption of micronutrients (Potter et al., 1993). Despite the toxicity concerns associated with the consumption of saponin containing plant materials, studies by Chan et al. (2014) revealed that phenolics-saponins fraction from defatted kenaf seed meal is rich in antioxidants and therefore, could serve as a potential active ingredient for nutraceuticals, functional foods as well as natural food preservatives. Likewise,  $\alpha$ -hederin and hederasaponin-C from *Hedera helix* and hederacolchisides-E and -F from *Hedera colchica* exhibited antioxidant activities that were comparable with standard antioxidants such as  $\alpha$ -tocopherol, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Gulcin et al., 2004).

The capabilities of saponins to ameliorate dyslipidemia have vastly been reported. Hypercholesterolemic rats administered with different combinations of saponins from *Glycyrrhiza glabra* (F. Fabaceae), *Withania somnifera* (F. Solanaceae), *Asparagus racemosus* (F. Liliaceae), *Chlorophytum borivilianum* (F. Liliaceae) and *Sesamum indicum* (F. Pedaliaceae) effectively reduced plasma and hepatic lipid profiles and increased fecal excretion of cholesterol, neutral sterol and bile acid along with increased hepatic HMG-CoA reductase activity and bile acid content (Visavadiya and Narasimhacharya, 2011). Plasma cholesterol lowering activity of saponins is also connected with their capabilities to precipitate cholesterol from micelles and interference with enterohepatic circulation of bile acids making it unavailable for intestinal absorption and hence reduce plasma cholesterol levels. Saponins can precipitate cholesterol from micelles and interfere with enterohepatic circulation of bile acids and thereby make cholesterol unavailable for intestinal absorption and eventual reduce plasma LDL-cholesterol levels (Harwood et al., 1993; Petit et al., 1995; Rajendran et al., 1996; Francis et al., 2002; Venkatesan et al., 2003). Another perspective showed that anti-hyperlipidemia saponins inhibit pancreatic lipase activity and reduce plasma triacylglycerol concentrations, thereby engendering reduction in plasma VLDL-C concentration (Howell et al., 1998; Han et al., 2002).

Related study showed that saponins from *Helicteres isora* caused increased gene expression of adipisin, GLUT-4 and peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) as well as reduced gene expression of glucose-6-phosphatase and fatty acid binding protein 4 (FABP4) enzymes, which improved hyperlipidemia and hyperglycemia in C57BL/KsJ-db /db mice (Bhavsar et al., 2009). Saponins extracted from *Entada phaseoloides* (L.) Merr exerted hypoglycemic and hypolipidemic activities through repression of chronic inflammation responses in Type II diabetic rats (Zheng et al., 2012). Also, saponins from *Solanum anguivi* Lam. fruits exhibited hypoglycemic, anti-peroxidative and anti-hyperlipidemic effects in Type I diabetic rats (Elekofehinti et al., 2013).

Charantin (XV) isolated from *Momordica charantia* L. possesses an insulin-like activity with which it promotes insulin secretion and thereby lowers hepatic glycogenesis (Ng *et al.*, 1986). Also, diverse saponins such as  $\beta$ -sitosterol (XVI) present in *Azadirachta indica* A., andrographolide (XVII), a diterpenoid lactone, obtained from *Andrographis paniculata* Nees and gymnemic acid IV (XVIII) isolated from *Gymnema sylvestre* R., are agents of glycemic control in animal models (Sugihara *et al.*, 2000; Yu *et al.*, 2003). The roles of bioactive principles in bringing glycemic control to bear in both experimental animals and humans have been exhaustively described elsewhere (Prabhakar and Dobie, 2008; Chikezie *et al.*, 2015). Adjuvant activities of saponins from traditional Chinese medicinal herbs such as *Panax ginseng*, *Astragalus species*, *Panax notoginseng*, *Cochinchina momordica*, *Glycyrrhiza uralensis* and *Achyranthes bidentata* have been previously described (Song and Hu, 2009). The immune-stimulatory activities of Quil A (consists of a mixture of related saponins) isolated from the bark of Quillaja (a tree), which is used as an adjuvant in selected veterinary vaccines has been acknowledged (Walsh, 2003).

More than five decades ago, Glauert *et al.* (1962) reported that toxic levels of saponins cause lytic action on erythrocyte membranes. The amphipathic nature of saponins allows for compatible interaction between aglycone moiety of the molecule and inner membrane cholesterol molecules, whereas the hydrophilic sugar moiety freely binds to outer membrane proteins. The insertion of saponins into biomembrane structure affects its fluidity and function with resultant introduction of holes and pores, which elicits leaky cells and eventually cells death. Saponins-induced disturbances of membrane stability and functionality are non-specific and may affect wide range of organisms such as bacteria, fungi and even competing plants (Enneking and Wink, 2000). Logically, saponins-biomembrane interactions are considered to be a resistance/defense factor in legumes against microbial infections and herbivorous predators.

**Tannins:** Tannins or tannic acid are water-soluble polyphenols that are present in many plant foods (Chung *et al.*, 1998). Tannins are bitter astringent, condensed or hydrolysable polyphenolic compounds that bind to and precipitate proteins and other various organic compounds including amino acids and alkaloids (Bate-Smith, 1973; Kumar and Vaithyanathan, 1990; Makkar *et al.*, 1993; Tadele, 2015). The astringency of tannins is what causes the dry and pucker feeling in the mouth following the consumption of unripe fruits or red wine. Likewise, the degradation or modification, which is most probably, connected with increased polymerization of tannins with time plays an important role in the ripening of fruit and the aging of wine (Goldstein and Swain, 1963). Both *in vivo* and *in vitro* studies have revealed the antioxidant potentials of tannins (Okamura *et al.*, 1993; Hagerman *et al.*, 1998; Amarowicz *et al.*, 2000; Chung *et al.*, 1998; Yokozawa *et al.*, 2011). Using cyclic voltammetry, metmyoglobin assay and deoxyribose assay, Hagerman *et al.* (1998) reported that the redox potentials of condensed and hydrolyzable tannins were similar to those of structurally related simple phenolics. They further noted that the tannins were 15-30 times more effective at quenching peroxy radicals than simple phenolics or Trolox. Specifically, polygalloyl glucose reacted in an order of magnitude more quickly with hydroxyl radical than mannitol (Hagerman *et al.*, 1998).

According to Reed (1995), hydrolyzable tannins are polymers of gallic or ellagic acid esterified to a core molecule, commonly glucose or a polyphenol such as radical scavenging catechin (Fig. 7). Similarly, notable condensed tannins such as procyanidins, prodelphinidins, epicatechin, epigallocatechin polymers with galloylated procyanidin or prodelphinidin from leaves, twigs and stem bark of *Canarium album* as well as crude tannins of canola and rapeseed hulls showed a very

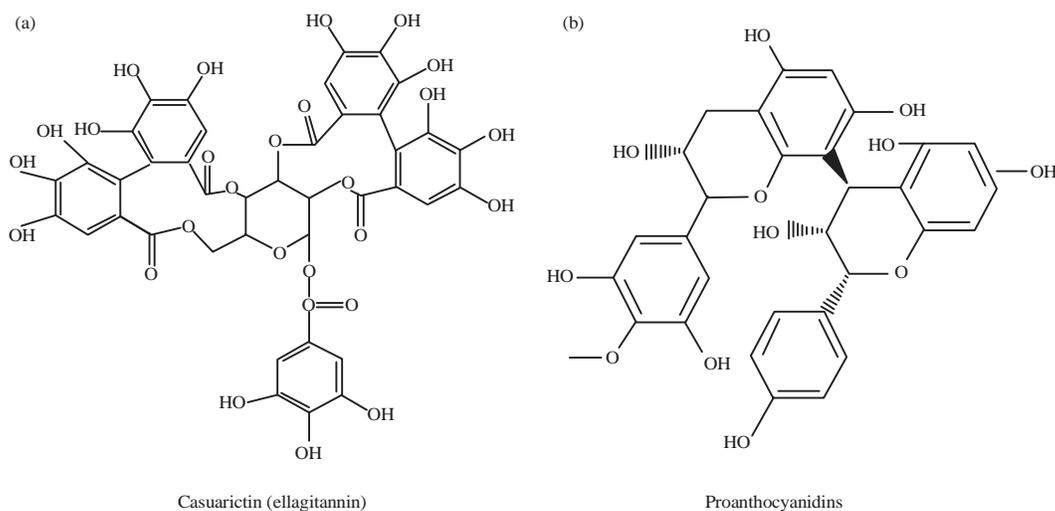


Fig. 7(a-b): Prototypes of (a) Hydrolyzable and (b) condensed tannins

good 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity and ferric reducing power (Amarowicz *et al.*, 2000). Also, proanthocyanidins (Fig. 7) from persimmon (*Diospyros kaki*), which is a known member of condensed tannins of specific group of polyphenolic compounds, exhibits powerful antioxidant activity in streptozotocin (STZ)-induced diabetic model rats and db/db Type II diabetic mice (Yokozawa *et al.*, 2011). Tannin supplements from *Ficus racemosa* attenuated oxidative stress engendered vascular tissue damage and ameliorated hyperglycemia and hyperlipidemia in streptozotocin-induced hypercholesteremia associated diabetic rats (Velayutham *et al.*, 2012). Overall, there appeared to be a relationship between the molecular configuration of tannins and their capacity to scavenge reactive oxidants. For instance, according to Hatano *et al.* (1988) the scavenging capacities of tannins having the ortho-trihydroxyl (pyrogallol) structure-(galloyl, hexahydrodiphenoyl (HHDP) groups in hydrolyzable tannins, galloyl group in acylated proanthocyanidins and the B-ring of some flavano-3-ol) were stronger than that of unacylated proanthocyanidins.

Using the hydroxyl radical scavenging activities by 2-deoxyribose oxidation system and salicylic acid system, superoxide anion scavenging activity and linoleic acid lipid peroxidation inhibition activity respectively, Gu *et al.* (2008) noted that high molecular weight condensed tannins {(epi)gallocatechin, epigallocatechin-3-O-gallate, epicatechin-3-O-gallate} are the major antioxidant composition in *D. kaki* pulp. Generally, tannins in certain fruits serve as a natural defense mechanism against microbial infections (Chung *et al.*, 1998). The mechanisms of anti-bacterial activity of tannins have been described (Scalbert, 1991). Likewise, proanthocyanidin polymers from *D. kaki* fruit exhibit anti-fungal properties as well as protective effect against diabetic oxidative stress with hyperlipidemia and anti-cancer activities (Yokozawa *et al.*, 2011; De Pascual-Teresa *et al.*, 2000; Santos-Buelga and Scalbert, 2000). Also, proanthocyanidins from *Pavetta owariensis* that are structurally similar with the proanthocyanidins A2 and cinnamtannin B1 and B2) have been shown to have anti-viral activity against herpes simplex virus (HSV) and coxsackie B virus (Balde *et al.*, 1990; Cushnie and Lamb, 2005).

Ingestion of tannin-rich grasses and agriculturally produced legumes and grains cause the precipitation of dietary proteins and gastrointestinal enzymes of herbivores and thereby reduce the digestibility and availability of proteins to the animal (Robbins *et al.*, 1987; Kumar and Vaithyanathan, 1990; Reed, 1995; Tadele, 2015). The anti-nutrient factor of tannins decreases

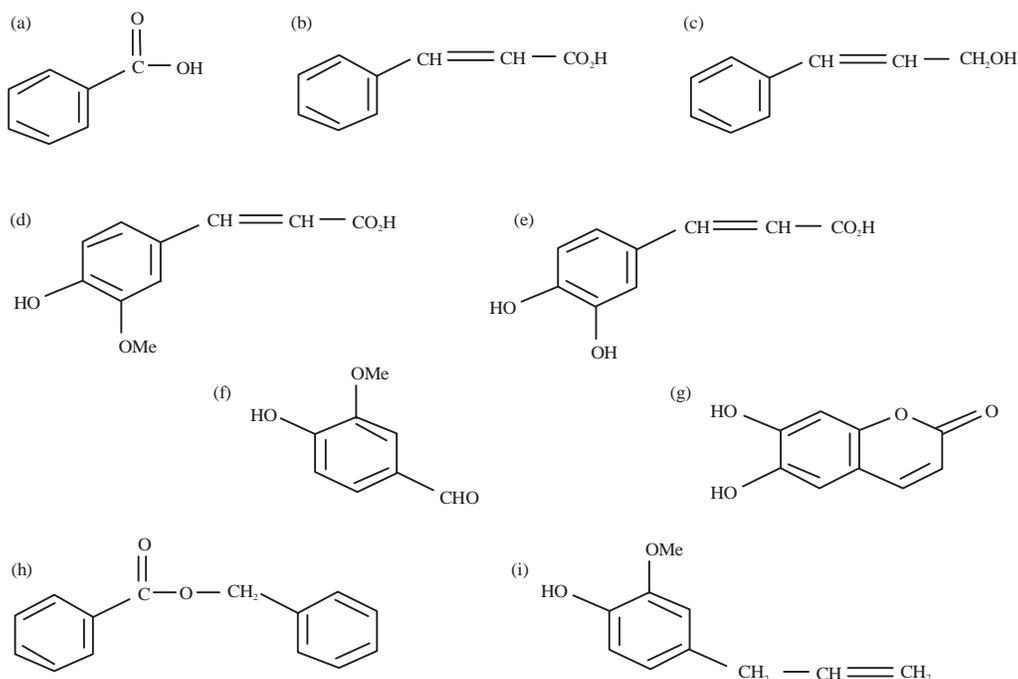


Fig. 8(a-i): Molecular structures of some phenols and phenolic acids (a) Benzoic acid (b) Cinnamic acid (c) Cinnamic alcohol (d) Ferulic acid (e) Caffeic acid (f) Vanillin (g) Esculetin (h) Benzyl benzoate and (i) Eugenol

feed intake, growth rate, feed efficiency, net metabolizable energy and protein digestibility in experimental animals (Chung *et al.*, 1998).

**Phenols and phenolic acids:** Phenolic compounds are generally synthesized via the shikimate pathway (Fig. 1). These bioactive principles are often associated with lignin as ester groups and are extracted either as components of alcohol insoluble fractions or bound to simple glycosides as alcohol soluble fractions (Liu, 2003; Ramawat *et al.*, 2009). Common phenolics among the angiosperms are p-hydroxyl-benzoic acids, protocatechuic acids, vanillic acid and syringic acid (Fig. 8).

Phenylpropanoids are phenolics, having a C<sub>6</sub>C<sub>3</sub> carbon skeleton (e.g. cinnamic acid, o-coumaric acid, p-coumaric acid, caffeic acid and ferulic acid), derived from shikimic acid pathway (Fig. 1) (Ramawat *et al.*, 2009). Additionally, simple phenylpropanoid forms conjugate with quinic acid to yield chlorogenic acid. Phenolic compounds having a C<sub>6</sub>C<sub>3</sub>C<sub>6</sub> carbon skeleton include flavonoids (including anthocyanins) and isoflavonoids (Ramawat *et al.*, 2009).

Polyphenolics from *T. cacao* exhibited anti-ulcer activity and modulated leukocyte function as exemplified by their ameliorative potentials against ethanol-induced gastric mucosal lesion in animal models (Osakabe *et al.*, 1998). There are claims by Kim *et al.* (2011) that regular or occasional consumption of polyphenol-rich cocoa exerts beneficial effects on blood pressure, increases cerebral blood flow and possibly, for treatment of dementia. According to Hu (2007) dietary polyphenolic supplementation exert desirable outcome in complementary therapy when ingested in large quantity. From the reports of Ranneh *et al.* (2013), experimental models confirmed that phenolics from *T. cacao* exhibited beneficial effects against platelet aggregation

(Steinberg *et al.*, 2003), high blood pressure (Buijsse *et al.*, 2006), atherosclerosis (Kurosawa *et al.*, 2005), hyperglycemia and hypercholesterolemia (Amin *et al.*, 2004; Ruzaidi *et al.*, 2005), inflammation (Selmi *et al.*, 2006), hepatocarcinogenesis (Amin *et al.*, 2004), DNA damage and clastogenic effect (Yamagishi *et al.*, 2001). Furthermore, flavonoids and polyphenol from *T. cacao* such as flavan-3-ols, epicatechin and catechin are potential inhibitors of pro-inflammatory mediators in tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )-sensitized Caco-2 cells *in vitro* and exhibited protective effect in colon cancer *in vivo* (Rodriguez-Ramiro *et al.*, 2013). Bioactive principles from *T. cacao* effectively down-regulated cyclo-oxygenase-2 and interleukin-8 (IL-8) as well as inducible nitric-oxide synthase activity by inhibiting Nuclear Factor (NF)- $\kappa$ B translocation and c-Jun N-terminal kinases (JNK) phosphorylation (Rodriguez-Ramiro *et al.*, 2013; Ranneh *et al.*, 2013). In another study, quercetin, the active phenolic component in kiwifruit, mediated by its free radical-scavenging activity, prevented hydrogen peroxide-induced inhibition of gap-junction intercellular communication in rat liver epithelial cells that is required for cell-cell communication in order to maintain homeostasis by facilitating direct exchanges of essential cellular metabolites and messengers less than 1-2 kDa (e.g., Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, cyclic AMP and ATP) (Kumar and Gilula, 1996; King and Bertram, 2005; Lee *et al.*, 2010). Additionally, quercetin possesses chemopreventive activity against azoxymethane-induced colonic tumorigenesis in mice and pre-neoplastic lesions in rat hepatocarcinogenesis (Lee *et al.*, 2010).

The nephrotoxicity associated with the use of anthraquinones from Rhubarb as laxatives has been successfully circumvented using rhubarb total free anthraquinone oral colon-specific drug delivery granules (RTFAOCDD-GN). The oral colon-specific drug delivery technology allowed anthraquinones to exert purgative effect devoid of intestinal absorption, which promoted their rapid excretion (Zhang *et al.*, 2015).

**Glycosides:** Glycosides are found in virtually every medicinal plant and have vast therapeutic efficacy and, certain cases, toxic effect depending on the plant of origin and the dose of plant product ingested. They are glycosylated bioactive principles in which the aglycone moieties are constituted of the alkaloids, vitamins, polyphenols, steroids, terpenoids or antibiotics etc. bound to a mono- or oligosaccharide or to uronic acid (Bernhoft, 2010). Glycobiology has revealed that the glycosidic residue is crucial for bioactivity; in other circumstances, glycosylation improves pharmacokinetic parameters and may serve as leads to the development of new and more active drugs, as typified by the recently developed antibiotics-vancomycin (Maneerat *et al.*, 2012). A precise overview of physiologic role of glycosyl residue in bioactive principles as well as the structure/activity relationship has been described (Kren and Martinkova, 2001). The most encountered glycosides of medicinal and toxicological importance are the vitamins glycosides, polyphenolic glycosides (anthraquinone glycosides), alkaloid glycosides, glycosides in the group of antibiotics (streptomycin), glycopeptides, cardiac glycosides, steroid and terpenoid glycosides, cyanogenic glycosides etc. (Obatomi and Bach, 1998; Enneking and Wink, 2000; Kren and Martinkova, 2001; Walsh, 2003; Prabhakar and Dobie, 2008; Tadele, 2015).

Anthraquinone glycosides are present in fairly limited distribution in plants. In traditional Chinese medicine, anthraquinone glycosides from *Rheum palmatum* (rhubarb) in the non-boiled form are administered when catharsis was the desired outcome (Yamagishi *et al.*, 1987; Zhang *et al.*, 2015). Aglycone anthraquinone are anti-fungal, impede renal tubular proliferation and ameliorate inflammations by partial inhibition of the cyclooxygenase pathway (Moroney *et al.*, 1988). Notable plants containing cardiac glycosides include: Dogbane (*Apocynum* sp.), Lily of the

Valley (*Convallaria* sp.), Foxglove (*Digitalis* sp.), Oleander (*Nerium oleander*), Yellow Oleander (*Thevetia* spp.) and Milkweeds (*Asclepias* sp.) (Bernhoft, 2010). Cardiac glycosides all contain steroids as the aglycone. Cardiac glycosides from foxglove (*Digitalis* sp.), *Rauwolfia caffra* sond, as well as lanoxin derivative from number of plants in low doses serve as medication for cardiac disorders in humans (Kumar *et al.*, 2011; Musabayane, 2012; Milugo *et al.*, 2013).

Persistent use or abuse of anthraquinone glycosides medications, beside its strong anti-bacterial, antioxidant and anti-diabetic activities, could elicit fluid and electrolyte loss, rhabdomyolysis, renal failure and acute hepatic failure (Vanderperren *et al.*, 2005; Yan *et al.*, 2006; Ghezala *et al.*, 2015). Cardiac glycosides derivatives of digitalis and strophanthus such as ouabain are notable inhibitor of Na<sup>+</sup>/K<sup>+</sup>-ATPase activity of biomembranes (Bender and Mayes, 2003; Kumar *et al.*, 2011). Similarly, cardiac glycosides have been linked with hyperkalaemia (Haden *et al.*, 2011). The diterpenoid glycosides or atractylosides and other analogues from *Coffea arabica* beans are naturally present in many plants of ethnomedicinal importance and animal grazing forage in Europe, Africa, South America and Asia. Fatal outcomes following the consumption of diterpenoid glycosides include renal proximal tubule necrosis and/or centrilobular hepatic necrosis in man and farm animals (Obatomi and Bach, 1998). Also, acute toxicity of diterpenoid glycosides is associated with competitive inhibition of adenine nucleoside carrier and thus blocks oxidative phosphorylation in isolated mitochondria cocktail (Obatomi and Bach, 1998). By their chemical nature, cyanogenic glycosides are  $\beta$ -linked glycosides of  $\alpha$ -hydroxynitriles. Cyanogenic glycosides are biosynthesized from at least 2, 650 species of plants (FSANZ, 2004). The L-amino acids are biosynthetic precursors of the cyanogenic glycosides. According to Vetter (2000) the amino acids are first hydroxylated to yield N-hydroxylamino acids, which are converted to aldoximes and subsequently to nitriles. Next, the hydroxylation of nitriles yields  $\alpha$ -hydroxynitriles, which are then glycosylated to yield cyanogenic glycosides. Consumption of cyanogenic glycosides containing plants results to the release of hydrogen cyanide into systemic circulation, which inactivates cytochrome oxidase in the mitochondrial electron transport chain of cells and thereby engenders decreased utilization of oxygen in peripheral tissues. Long-term exposure to cyanide toxicity causes upper motor neuron characterized by irreversible paralytic disorder, tropical ataxic neuropathy, optical atrophy, angular stomatitis; sensory gait ataxia; and neurosensory deafness, goitre and cretinism. Cyanogenic glycosides are present in species of *Rosaceae* (rose family) in particular in *Prunus* spp., cassava (*Manihot esculanta* Crantz), Cherry (*Prunus cerasus*), as well as other *Prunus* species such as peach (*Prunus persica*), plum (*Prunus domestica*), almond (*Prunus dulcis*) and apricot (*Prunus armeniaca*) (FSANZ, 2004; Bernhoft, 2010; Brimer, 2010). Some notable cyanogenic glycosides present in edible parts of plants include: amygdalin (almonds), dhurrin (sorghum), linamarin (cassava, lima beans), lotaustralin (cassava, lima beans), prunasin (stone fruit) and taxiphyllin (bamboo shoots) (FSANZ, 2004).

**Terpenoids:** Terpenoids are derived from five carbon isoprene units that are assembled in numerous combinations to generate vast arrays of terpene derivatives, collectively referred to as isoprenoids. Most terpenoids are present in the glycosidic form rather than the non-polar or low polarity terpene aglycone form (Attard and Pacioni, 2012). The terpenoids encompasses other classes of bioactive principles in diverse collections of plants. Notable examples include: mono- and sesquiterpene volatile derivatives from *Antirrhinum tortuosum* (Nagegowda *et al.*, 2008), mono- and sesquiterpenes from *Phlomis fruticosa* (Amor *et al.*, 2009), saponins and sapogenins from *Asparagus aphyllus* (Shao *et al.*, 1996), sesquiterpene lactones from *Palaeocyanus crassifolius* (Koukoulitsa *et al.*, 2002) tetraterpene carotenoids from *Arum italicum* (Bonora *et al.*, 2000),

triterpenoids from *Olea europaea* (Caputo *et al.*, 1974; Elamrani, 2011) and  $\beta$ -sitosterol; a triterpene-like compound from *Acanthus mollis* (Loukis and Philianos, 1980) that exhibits plasma cholesterol lowering properties.

Studies have shown that the terpenoids possesses anti-microbial, anti-fungal, anti-parasitic, anti-viral, anti-allergenic, anti-spasmodic, anti-hyperglycemic, anti-inflammatory and immune modulatory properties (Wagner and Elmadfa, 2003; Rabi and Bishayee, 2009; Kumar *et al.*, 2011). Although early experimental data showed that the most common terpenes (D-limonene) caused increased incidence of renal tubular tumors in male rats, no evidence of any tumor was observed in female rats and mice of both sexes (Sun, 2007). Further evidence from a phase I clinical trial demonstrated that a patient with breast cancer showed a partial response to the chemopreventive activity of D-limonene. Additionally, D-limonene has been used clinically to dissolve cholesterol-containing gallstones and alleviation of gastroesophageal reflux (GERD) (Sun, 2007).

**Coumarins:** The coumarins display molecular/pharmacological diversities and are natural compounds found in diverse plant sources in the form of benzo[a]pyrene derivatives. Aside the medicinal properties of the coumarins, it's the first synthetic substance to be used as fragrance and aroma present in essential oils and industrially processed food products (Karayil *et al.*, 2014). Some naturally occurring coumarin derivatives include umbelliferone (7-hydroxycoumarin), aesculetin (6, 7-dihydroxycoumarin), herniarin (7-methoxycoumarin), psoralen and imperatorin. Other notable coumarins are presented in Fig. 9.

The coumarins are antimicrobial, anti-inflammatory (Sardari *et al.*, 2000; Theis and Lerdau, 2003; Khan *et al.*, 2005), antioxidant (Sardari *et al.*, 2000; Hamauzu *et al.*, 2005; Aqil *et al.*, 2006; Jain *et al.*, 2011; Patel and Patel, 2011; Prabakaran and Ashokkumar, 2013; Matos *et al.*, 2015), anti-diabetic (Patel *et al.*, 2012; Prabakaran and Ashokkumar, 2013), hepatoprotective (Prabakaran and Ashokkumar, 2013), anti-thrombotic (Sardari *et al.*, 2000; Binks and Davies, 2007; Jain *et al.*, 2011), anti-fungal (Sardari *et al.*, 2000; Khan *et al.*, 2005), anti-viral (Hamauzu *et al.*, 2005), analgesic (Khan *et al.*, 2005) and anti-carcinogenic (Marshall *et al.*, 1989; Liu, 2003; Thati *et al.*, 2007) agents.

Coumarin poisoning following exposures to coumatetralyl and subsequent development of elevated international normalized ratio (INR>9.5) and partial thromboplastin time (PTT = 83 s) have been described (Kay *et al.*, 2011). Coumarins poisoning is mostly as a result of inhibition of post-translational carboxylation of several blood clotting factors (Binks and Davies, 2007).

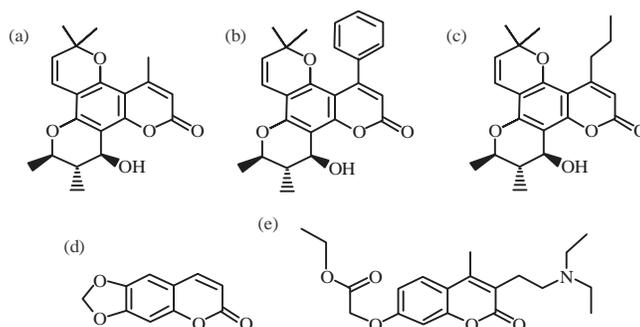


Fig. 9(a-e): Some natural bioactive coumarins (a) (+)-cordatolida A (b) (+)-inophyllum B (c) (+)-calanolide A (d) Ayapin and (e) Carbochromen

## CONCLUSION

Plant materials are composed of vast array of bioactive principles of which their isolation, identification and characterization for analytical evaluation requires expertise with cutting edge analytical protocols and instrumentations. Bioactive principles are responsible for the therapeutic activities of medicinal plants and provide unlimited opportunities for new drug leads because of their unmatched availability and chemical diversity. For the most part, the beneficial or toxic outcomes of standardized plant extracts depend on the chemical peculiarities of the containing bioactive principles. The main objective of this review has been to emphasize that whereas bioactive principles display therapeutic benefits and have served as leads to the development of new drugs, studies have also shown that bioactive principles exhibit toxic outcomes; depending on the their sources, molecular and chemical peculiarities.

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