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Polyphenols: Phytochemistry and health benefits

Sonali Kulasari, Mamta F Singh and Shradha Bhandari

Abstract
Phenolic compounds are the phytoconstituents from plants with diverse chemical properties and bioactivities. Since the ancient time polyphenols compounds are widely used in Indian medicine system due to their health benefits. The phenolic compounds are subdivided into five major classes, phenolic acids, flavonoids, tannins, lignans, and coumarins. Phenolic acids are the derivative of esters and glycosides which is associated with flavonoid, alcohols, hydroxy fatty acids, sterols, and glucosides. flavonoids are a group of bioactive compounds which includes flavonols, flavones, flavanones, flavonoid glycosides isoflavones, and anthocyanins. Tannins are the secondary metabolites which have an activity to precipitate protein. Lignans and coumarins are one of the most important groups of plant secondary metabolites. The phenolic compounds show various pharmacological activities such as anti-inflammatory activity (Vanillic acid, and catechin), anti-asthmatic activity (Protocatechuic acids), antidiabetic activity (Cinnamic acid), and cardioprotective activity (Daidzein). This review addresses the introduction of phenolic compounds, their classifications, chemical structure, and pharmacological activities.

Keywords: Phytoconstituents, bioactivites, polyphenols, precipitate

Introduction
Phenolic compounds are the diverse group of phytochemicals which are expanded in the plant kingdom. These are plants secondary metabolites containing an aromatic ring substituted with hydroxyl groups [1]. Additionally, 8,000 phenolic structures have been believed to present in plant kingdom which is categorized according to simple low- molecular weight compounds to large complex tannins and polyphenols [2]. Phenolic compounds are synthesized by two metabolic pathway: the shikimic acid pathway and the acetic pathway. In shikimic acid, pathway phenylpropanoids are formed whereas in acetic acid pathway simple phenols are formed. The junction of this pathway leads to the formation of flavonoids and after the condensation process, non-hydrolysable tannins are formed. Phenolics compounds are present in the bound form with sugars (Glycoside residue) and proteins inside the cell vacuoles. In free form, they are toxic in nature [3]. The biochemist explains that the phenol makes a complex structure with protein by hydrogen bonding. During the isolation process, the phenolic content decreases. Phenols are very sensitive to enzymatic oxidation thus the extraction with boiling alcohol may limit the enzymatic oxidation [4]. The dietary phenolic compounds include flavonoids, phenolic acids, and polyphenols which shows various pharmacological activity

Phenolic compounds show various function in plants such as
1. Show the defense mechanism for herbivores and pathogens [5].
2. Attract pollinators and fruit dispersers [5].
3. Reduce the growth of nearby competing plants [5].
4. Involves in plants sensorial properties like color, aroma, taste, and astringency [3].
5. Responsible for the germinating process of seed after harvesting and growth as well as development and reproduction [3].

Classification
The classification of phenolic compounds is determined by a large number of heterogeneous structures which covers the area of simple molecules to higher polymerized compounds [3]. According to the circulation in nature, phenolic compounds are categorized into three classes:
1. ***Shortly distributed*** includes simple phenols, pyrocatechol, hydroquinone, resorcinol, and aldehyde derived benzoic acid.
2. ***Widely distributed*** includes flavonoids and their derivatives, coumarin and phenolic acids such as benzoic acid and cinnamic acid and their derivatives.
3. ***Polymers*** include tannins and lignin [6].

According to the presence of the phenolic compound in plants as a free or bound state, they are classified as

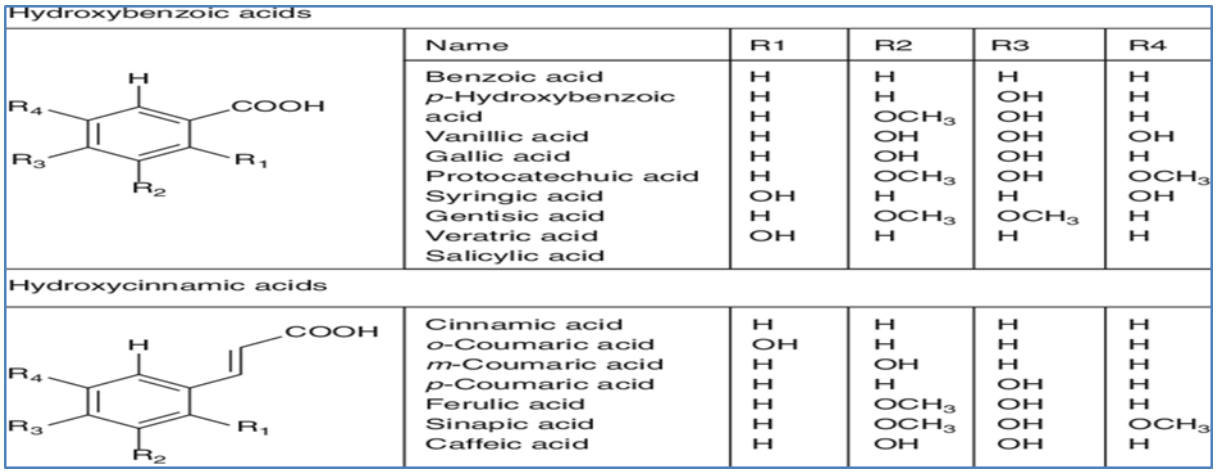
1. ***Soluble compounds*** include simple phenols, flavonoids, and tannins of low molecular weight which is not bound to membrane compounds.
2. ***Insoluble compounds*** include condensed tannins, phenolic acids and low molecular weight compound which is bound to cell wall polysaccharides or protein [3].

Due to the presence of a carbon chain in phenolic compounds, they can be divided into 16 important classes. The main classes include phenol and phenolic acids, flavonoids, tannins, lignans, and coumarins [3, 4].

Main classes of phenolic compounds

Phenol and phenolic acids

Phenolic acids are derivative of esters and glycosides which is associated with flavonoid, alcohols, hydroxy fatty acids, sterols, and glucosides [7]. Due to the presence of phenols with the carboxylic acid, it is named as phenolic acids [8]. Phenolic acids comprise two types of broadly distributed hydroxybenzoic acid and hydroxycinnamic acids. In which hydroxycinnamic acid formed simple esters with glucose or hydroxyl carboxylic acid [7]. Phenolic compounds contain carbon chain at the lateral side of the ring which divided it into C6-C3, C6-C2, and C6-C1 compounds. C6-C3 compounds are derived from hydroxycinnamic acids and C6-C1 compounds are derived from hydroxybenzoic acids [8].



Hydroxybenzoic acids

Name	R1	R2	R3	R4
Benzoic acid	H	H	H	H
p-Hydroxybenzoic acid	H	H	OH	H
Vanillic acid	H	OCH_3	OH	H
Gallic acid	H	OH	OH	OH
Protocatechuic acid	H	OH	OH	H
Syringic acid	H	OCH_3	OH	OCH_3
Gentisic acid	OH	H	H	OH
Veratric acid	H	OCH_3	OCH_3	H
Salicylic acid	OH	H	H	H

Hydroxycinnamic acids

Cinnamic acid	H	H	H	H
o-Coumaric acid	OH	H	H	H
m-Coumaric acid	H	OH	H	H
p-Coumaric acid	H	H	OH	H
Ferulic acid	H	OCH_3	OH	H
Sinapic acid	H	OCH_3	OH	OCH_3
Caffeic acid	H	OH	OH	H

Fig 1.1: Substitution in hydroxybenzic acids and hydroxycinnamic acids.

Table 1: The Pharmacological activity of Phenolic acids

Hydroxybenzoic acids	Pharmacological activity	Mechanism of action
P-hydroxybenzoic acid	As Antisickling Agent	P-hydroxy benzoic acid prevent the polymerization of sickle Hb which is monitored by UV spectrophotometer. It also exerts analgesic as well as anti-inflammatory action [9]
Vanillic acid	Anti-inflammatory and immune supressant	vanillic acid significantly suppressed the expression of cyclooxygenase-2 and the activation of transcription nuclear factor-kappaB p65 in DSStreated colon tissues [10]
Protocatechuic acids	Neurological activity	PCA inhibited the cytotoxicity, apoptotic morphology, reduction of TH expression and abnormal oligomerization of α-synuclein in PC12 cells [11]
Cinnamic acid	Antidiabetic activity	Cinnamic acid shows insulin secreting activity due to the presence of p-hydroxy and m-methoxy group in the ring. Also responsible for the release of insulin from the beta-cells [12]
Sinapic acid	Anxiolytic activity	Sinapic acid might act like the agonist of a specific gamma-aminobutyric acid (GABA) receptor (ligand-gated ion channel: GABAA). It was found that sianpic acid was the most effective at a dose of 4 mg/kg. It was concluded that the anxiolytic-like effects of sinapic acid are mediated via GABAA receptors and potentiating Cl− currents [13]

Flavonoids

Flavonoids are a group of bioactive compounds which are secondary metabolites of plants. Flavonoids are active in many ways and their subcellular interaction shows multiple activities in microbes, plants, and animals [14]. They protect the plant from harmful UV radiation, also control the gene expression and shows antioxidant, antiviral and antibacterial action [15]. Synthesis of flavonoids occurs in every part of the plants which is responsible for color, fragrance, and taste of fruits, flowers, and seeds [16]. These yellow and white plant pigments show various health benefits and were reported as 'phytoalexin' [17].

The basic structure of flavonoid is 2-phenlybenzopyrone, in which the three- carbon bridge between the phenyl groups is commonly cyclized with oxygen [18]. These are polyphenolic compounds present in both free aglycones state and respective glycosides [19]. The solubility of flavonoids is more in water and alcohol, but less in organic solvents. When they interact with the alkalis, they show a yellow color and with acid become colorless [19]. The glycosylation increases the polar characteristic of flavonoid and increases the water solubility [18]. The three molecules of malonyl-CoA and one molecule of p-coumaroyl-CoA condensed together and produce chalcone, which is catalyzed by chalcone synthase. Chalcone isomerase enzyme isomerizes the chalcone into flavanone and starts the synthesis of different classes of flavonoids including aurones, dihydrochalcones, flavonols, isoflavones, flavones, flavonols, leucoanthocyanidins, anthocyanins, and proanthocyanidins [18]. In 1938, Hungarian Physiologist Albert Szent studied about the flavonoid activity. He reported the citrus peel flavonoid having a preventive action against capillary bleeding and fragility [20].

Table 2: Flavonoids classification:

Classes of flavonoids	Examples
Flavonols	Quercetin, Kaempferol, Myricetin and Fisetin
Flavones	Luteolin, Apigenin
Flavanones	Hesperetin, Naringenin
Flavonoid glycosides	Astragalin, Rutin
Flavonolignans	Silibnin
Isoflavones	Genistein, Daidzein
Anthocynidins	Cyanidin, Delphinidin
Aurones	Leptosidin, Aureusidin
Leucoanthocyanidins	Teracacidin
Neoflavonoids	Coutareagenin, Dalbergin

Flavonols

Flavonols are the subclasses of flavonoids, found in high concentration in a variety of plants. The activity of flavonols changes because of the impact of light, maturity, degree of ripeness and processing. The food containing flavonols are apples, apricots, beans, broad beans, broccoli [21].

Chemistry of flavonols

The structure of flavonols consists of C15 flavone nucleus. One oxygen-containing pyrone ring is connected to two benzene rings (Ring A and ring B). In flavonol molecules, the double bond is present between position 2 and 3, and oxygen in position 4 of the carbon ring. The majority of flavonols are present as O-glycosides and very rarely as C-glycosides. The basic structure of flavonol is 3-hydroxyflavone. Flavonols increase the activity of erythrocyte superoxide dismutase and also increases plasma antioxidant activity [20, 22, 23].

Table 3: Principle structure of flavonols

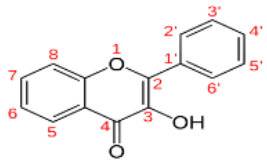
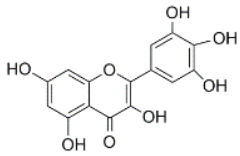
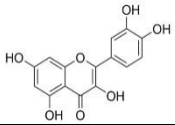
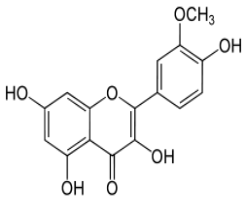
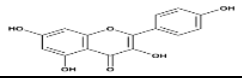
Flavonols		Myricetin	
Quercetin		Isorhamnetin	
Kaemferol			

Table 4: The Pharmacological activity of Flavonols

Flavonols	Pharmacological action	Mechanism of action
Quercetin	Direct free radical scavenging action	Quercetin acting as free radical scavengers was shown to exert a protective effect in reperfusion ischemic tissue damage. One way is the direct scavenging of free radicals. By scavenging free radicals, Quercetin prevent LDL oxidation. This action protects against atherosclerosis [24]
Kaemferol	Antiaging activity	kaempferol might increase the proliferative potential of keratinocytes by regulating ECM proteins such as integrin α6 and integrin β1. Manipulation in cell ECM interation can control the skin disease [25]
Myricetin	Protective effect in CNS Disorders	The compound is known to have protective effects against the progression of Parkinson's disease (PD) and Alzheimer's disease (AD).The protective effects of myricetin stem from the effect of the compound against specific proteins, known as tau proteins, which are abundant in the distal portions of axons and serve to provideflexibility and stability to microtubules. Myricetin was found to produce an anti-tau effect at a concentration of 50micrometer in HeLa-C3 cells [26]
Isorhamnetin	Cardio protective activity	Isorhamnetin prevents endothelial dysfunction, superoxide production, and over expression of p47phox induced by angiotensin II in rat aorta1.Isorhamnetin has a tremendous protective effects on cardiomyocytes against anoxia/reoxygenation-induced injury is mediated by SIRT1likewise in vivo and in vitro studies give a sufficient report of isorhamnetin has cardiotoxicity against doxorubicin as an inducerin another case isorhamnetin attenuates atherosclerosis by inhibiting macrophage apoptosisvia PI3K/AKT activation and HO-1 induction [27]

Flavones

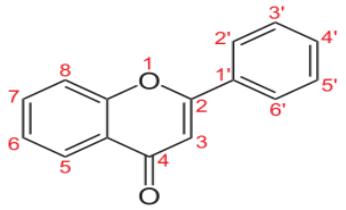
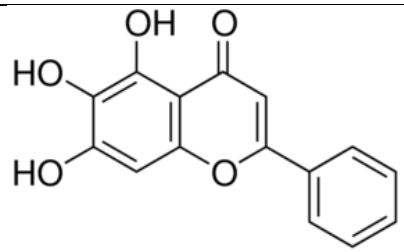
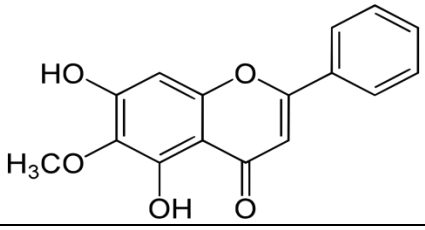
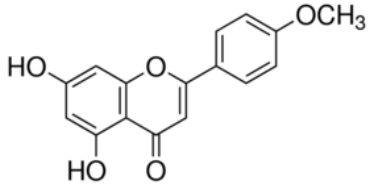
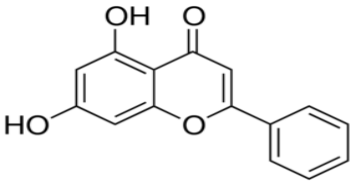
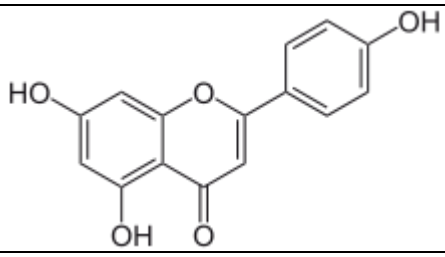
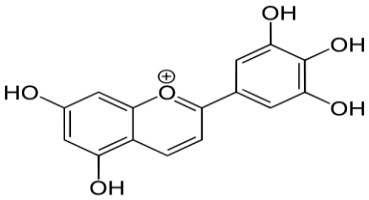
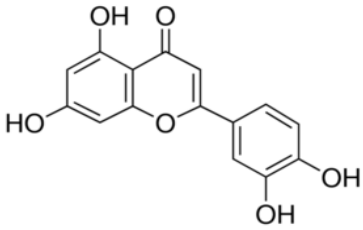
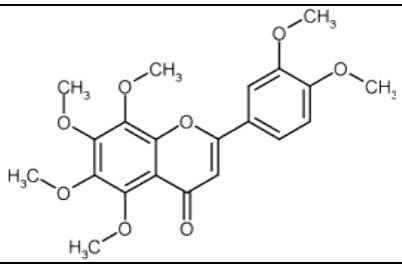
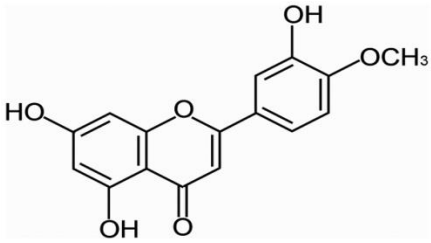
Flavones are yellow pigments which are essential components of human diets [28]. They are widely distributed in plants in a free state or associated with glycosides and tannins [29]. The oxidases enzymes catalyzed flavonones and produce flavones. The cytochrome p-450 dependent monooxygenase enzyme system designated flavones synthase 2nd catalyzed flavones formulation [30].

Chemistry of flavones

Flavones contain a backbone of 2-phenylchromen-4-one with three ring skeleton structure of C_6-C_3-C_6. The molecular formula of flavones is $C_{15}H_{10}O_2$. The ring consists of three functional groups including hydroxyl, carbonyl, and conjugated double bond. These crystalline substances are soluble in water and ethanol [31].

Structure of principle flavones

Table 5: Principle chemical structure of Flavones

Flavones		Baicalein	
Oroxylin A		Acacetin	
Chrysin		Apigenin	
Tricetinidin		Luteolin	
Nobiletin		Diosmetin	

Pharmacological activity of flavones

Table 6: Pharmacological activity of Flavones and their mechanism of action

Flavones	Pharmacological activity	Mechanism of action
Oroxylin A	Anti-inflammatory effect	Oroxylin A induces estrogen-responsive gene expression and promoter activity. In macrophages, Oroxylin A treatment significantly attenuates lipopolysaccharide (LPS)-induced but not basal inflammatory response, including nitric oxide (NO)production and the expression of inflammatory mediators (i.e., iNOS and COX-2) and cytokines (i.e., TNF-α, IL-1β,and IL-6), in an estrogen receptor (ER)-dependent manner. Oroxylin A is a novel phytoestrogen and exhibits anti-inflammatory effects that are mediated by ER activity [32]
Chrysin	Anti-depressant effects	The therapeutic role of chrysin as antidepressant compound has been previously assessed using animals subjected to chronic unpredictable mild stress (CUMS). Oral treatment with chrysin (20 mg/kg) attenuated the decrease in BDNF and NGF (nerve groeth factor) levels in mice subjectedto CUMS, comparable to fluoxetine. Chrysin also attenuated the increase in glutathione reductase (GR), glutathione peroxidise (GPx) and catalase (CAT) activities in mice exposed to CUMS. This suggests that the upregulation of BDNF and NGF, together with the potent antioxidant function of chrysin, is theprimary mechanism to explain the anti-depressant effect of chrysinin vivo [33]
Baicalein	Anti-inflammatory activity	When the cornea is injured, platelet-activating factor (PAF),a lipid inflammatory mediator is accumulated as a response, with lyso-PAF acetyltransferase acting as a vital enzyme in the final key step of PAF synthesis. In bovine corneal epithelium,baicalein effectively inhibited lyso-PAF acetyltransferase, without the participation of the lipoxygenase (LOX) pathway. Since PAF was reported to also delay the corneal wound healing process,45 baicalein-induced inhibition of PAF production may be beneficial in cornea repair [34]

Apigenin	Effect on cardiovascular system	Apigenin may protect the vascular endotheliumvia the increment of nitric oxide level in the aorta, andit possesses the direct reduction of blood pressure via the inhibition of angiotensin-conventing enzyme activityand improvement of cardiac hypertrophy. Apigenin can reduce the expressions of cell adhesion molecules, including vascular cell adhesion molecule-1 and E-selectin in oxidized LDL-stimulated human umbilical vein endothelial cells. Apigenin can also decrease the atherogenesis via theinduction of macrophage apoptosis in ApoE(–/–) mice, which leads tothe reduction of inflammatory cytokines, such as tumor necrosisfactor-a (TNF-a), interleukin (IL)21b, and IL-6 [35]
Luteolin	Nutritional and Inflammatory Disorders	Luteolin inhibits NF-kappa B activity at concentrations in the low micro molar range that increases the expression of pro inflammatorycytokines, chemokines and enzymes (e.g. TNF, IL-1, IL-6, IL8, COX-2, iNOS).The enzymes cyclooxygenases (COX), lipoxygenases (LOX) and inducible nitric oxide synthase (iNOS) are known to play importantroles in inflammation by participating in the synthesis of eicosanoids (e.g. prostaglandins, leukotrienes) and in the production ofreactive species. Some reports have shown that luteolin can inhibit COX-2, LOX and iNOS. The inhibitory effects of luteolin on thesepro-inflammatory enzymes may contribute to its anti-inflammatory activity. Luteolin have abilities to inhibit enzymes for the synthesis of thromboxane B2 and leukotriene B4 as well as hydrogen peroxide scavengingactivity. Luteolin exhibited a high inhibitory activity against both thromboxane and leukotriene synthesis [36]

Isoflavones

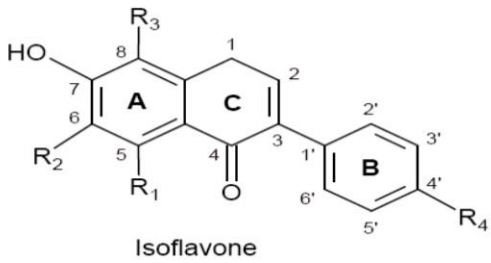
Isoflavones are well-known phytoestrogens their oestrogenic activity was recognized in the 1940s when the sheep suffered from infertility by grazing *Trifolium subterraneum*. Naturally found isoflavones having strong estrogenic activity are the aglycones, genistein, daidzin, and glycones. Most isoflavones are biologically inactive from when the colonic bacterial metabolize them, which remove the sugar moiety. Isoflavones are non-steroidal, diphenolic structures that have the ability to bind estrogen receptors (Alpha and beta). Isoflavones content of soy protein preparations can vary widely and is affected by production techniques. Daidzein and genistein are the main soy isoflavones. Kudzu root is used in some dietary supplements, also contains an appreciable amount of daidzein. Genistein and daidzein have a similar structure to estrogen and they mimic the activity of estrogen by binding with estrogen receptors [37].

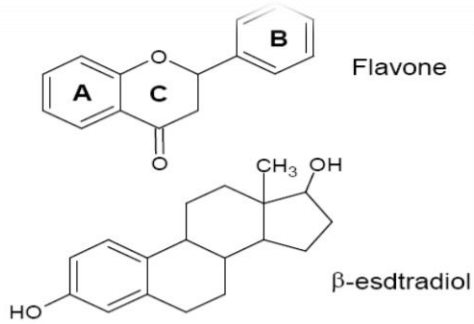
Very early, in the premature phase of the research in this field of study, it became obvious that isoflavones were less potent than endogenous and synthetic hormones but it also became obvious that they had few side effects [38, 39].

Chemistry of isoflavones

Isoflavones are a group of flavonoids where the B ring attachés to the C ring at the position third and have a similar structure to 17-beta-estradiol. Aglycone shows different structure from isoflavones due to their arrangements of the substituent. The hydroxyl group of 7th position binds to one molecule of glucose and form 7-O-glucoside of isoflavone. In plant acetyl glycosides and malonyl, glycosides are present [40].

If the parent isoflavone X_1 and X_2 are substituted with hydroxyl group this lead to the formation of genistein and if X_1 and X_2 are substituted with one molecule of the hydroxyl group and hydrogen group this lead to form daidzein [41].





Compound	R1	R2	R3	R4	Substitution
Daidzein	H	H	H	OH	7,4'-$(OH)_2$
Genistein	OH	H	H	OH	5,7,4'-$(OH)_3$
Glycitein	H	OCH_3	H	OH	7,4'-$(OH)_2$, 6-OCH_3
Formononetin	H	H	H	OCH_3	7-OH, 4'-OCH_3
Biochanin A	OH	H	H	OCH_3	5,7-$(OH)_2$, 4'-OCH_3

Fig 1.2: Substitution in parent isoflavone lead to formation of sub isoflavone compounds

The pharmacological activity of isoflavones

Table 7: Pharmacological activity of Isoflavones and their mechanism of action

Isoflavones	Disorder	Pharmacological activity	Mechanism of action
Daidzein	Menopausal health	Anti-Cardiovascular Diseases	Daidzein exhibited anestrogen-like effect on endothelium-dependent vasorelaxation and inhibited caveolin-1 leading to an increase in nitric oxide bioavailability and as a result, daidzein improved endothelium dysfunction [42]
		Neuroprotective	Reduces the oxidative stress of hippocampal neurons, generated by glutamate and beta-amyloid. Decrease the expression of caspase-3 in the hippocampus and cortex lead to decrease neurotoxicity [43]
Genistein		Bone disease	Genistein interact with ER-beta in osteoblast and inhibit the tyrosine kinase activity which leads to decrease the cell growth and acid transport in bone cells, hence prevent the osteoclast activity [44]
		CVS effect	Enhances the lipolysis and reduces lipogenesis by increasing the hepatic expression of apoprotein –E. Also inhibits the activity of lipoprotein lipase activity [45]
		Cognitive effect	Increases the growth of nerve growth factor in the hippocampus. Which enhances the production of acetylcholine in the hippocampus, hence improve the learning and memory [46]
		Vasomotor effects	Reduces the hot flashes in postmenopausal women [47]

Flavan-3-ols

Flavan-3-ols are active biomolecules containing monomeric and polymeric compounds and show a significant role for human health [48]. They are also known as proanthocyanidins with having the capability to defend the body from the pathogens. This antioxidative molecule inhibits the effect of free radicals and reactive oxygen species [49]. According to the recent studies chocolate and flavan-3-ols have anti-oxidant, anti-thrombotic and anti-inflammatory effect thus shows a positive effect on human health. Other studies project their beneficial effect on cardiovascular diseases such as metabolic disorders [50].

Chemistry of flavan-3-ols

Flavan-3-ols are the type of flavonoids which contain C6-C3-C6 skeleton. These structurally complex compounds classified as monomers (catechin and epicatechin), oligomers (decamers) and polymers(>10mers) [51]. 2,3-trans-(+)-catechin or 2,3-cis-(–)-epicatechin are structurally different compound due to the presence of asymmetric carbon on C-ring. Flavan-3-ols contains two chiral centers and during hydroxylation, they bring out four isomers. The two isomers of flavan-3-ols (+)-C(17) and (-)-EC(20) are present in higher amount in nature whereas (-)-C (18) and (+)-EC(19) are present in the lower amount [52]. The C4 position at flavan-3-ol contain the extender unit and the C8 position contains terminal units, hence they formed proanthocynidins [53]. Due to the alteration in heterocyclic ring, catechins are classified into two groups as free catechins includes: (+)-catechin, (+)-gallocatechin, (-)-epicatechin and (-)-epigallocatechin, as well as galloyl catechins: (-)-epicatechingallate, (-)-epigallocatechin gallate and (-)-gallocatechingallate [54].

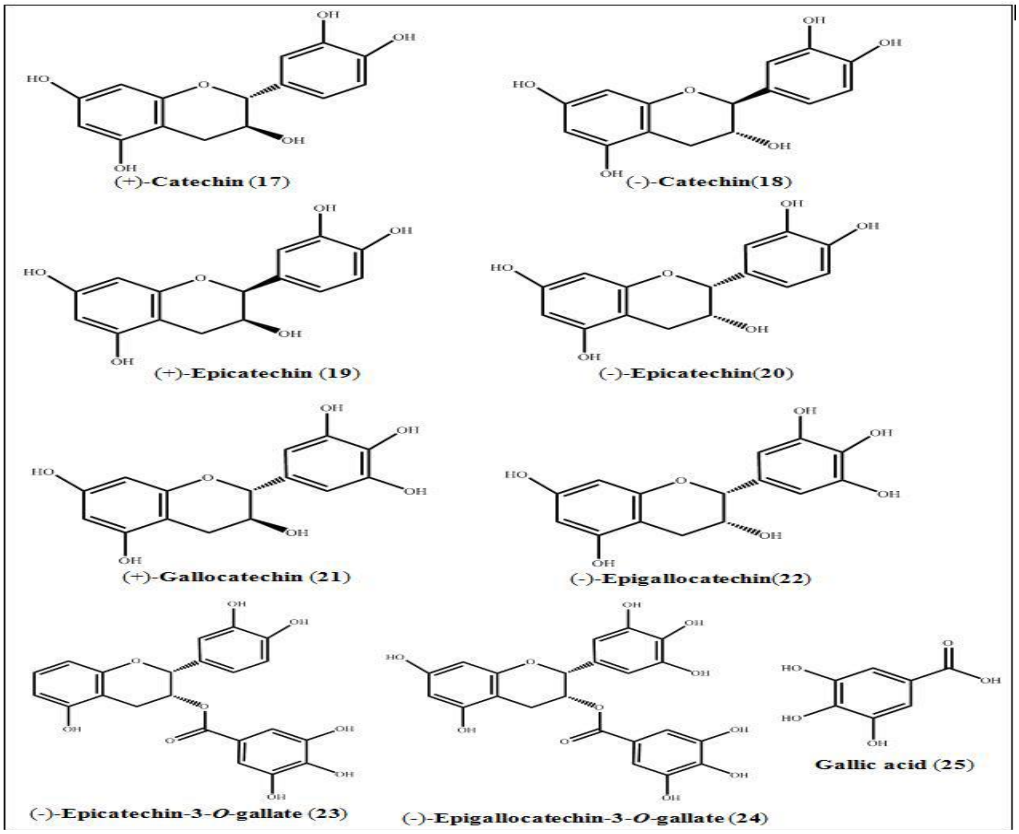


Fig 1.3: Different chemical structure of flavan-3-ols

The pharmacological activity of flavan-3-ols

Table 8: Pharmacological activity of Flavan-3-ols and their mechanism of actions

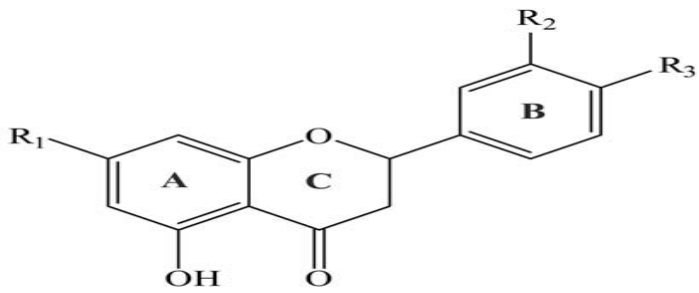
Flavan-3-ols	Pharmacological activity	Mechanism of action
Catechin	Anti-inflammatory and respiratory protective	It has been reported that the polyphenolic agent catechin is a potent inhibitor of STAT-1 phosphorylation and activation. The JAK/STAT pathway has been shown to be essential for human and murine iNOS expression and in ICAM-1 induction responsible for the pleural injury. Catechins down regulate STAT-1 action reducing pulmonary injury caused by lung inflammation [55]
Epicatechin	Antiviral activity	Epicatechin inhibited expression of viral protein12 and host factors of Epstein-Barr virus. Epicatechin was shown to agglutinate influenza viruses, thus preventing it from absorbing to Mardin-Darby canine kidney (MDCK) cells. Hence, reduced the infectivity of influenza virus. This was an in vitro study. Green tea extract had aninhibitory effect on the acidification of intracellular compartments such as endosomes and lysosomes, resulting in inhibition of growth in influenza virus [56]

Flavanones

Flavanones are the aromatic ketones with molecular weight $C_{15}H_{12}O_2$ which presents in the plant as glycosidic form. These colorless ketones are produced by flavones [57]. Flavanones show a number of biological activities in animal models. They inhibit cell proliferation and angiogenesis, reduce cholesterol, and triglycerides, scavenge free radicals, show estrogenic activity, modulate nitric oxide (NO) level, and decrease platelet aggregation and lymphocyte immobilization [58]. As a part of flavonoid, flavanone was not concerned in past decades, like chalcones, dihydrochalcones, dihydroflavonols, and aurones. Now the number of flavanones has been increased up to 350 flavanone aglycones and 100 flavanone glycosides [59].

Chemistry of flavanones

Flavanones are one of the main classes of flavonoids, with 350 aglycones and 100 glycosylated forms identified so far. Their structure is based on the generic structure of flavonoids, a flavan nucleus formed of two aromatic rings (A and B) linked through a dihydropyrone ring (C). The lack of a C2–C3 double bond, the presence of a chiral carbon atom at the C2 position and the lack of substitution at the C3 position of the C ring mark the structural differences characterizing flavanones as separate from the other two classes of flavonoids present in Citrus, flavones, and flavanols. The latter group encompasses an array of compounds with a sugar moiety bound to the aglycone hydroxyl groups through the formation of an O-glycosidic linkage, most commonly found at the C-7 position (A ring) [59].



Structure assignment	R_1	R_2	R_3
Naringenin	OH	H	OH
Hesperetin	OH	OH	OMe
Isosakuranetin	OH	H	OMe
Eriodictyol	OH	OH	OH
Narirutin (Naringenin 7-*O*-rutinoside)	*O*-Ru[a]	H	OH
Naringin (Naringenin 7-*O*-neohesperidoside)	*O*-Nh[b]	H	OH
Hesperidin (Hesperetin 7-*O*-rutinoside)	*O*-Ru[a]	OH	OMe
Neohesperidin (Hesperetin 7-*O*-neohesperidoside)	*O*-Nh[b]	OH	OMe
Didymin or Neoponcirin (Isosakuranetin 7-*O*-rutinoside)	*O*-Ru[a]	H	OMe
Poncirin (Isosakuranetin 7-*O*-neohesperidoside)	*O*-Nh[b]	H	OMe
Eriocitrin (Eriodictyol 7-*O*-rutinoside)	*O*-Ru[a]	OH	OH
Neoeriocitrin (Eriodictyol 7-*O*-neohesperidoside)	*O*-Nh[b]	OH	OH

[a] *O*-Rutinose; [b] *O*-Neohesperidose

Fig 1.4: Substitution of parent flavanones ring

The pharmacological activity of flavanones

Table 9: Pharmacological activity of Flavanones and their mechanism of actions

Flavanones	Sources	Pharmacological activity	Mechanism of action
Naringenin	Grapefruit juice	Analgesic effect	Analgesic effect, through activation of NO-cGMP-PKG-ATP-sensitive potassium channel pathway. Reduction of neutrophil recruitment, tissue oxidative stress, and cytokine production (IL-33, TNF-alpha, and IL-1). Decrease the expression of gp91phox, cyclooxygenase (COX)-2, and preproendothelin-1. Increase the expression of nuclear factor(erythroid-derived 2)-like 2 (Nrf2) mRNA, and heme oxygenase (HO-1) mRNA, and NF-kappa B [60]
Hesperetin	Citrus fruit	Protective activity in prostate cancer	The apoptotic process is an important target in treatment of cancer. Hesperetin induces apoptosis and lead to inhibition of cell proliferation in the prostate cancer PC3 cells [61]

Anthocyanidins

Anthocyanidins are water-soluble compounds which provide colors to vegetables and flowers. Anthocyanin has been taken from Greek words where anthos means flowers and kyanos means dark blue [62]. These plant pigments contain anti-oxidant activity thus they are used to treat the cardiovascular disorder, cancer and inflammatory disease [63]. The glycosidec form of anthocyanidins is polyhydroxylated or polymethoxylated glycosides or acyl glycosides. They are oxygenated derivatives of 2-phenylbenzopyrylium or flavylium salts. The distinct color produces by the anthocyanidin the substitution pattern of the Bring of the aglycone, the pattern of glycosylation, and the degree and nature of esterification of the sugars [64].

Chemistry of anthocyanidins

The anthocyanidins are categorized into 6 classes due to the presence of hydroxyl groups on the flavan nucleus and are named cyanidin (Cy), delphinidin (Dp), malvidin (Mv), peonidin (Pn), pelargonidin (Pg) and petunidin (Pt) [65]. The 3-glucosides of the anthocyanidins possess anthocyanins, anthocyanidins with sugar group. The sub category of anthocyanins includes the sugar-free anthocyanidin aglycones and the anthocyanin glycosides. The pigments of anthocyanidins combines and from two different streams of chemical raw materials in the cell: both starting from the C_2 unit acetate (or acetic acid) derived from photosynthesis, one pathway involves the shikimic acid pathway to generate the amino acid phenylalanine. The other stream (the acetic acid pathway) produces 3 molecules of malonyl-Coenzyme A, a C_3 unit [66].

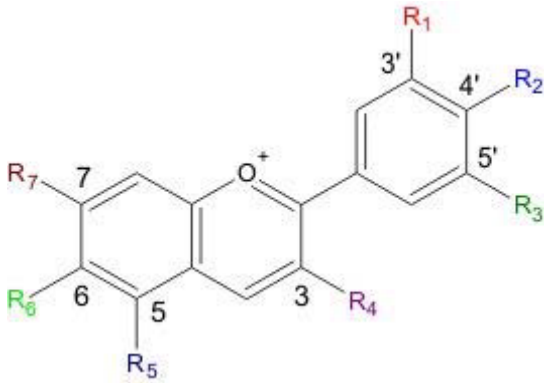


Fig 1.5: There are 7 different side groups on the flavylium ion. These side groups can be a hydrogen atom, a hydroxide or a methoxy-group.

There are three rings present in anthocyanidins structure which contain an aromatic ring [A] attached to a heterocyclic ring [C] that consist of oxygen, which is also bonded by a carbon-carbon bond to a third aromatic ring [B]. The glycosidic form of anthocyanidins (bonded to a sugar moiety) is known as anthocyanins. The main differences between them are the number of hydroxylated groups, the nature and the number of bonded sugars to their structure, the aliphatic or aromatic carboxylates bonded to the sugar in the molecule and the position of these bonds [67].

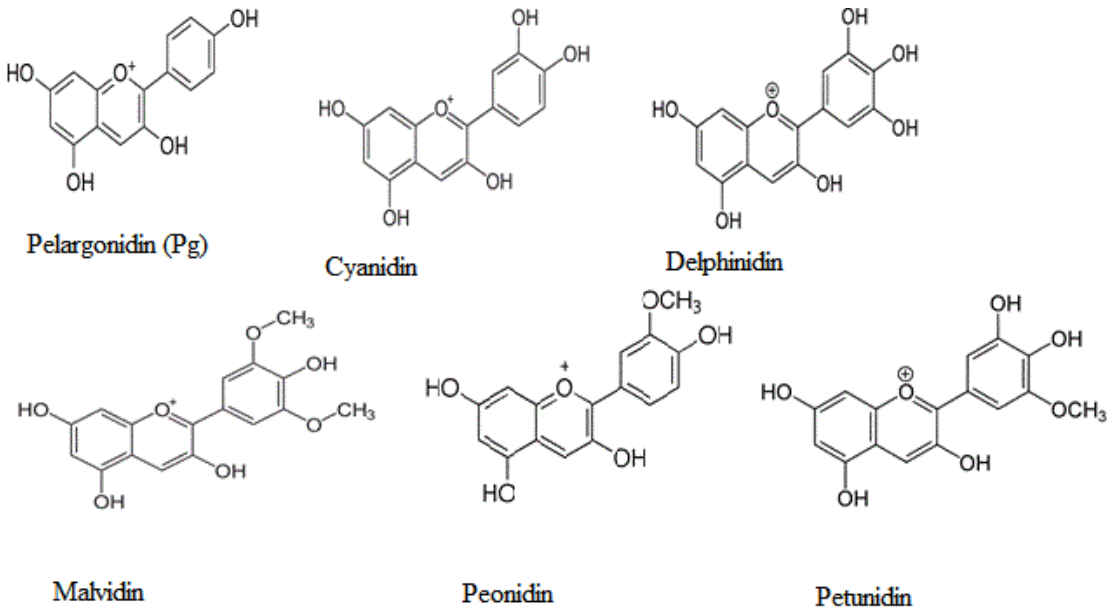


Fig 1.6: Structures of naturally occurring anthocyandin in fruits

The pharmacological activity of anthocyanidins

Table 10: Pharmacological activity of Anthocyanidins and their mechanism of actions

Anthocyanidins	Pharmacological activity	Mechanism
Cyanidin	Anti-oxidant activity	Reduces lipid peroxidation and DNA damage. Also, destroy the dene gerous hydroxyl radical [68]
Malvedin	Anti-hyperglycaemic activity	Decline the activity of tissue necrosis factor – alpha mRNA levels and decreases the oxidative stress to protect beta pancreatic cells. Decreases glucose production by increasing the activity of AMPK [68]
Peonidin	Effect on the CVS system	Increases the capillary permeability, inhibit platelet formation and increase nitric oxide production lead to vasodilation. Also decreases the lipid peroxidation and protect the cell membrane lead to prevent the damage of blood vessels and DNA [68].
Delphinidin	Neuroprotective activity	Decreases the activity of peroxynitrite free radical and shows neuroprotective activity [68]
Pelargonidin	Anti-inflammatory activity	Decreases the activity of cyclooxygenase which leads to decrease in the production of the nitric oxide free radical and prostaglandins [68].
	Anti-carcinogenic activity	Increases the apoptosis of mutated cells and arrests the cell cycle. Inhibits the proliferation of human cancer cell lines AGS (stomach), HCT-116(colon) MCF-7(breast) and SF-268(CNS)(c75) [68]
	Obesity	Reduces fat accumulation in the body. Also decreases the synthesis of lipid in liver and white adipose tissue. Up regulated the expression of adiponectin and increases the sensitivity of insulin for adipocytes [68].

Tannins

Tannins are the natural polyphenols which came from the French word called 'tanin'. These secondary metabolites work to modify the plant-herbivore interaction and provide protection against infection. Due to their activity to precipitate protein and acid taste their function is known as herbivore deterrents [69]. Tannins contain astringent property and have the ability to bind with proteins that lead to shrink protein. Their binding property with basic compounds, pigments large molecular compounds and met allic ions differentiates from other polyphenols [70]. During the ancient time tannins used to make leather from the animal hides. (Tannin chemistry) Utilization of tannins has been increased due to their antibacterial, antitumor and antiviral activity; also have the ability to selectively inhibit HIV replication [69].

Classification

The structure of tannin contains two or three phenol hydroxyl group attached to the phenyl ring. According to the presence of polyphenol group they were classified as pyrogallol type tannins and catechol type tannins [70]. After the development in tannin chemistry, they are classified as –

1. ***Hydrolyzable tannins*** they are present in low amount in plants and have the ability to interact with toxic metal ions and decreases their bioavailability [71]. They are derived from gallic acid. Esterification of gallic acid to core polyol and galloyl groups may lead to the formation of complex tannins [72].

2. ***Condensed tannins*** they are also known as proanthocyanidins and have the ability to convert in anthocyanidins in the presence of heated ethanol solution. These oligomers and polymers contain flavan-3-ols nuclei [73]. Classification of tannins according to their hydrolytic activity and structural characteristics

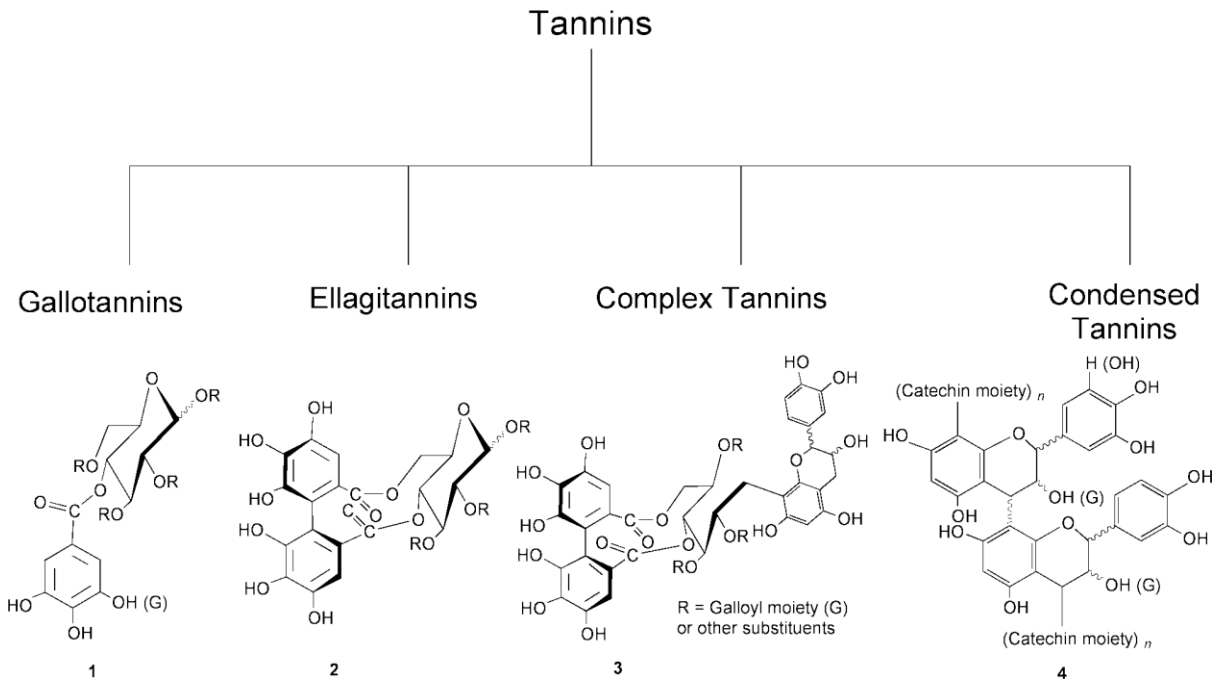


Fig 1.7: Molecular structure of types of tannins

The Pharmacological activity of tannins

Table 11: Pharmacological activity of Tannins and their mechanism of actions

Tannins	Pharmacological action	Mechanism of action
Gallotannins	Neuroprotective potential	Gallotannin, a complex mixture of tannins purified from the oak gall, has been shown to inhibit PARG (PARP (poly(ADP-ribose) glycohydrolase – a key enzyme degrading ADP-ribose polymers) activity. It significantly reduced oxidative (H2O2)-induced cell death (after 24and 72 h of H2O2 exposure; 100 nM of gallotannin) in murine astrocytes cell culture with 10-fold more potent activity than the PARG inhibitor benzamide in preventing such process [74].
Ellagitannins	Anti-inflammatory action	Ellagic acid has been found to mitigate inflammation and reduce the duration of the disease. In addition, it reduces the level of proinflammatory cytokines IL-6 and increases that of anti-inflammatory cytokines IL-10 [75].
Complex tannins	Hepatoprotective effect	Exhibited inhibitory effects on hepatotoxicity induced by acetaminophen and CCl4. The suppression of bleomycin-induced genotoxicity in cultured Chinese hamster ovary cell and of the proliferation of H-ras-transformed NIH3T3 cells shows their antioxidant activity. These effects aredue, in part, to decreases in intracellular superoxide levels, which may modulate downstream signaling of Ras protein [76].
Condensed tannins	Protein precipitating activity	Low levels of CT (3.4%) protect proteins from rumen degradation14. Concentrations of CT between 6-12% dry matter (DM) depress voluntary feed intake, digestive efficiency and animal productivity, moderate levels of CT (2-4% DM) may exert beneficial effects14 on protein metabolism inruminants by reducing the degradation of dietary protein into ammonia by rumen microorganisms and increasing the flow out of the rumen of protein, as well as resulting in an increased absorption of amino acids in the small intestine15 [77].

Lignans

Lignans are one of the most important groups of plant secondary metabolites originated from the phenylpropanoid pathway. They have a significant role in plant defense and are most effective in human nutrition and medicine. Lignans were isolated from more than 60 families of vascular plants and from their different parts namely roots, rhizomes, woody parts, stems, leaves, fruits, seeds and in other cases, from exudates and resins [78].

Chemical structure of lignans

Their basic chemical structure consists of two phenylpropane units linked by a C-C bond between the central atoms of the respective side chains (position 8 or β), also called β-β' bond. 3-3′, 8-O-4′, or 8-3′ bonds are observed less frequently; in these cases, the dimers are called neolignans. Furthermore, there is considerable variability regarding the oxidation level of both the propyl side chains and the aromatic rings. They are not present in the free form in nature, but linked to other molecules, mainly as glycosylated derivatives [79].

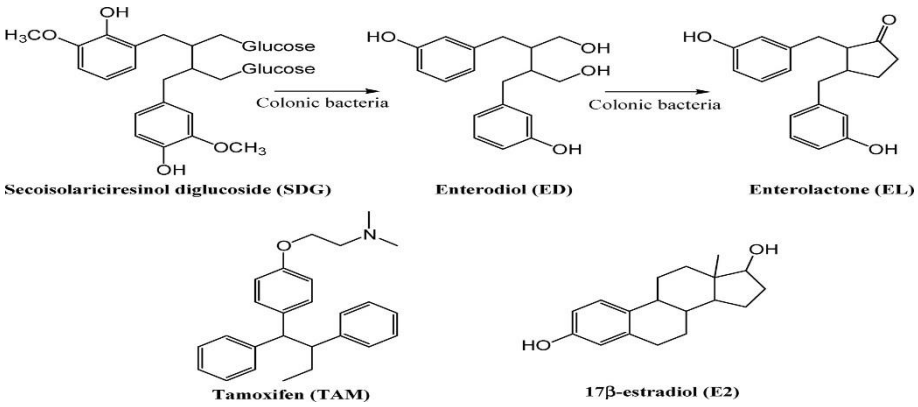


Fig 1.8: Molecular structure of metabolite of lignans

The pharmacological activity of lignans

Table 12 Pharmacological activity of lignans and their mechanism of actions

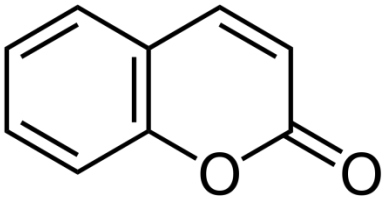
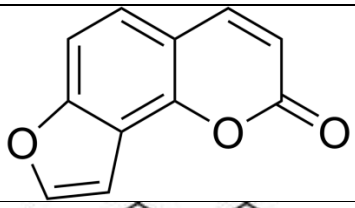
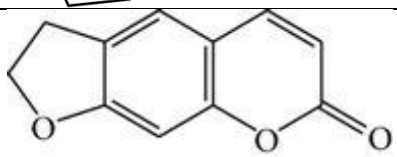
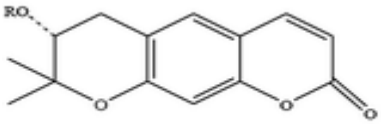
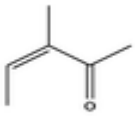
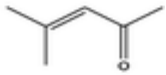
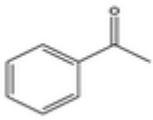
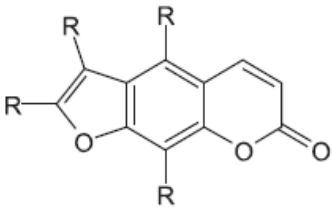
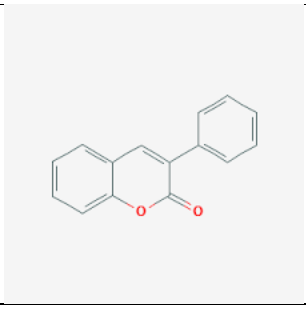
	Pharmacological activity	Mechanism
Lignans	Antimitotic activity	Arrest the cell culture at metaphase and bind to purified tubulin preparation [80].
	Antiviral activity	Reduce the cytopathic effect of herpes simplex type 2, influenza A and vaccine viruses. Lignans prevent the microtubule formation in viruses [80].
	Anti- tumour activity	Shows the specific effect on the certain enzyme-catalyzed process of malignant tissues. Also inhibit siccinoxidase, NADH-oxidase and mitochondrial energy transfer [80].
	Cathartic activity	Decreases the initial rate ofan amplitude of rhythmic contraction of gut preparationand increases the force of contraction and loss of tone [80]

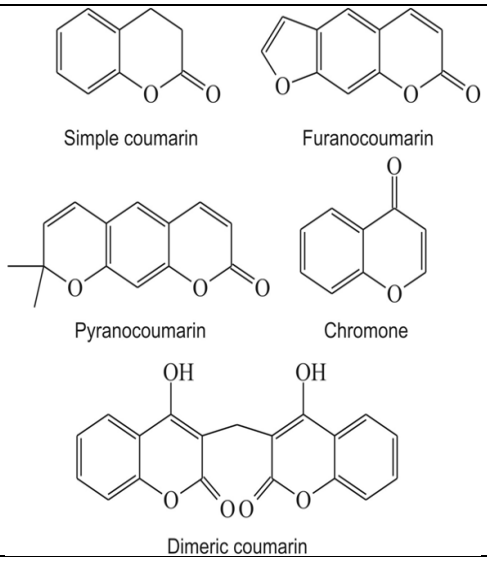
Coumarins

Coumarins from elite classes of naturally occurring compounds, which occupy a special role in nature and interest in its chemistry continue unabated because of its usefulness as biologically active agents. Coumarins (2*H*-1-benzopyran-2-one),consist of a large class of phenolic substances found in plants and are made of fused benzene and α-pyrone rings. The prototypical compound is known as 1,2-benzopyrone or, less

commonly, as *o*-hydroxycinnamic acid and lactone, and it has been well studied [81]. Coumarin is planted flavonoids widely distributed in nature. Natural coumarins are known to have antidiabetic activity, anabolic antioxidant and, hepatoprotective activities. Substituted coumarins derivatives have been reported to have a variety of biological activities [82]. Coumarin, the parentsubstance of the benzo-a-pyrone group, was first isolated from tonka beans in 1820. Coumarin was initially considered to be a benzoic acid derivative, but its synthesis by W. H. Perkin, Sr., (160) from salicylaldehyde by means of his classical reaction established its relation to o-hydroxy cinnamic acid, which loses a molecule of water in forming the lactone ring [83].

Table 13: Principle structure of Coumarins

Type of coumarin	General chemical structure	Example
Simple coumarins		Coumarin Esculetin Ammoresinol Ostruthin Osthole Novobiocin Coumermycin
Furano coumarins		Imperatorin Psoralen Bergapten Methoxsalen Marmalde, Marmelosin
Dihydrofurano coumarins		Anthogenol] Felamidin Marmesin, rutaretin
Linear type		Compound / R Agasyllin (56)  Grandivittin (57)  Aegelinol benzoate (58)  Aegelinol (59) H
Angular type		Inophyllum A, B, C, E, P, G1, andG2 ,Calanolide A, B, and F (+)-Dihydrocalanolide A and B Pseudocordatolide C
Phenyl coumarins		Isodispar B, dispardiol B, mammea A/AB cyclo E, mammea A/ABdioxalanocyclo F, disparinol D,disparpropylinol B

Bicoumarins		Dicoumarol

The pharmacological activity of coumarins

Table 14: Pharmacological activity of Coumarins and their mechanism of actions

Coumarins	Pharmacological activity	Mechanism
Esculetin	Anti-inflammatory activity	Increases the activity of phagocytizes and enzymes which remove the odema fluid and protein and lead to proteolysis [84].
Dicoumarol	Anti-coagulant activity	Coumarin is Vit K antagonist, restrict the interconversion of Vit K and its epoxide, also inhibit the carboxylation of anticoagulant regulatory proteins. Hence inhibit the VitK conversion cycle [84].
Ammoresinol and ostruthin	Anti-bacterial activity	Show activity against a wide spectrum of gram- positive bacteria [84].
Inophyllum A Inophyllum B Inophyllum C	Antiviral activity	Inhibits HIV transcriptase with IC_{50} values of 38 and 13nM [84].
Imperatorin	Antiviral activity	Inhibits vesicular stomatitis virus pseudotyped and gp160-enveloped recombinant HIV infection in several T-cell lines [85].
Osthole	Anticancer activity	Reduces ovarian cell proliferation. Prevent the activity of mitochondrial transmembrane depolarisation potential and regulates mitochondrial BCL-2 family pathway. Increase the pro-apoptotic factors, Bid,Bad, and Box expression and decrease the expression of Bcl-X1 and Mcl-1 [85].

Conclusion

Phenolic compounds are plants secondary compounds which possess various nutritional properties. Phenolic compounds include various classes of phytoconstituents like phenolic acids, flavonoids, tannins, and coumarins, etc. The phenolic compounds contain hydroxybenzoic acid and hydroxycinnamic acid which possess pharmacological activities such as anti-asthmatic, anti-diabetic and anti-mutagenetic activity. Flavonoids are the compounds which show multiple activities in plants, microbes, and animals. Flavonoids include flavonols, flavones, flavanones, flavonoid glycoside, isoflavones, and anthocyanidins. The basic structure of flavonols is 3-hydroxyflavone and substitution of hydroxyl group which provides different chemical compounds. They show different pharmacological activity such as direct radical scavenging activity (Quercetin), protective activity (Myricetin) and cardiovascular protection (Isorhamnetin). Flavones are yellow pigments and widely associated with glycosides and tannins. Their pharmacological activities are an anti-inflammatory effect (Oroxylin A) and anti-depressant effect (Chrysin). Isoflavones are well-known phytoestrogens and are their oestrogenic activity was recognized in the 1940s when the sheep suffered from infertility by grazing *Trifolium subterraneum*. Naturally found isoflavones having strong estrogenic activity are the aglycones, genistein, daidzin, and glycones. Due to their estrogenic activity, they relief the postmenopausal symptoms like vasomotor symptoms, osteoporosis, CVS and CNS disorders. Flavan-3-ols, flavanones, and anthocyanidins are the other flavonoids which show antiviral effects (Epicatechin), analgesic effects (Naringenin), anti-oxidant, anti-hyperglycemic, neuroprotective and anti-inflammatory effect (delphinidin, cyaniding, peonidin, and pelargonidin). Tannins contain astringent property and have the ability to bind with proteins that lead to shrink protein. Tannins include hydrolyzable tannins and condensed tannins which show neuroprotective potential, hepatoprotective effect, and protein precipitating activity. Lignans and coumarins also contain therapeutic potential and show anti-inflammatory, anticoagulant, anti-viral and anti-cancer activity. Polyphenols are the phytoconstituents which are investigated extensively due to their potential to prevent various chronic diseases such as diabetes, cancer, and cardiovascular diseases, etc. The above review concludes that consumption of plant and diet which are rich in polyphenols can protect human beings from various diseases. Intake of polyphenols approx 1g/day is recommended for better health.

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