Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2020; 9(2): 1270-1275
Received: 10-01-2020
Accepted: 12-02-2020

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Ethnomedicinal plants: A source of phytochemical compounds against snake venom PLA_2s activity

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Abstract
Ethnomedicinal plant extracts and their isolates have demonstrated significant inhibitory effect against various snake venom PLA_2s enzymes activities and therefore can be used as an alternative against snake envenomation. Different phytochemicals capable of inhibiting PLA_2s from different snake venoms have been isolated, these include Ikshusterol-3-O-glucoside, Betulin and Betulinic acid, Ar tumerone, 12-methoxy-4-methylvoachalotine, aristolochic acid, luteolin, kaempferol, isoquercitin, rutin, ellagic acid, gallic acid quinic acid, ferulic acid, caffeic acid, propylgallate, epigallocatechin gallate, 4-nerolidylcatechol, sitosterol, stigmasterol, 7-methoxy-coumarin, 6,7- methylenedioxy-coumarin, umbelliferone and tannic acid. These phytochemicals might provide a cheaper and new strategy for the development of new pharmaceutical drugs and alternative approaches for the treatment of snake envenomation. This review, presents a compilation of important phytochemicals that are effective against snake venom PLA_2s activity due to their neutralization effect.

Keywords: Ethnomedicinal plant, phytochemicals, snake venom, phospholipase A_2, inhibitors

Introduction
Snake envenomation is a serious and frequently neglected public medical issue in developing countries (Muthusamy *et al.*, 2017) [21]. It is a common hazard among the poorest populations that live in endemic snakebite areas, it affects mainly people involved in farming activities, fisherman and hunters that have vital socio-economical important (Guimarães *et al.*, 2014) [16]. Generally, these populations have poor access to healthcare services and poor access to specific treatment, due to lack of proper healthcare services and health facilities in rural setting (Felix-Silva *et al.*, 2017) [11] of developing countries, this often leading to poor outcome and higher morbidity and mortality rates (WHO, 2010) [29, 30]. Snakebites have been classified as a neglected tropical disease by WHO in June 9th, 2017 WHO (Chippaux, 2017) [6]. There are about 5.4 million snake bites occur each year, resulting in 1.8 to 2.7 million cases of envenomings .There are between 81 410 to 137 880 deaths and around three times as many amputations and other permanent disabilities each year (WHO, 2018) [31]. Venomous snakes are snakes capable of producing and storing venom in specialized salivary glands situated in the upper jaw ventral and posterior to the eyes. Venomous snakes are distributed into four families: Viperidae; Atractaspididae; Elapidae and Colubridae (Fox and Serrano, 2008) [12] of these, Naja nagricolis and kraits of Elapidae family cause maximum envenomations (W.H.O., 2010) [29, 30]. Snake venom contained various protein toxins including cardiotoxin, neurotoxin and various enzymes which resulted to hemorrhage, edema and local tissue necrosis (Molander *et al.*, 2014) [19], hence the pathology of snakebites includes systematics and local tissue necrosi (Machiah and Gowda, 2006) [18]. Snake envenomation is a life threatening condition that requires an immediate medical attention (Ameen, 2015) [2].
Anti-snake venom (AVS), the only authorized available drug of choice for the effective and immediate treatment of snakebites (Gopi *et al.*, 2015) [15] is expensive and requires ideal storage facilities (Abubakar *et al.*, 2006) [1] which might be lacking in the rural areas of tropical African countries (Felix-Silva *et al.*, 2017) [11]. Therefore, scientific investigation for the alternative treatment for snakebite is necessary needed.
Ethnomedicinal plants constitute bioactive compounds alternative for snakebite remedy, displaying a large biodiversity of phytochemical compounds with several pharmacological activities of medical interest (Pithayanukul *et al.*, 2010) [24]. This paper review described the anti-venom potential of different phytochemical constituents of ethnomedicinal plants against Phospholipase A_2 (PLA_2) of the various species of the snake families. Data were collected during March to July 2018 using Science Direct, Pubmed, Google Scholar and web of Science Hub.

PLA_2 inhibitors from plants extract

Phospholipase A_2 (PLA_2) (phosphatide 2-acylhydrolase: EC. 3. 1. 14.), is one of the most damaging components of snake venoms (Dos Santos *et al.,* 2011) [10], it play a crucial role in myonecrosis (Kang *et al.,* 2011) [17] neurotoxicity, anticoagulant, hemorrhagic, cardiotoxicity and edema-inducing effects. Scientific investigation on the interaction between the PLA_2s and their natural inhibitors (phytochemicals) might provide alternative treatment for snakebite envenomation. Flavonoids, steroids coumestan, alkaloids, and terpenoids (mono-, di-, and triterpenes), and polyphenols are the bioactive components of the ethnomedicinal plants that inhibit classes of PLA_2 (Carvalho *et al.,* 2013) [5].

Phytochemical compounds against snake envenomation

Flavonoids

Polyphenolic secondary metabolites existing in both free and glycosidic forms, they occur naturally in fruits, vegetables, nuts, seeds, flowers, and bark (Cook and Samman, 1996) [7], polyphenolic compounds have ability to bind to macromolecules, and some of these have been shown to inhibit PLA2s, these include quercetin (Singh *et al.,* 2017) [26], a strong lipoxygenase inhibitor (Carvalho *et al.,* 2013) [5], luteolin, kaempferol, and isoquercitin, rutin among several other flavonoids. Flavonoid compounds exert their inhibitory effect through hydrophobic interactions with the A and B rings as well as the hydrophobic amino acid residues of the protein structure of the enzymes (Da silva *et al.,* 2012) [8]. Quercetin and aristolochic acid completely neutralized the activity of PLA_2 of *Naja nigricolis* (Shabbir *et al.,* 2014) [25]. Muthusamy, *et al*. (2017) [21] investigated the computational and in vitro insight on snake venom phospholipase A_2 inhibitor. *Ikshusterol-3-O-glucoside* isolated from *Clematis gouriana* Roxb Ex DC was found to be a potent inhibitor PLA2 activity of Naja nagricolis. The structure of the phytochemical was characterized via various spectroscopic techniques UV, NMR, FTIR, and GC-MS-EI. Molecular dynamics simulation revealed the stability of the *ikshusterol-3-O-glucoside* in the active site of PLA_2 enzyme of *Naja naja* (Indian cobra) venom. In a similar research conducted by Gopi *et al.* (2015) [15], ellagic acid, gallic acid and quinic acid isolated from *Euphorbia hirta* were able to completely inhibit *Naja naja* venom induced toxicity under *in vivo* as well as ex vivo conditions. Perenanez *et al* (2011) [23] Reported that phenolic compounds; gallic acid, ferulic acid, caffeic acid, propylgallate and epigallocatechin gallate inhibite the enzymatic activity of a phospholipase A_2 (PLA_2) using egg yolk as substrate, they further stated that propylgallate and epigallocaechingallate are two novel natural products with anti-myotoxic potential. Da sival *et al* (2008) [9] in their research aimed to evaluate the half maximum inhibitory concentration of (IC_{50}) of ellagic acid isolated from *Casearia sylvestris* against BthTX-II, a basic Asp 49-PLA_2 isolated from *B jararacus* snake venom, concluded that ellagic acid competitively inhibited PLA_2 activity, myotoxicity and edema inducing activity of the *B. jararacus* snake venom. The phenolic content of methanolic extract of fresh leaves of Camellia sinensis (tea leaves) inhibited phospholipase A_2 activity of *Naja naja kauothia* Lesson (Elapidae) and *Calloselasma rhodostoma kuhl* (Viperidae) venom in a dose dependent manner (Pithayanukul *et al.,* 2010) [24]. 4-nerolidylcatechol, a hydroxylated phenolic compound isolated from *Piper umbellatum* and *Piper pethatum* demonstrated inhibitory effect against group I, II and III PLA_2S activities (N´u˜nez *et al.,* 2005) [22].

Steroid compounds

The combination of sitosterol and stigmasterol (3:1,100µg) active components from the methanol root extract of *Pluchea indica* strongly inhibited the activity of phospholipase A_2 of *Naja kaouthia* venom (Gomes *et al.,* 2007) [14]. In a similar researched conducted to investigate the Anti-myotoxic and Anti-hemorrhagic effects of the *Eclipta prostrata* (Asteraceae) extract and its components, the result revealed that sitosterol and stigmasterol were the potent inhibitors against *B. jararaca*, *B. jararacussu*, and *Lachesis muta* snake venom (Mors *et al.,* 2000) [20].

Coumarins

Coumarin compound is classified as a member of the benzopyrone family, which consist of a benzene ring joined to a pyrone ring. It's widely distributed in plants, fungi and bacteria. Herniarin (7-methoxy-coumarin) and ayapin (6, 7-methylenedioxy-coumarin), isolated from *Eupatorium triplinerve* were reported to have remedies against snake bite (Guimarães *et al.,* 2014) [16]. Toyama Dde *et al* (2011) [28] suggested that interaction of umbelliferone with phospholipase A_2 (PLA_2) isolated from *Crotalus durissus collineatus* venom, induce structural modifications that lead to a significant decreased of the phospholipase A_2 activity.

Tannin compounds

Polyphenols and tannins isolated from *Musa paradisiaca* significantly inhibit phospholipase A2, myotoxic and hemorrhagic activities, and lethality induced by *Crotalidae* venoms (Borges *et al.,* 2005) [4]. A similar research revealed the inhibitory effect of tannic acid (gallotannin) on the activity hyaluronidase enzyme and hemorrhagic neutralizing effect induced by *Crotalus adamanteus* venom (Girish and Kemparaju, 2005) [13].

Terpenoid compounds

Betulin and Betulinic acid isolated from *Betula alba* (Betulaceae) significantly inhibit the activity of PLA2. Also molecular docking and structural simulation revealed betulinic acid as the best PLA2 inhibitor due to its direct binding to the active site of the PLA_2 enzyme with a very low energy level (Soares *et al.,* 2005) [27]. Sesquiterpene ketone (Ar tumerone) isolated from a hexane extract of *C. longa* (Zingiberaceae) roots, neutralized both the hemorrhagic activity of *B. jararaca* venom and the lethality of *C. durissus terrificus* venom in mice (Guimarães *et al.,* 2014) [16]

Alkaloid

12-methoxy-4-methylvoachalotine isolated from *Tabernaemontana catharinensis* (Apocynaceae) reported to be a portent inhibitor against lethality and myotoxic activities induced by *C. d. terrificus* venom (Batina *et al.,* 2000) [3]. Also the enzymatic and pharmacological activity of the basic PLA2 from *V. russelli* venom was strongly inhibited by aristolochic acid isolated from *Aristolochia radix* and *Aristolochia odoratissima* (Guimarães *et al.,* 2014) [16]

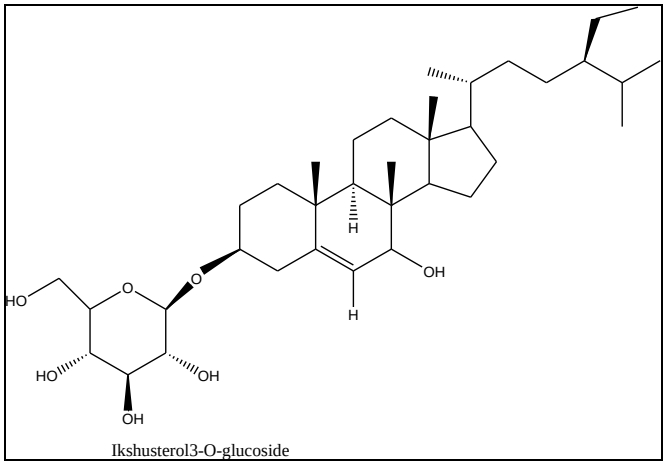
Conclusion

Ethnomedicinal plant extracts and their isolated compounds have demonstrated significant inhibitory effect against various snake venom PLA_2s enzymes activities, this reveals the potential use of these phytochemicals in the development of

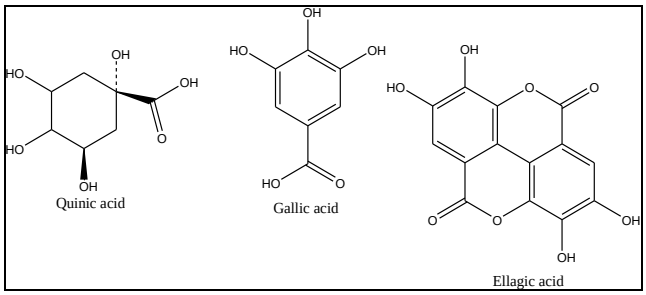
new anti-snake therapies. Thus, ethnomedicinal plants are the most significant source of bioactive compounds that leads for new anti-venom serum development.

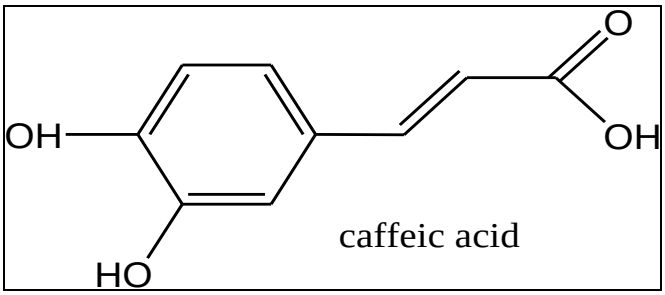
Table 1: List of phytochemicals with their venom neutralization ability

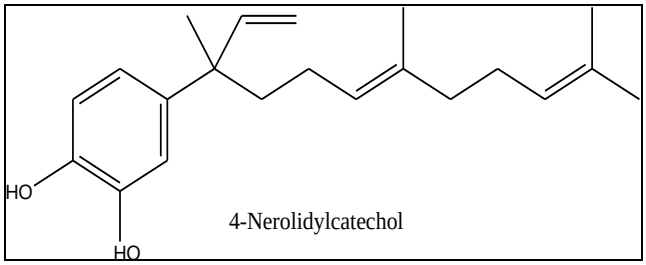
S/NO	Plant	Phytochemicals	Mode of action	Reference
1	*Mouriri pusa*	Quercetin	Neutralized the activity of PLA_2	(Guimarães *et al.*, 2014) [16]
2	*Aristolochia radix*	Aristolochic acid	Neutralized the activity of PLA_2	(Shabbir *et al.*, 2014) [25]
3	*Clematis gouriana*	*Ikshusterol-3-O-glucoside*	Potent inhibitor PLA2 activity	(Muthusamy *et al.*, 2017) [21]
4	*Euphorbia hirta*	Ellagic acid,	Inhibit *Naja naja* venom induced toxicity under *in vivo* as well as ex vivo conditions	(Gopi *et al.*, 2015) [15]
5	*Euphorbia hirta*	Gallic acid	Inhibit *Naja naja* venom induced toxicity under *in vivo* as well as ex vivo conditions	(Gopi *et al.*, 2015) [15]
6	*Euphorbia hirta*	Quinic acid	Inhibit *Naja naja* venom induced toxicity under *in vivo* as well as ex vivo conditions	(Gopi *et al.*, 2015) [15]
7	*Musa paradisiaca*	Gallic acid	Inhibition of PLA_2s	(Perenanez *et al.*, 2011; Guimarães *et al.*, 2014) [23, 16]
8	Plant not specified	Ferulic acid	Inhibition of PLA_2s	(Perenanez *et al.*, 2011) [23]
9	Plant not specified	Caffeic acid	Inhibition of PLA_2s	(Perenanez *et al.*, 2011) [23]
10	Plant not specified	Propylgallate	Inhibition of PLA_2s, Anti-myotoxic potential	(Perenanez *et al.*, 2011) [23]
11	Plant not specified	Epigallocatechin gallate	Inhibition of PLA_2s, Anti-myotoxic potential	(Perenanez *et al.*, 2011) [23]
12	*Casearia sylvestris*	Ellagic acid	competitively inhibited PLA_2 activity, myotoxicity and edema inducing activity	(Da sival *et al.*, 2008) [9]
13	Camellia sinensis (tea leaves; fresh leaves)	The phenolic content of methanolic extract	Inhibition of PLA_2s	(Pithayanukul *et al.*, 2010) [24]
14	*Piper umbellatum*	4-Nerolidylcatechol	Inhibitory effect against group I, II and III PLA_2S activities	(N´u˜nez *et al.*, 2005) [22]
15	*Piper pethatum*	4-Nerolidylcatechol	Inhibitory effect against group I, II and III PLA_2S activities	(N´u˜nez *et al.*, 2005) [22]
16	*Pluchea indica*	Sitosterol	Inhibition of PLA_2s	(Gomes *et al.*, 2007) [14].
17	*Pluchea indica*	Stigmasterol	Inhibition of PLA_2s	(Gomes *et al.*, 2007) [14].
18	*Eclipta prostrata*	Sitosterol, Stigmasterol	Anti-myotoxic and Anti-hemorrhagic effects	(Mors *et al.*, 2000) [20].
19	*Eupatorium triplinerve*	Herniarin (7-methoxy-coumarin)	have remedies against snake bite	(Guimarães *et al.*, 2014) [16]
20	*Eupatorium triplinerve*	Ayapin (6,7-methylenedioxy-coumarin)	have remedies against snake bite	(Guimarães *et al.*, 2014) [16]
21		Umbelliferone	Inhibition of PLA_2s	(Toyama Dde *et al.*, 2011) [28]
22	*Musa paradisiaca*	Polyphenols and tannins	Inhibition of PLA_2s, Myotoxic, Hemorrhagic activities, and lethality induced by *Crotalidae* venoms	(Borges, et al., 2005) [4].
23	Plant not specified	Tannic acid (gallotannin)	Inhibition of hyaluronidase activity, Hemorrhagic neutralizing effect induced by *Crotalus adamanteus* venom	(Girish and Kemparaju, 2015)
24	*Betula alba*	Betulin and Betulinic acid	Inhibition of PLA_2s	(Soares *et al.*, 2005) [27]
25	*C. longa* (Zingiberaceae)	Sesquiterpene ketone (Ar tumerone)	Neutralized both the hemorrhagic activity of *B. jararaca* venom and the lethality of *C. durissus terrificus* venom in mice	(Guimarães *et al.*, 2014) [16]
26	*Tabernaemontana catharinensis*	12-methoxy-4-methylvoachalotine	Portent inhibitor against lethality and myotoxic activities induced by *C. d. terrificus* venom	(Batina *et al.*, 2000) [3]
27	*Aristolochia radix* and *Aristolochia odoratissima*	Aristolochic acid	Inhibition of basic PLA2 from *V. russelli* venom	(Guimarães *et al.*, 2014) [16]

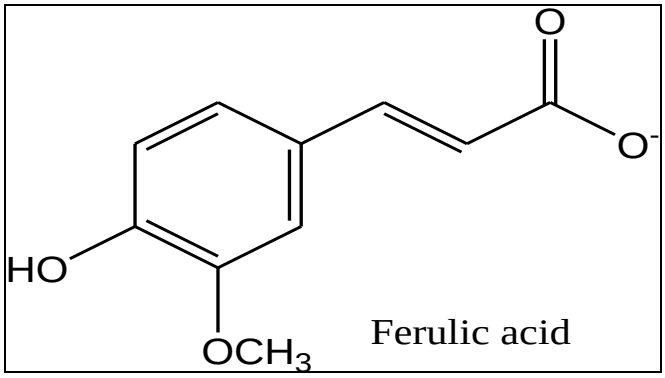


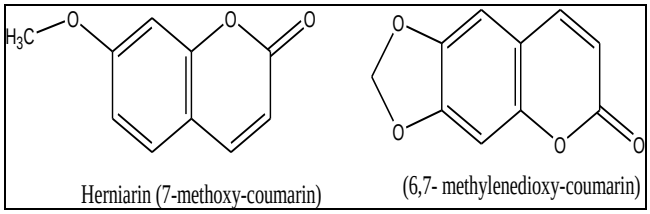
Ikshusterol3-O-glucoside

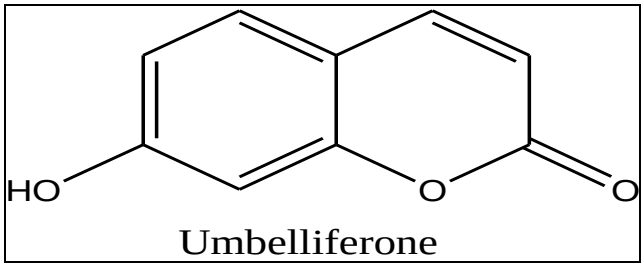

Quinic acid
Gallic acid
Ellagic acid

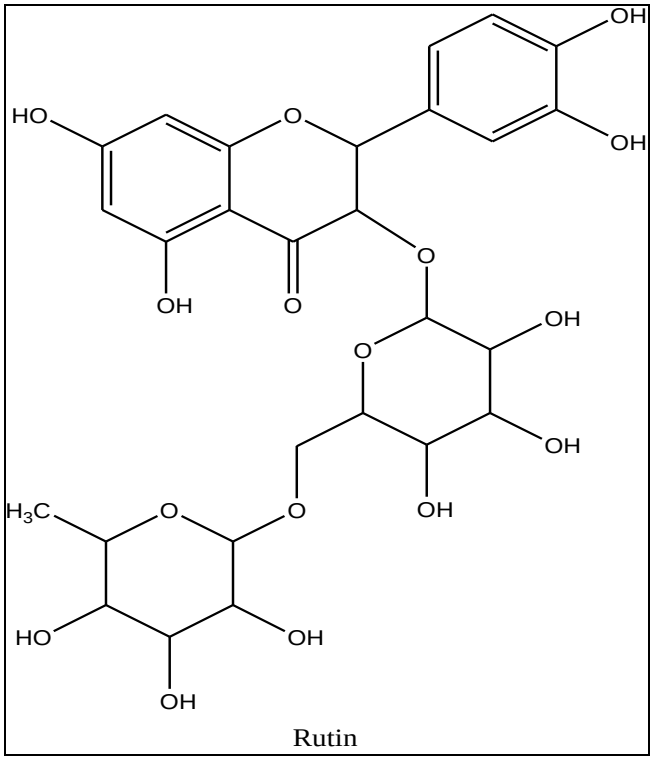

caffeic acid

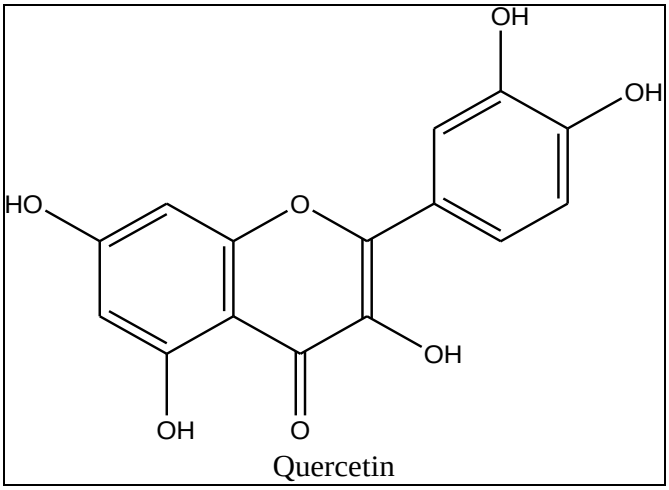

4-Nerolidylcatechol

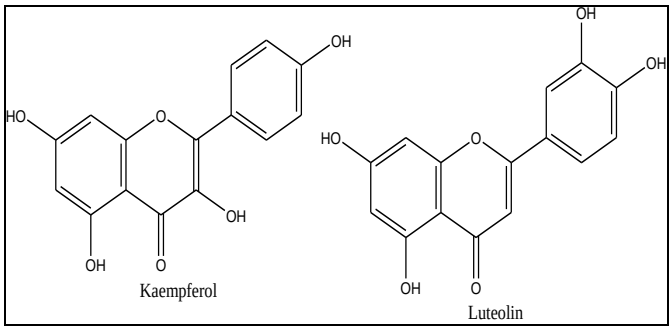

Ferulic acid

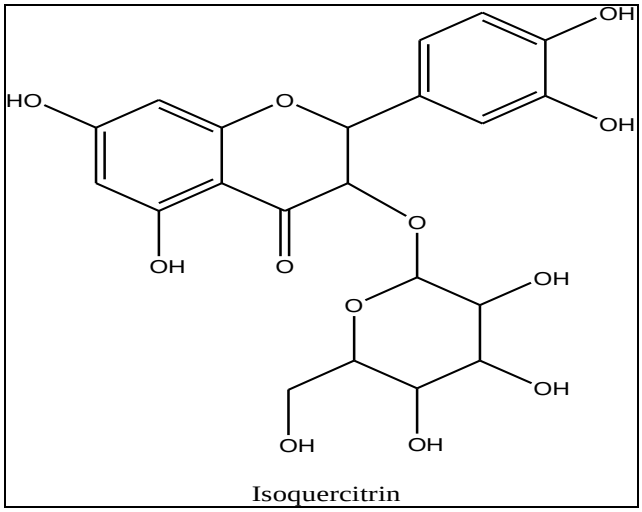

Herniarin (7-methoxy-coumarin)
(6,7- methylenedioxy-coumarin)

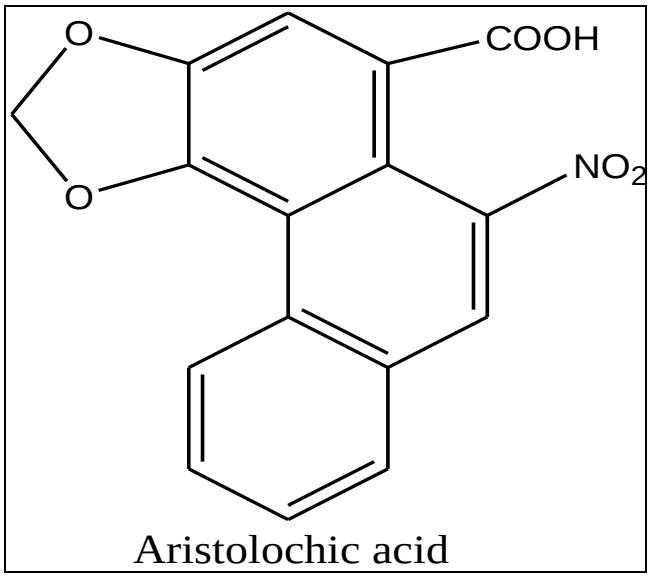

Umbelliferone


Rutin

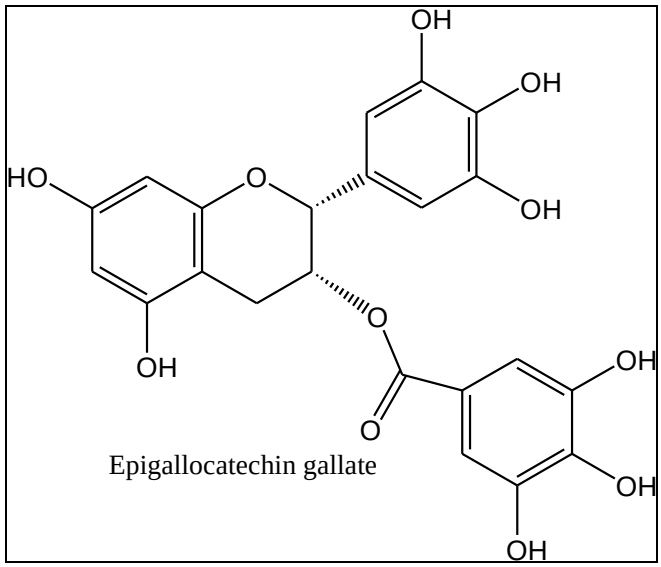

Quercetin


Kaempferol
Luteolin

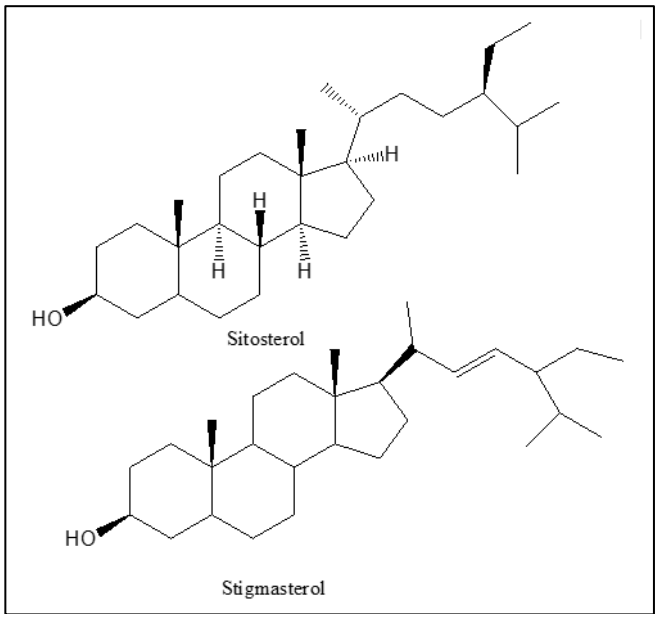

Isoquercitrin

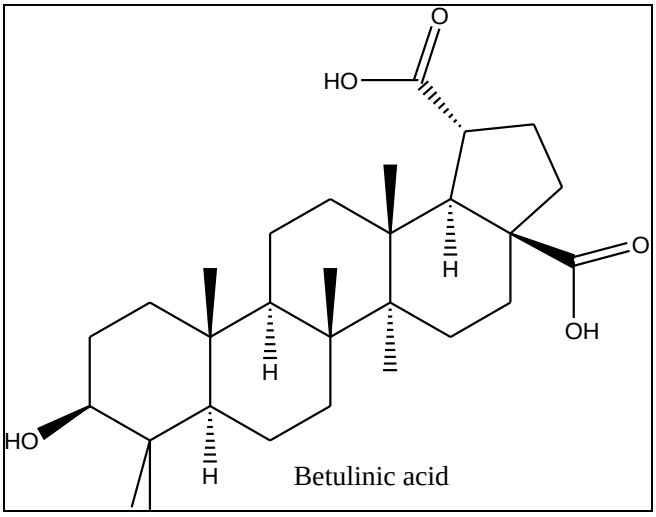


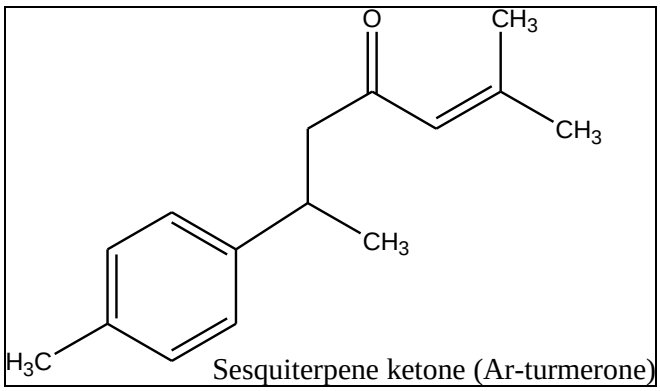
Aristolochic acid

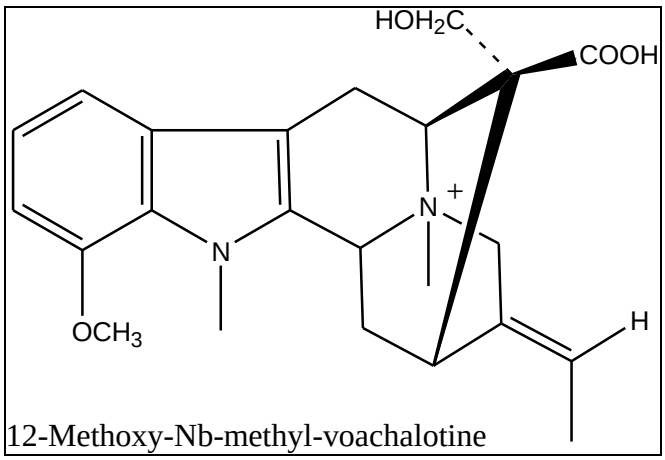


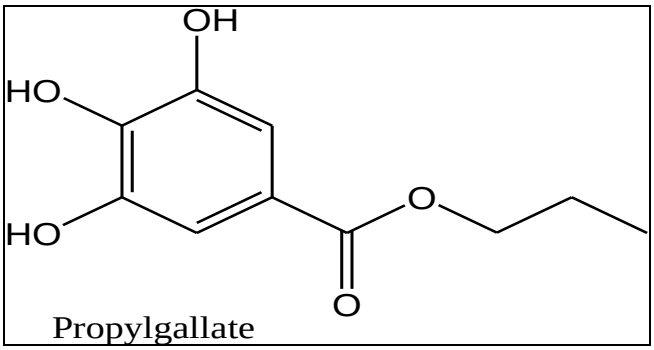
Epigallocatechin gallate











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