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Pharmacological and phytochemical review on *Phyllanthus species*

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ABSTRACT

The genus of *Phyllanthus* (Euphorbiacae) is widely distributed and possesses diverse morphological characters. A number of plants have been used in the treatment of many ailments. A lot of work has been done on pharmacological and phytochemical aspects, and a number of chemical constituents have been isolated by various workers. In the present article, we have reviewed the work done on the plants namely *P.amarus, P.niruri, P.fraternus. P.maderaspatensis, P.emblica, P.debelis, P.acidus, P.urinaria, P.sellowianus, P.stipulatus, P.corcovadensis, P.chamaecristoides, P.caroliniensis, P.tenellus, P.orbiculatus, P.acuminatus, P.myrtifolius, P.discoides, P.virgatus* and *P.mummuariifolius* possessing different biological activities namely antihepatotoxic, anti-HIV, anticarcinogenic, anti-inflammatory etc. with special emphasis on antihepatotoxic activity.

KEYWORDS

Antihepatotoxic activity;
Anti-HIV activity;
Euphorbiacae;
Phyllanthus niruri;
Phyllanthus amarus;
Phyllanthus urinaria.

INTRODUCTION

The genus *Phyllanthus* (Euphorbiacae) possesses diverse pharmacological properties; some of them find use in the indigenous system of medicine[1,48,121]. For example, in jaundice or other liver ailments in general, several drugs such as Hepex, Liv 52, Vimliv, Nirocil, Livocin, Livcure, Livol etc. wherein *Phyllanthus* plants have been used. There are about 25 *Phyllanthus* species having hepatoprotective activity, some of them possess significant activity such as *P.amarus, P. niruri, P.fraternus. P.maderaspatensis, P.emblica, P.debelis, P.acidus, P.urinaria, P.sellowianus, P.stipulatus, P.corcovadensis, P.chamaecristoides, P.caroliniensis, P. tenellus, P.orbiculatus, P.acuminatus, P.myrtifolius, P.discoides, P.virgatus* and *P.mummuariifolius*. Phytochemical studies carried out on these plants have reported a number of compounds including alkaloid, flavonoid, lignan and terpene etc. The morphological, biological and phytochemical aspects of the various species of the genus have been described here.

Phyllanthus amarus

Morphological characters

Erect annual herbs, 10-60cm tall; main stem simple or branched, terete, smooth, or scabridulous in younger parts. **Cataphylls:** Stipules 1.5-1.9mm long, deltoid-acuminate. Deciduous branch lets 1.5-14cm long, subterete, smooth, or a few lower nodes sometimes scabridulous with 13-30 distichous leaves. **Leaves**: 3-11×1.5-6mm, elliptic-oblong, obovate-oblong, or even obovate, obtuse, or minutely apiculate at apex, obtuse or slightly in equilateral at base; petioles 0.3-0.5mm long; stipules 0.8-1.1mm long. Triangular-acuminate.

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Flowers: Flowers in auxiliary unisexual and bisexual cymules on deciduous branch lets; proximal 2-3 axils with unisexual cymules of (1-) 2(-3) male flowers; all succeeding axils with bisexual cymules, each consisting of 1 male and 1 female, or 2(-3) males and 1 female, or 1 male and 2(-3) female flowers or combinations thereof. **Male flowers:** Pedicels at anthesis ca 1mm long. Calyx lobes 5 (rarely 6), subequal, each ca 0.7×0.3 mm, elliptic or oblong-elliptic and abruptly acute at apex, hyaline, with unbranched midrib. Disc segments 5, roundish. Stamens 3 (rarely 2): filaments connate into a column 0.2-0.3 mm high: anthers sessile atop the column, dehiscing longitudinally. **Female flowers:** pedicels 0.8-1 mm long, obtusely 4-gonous, dilated above, ca 1.5mm in fruits. Calyx lobes 5 (rarely 6), subequal, ca 0.6×0.25mm ca 1.0×0.3mm in fruits, ovate-oblong, or oblong, acute at apex: mid-sepline band green, about a third broad, margin hyaline. Disc flat, deeply 5-lobed, lobes sometimes toothed at apex. Styles 3, free, more or less spreading, shallowly bifid at apex; arms divergent. Capsules ca 1.8mm across, oblate, rounded. Seeds ca 0.9mm long, triangular with 6-7 longitudinal ribs and numerous minute transverse straie on back[2].

Biological properties

It is one of the most important medicinal plants, used as a traditional medicine in India, and elsewhere[3]. Entire plant is used in India to treat hepatitis, dysentery, irritating sores[4] and jaundice[5]. It is used in Tanzania for non-insulin dependent diabetes mellitus (NIDDM). The aqueous extract of the aerial part is drunk and leaves are chewed against persistent cough and leaves are used for stomaches[6].

Liver disease

There are five hepatitis viruses knows as hepatitis viruses such as hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, HDV and HEV. Based on substantial body of data HBV has been proved as a major viral pathogen producing chronicity in liver disease[7].

Several authors namely Sankaran[8], Sundaravalli et al.[9] have shown the effect of certain indigenous preparations, which have *Phyllanthus amarus* as one of their ingredients to be useful in treatment of undifferentiated viral hepatitis patients. The first ever designed *in vitro* antiviral study on *Phyllanthus niruri* against any hepatitis virus with (HBV) as model was reported by Thyagarajan[10] from India (madras). Subsequently Thygarajan et al.[11] have shown the whole plant extract of *P.niruri* from several solvents brought about binding of surface antigen (HbsAg). These plants were later identified by Unander as *P.amarus*.

Venkateswaran et al.[12] and Blumberg et al.[13] have shown that aqueous extract of *P.amarus* bound the surface antigen of HBV *in vitro*, have inhibited the viral DNA polymerase (DNA_p) of HBV and viral woodchuck hepatitis virus (WHV) *in vitro* at 50% inhibitory concentration (IC_{50}) of 59 and 140μg respectively; the IC_{50} values for calf thymus DNA_p was 115μg/ml and DNAP's of *Escheria coli* ranged from 120-460g/ml. When administered i.p. to WHV infected woodchucks, acutely infected animals lost the viral surface antigen: the surface antigen titer dropped in some chronically infected animals was lower than the untreated controls. *P.amarus* extract is significant against both in acute hepatitis B and against chronic HBV carriers[14].

In a clinical trial, carriers of HBV were treated with a preparation of the plant *P.amarus* for 30 days. 59% treated patient had lost hepatitis B surface antigen when treated 15-20 days after the end of the treatment compared with only 4% placebo treated controls. Some subjects have been followed for up to 9 months. In no case has the surface antigen returned[15].

The extract of *P.amarus* has been shown to inhibit the DNA polymerase of HBV and woodchuck hepatitis virus (WHV) *in vitro*[16]. The different fractions as hexane, chloroform, butanol and aqueous extract of *P.amarus* were tested for *in vitro* effects on HbsAg, HbeAg and HBV-DNA in serum samples. The extracts were effective against HBV antigens. The butanol extract being the most potent[17].

Aqueous extract of *P.amarus* was observed to inhibit the interaction between HbsAg/HbeAg and corresponding antibodies suggesting Anti-Hbe-like activity and an effect on HBV-DNA. It also inhibited the secretion of HbsAg from Alexander cell line (a human hepatocellular derived cell line *in vitro*) for a period of 48 hrs at a concentration of 1mg/ml on a single dose. This experiment proved the Anti-HBV property of *P.amarus* at cellular level and further confirms its beneficial use in the treatment of acute and chronic hepatitis B and healthy carriers of HBV[18].

P.amarus[19] inhibited HBV polymerase activity,

decreased episomal hepatitis B virus DNA content and suppressed virus release into culture medium. We use G26 hepatitis B virus transgenic mice, which produce serum HbsAg but neither HbcAg nor virion particle. When *P.amarus* was administered to transgenic mice hepatitis HbsAg mRNA levels decreased indicating transcriptional or post transcriptional down regulation of transgene. Disruption by *P.amarus* of HBV polymerase activity mRNA transcription and replication supports its role as an antiviral agent.

It suppressed[20] HBV mRNA transcription *in vitro* and exhibited therapeutic potential in chronic HBV carriers. Mechanism of action involve inhibition of HBV enhancer I activity to identify inhibition liver enriched cellular transcription factors were in HuH-7 cells. The C/EBP alpha and beta, as well as HNF-3 alpha and beta transcription factors significantly unregulated the HBV enhancer I activity. In contrast co transfaction of HNF-I alpha or beta had no effect upon HBV enhancer I activity, where as HNF-3 alpha or beta mediated up regulation of HBV enhancer I was unaffected. *P.amarus* suppresses hepatitis B virus by interrupting interaction between HBV enhancer and cellular transcription factors. It also demonstrated to suppress the HbsAg expression in human hepatoma cell, which was suggested to contribute the antiviral activity *in vivo*[21].

Its compound has remarkable effect for chronic viral hepatitis in the recovery of liver function and inhibition of the replication of HBV[22]. Niujz and co-workers also demonstrated the efficacy of *P.amarus* to eradicate duck hepatitis B virus replication *in vivo*[23]. Its efficacy was evaluated in parallel to another drug essentials in acute HBV group, *P.amarus* treated patient recovered faster than the essential treated group[24]. In Thailand, it was demonstrated to possess minimal effect on eradication of HbsAg from Thai adult asymptomatic chronic carriers[25].

Anti HIV activity

The aqueous/alcoholic extract blocks HIV-1 attachment and the HIV-1 enzymes integerase, reverse transcriptase and protease to different degrees[26,27].

Anticarcinogenic activity

The extract reversibly inhibited cellular proliferation and suppressed HbsAg production in cultured hepatoma cell line Hep A2[28]. Aqueous extract of *P.amarus* exhibited potent anticarcinogenic activity against 20-methyl cholanthrene (20 MC) induced sarcoma development and increased the survival of tumor harboring mice[29]. *P.amarus* extract inhibited gastric carcinogenesis induced by N-methyl N'-nitro-N-nitroso guanidine (MNNG)[30].

Ant mutagenic and Antigenotoxic activity: Aqueous extract of *P.amarus* possessed antimutagenic and antigenotoxic properties. It was examined using the bacterial preincubation mutation assay and *in vivo* alkaline dilution method for DNA single strand breaks in hamster liver cells[31]. Antigenotoxic property was evaluated using the root meristem of *vicia faba* L as the *in vivo* test system[32].

Insecticidal activity

Ethanolic root extract of *P.amarus* possessed significant insecticidal activity against *T.castaneum*[33].

On reproductive organs: The aqueous crude extract of *P.amarus* and *E.hirta* caused varying degrees of testicular degeration as well as reduction in the mean seminiferrous tubular diameter (STD) in the treated rats[34].

Hexane extract of *P.amarus* produces antialloynia and antiedema in two models of inflammatory and neuropathic pain[35].

Hypoglycemic activity

Methanolic extract of *P.amarus* was found to have antioxidant activity and hypoglycemic effect. The extract reduced the blood sugar in alloxan diabetic rats at 4th hr by 6% at a dose level of 200mg/kg body wt and 18.7% at a concentration of 100mg/kg body wt continued administration of extract for 15 days produced significant reduction in blood sugar[36].

Anti-inflammatory activity

P.amarus has anti-inflammatory potential by inhibition of endotoxin-induced nitric oxide synthatase, COX-2 and cytokines via the NF- Kappa B pathway[37]. Methanolic extract at a dose of 50, 200 and 1000 mg/kg body wt significantly inhibited gastric lesions, induced by intragastric administration of absolute ethanol (8ml/kg). Aqueous and methanolic extract of *P.amarus* produced an inhibition of rat paw edema upto 42% compared to control in 3 hr and continued upto 8 hr[38]. The extract of *P.amarus* 100(mμg/ml)

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decreased the specific binding of [(3) H]- PAF in mouse cerebral cortex membranes and showed anti-inflammatory activity[39].

Contraceptive effects

Antifertility effects of an alcohol extract of the whole plant, *P.amarus* at a dose of 100mg/kg body wt for 30 days orally was investigated in cyclic adult female mice[40].

P.amarus extract was found to inhibit cytochrome P450 enzyme both *in vivo* as well as *in vitro*[40].

Antimicrobial potentiality of methanolic extract of *P.amarus* against drug resistant pathogens was observed[41]. Anti-diarrheal and gastro intestinal protective potentials of aqueous extracts of leaves of *P.amarus* were investigated in mice[42]. It showed diuretic, hypotensive effect and hypoglycemic effect[43]. Its hexane extract was found to have inhibitory effect on α-amylase[44]. It also showed radioprotective effect[45].

Phytochemical aspects

Isolated compounds niranthin exhibited anti-inflammatory and antiallodynic actions, which are probably mediated through its direct antagonistic action on the PAF receptor binding sites[35]. Two new securinege type alkaloids isobubbialine **(1)** and epibubbialine **(2)** and three known alkaloid phyllanthine, securinine and norsecurinine were isolated[46]. Two new secosterols named as amarosterol-A **(3)** characterized as 13, 14-*seco*-stigma 5(6), 14(15)-diene-3-α-ol and amarosterol -B **(4)** characterized as 13, 14-seco-stigma 9(11), 14(15)-diene-3-α-ol were isolated from whole plant[47].

Phyllanthus niruri

Morphological characters

It is an erect annual herb, leafy shoot is less than 5 cm long, acute and terete and flower bears 6 tepals in two whorls of three each, distributed in Tropical Asia from India to Malaysia[48].

Biological properties

The plants are used in the indigenous system of medicine such as ayurveda, which describes its use in bronchitis, leprosy, anemia, urinary discharge, asthma, diuretic and menorragia. Unani system of medicine prescribed it for sore and chronic dysentery, in tubercular ulcers wounds bruises scabies ringworm etc. fresh root is said to be excellent remedy for jaundice[49].

Several preparations such as Nirocil, Liv-52, Hepex, Livosin, Vimliv, Livol, etc are being used in the traditional system of medicine and these have *P.niruri* as one of the major ingredients and are reported to be successful in the treatment of jaundice and liver cirrhosis.

Urolithiasis

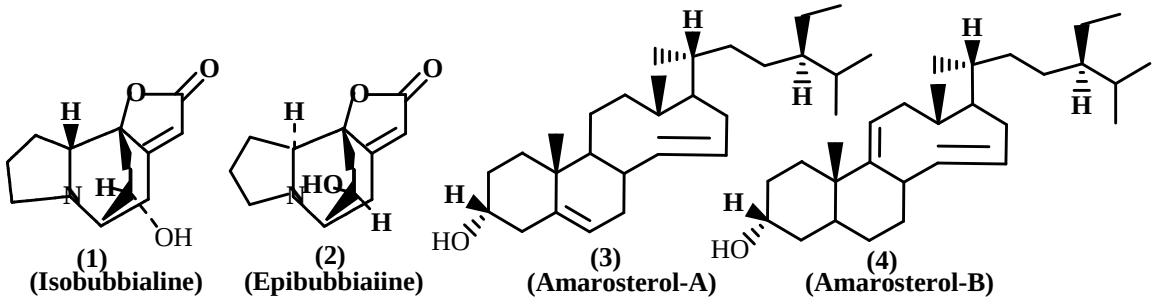
P.niruri known as stone breaker. Aqueous extract of *P.niruri* inhibit Calcium oxalate crystallization *in vitro*[50]. It is used for the treatment of urolithiasis and also inhibited *in vivo* model[51-55].

Antiplasmodial activity

The *in vitro* and *in vivo* antiplasmodial activity of the ethanolic and dichloromethane extract as well as the toxicity of the lyophilized aqueous extract from *P.niruri* was reported[56]. Dichloromethane fraction (rich in terpenic constituent) of ethanolic extract of callus culture exhibited higher activity than its isoamyl fraction rich in flavonoid[57].

Antihepatitis activity

Fresh roots have been reported to be potent remedy for jaundice[58]. It showed potency against hepatitis B virus[59]. Extract showed potential therapeutic action in the management of hepatitis B[60].



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Hepatoprotective activity

The hexane isolated fractions of *P.niruri* have been reported to be hepatoprotective against carbon tetrachloride and galactosamine induced cytotoxicity in primary cultured rat hepatocytes[61]. Isolated fraction protected liver from nimesulide induced oxidative stress[62].

Anti HIV

P.niruri inhibit HIV-1 RT[63,64]. It showed anticancer[65], antidiabetic[66], analgesic[67] and lipid lowering activity[48]. An aqueous infusion of the whole plant, which is a typical preparation, is employed as a stomachic, aperitive, antispasmodic, laxative, diuretic, and carminative against constipation, fever including malaria, hepatitis B, dysentery, gonorrhea, syphilis, tuberculosis, cough, diarrhea, and vaginitis[69,70]. It inhibits avian myeloblastosis virus reverse transcriptase[71].

Phytochemical aspects

It showed the presence of number of alkaloids, triterpenes, flavonoides, lignans, tannins, glycosides and some steroidal substances.

Terpenes: An acyclic triterpene (3, 7, 11, 15, 19, 23-hexamethyl-2Z, 6Z, 10Z, 14E, 18E, 22E-tetracohexen-1-ol)[72] **(5)** has been isolated from the hexane extract of the plant. Three euphane triterpenoides viz. phyllanthenol **(6)**, phyllanthenone **(7)**, phyllantheol **(8)** and an acyclic diterpene, trans-phytol have been isolated from the hexane extract[73].

Alkaloids: It showed the presence of alkaloid in methanolic extract and isolation of ent-norsecurinine **(9)** and tetrahydro ent- securinine[74] has been reported from methanolic extract of whole plant. Two more alkaloids norsecurinine **(10)** and securinine **(11)** have been isolated[75]. Three securinine type alkaloids have been isolated from chloroform extract, viz. 4-methoxy dihydro norsecurinine **(12)**, 4-methoxy tetrahydro securinine **(13)** and 4-hydroxy securinine[76] **(14)** along with eight known alkaloids like securinine and norsecurinine[77], dihydro securinine, tetrahydro securinine, securinol-A, securinol-B[78], phyllanthine[79], allosecurinine[80].

Flavonoids: A number of flavonoids like quercetin, quercitrin, isoquercitrin, asragalin, rutin[81], kaempferol-4′-rhamnopyranoside, eridictyol-7-rhamnopyranoside, 3,5,7-trihydroxy flavanol-4′-o-α-L-(-) rhamnopy ranoside[82] **(15)**, fisetin-4′-glucopyranoside[83] **(16)** etc have been reported in the plant.

Glycosides: It showed the presence of niruriside[84] **(17)**, nirurin **(18)** and nirurinetin[85] **(19)**, in methanolic extract.

Sterols: A new phthalic acid bis-ester, named as phyllester **(20)** together with β-sitosterol, dotriacontanoic acid and a rare sterol, 24-isopropyl cholesterol have been isolated from the hexane extract of the aerial parts[86].

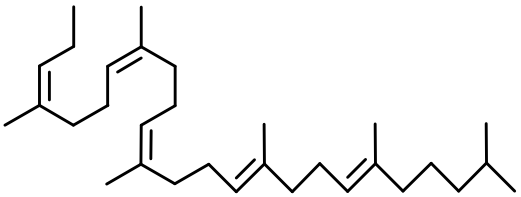
Lignans: A new new lignan, nirphyllin **(21)**, established as 3,3′,5,9,9′-pentamethoxy-4-hydroxy-4′,5-methylene dioxylignan and neolignan phyllnirurin **(22)** established as 3,4-methylene dioxy-5′-methoxy-9′-hydroxy-4′,7-epoxy-8,3′-neolignan have been isolated from n-hexane extract of dried aerial parts of the plant[87]. Seven lignans have been isolated as lintetralin[88-90] **(23)**, isolintetralin[91] **(24)**, hypophyllanthin[88,91,92] **(25)**, nirtetralin[88,90] **(26)**, niranthin[90,92], phyllanthin[90,93] **(27)** and honikin[93] from the ethanol extract of *P.niruri* growing in Taiwan. The antihepatotoxicity of plant was found to be due to the presence of lignans and acyclic compounds. The unusual secolignan **(28)** and two new hydroxylignan as seco-isolariciresinol trimethylether **(29)** and hydroxy niranthin **(30)** have been isolated[61]. β-glucogallin **(31)**, quercetin 3-O-β-D-glucopyranosyl-(2→1)-O-β-D-xylopyranoside **(32)**, 1-O-galloyl-6-O-luteoyl-α-D-glucose **(33)**[93].

Dibenzyl butyrolactone **(34)** was isolated and reported to exhibit antitumor activity[61]. Repandusinic acid-A isolated from the aqueous extract of *P.niruri*, which inhibited human immunodeficiency virus type-1 reverse transcriptase inhibitor (HIV-1 RT)[95]. It afforded alkaloides[96], lignans[97,98,99], flavonoids[100,101], lup-20 (29)-en-3β-ol[102], phthalic acid ester, fatty acid[103], vitamin C[104], ellagic acid, geraniin and gallic acid[105].

Phyllanthus maderaspatensis

Biological properties

It is traditional herbaceous medicinal plant. The



(5) (3,7,11,15,19,23-Hexamethyl-22,62,102, 14E,18E,22E-tetracohexen-1-ol)

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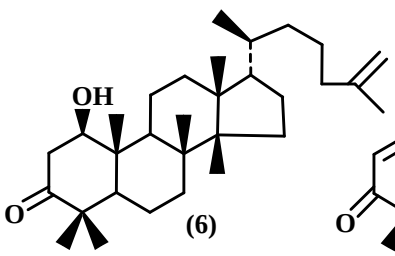
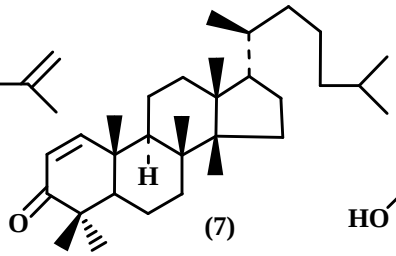
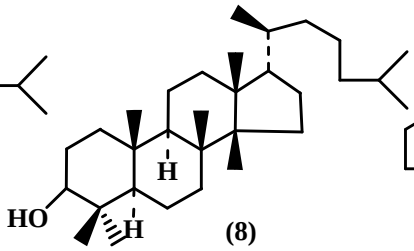


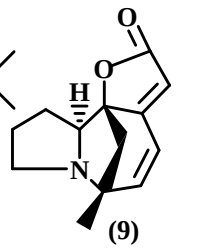
(6) (Phyllanthenol)



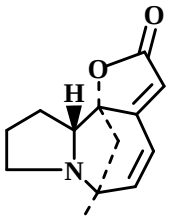
(7) (Phyllanthenone)



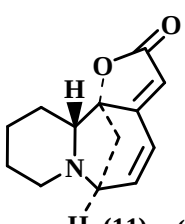
(8) (Phyllantheol)



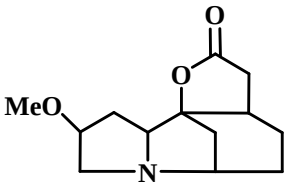
(9) (Ent-norsecurinine)



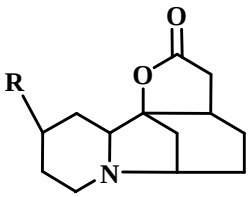
H (10) (Norsecurinine)



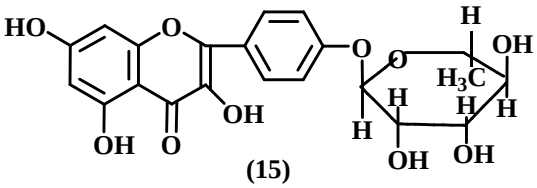
H (11) (Securinine)



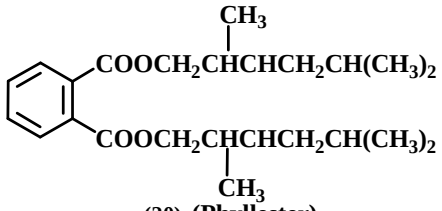
(12) (4-Methoxy- dihydro-norsecurinine)



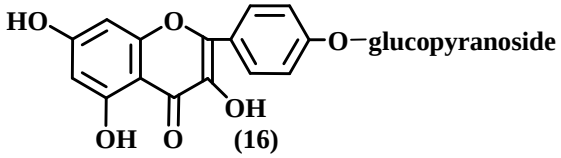
(13) R =OMe (4 -Methoxy tetrahydro-securinine)
(14) R = OH (4-Hydroxy securinine)



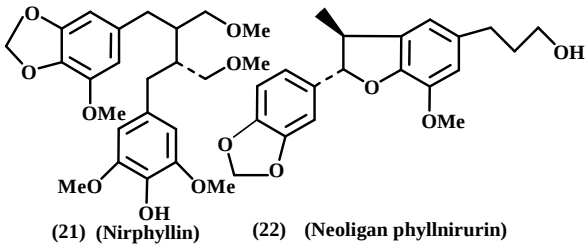
(15) (3,5,7-Trihydroxy flavonol-4'-O-alpha-L-(-) rhamnopyranoside)



(20) (Phyllester)

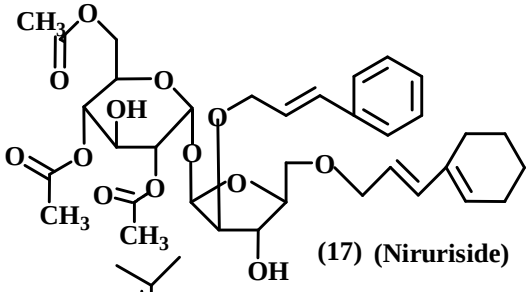


(16) (Fisetin-4'-O-glucopyranoside)

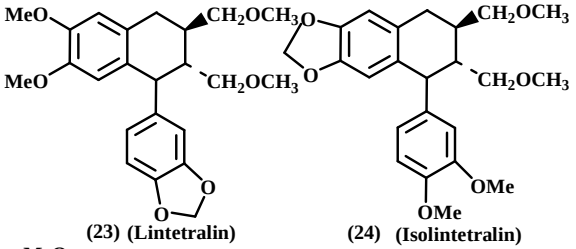


(21) (Nirphyllin)

(22) (Neoligan phyllnirurin)

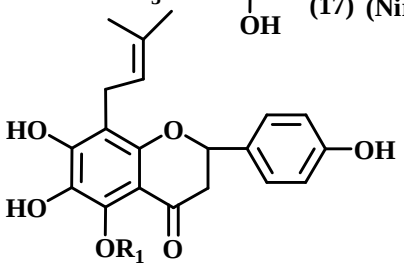


(17) (Niruriside)

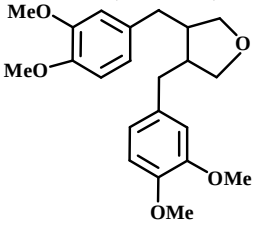


(23) (Lintetralin)

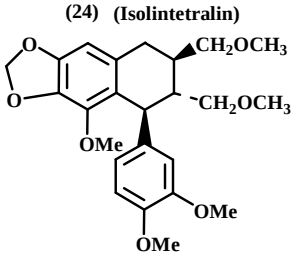
(24) (Isolintetralin)



(18) R_1 = Rhamnoglucosyl (Nirurin)
(19) R_2 H (Nirurinetin)

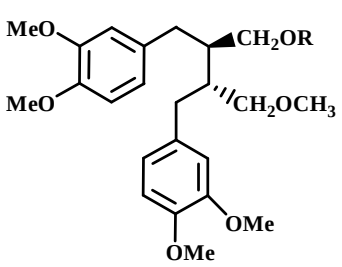


(25) (Hypophyllanthin)

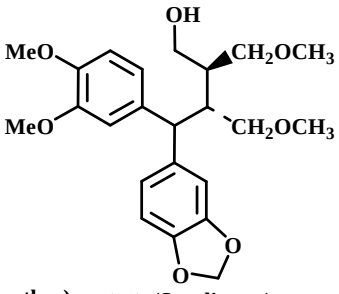


(26) (Nirtetralin)

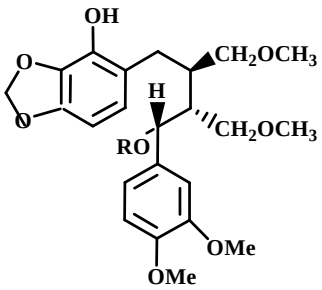
Review



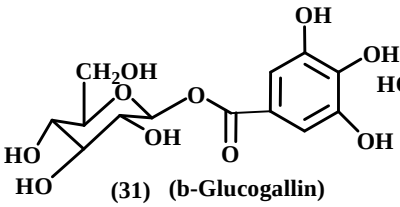
(29) R = H (Seco-isolariciresinoltrimethy ether)
(27) R = CH_3(Phyllanthin)



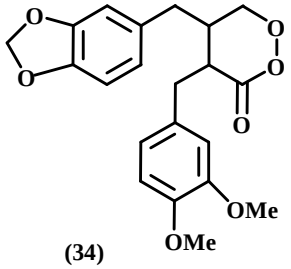
(28) (Secolignan)



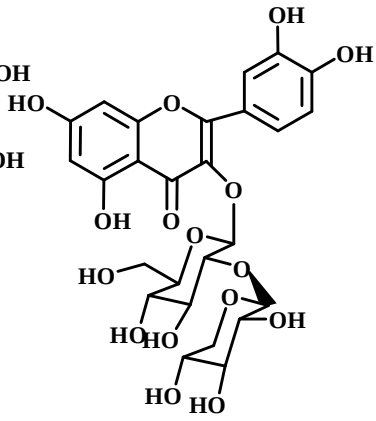
(30) (Hydroxy niranthin)



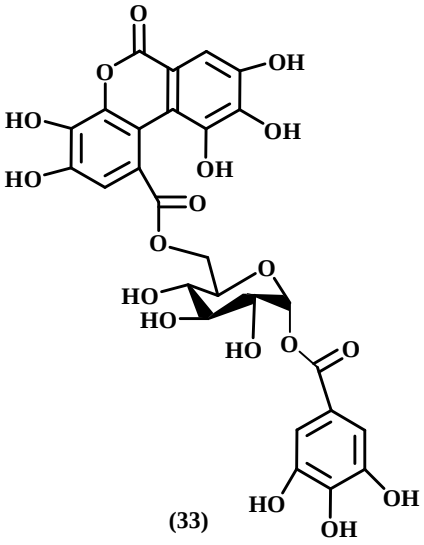
(31) (b-Glucogallin)



(34)
(Dibenzyl butyrolactone)



(32)
Quercetin 3-O--D-glucopyranosyl-
(2→1)-O-b-D-xylopyranoside



(33)
(1-OGalloyl-6-O-luteoyl-a-D-glucose)

leaves are expectorant, diaphoretic and used in strangury and sweats. The seeds have a bad taste and are carminative, laxative, toxic to liver, diuretic, and used in bronchitis, earache, gripping, opthalmia and asites[106]. In South India an infusion of the leaves is given for headeche[107].

Hepatoprotective activity

The remarkable hepatoprotective activity of this plant powder (water suspension) at a dose of 500mg/kg against acetaminophen induced liver damage in Wistar rats[108]. Antihepatotoxicity of the hexane extract was found to be better than silymarin, a standard hepatoprotective herbal drug. The ethyl alcohol and water extract showed moderate activity. The hexane extract exhibited cholerectic activity, hydroxyl radical scavenging activity and inhibition of lipid peroxidation[106].

Phyllanthus urinaria

Biological properties

It has been used in folk medicine for liver protection, diabetes, hepatitis, jaundice and dropsy[109]. The hydro alcoholic extracts of stems, leaves and roots of *P.urinaria* caused graded contraction in guinea pig trachea[110] and urinary bladder[111].

Hepatoprotective activity

The extract exhibited hepatoprotective action by inhibiting CCl_4 induced decrease of mobility of membrane of liver cells and increase of intracellular free Ca^{2+} concentration of liver cells[112].

Anti-HBV

The anti duke hepatitis BV effect- the duck hepatitis BV model was treated with *P.urinaria* of different area and combined with Sphora flavesceus as well as

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ciprofloxacin once a day for one month, the result indicated Guangxi and Yunnan. *P.urinaria* could lower the serum DHBV DNA significantly (P<0.05) but chongging *Phyllanthus* could not. The antiviral effect of Guangxi P combined with ciprofloxacin seen to be strengthened (P<0.05)[113].

Anticancer activity

It showed antitumor effect on mice bearing lewis lung carcinoma[114,115]. The water extract induces apoptosis in human cancer cells[116].

Antidiabetic activity Oral administration of 50% methanolic extract decreased the blood glucose by 24% after 3 hrs in streptozocin induced diabetic rats[117].

Phytochemical aspects

A novel polyphenolic compound phyllanthusin F was isolated[118]. A novel ellagitannins named phyllanthusiin G(1-O-galloyl-2-phyllanthoyl-3, 6-(···)-HHDP-β-D-glucose) was isolated[119]. Two new phenolic compounds crystal VI (methyl brevifolincarboxylate) and crystal IX (trimethyl ester dehydrochebulagic acid) and eight known compounds have been isolated as n-octadecane, β-sitosterol, ellagic acid, daucosterol, kaempferol, quercetin, gallic acid, rutin[120]. Four lignans namely 5-demethoxyniranthin **(35)**, urinatetralin **(36)**, dextro bursehernin **(37)**, urinaligran **(38)** together with nine known lignans as phyllanthin, niranthin **(39)**, phyltetralin **(40)** hypophyllanthin, nirtetralin, lintetralin, isolintetralin, heliobuphthalmin lactone **(41)**, virgatusin[121] **(42)**.

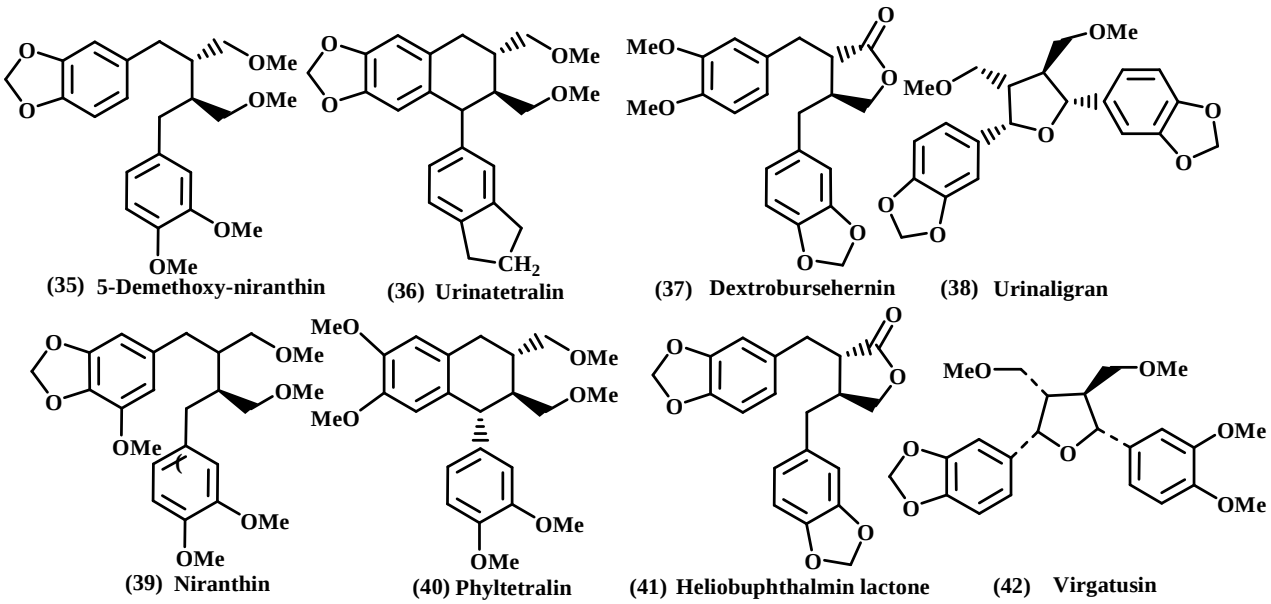
Ellagic acid was isolated from *P.urinaria*, which blocks effectively Hbe Ag secretion in Hep G2 2.2.15 cells. It active against immune tolerance in HBV infected individuals[122].

Seven ellagitannins were isolated from *Phyllanthus myrtifolius* and *P.urinaria*. All these compounds have the same moiety of corilagin and differ from each other by different substitution at C-2 and C-4 at the glucose core. These tannins are active against viral DNA polymerase[123].

Phyllanthus fraternus

Morphological characters

It is distributed in Pakistan and India and has been introduced into Africa and West Indies. It is an erect annual herbs 7-50cm tall; main stem terete and mostly naked below, rarely when young with inconspicuous normal leaves in lower 2-3 nodes, 4-gonous above, often with a few slender, lateral branchlets with age. **Cataphylls:** Stipules 0.8-1.2mm long, lanceolate, not dilated at the base; blade narrower. Deciduous branchlets (2-) 4-11cm long with 10-30 leaves, 4-gonous with decurrent leaf bases on either side conspicuously winged-edge. Leaves 3-16×2-8mm, elliptic oblong, rounded at apex, obtuse or cuneate at base, dark green above, paler beneath with prominent midrib and 4-5 faintly raised lateral nerves; petiols0.3-0.6cm long: stipules similar to cataphyll stipules. **Flowers** in



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axillary cymules on deciduous branchlets; proximal (2-) 3-4(-5) axils with 2-3 male flowers, succeeding axils with solitary female flower; transitional axil occasionally with a bisexual cymules. **Male flowers:** pedicels at anthesis 0.5-0.8mm long. Calyx lobes 6, subequal, membranous, hyaline, each 0.6-0.7×0.4-0.5mm. elliptic, acute or subacute at apex, with unbranched midrib. Disc segment 6, irregularly angular or lobed. Stamens 3; filaments connate into a column about 0.3 mm high; anthers sessile atop the column, dehiscing longitudinally. **Female flowers:** Pedicels Ca 1.2mm long, obtusely 4-ganous, dilated above, becoming 1.5-2mm in fruits. Calyx lobes 6, unequal, each 1-1.2×0.4-0.5 mm, upto 1.5×0.7mm in fruits, elliptic, obovate, or even spathulate, rounded to subacute at apex; green mid sepline band unbranched, about a third broad: margin hyaline. Disc of three broad, irregularly laciniately toothed segments, each deeply 2-3 lobed with age (i.e. of 6-9 lacerated and toothed segments) style 3, free, erect and spreading, each briefly bifid at apex; style arms knob like, diverging. Capsules ca 2m across, oblate, rounded. Seeds ca 0.9 mm long, with 6-7 longitudinal ribs and many fine transverse striae on the back[2].

Biological properties

It is an herb reported to possess astringent, deobstruent, stomachic, diuretic, febrifugal and antiseptic properties. It is used in stomach trouble and is also employed in dropsy and urogenital disease[121].

Antihepatotoxic effect

Administration of rat with an aqueous extract prior to hepatotoxic administration showed significant protection on the CCl_4[125] and alcohal[126] induced mitochondrial dysfunction. Different fraction of alcoholic extract of aerial parts and roots of *P.fraternus* were screened for antihepatotoxic activity of CCl_4 induced liver damage in albino rats. The methanol fraction was found to be most potent, which was further supported by a significant recovery of hepatocytes in histopathological study of the liver[127].

The hydroalcoholic extract of the *P.fraternus* given i.p. inhibited the capsaicin-induced neurogenic pain[128].

Phytochemical aspects

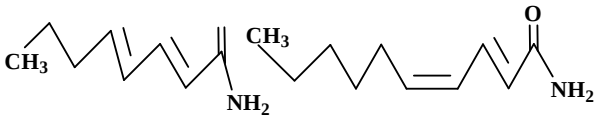
Two alkamides E,Z-2,4-octadienamide **(43)** and E,Z-2,4-decadienamide **(44)** were isolated[129].

Phyllanthus emblica

Biological properties

Hepatoprotective

The extract of *Phyllanthus emblica* at the dose of



(43) **(44)**

(E,Z-2,4-Octadienamide) **(E,Z-2,4-Decadienamide)**

100mg/100gm produced significant hepatoprotective against liquor and paracetamol administration in albino rats and mice respectively[130].

Anticancer activity

Aqueous extract of edible dried fruits of *P.emblica* showed cancer prevention when fed to mus musculus for seven consecutive days prior to treatment with different doses of metal[131,132].

On oral administration it was found to enhance natural killer cell activity and antibody dependent cellular cytotoxicity (ADCE) in synergic BALB/C mice bearing Dalton's lymphoma asites (DLA) tumor[133].

Anti-inflammatory activity

P.emblica showed anti-inflammatory activity due to inhibition of prostanoid and leukotriene synthesis by polar compounds present in leaves[134].

Anti-HIV[124], antiatherogenic[135], nitric oxide radical scavenging activity[136].

Phytochemical aspects

Besides Vit C, norsesquiterpenoides[137,138] as phyllaemblicin A**(45)**, phyllaemblicin B**(46)**, phyllaemblicin C**(47)**, phyllaemblic acid **(48)**, organic acid gallates as L-malic acid 2-O-gallate **(49)** and mucic acid 2-O-gallate **(50)** [139] were isolated from *P.emblica*. Hydrolysable tannins as 1-O-galloyl-β-D-glucose**(51)**, corilagin**(52)**, chebulagic acid **(53)**, eleocarpusin **(54)**, putrajivain **(55)**, geraniin **(56)**, phyllanemblinin C **(57)**, phyllanemblinin E **(58)** and flavonoides and condensed tannins as prodelphinidin B_1 **(59)**, prodelphinidin B_2 **(60)**, epigallocatechin 3-O-gallate **(61)**, (S)-eriodictyol 7-(6''-O-*trans*-coumaroyl) -β-D-glucoside **(62)**[140, 141] was isolated.

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A proanthocyanidin polymer phyllemtannin **(63)** was isolated from aqueous acetone extract of roots of *P.emblica*, this polymer composed of epicatechin, epigallocatechin, epicatechin 3-O-gallate and epigallocatechin 3-O-gallate in the chain extension part, and of catechin, epicatechin, gallocatechin and epigallocatechin units in the chain termination part[142].

A novel compound 3-ethyl gallic acid and isostrictiniin was from *P.emblica* for the first time[143]. Antiatherogenic effect of corilagin and dgg 16(1-O-galloyl-β-glucose) was reported[144]. Gallic acid, methyl gallate, corilagin, furosin and Geraniin showed nitric oxide scavenging activity *in vitro*. Geraniin showed highest nitric oxide scavenging activity[145].

Phyllanthus sellowianus

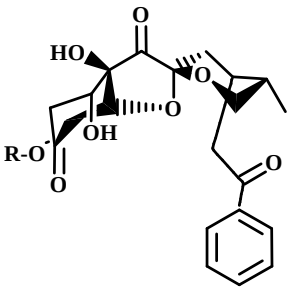
Dichloromethane and methanolic extract of leaves and stems of *P.sellowianus* inhibit the classical complementary pathway activity and aqueous extract inhibited the alternative complementary pathway[146]. It was found to inhibit the polymerase and ribonuclease activities of HIV-1 reverse transcriptase[147]. Alkaloid fraction showed prominent antispasmodic effect on isolated strip of guinea pig ileum and rat uterus[148].

Phytochemical aspects

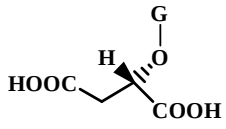
Already reported two ellagitannins geraniin **(64)** and furosin **(65)** were found in ethanolic extract of the leaves, both exhibited antinociceptive action[147]. This also showed the presence of new alkaloid phyllanthimide[149].

Phyllanthus stipulatus

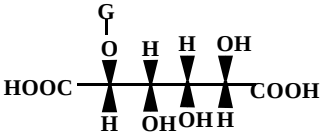
The methanolic extracts obtained from callus cultures of *P.stipulatus* caused significant inhibition into the late phase of the formalin test[150]. The hydroalcohalic extract of the *P.stipulatus* exhibited antinociceptive properties (analgesic) when given i.p.[151].



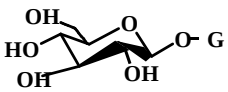
(45) R = Glu (Phyllaemblicin A)
(46) R = Glc^2-glc (Phyllaemblicin B)
(47) R = Glc^2-glc^2-ara (Phyllaemblicin C)
(48) R = H (Phyllaemblic acid)



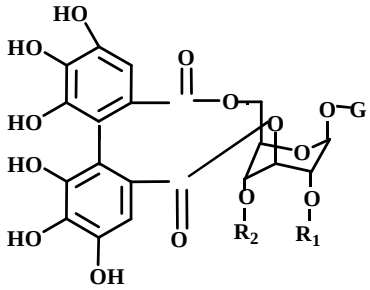
(49) (L-Malic acid 2-O-gallate



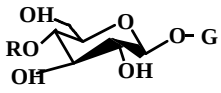
(50) (Mucic acid 2-O-gallate)



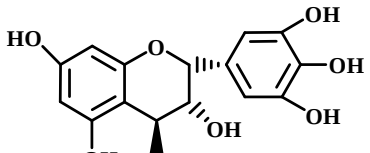
(51) (1-O-Galloyl-b-D-glucose)



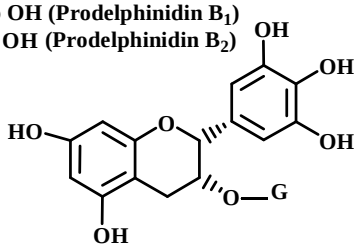
(52) R_1= R_2 = H (Corilagin)
(53) R_1 , R_2= Chebuloyl (Chebulagic acid)
(54) R_1 , R_2 = Ela (Elaeocarpusin)
(55) R_1 , R_2 = Put (Putranjivain)
(56) R_1 , R_2 = DHHDP (Geraniin)
(57) R_1, R_2 = A (Phyllanemblinin)



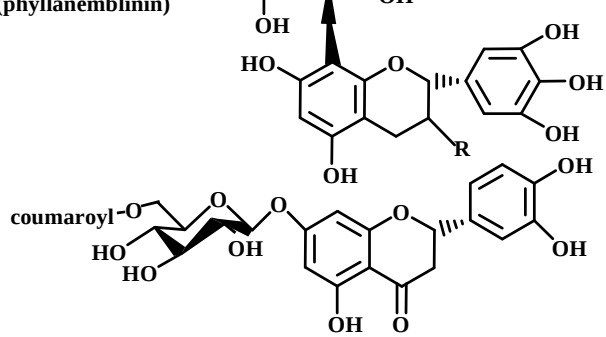
(58) R = Neochebuloyl (phyllanemblinin)



(59) R = b OH (Prodelphinidin B_1)
(60) R = a OH (Prodelphinidin B_2)



(61) (Epigallocatechin-3-O-gallate)



(62) (s)- Eriodictyol-7-(6''-O-trans-coumaroyl)-b-D-glucoside

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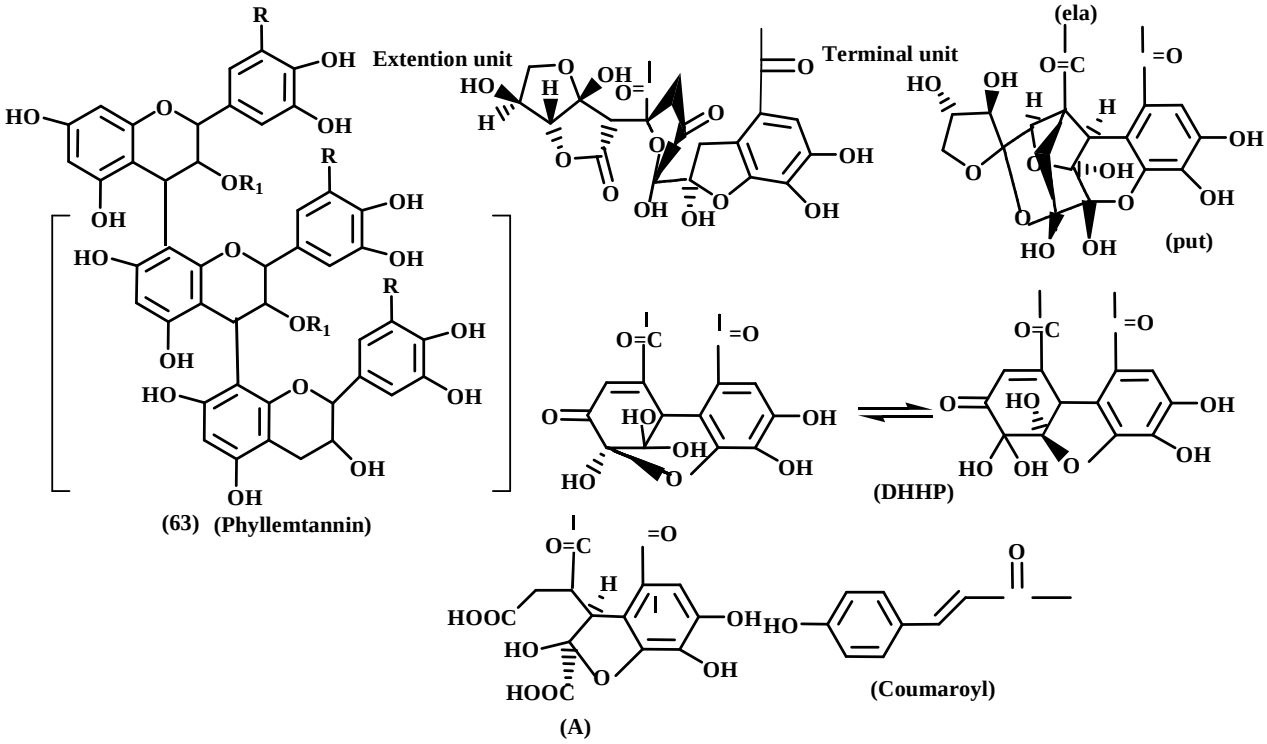

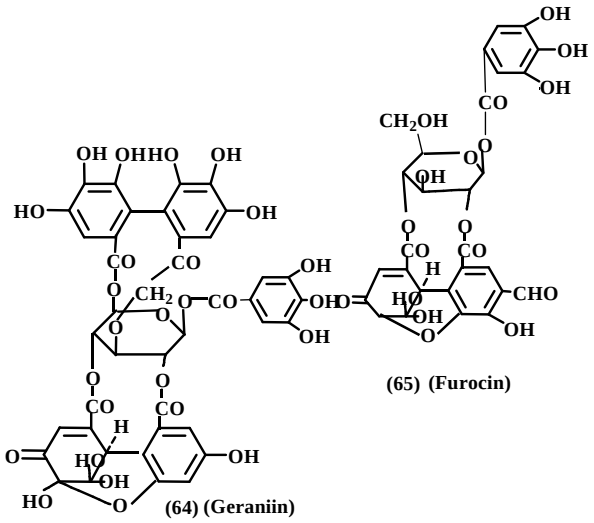

Phyllanthus corcovadensis

The methanolic extract from callus culture[152] and hydroalcohalic extract[153] was exhibited analgesic effect by inhibiting abdominal constrictions induced by acetic acid. It showed antinociceptive action in mice due to the presence of stigmasterol and stigmasterol acetate[154].

Phyllanthus chamaecristoides

The stem extract showed *in vitro* inactivity of HbsAg[155].

Phyllanthus caroliniensis

The methanolic extract of callus culture of *P.caroliniensis* causes significant inhibition into the late phase of the formalin test[150]. Phytosterols, quercetin, gallic acid ethyl ester and geraniin are isolated from hydroalcohalic extract of *P.caroliniensis*[156].

Phyllanthus orbiculatus

The Hydroalcohalic extract of *P.orbiculatus* exhibited antinociceptive properties[151].

Phyllanthus tenellus

The methanolic extract exhibited analgesic effect by inhibiting abdominal constrictions induced by acetic acid[152].

Phyllanthus acuminatus

It showed antitumor activity against murine B-16 melanoma and P-388 leukemia in monkey and dog probably due to the presence of phyllanthoside[157].

Phytochemical aspects

A new glycoside phyllanthostatin **(66)** was isolated along with didesacetyl phyllanthostatin-3 and descinnamoylphyllanthocindiol and phullanthostatin-A from roots[158].

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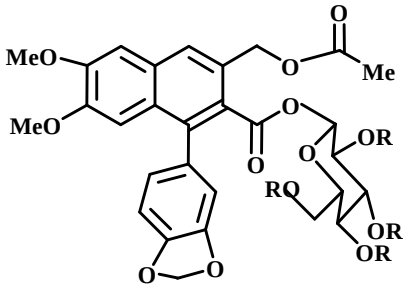
Phyllanthus myrtifolius

Isolated lignans (phyllamycin and retojusticilin) demonstrated to have prominent inhibitory effect on HIV reverse transcriptase activity[159].

Phyllanthus discoides

The extract from leaves has been found to show

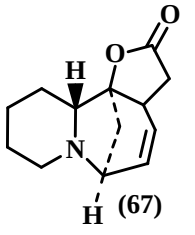


(66) (Phyllanthostatin)

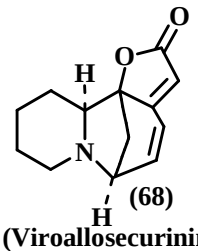
antibacterial[160] and uterotonic activities[161]. Phyllanthine[162], phyllochrysine[163] **(67)**, viroallo securinine[164] **(68)** and phyllalbine[165] **(69)** are isolated from *P.discoides*.

Phyllanthus virgatus

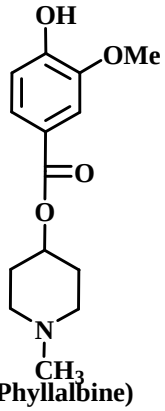
It showed the presence of five new compounds including lignan 2-(3,4-methylenedioxy phenyl)-3-butyne-1,2-diol named virgatyne **(70)**, a hydrolysable tannin, virganin **(71)** and three flavonoid sulfonates as galangin-8-sulfonate **(72)**, galangin-3-O-β-D-glucoside-8-sulfonate **(73)** and kaempferol-8-sulfonate[166] **(74)**.



(67) (Phyllochrysine)



(68) (Viroallosecurinine)

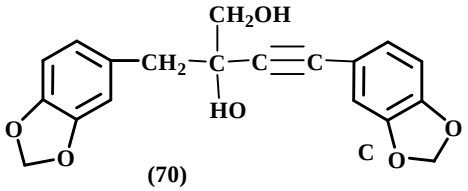


(69) (Phyllalbine)

Phyllanthus mummuariifolius

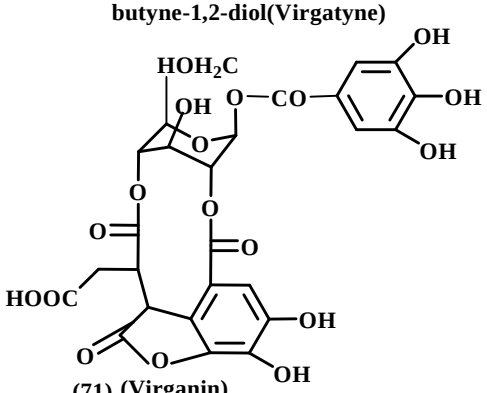
It was tested positively for the presence of terpenoides and steroids[167].

Phyllanthus debelis

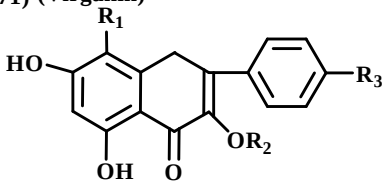


(70)

2- (3,4-Methylenedioxyphenyl)-3-butyne-1,2-diol(Virgatyne)



(71) (Virganin)



(72) $R_1 = SO_3Na$, $R_2 = R_3 = H$ (Galangin-8-sulfonate)

(73) $R_1 = SO_3Na$, R_2=gluco, $R_3 = H$ (Galangin-3-o-b-D-glucoside)

(74) $R_1 = SO_3Na$, R_2=H, $R_3 = OH$ (Kaempferol-8-sulfonate)

Morphological aspects

It is distributed in India, Sri Lanka, Burma, Indonesia, Pacific Islands and the West Indies. It commonly grows as a weed in rice fields, moist lands and muddy flats amidst grasses. It is restricted to the coastal regions. On the other hand *P.fraternus* and particularly *P.amarus* are ubiquitous species and found almost throughout India. It is an erect annual herbs 10-70cm tall: main stem usually sparingly branched with conspicuous normal leaves in lower about ten nodes (also in a few lower branches) when young, becoming leafless, woody and sometimes much branched (even from base) with age, terete or sub-terete below, 4-gonous with more acutely angled leaf-bases on either sides decurrent between the nodes, smooth, with 7-35 leaves. Leaves variable, dark green above, paler beneath with prominent midrib and 4-5 faintly raised lateral nerves; those on main stem and primary branches 10-35×1-3 mm. Linear, linear-elliptic-lanceolate or oblanceolate,

acute, subacute or obtuse at apex, obtuse or attenuate at base: those on branchlets 4-20×1.5-6mm. linear, linear-lanceolate, ob-lanceolate, elliptic or even obovate-elliptic, acute, subacute or obtuse at apex, attenuate or obtuse at base: petioles 0.5-1mm long: cataphylls: stipules1.2-1.8×0.6-0.8mm. triangular-acuminate, one side somewhat dilated at base : blade about same in length, narrowly lanceolate, acuminate. Stipules similar to cataphyll stipules, but narrower and not dilated at the base.

Flowers in axillary unisexual cymules on deciduous branchlets: proximal (2-) 3-5 axils with 3-4 male flowers, succeeding axils with solitary female flowers; transitional axil occasionally with a bisexual cymule, or a few transitional axils sometimes even barren. Male flower: pedicels at anthesis 0.5-0.8 mm long. Calyx lobes 6, biseriate, subequal, membranous, hyaline, each 0.5-0.6×0.5 mm, obovate and somewhat cuculate at apex, with unbranched midrib. Disk segment 6, roundish. Stamens 3; filaments connate into a column about 0.3mm high; anthers sessile atop the column, dehiscing horizontally. Female flower: Pedicels ca 1.2mm long, obtusely 4-gonous, dilated above, becoming ca 1.2mm in fruit. Calyx lobes 6, biseriate, subequal, each 1.5×0.8-0.9 mm, becoming ca 2.0×1.1 mm in fruit, oblong-obovate, or oblong-elliptic, subacute or obtuse at apex: midsepline band green, unbranched, about a third broad, margin hyaline. Disc saucer shaped, obtusely and shallowly 6-lobed along margin. Style 3, free, appressed to ovary, each bifid at apex; style arms recurred. Capsules ca 2.5 mm, across, oblate, rounded.

Seeds 1.0-1.1mm long, trigonous, with 7-8 longitudinal ribs and many transverse striae on back[2].

Biological properties

Aqueous extract of leaves showed strong anticomplement effect on both the classical and alternate pathways of the human complement system *in vitro*[146,168].

Phyllanthus simplex

It has been already reported to have antiseptic properties[124]. In Philippines the juice of the leaves is employed in eye disease and fresh leaves, flowers, fruits with cumin seeds and sugar are used in gonorrhea. A preparation of root is applied to mammary abscesses [169].

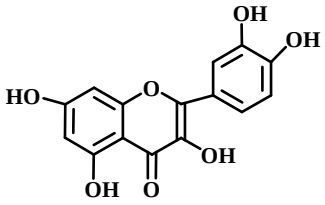
The brevifolin and 8, 9-single-epoxybrevifolin isolated from *P.simplex* showed protective effect against acute and chronic liver injuries[170].

Phyllanthus acidus

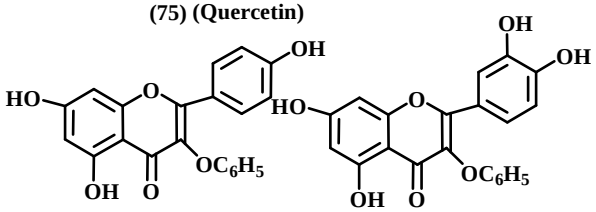
The methanolic extract showed hepatoprotective and antioxidant effect[171]. Phyllanthusols A, phyllanthusols B[172], adenosine, kaempferol and hypogallic[173] are isolated from *P.acidus*.

The extract of five Australian *Phyllanthus* species e.g. *P.hirtellus, P.gunni, P.gastroemi, P similis, and P.tenellus* caused 50% inhibition of DHBV DNA polymerase activity at concentration of dry wt 350-800µg/ml[174].

P.niruri, P.urinaria, P.orbiculatus were found to have five flavonoides- quercetin **(75)**, isoquercetin, astragalin **(76)**, quercitrin **(77)** and rutin[86].



(75) (Quercetin)



(76) (Astragalin) **(77) (Quercitrin)**

CONCLUSIONS

The present review article has shown that the genus phyllanthus possesses a wide variation in occurrence, and morphological characters, and in distribution. It contains plants of medicinal importance, which have used in many commercial herbal preparations for the treatment of various ailments of liver and other diseases. A large number of chemical constituents belonging to various classes have also been reported from plants of the genus. Some of them possessed some important biological properties.

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