

Phyto-Pharmacology of *Phyllanthus amarus*, an overview

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Summary

Phyllanthus amarus (PA) is a small herb indigenous to Amazon Basin. It is well known for its medicinal properties and widely used by oriental countries. It is reported to contain lignans, alkaloids, flavonoids, galloatanoids, glycosides and alkaloids. It possesses antiviral, antiparasitic, antimalarial, antimicrobial, anticancerous, anti-diabetic and anti-Cholesterol agents. It acts on kidney stones & Uric Acid. It protects liver & detoxifies the toxicity. It has cellular protective and wound-healing properties. Further activity guided phytochemical phytoanalytical studies may indicate to development of novel agents to be used in various disorders. An overview of chemical constituent in the plant and their pharmacological actions are given in the present paper.

Keywords: *Phyllanthus amarus*, chemical constituent, pharmacological properties.

Introduction

Since pre-historic day attempts are being made to find out suitable drugs from natural source for the treatment of diseases. As synthetic medicines cause various inevitable side effects; recently, much important has been imparted to develop the formulations from the plant source which are almost free from toxic actions. The plant families are the rich source of organic compounds, many of which are well known for their therapeutic properties.

Phyllanthus amarus Schum. Thonn. (Euphorbiaceae) is an annual herb grows to a height 6 inches-15 inches. Stem is angular with numerous distichous, elliptic oblong leaves. Flowers are yellow and numerous in numbers.

Fruits are capsule shaped, very small, globose, and smooth. The flowering time in Indian climate is July to August. It is found widely distributed all over the world. This species is indigenous to the rainforests of the Amazon and other tropical countries like India, China, Bahamas.

The therapeutic effects has been acknowledged as an anti-diabetic, and anti-cholesterol properties, anti-cancerous and cellular protective actions, liver protective and detoxification actions, antiviral actions, antispasmodic, pain-relieving anti-inflammatory activity and normalizes elevated urinary calcium levels in calcium stone forming patients. Furthermore extracts of PA possess antiparasitic, antibacterial and antimicrobial activity. It is also used for its wound healing properties. Several biologically active compounds including alkaloids, flavonoids, lignans, phenols and terpenes were identified from this species and most of them interact with the key enzymes of the body.

Together this data strongly supports the view that this plant has the beneficial therapeutic effects to manage, balance, detoxify and to tone the whole body.

Phytochemical constituents

The main active constituents are lignans (phyllanthin, hypophyllanthin, nirurin etc), flavonoids (quercetin, quercetrin, rutin etc), terpenes, tripenes, alkaloids etc. The leaves are the rich source of phyllanthin a diarylbutane and hypophyllanthin an aryltetrahydronaphthalene type of lignan. The 15% hot aqueous-KOH extract yielded a linear beta (1---4) linked xylan and 2% aqueous-KOH provided a complex acidic heteroxylan with a (1---4) linked beta xylan chain, substituted by rhamnose, arabinose, and 4-O-methylglucuronic acid side chains (1). These molecules contain non-reducing end – units of arabinose, xylose, galactose glucose and non-methylated glucuronic acid. High performance liquid chromatographic (reversed phase) analysis proved the presence of phenolic constituents in aqueous extract of PA. The tannin groups found in PA are ellagitannins or hydrolyzable tannins and condensed tannins. On the hydrolysis the ellagitannins finally afforded ellagic acid and gallic acid. The isolation process of geraniin, corilagin and their chemical structure are now established (2). Aqueous extraction of the total plant yielded an acidic arabinogalactan. Bioassay – guided analysis of the extract showed the presence of lignan niranthin. Methanolic extract from the leaves of were fractionated by resin chromatography led to the isolation of phyllanthin and antihyperuricemic lignan. (2). The presence of Pyrrolizidine types of alkaloids are reported in extract of PA, these are securinine, dihydrosecurinine, tetrahydrosecurine, Securinol- B, Phyllanthine, allosecurine, norsecurinine etc.

The presence of other securinine type of alkaloids is also proved. From the methanolic extract three alkaloids namely 4-methoxy dihydrosecurinine, 4-methoxytetrahydrosecurinine and 4-hydrosecurinine have been isolated.

It is also reported the presence of steroids and aliphatic type of compounds (4). Three euphane triterpenoids designated as phyllanthanol, phyllanthone and phyllanthol were identified from the hexane extract (5).

Pharmacological studies

Antiviral:

Niranthin, nirtetralin, geraniin suppressed effectively both HbSAg and HBeAg expression with the highest inhibition at 74.3%, 45.3%, 33.9%, 68.1%, and 52.3%, 46.6% respectively (6). PA down-regulates HBV mRNA transcription by a specific mechanism involving interactions between HBV enhancer I and C/EBP transcription factors (7). The aqueous extract, butanol and alcoholic extract of *Phyllanthus amarus* were described for the treatment of chronic hepatitis B virus infection on duck hepatitis B virus at the doses of 25, 50, and 200 mg/kg body weight (8). A clinical study was carried out for the eradication of hepatitis B virus with this plant extract. This species were collected from Central Thailand. Sixty-five adult asymptomatic chronic carriers were treated. Thirty four received PA extract at a dose 600mg per day for 30 days and thirty on received placebo in identical capsules, at day 30 the conversion rate of HbsAg was 6% in the experimental group. A further 30 days treatment were given to 20 subjects in the PA group and twenty placebo recipients given PA 1,200 mg per day for 30 days. The study indicated that the whole plant extract except root had a minimal effect to eradicate HBsAg (9). Another clinical study on chronic carrier of hepatitis B virus was encouraging and recommended continued evaluation of this plant. In this preliminary study, carriers of hepatitis B virus were treated with PA for 30 days. Fifty nine percent subjects had lost hepatitis B surface antigen when tested 15-20 days after the end of the treatment compared with only 4% placebo treated controls (10).

Actions on Kidney Stones & Uric Acid

In a clinical study it is reported that a significant increase in diuresis and sodium and creatine excretion after 1-3 months treatment with PA tea (11).

Calcium oxalate crystals are the building blocks of most kidney stones can be prevented by the administration of (PA) proved in an *in-vitro* clinical study (12). PA also increased bile acid secretion (demonstrated choleric activity) and significantly lowered blood cholesterol levels in rats.

Antispasmodic, Pain-Relieving, & Anti-inflammatory Actions:

Researchers proved PA's antispasmodic properties including uterine relaxant effect and finally it is concluded that "smooth muscle relaxation within the urinary or biliary tract probably facilitates the expulsion of kidney or bladder calculi" (13). The pain-relieving effects of PA were also performed against six

different laboratory-induced pain models. The hydrolysable tannin geraniin (14) of PA was seven times more potent as a pain reliever than aspirin or acetaminophen; it is also effective for its antiulcerous properties and to protect the gastric tract.

Liver Protective & Detoxification Actions:

An antihepatotoxic effect of PA is now proved in animals as well as in humans (15).

The two principles bioactive of PA are phyllanthin and hypophyllanthin lignans has been attributed their hepatoprotective properties (16).The worker has also been reported cholesterol lowering activity of this species. The different types of chemical induced liver toxicities in different animal models were also controlled pronouncedly (17, 18). Researcher of different parts of world established that PA extract is the single drug in the treatment of jaundice in children.

Anticancerous & Cellular Protective Actions

Numerous studies were documented that treatment with PA enhanced the life span of animals with liver cancer (19).When the aqueous extract of PA was administered to cancer bearing mice it lowered the tumor incidents, level of carcinogen-metabolizing enzymes, levels of liver cancer markers dose dependently (20).It is also established that extracts of PA have prevented or stopped the cells from mutation with the existence of chemical agents those are known to create cellular mutation and breaking down of DNA strands and finally leads to the formation of cancerous cells (21).These experimental data indicated that PA possesses the ability to inhibit the unusual enzymatic pathways peculiar to cancer cells proliferation and growth rather than a direct toxic effect of killing the different types of cancer cells.

The extract of PA has been administered orally (750mg/kg and 250mg/kg body weight) in the radiation (6Gy) induced BALB/c mice for its protective activity against carcinogenesis. The WBC count, bone marrow cellularity and α -esterase activity increased significantly as compared to only radiation – exposed mice. The antioxidant enzymes such as superoxidized dismutase (SOD),Catalase(CAT),Glutathione-S-transferase (GST), glutathione peroxidase (GPX),and glutathione reductase, both in blood and tissue, which were reduced by radiation induced (22).The life span of hepatocellular carcinoma induced by N-nitrosodiethylamine (NDEA) bearing rats increased significantly after treatment with the aqueous extract of PA (150mg/kg body weight). Likewise the increased glutathione and GST content in NDEA+PA treated group were also controlled (23). N-methyl N'-nitro-N-nitrosoguanidine (MNNG) induced stomach cancer in Wistar rats was significantly inhibited by the administration of PA extracts; it also reduced the incidence of gastric neoplasms in rats (44%) as well as their numbers. The elevated enzymes levels in the stomach were also found to reduce by PA treatment (24).

Anti-Diabetic & Anti-Cholesterol Actions

The extract (Methanolic) were administered 200mg/kg and 1000mg/kg body weight in alloxan induced diabetic rats and found to normalize the elevated blood sugar by 6% and 18.7% respectively. The anti-oxidant potentiality of the extract was also established by inhibiting the lipid peroxidation, scavenge hydroxyl and superoxide radicals *in – vitro* (25). The antidiabetic activity of the aqueous extracts of leaf and seed of PA was studied at oral dose of 150,300 and 600 mg/kg body weight. The experiment showed dependent decrement of the fasting plasma glucose level and cholesterol content and reduction of body weights in treated mice in a dose-dependent manner (26).

Antiparasitic, Antimalarial, Wound-Healing, & Other Antimicrobial Actions

PA showed its potentiality on wound healing (27). The methanolic extract of PA also possesses the antimicrobial activity; it was examined against some drug resistant pathogenic bacterial strains by disc diffusion and agar dilution process. The plant extract showed that it was more active to inhibit the growth of bacteria particularly against gram-negative bacteria (28).

Miscellaneous activities

Methyl brevifolin Carboxylate was isolated from the leaves of PA which showed vasorelaxant effect against norepinephrine induced contraction of rat aortic ring with or without endothelium. This compound inhibited NE induced vasoconstriction through receptors operated Ca²⁺ channels in the presence of nicardipine (29).

The lipid Triton (WR-1339) and cholesterol (25mg/kg bw) induced hyperleemic condition in rats was inhibited by oral feeding of PA extract (250mg/kg bw). Continuous administration of the extract for 30 days to rats lowered the lipid and apoprotein levels of VLDL and LDL (30).

The ethanolic extract of root and the aerial parts of PA significant insecticidal activity against stored grain pest *Tribolium castaneum* (31). The alcoholic extract of PA was found to be reduced cytochrome P-450 enzymes both in *–vivo* as well as *in-vitro* (21). The genotoxic effect of two types of tannary effluent (Raw-to-welblue and welblue to –Finish) and the antigenotoxic property of the crude extract of PA (2.5, 0.5, 0.75, 1%) was measured using the root meristem of *Vicia faba* L. *as in vitro.*)

Conclusion

PA possesses flavonoids, alkaloids, lignans etc. The pharmacological evaluation mentioned in this review establish the therapeutic value of this herb. Thus activity guided phytochemical and phytoanalytical may leads to development of novel agents for various disorders. The available literature regarding the chemical compositions and pharmacological activities appear to be very impressive.

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