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REVIEW ARTICLE

Pleiotropic Multifaceted Therapeutic Potential of *Phyllanthus amarus*

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ABSTRACT

Herbal drugs constitute a major share of all the officially recognized systems for the treatment of a wide range of diseases. More than 70% of world's population still uses the non-allopathic systems of medicine. Indian medicinal plants provide a rich source for health care moieties to prevent different diseased states. In spite of the great progress observed in modern medicinal systems in recent decades, herbal drugs still make an important involvement to health care. *Phyllanthus amarus*, a distinguished botanical worldwide, has been used since many years because of its rich medicinal importance. *Phyllanthus amarus* is a small, erect, annual herb having large number of phytochemicals that are attributed to its leaves, stem and roots. A wide array of studies anti-inflammatory, antidiabetic, antimicrobial, antihyperlipidemic, antioxidant, anticancer, hepatoprotective, antifertility, antidiarrhoeal, antiallodynic, antioedematogenic, antispasmodial, chemoprotective, antihypercalciuric, antiviral, antispasmodic, antinociceptive and diuretic properties associated with *Phyllanthus amarus*. The present review article summarizes about the phytochemicals associated with the plant. Moreover, numerous pleiotropic properties exhibited by the plant are also clearly discussed.

Key Words: Herbal, *Phyllanthus amarus*, Pleiotropic

INTRODUCTION

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of health viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. In the last few decades there has been an exponential growth in the field of herbal medicine which is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Recent years have seen considerable advances in our understanding of natural-product biosynthesis [1]. *Phyllanthus amarus* is an annual herb that grows upto 10-60 cms tall, erect, stem terete, younger parts rough, cataphylls 1.5-1.9 mm long, deltoid acuminate; leaf 3.0-11.0 by 1.5-6.0 mm, elliptic oblong to obvate, obtuse or minutely apiculate at apex, obtuse or slightly inequilateral at base; flowers axillary, proximal 2-3 axils with unisexual 1-3 male flowers and all succeeding axils with bisexual cymules; indigenous to the rainforests of the Amazon and other tropical areas including Bahamas, southern India and China [2].

Phyllanthus amarus has a long history of usage by the folk because of its rich medicinal values that has been reported to possess potent anti-inflammatory, antihepatotoxic, antilithic, analgesic, hypotensive, antispasmodic, antiviral, antibacterial, diuretic, antimutagenic and hypoglycemic properties (Fig I) [2]. Moreover, a large number of phytochemicals have been found only in the Phyllanthus genus. Many of the active constituents present in various parts of the plant are lignans, glycosides, flavonoids, alkaloids, ellagitannins and phenylpropanoids found in the leaf, stem and root of the plant. Common lipids, sterols and flavonols also occur in the plant [3]. The present review article discusses about the various phytochemicals present in the plant. Moreover, the pleiotropic pharmacological properties afforded by the plant have been delineated.

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PHYTOCHEMISTRY IN SUPPORT OF HERB

Phytochemistry is regarded as the heart of herbal therapy and the phytochemical research plays an important role in the development of herbal medicines. It constantly addresses a challenge because of the large number of compounds present as mixture in the extract in trace amounts. However screening of prefractionated extracts allows quick identification and dereplication of extract that depicts compound whose activity is masked in crude extracts. Though, the phytochemical research is comparatively slow as compared to synthetic but by all advanced methods including dereplication, mechanism based cleaning, drug design using natural molecules, have the potential to discover and develop active new chemical entities of rich medicinal values [4]. *Phyllanthus amarus* has been reported to possess two lignans namely phyllanthin and hypophyllanthin obtained from the leaves of the plant that has been noted to enhance the cytotoxic responses with cultured multidrug-resistant cells [5-6]. Niranthin, nirtetralin, phyltetralin and lintetralin; the four flavanone glycoside has been reported to be obtained from the leaves of *Phyllanthus amarus* [7-8]. Surprisingly, a steroidal hormone namely estradiol has been noted to be present in root and bark of the plant [9]. Quercetin quercitrin astragalin and fisetin-41-o-beta-d-glucoside were the two flavanoids that have been reported to be isolated from the entire plant of *Phyllanthus amarus* [10]. Phyllanthenol, phyllanthenone and phyllantheol are the three triterpenes obtained from aerial parts of plant [11]. Moreover, singh et al. reported nirphyllin and phyllnirurin, the two lignins that were isolated from the aerial parts of *Phyllanthus amarus* [12]. Additionally, Quercetin-3-o-beta-d-glucopyranosyl-(1-4)-alpha-lrhamno pyranoside, a flavanol was obtained from stem of the plant [13]. Moreover, the structure of three new lignans namely 2,3-desmethoxy seco-isolintetralin, 2,3-desmethoxy seco-isolintetralin diacetate and demethylenedioxyniranthin were determined from leaves of Phyllanthus niruri [14]. An unusual ellagitannin, Phyllanthusiin D (I), was found to be isolated from the biological active polar fraction of aerial parts of *Phyllanthus amarus* whose structure was established as 1-galloyl-2,4-(acetonyl-dehydrohexahydroxydiphenoyl)-3,6-hexahydroxy di phenoyl-glucopyranoside by chemical and spectroscopic methods [15]. In addition, novel cyclic hydrolysable tannin namely amarulone was obtained from the whole plant of *Phyllanthus amarus* [16]. Further, *Phyllanthus amarus* has been reported to possess di-dehydrohexahydroxyldiphenoyl hydrolysable tannin named amariin. In addition, geranin, corilagin, 1, 6-digalloylglucopyranoside, rutin, quercetin-3-o-glucopyranoside were isolated from the polar fraction of aerial parts of *Phyllanthus amarus* [17]. Chemical examination of the polar extractives of the aerial parts of *Phyllanthus amarus* led to the isolation of amariinic acid, a novel ellagitannin, together with 1-o-galloyl-2,4-dehydrohexahydroxydiphenyl-glucopyranose, elaeocarpus in, repandusinic acid A and geraniinic acid B [18]. In addition, two new Securinega-type alkaloids isobubbialine and epibubbialine were isolated from the leaves of *Phyllanthus amarus*. Other known alkaloids are securinine, norsecurinine, and phyllanthine the structures of which have been detected by means of UV, IR, mass and NMR spectroscopy [19]. The whole plant of *Phyllanthus amarus* has afforded new secosterols named as amarosterol-A characterized as 13, 14-seco-stigma-5(6), 14(15)-diene-3-a-ol (I) and amarosterol-B characterized as 13, 14-seco-stigma-9(11), 14(15)-diene-3-a-ol (II) whose structures have been elucidated on the basis of spectral and chemical studies [20]. In addition, 2, 3, 5, 6-tetrahydroybenzyl acetate and Phyllangin are the two new compounds isolated from the whole plant of *Phyllanthus amarus* [21].

PLEIOTROPIC PHARMACOLOGICAL PROPERTIES OF THE HERB

Phyllanthus amarus has a long history in herbal and folk medicinal systems to possess various beneficial properties referred to as its pleiotropic properties (Fig I). The anti-inflammatory property of the extracts and purified lignans obtained from *Phyllanthus amarus* was confirmed by the fact that given orally, the hexane extract (HE), the lignan-rich fraction (LRF) and the lignans phyltetralin, nirtetralin, niranthin inhibited carrageenan (Cg)-induced paw oedema and neutrophil influx. Additionally, bradykinin (BK), platelet activating factor (PAF) and endothelin-1 (ET-1)-induced paw oedema were significantly inhibited by the HE or LRF confirming its anti-inflammatory potential [22]. The methanolic extract of *Phyllanthus amarus* was found to inhibit lipid peroxidation, and scavenge hydroxyl and superoxide radicals in diabetic models and thus

showed potent antidiabetic activity [23]. The methanolic extract of *Phyllanthus amarus* was studied against some drug resistant pathogenic bacterial strains for its antimicrobial potentiality by disc diffusion and agar dilution method. The extract showed significant concentration dependent antibacterial activity particularly against gram-negative microbes in dysenteric and diarrheal infections alongwith fever [24]. Moreover, the antimicrobial effect of the plant extracts was further supported by the fact that the organic solvent and aqueous solvents of *Phyllanthus amarus* inhibited the growth and development of S. faecalis [25]. Further, *Phyllanthus amarus* has been reported to possess potent antioxidant effect which was proved by the fact that elevation of the antioxidant enzymes in the intestine and decrease in the lipid peroxidation levels were observed after its administration. Histopathological evaluations of the intestine revealed decreased damage to intestinal cells that further demonstrated that *Phyllanthus amarus* protected the intestine by oxidative damage. In addition, *Phyllanthus amarus* treatment also increased the activity of various antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPX) and glutathione reductase (GR) both in blood and tissue further evidencing the antioxidant potential of the plant [26]. The treatment with the aqueous extract of *Phyllanthus amarus* exhibited potent anticarcinogenic activity against 20-methylcholanthrene (20-MC) induced sarcoma development. The antitumour and anticancer activity of *Phyllanthus amarus* may be attributed to its inhibition of metabolic activation of carcinogen as well as the inhibition of cell cycle regulators and DNA repair confirming the significant anti-mutagenicity of the plant extract [27]. Moreover, *Phyllanthus amarus* possessed a potent hepatoprotective effect against aflatoxin B(1)-induced hepatic damage by a mechanism involving reduction in the intracellular level of reactive oxygen species by enhancing the level of both enzymatic and non-enzymatic antioxidants. In conclusion, data obtained suggest that the protein fraction show hepatoprotective effect against nimesulide-induced oxidative stress probably via promotion of antioxidant defence mechanisms [28]. The antifertility effects of an alcoholic extract of *Phyllanthus amarus* was demonstrated by the fact that change in 3-beta and 17-beta hydroxy steroid dehydrogenase (HSDs) levels, probably affecting hormonal conversions in the female mice were observed by its treatment. Cohabited females with normal male mice were unable to become pregnant as their cyclicity was affected. These factors are related to a change in the hormonal milieu that governs female reproductive function. Thus this extract manifests a definite contraceptive effect in female mice [29]. Further, the anti-diarrhoeal and gastro-intestinal protective potentials of aqueous extract of leaves of *Phyllanthus amarus* were investigated in mice. Graded doses of the aqueous extract (100-800 mg/kg) administered orally produced a dose-related inhibition of gut meal travel distance in normal mice. *Phyllanthus amarus* extract (400 mg/kg) delayed the onset of diarrhoea, reduced frequency of defecation and reduced gut meal travel distance. In addition, the activities of some intestinal mucosal enzymes (maltase, sucrase, lactase and alkaline phosphatase) in mice pretreated with extract was also found to be increased that further confirmed the antidiarrhoel potential of the plant [30]. Additionally, the anti-allodynic and anti-oedematogenic effects of the HE, LRF and purified lignans were investigated from a plant used in the traditional medicine, *Phyllanthus amarus*, in the inflammatory and neuropathic models of nociception. The HE inhibited the allodynia and the oedema induced by the intraplantar injection of complete Freund's adjuvant (CFA). Moreover, the treatment with HE inhibited the increase of myeloperoxidase activity, either following intraplantar injection of CFA or after sciatic nerve injury that accounts for antoallodynic and antioedematogenic potential of the plant [31]. Furthermore, the chemoprotective effect of 75% methanolic extract of the *Phyllanthus amarus* plant was studied against cyclophosphamide (CTX) induced toxicity in mice. Administration of CTX produced significant myelosuppression as seen from the decreased WBC count and bone marrow cellularity. Administration of *Phyllanthus amarus* extract at doses 250 and 750 mg/kg body weight significantly reduced the myelosuppression and improved the WBC count, bone marrow cellularity as well as the number of maturing monocytes that accounted for its chemoprotective activity [32]. Moreover, the diuretic, hypotensive and hypoglycemic effects of *Phyllanthus amarus* on human subjects were assessed. Significant increase in urine volume, urine and serum Na levels was observed after treatment with the extract obtained from *Phylanthus amarus*. A

significant reduction in systolic blood pressure in non-diabetic hypertensive subjects was noted that further confirmed the diuretic potential of the plant [33].

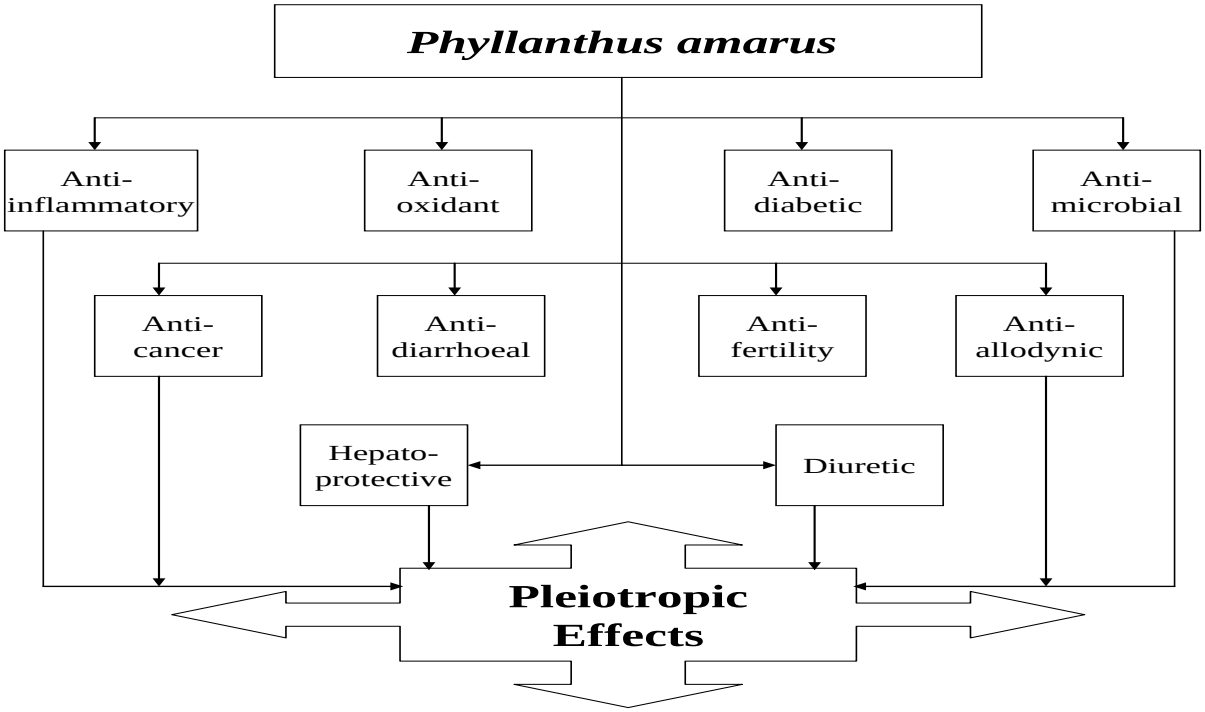

Fig 1: Diagram showing pleiotropic effects of *Phyllanthus amarus*.

CONCLUSION

Phyllanthus amarus has been used since ages by the folk because of its rich ethanomedicinal importance. A number of phytochemicals associated with the herb renders it a broad spectrum medicinal valued herb. Therefore, the chemical standardization of the raw material of plant and the formulations containing *Phyllanthus amarus* is under immense invention and thus more work is required to ascertain *Phyllanthus amarus* as a valuable herb for treatment of various impediments. The plant possesses a number of pleiotropic effects that makes the plant to be investigated with more doors open. Together with the vast improvements in the approaches for natural-product isolation, characterization and synthesis, this could be opening to a new epoch in the investigation of natural products in academia and industry. This would clearly indicate large share of natural product in new drug discovery and it is strongly advocated to expand the exploration of nature as novel active agents that may serve as scaffolds to develop more efficatious drugs.

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