Nucleus (2022) 65:437–472
https://doi.org/10.1007/s13237-022-00409-z

REVIEW ARTICLE

An insight into the potent medicinal plant *Phyllanthus amarus* Schum. and Thonn.

Aparupa Bose Mazumdar Ghosh[1] · Anindita Banerjee[2] · Sharmila Chattopadhyay[1]

Received: 27 May 2022 / Accepted: 7 October 2022 / Published online: 12 November 2022

Abstract

Phyllanthus amarus Schum. and Thonn., a globally distributed herb is known for its several therapeutic potentials. *P. amarus* has a long history of use in the traditional system of medicine for over 2000 years owing to its wide array of secondary metabolites that confer significant medicinal attributes. Research on various aspects including ethnobotany, phytochemistry to bioactivity, or pharmacological studies has been conducted over the past several decades on this potent herb. *P. amarus* extracts have shown a broad range of pharmacological activities like hepatoprotective, antioxidant, antiviral, antimicrobial, antidiabetic, anti-inflammatory, anticancer, antimalarial, nephroprotective, diuretic, and several other properties. The present review compiles and covers literature and research of several groups across past decades to date and focuses on how the therapeutic significance of this plant can be further explored for future research either as herbal formulations, alternative medicine, or in the pharmaceutical industry.

Keywords Bioactivity · Genomics · Hepatoprotective · *P. amarus* · Secondary metabolites · Therapeutic efficacy

Introduction

The eclectic botanical cornucopia representing varied plant products has been used by humans since antiquity, not only as the main source of food but also to relieve and treat several diseases. Few fossil records have revealed that humans used plants to cure diseases back at least 60,000 years [118, 392]. The knowledge of thousands of years of traditionally used plant-derived medicines still aids in overcoming several medical problems of present generations. Thus, medicinal plants are the major source of both traditional as well as modern medicines.

The genus *Phyllanthus* of the Phyllanthaceae family was described for the first time by Linnaeus in 1737, and, is of substantial medicinal significance. This genus (phyllon = leaf, anthos = flower) consists of approximately 550–750 species that are further subdivided into 10–11 subgenera, including *Isocladus, Kirganelia, Cicca, Emblica, Conani, Gomphidium, Phyllanthodendron, Xylophylla, Botryanthus, Ericocus,* and *Phyllanthus* [76, 441]. They are distributed throughout the tropical and subtropical regions of both hemispheres. Distribution of approximately 200 species of plants belonging to the genus *Phyllanthus* are believed to be in the Americas—mainly in the Caribbean islands and in Brazil [76, 442–444].

Phyllanthus amarus Schum. and Thonn., belonging to this genus, is one such significant medicinal plant that grows throughout the world including India. This plant has been known for its usage in the 'Ayurvedic' system of medicine for over 2000 years. *P. amarus* have been used for treating multi-faceted diseases like hepatitis B, jaundice, diarrhoea, dysentery, dropsy, intermittent fevers, Herpes Simplex virus, inflammation, oxidative stress, hypotensive, urinary disorders, etc. [76, 241]. In Unani literature, *P. amarus* is described by the name of 'Bhuti' which means Bhum Amlak—Amla of Land [220]. It has been described by the Sanskrit name Bhoomyaamalakee, Taamalakee, and Bhoodhatree in Ayurveda. In India, several common names in different languages have been assigned to this species

Corresponding Editor : Umesh C. Lavania; Reviewers : Rita Kundu, Parames C. Sil, Narendra Kumar.

✉ Sharmila Chattopadhyay
sharmila@iicb.res.in; chattopadhyay62@gmail.com

[1] Plant Biology Lab, Organic & Medicinal Chemistry Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Kolkata 700032, India

[2] Undergraduate, Postgraduate, and Research Department of Microbiology, St. Xavier's College (Autonomous), 30 Mother Teresa Sarani, Kolkata 700016, India

viz. 'Bhuiamla' or 'sadahazurmani' in Bengali, 'Jaramla' or 'bhuianvalah' in Hindi, 'bhonyaanmali' in Gujrati, 'bhuiavala' in Marathi, and so on, because it bears a close resemblance to amla [419]. In Spain, "chanca piedra," is the common name of *P. amarus*, which translates to stone-breaker. However, a great deal of confusion among scientists regarding plant identification still persists. Further, misidentification of the plant in many cases has made evaluation of published information difficult. Either *P. amarus* and *P. sellowianus* are often considered a variety of *P. niruri*, or no distinction is made among these three species in published clinical research [415]. It has been reported that one name is repeatedly indicated to be synonymous with another. Again, both names sometimes have been used interchangeably as if referring to one plant. Due to this utter confusion, a major reorganization of the *Phyllanthus* genus was conducted in the 1990s that classified *P. amarus* as a type of *P. niruri* [415].

A thorough and in-depth literature search on *P. amarus* was undertaken. All the papers published since 1985 until August 2022 were included in the study. A systematic literature review was performed using a three-step process described by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The flow diagram showing the process has been mentioned in Fig. 1. The research was conducted using the online databases Google Scholar, Scopus, Web of Science and performed with six keyword combinations—"*Phyllanthus amarus* geographic distribution", "*Phyllanthus amarus* morphology and nomenclature", "*Phyllanthus amarus* phytochemical studies", "*Phyllanthus amarus* ethnopharmacology", "*Phyllanthus amarus* pharmacological studies", "*Phyllanthus amarus* bioactivity and medicinal properties".

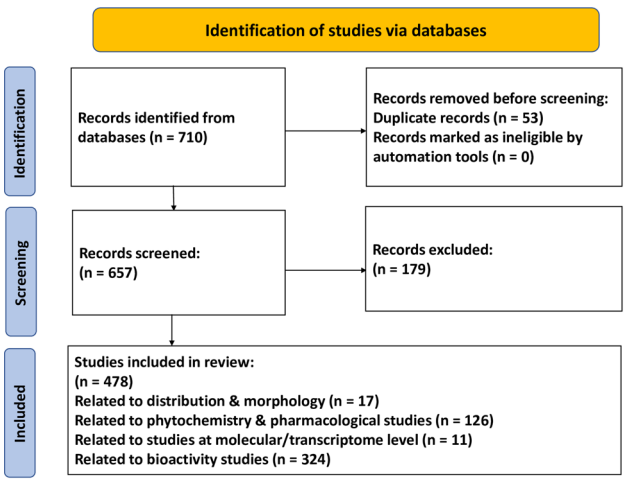

Fig. 1 The PRISMA flow diagram showing the number of documents obtained in the procedure of including studies in this review

Morphology and distribution of *P. amarus*

P. amarus is an annual, glabrous, erect herb growing up to about 10—60 cm tall. The main stem of the herb is either simple or branched and terrete smooth or scabridulous in younger parts. Owing to its immense medicinal properties, this plant has been valued in many countries for a variety of ailments. The nutritional and phytochemical components of the plant including its fruits and seeds have been evaluated in a study, where it is shown that they contain a moderate amount of protein, also rich in carbohydrates, and are low in fat, ash, and crude fiber. Some of the other constituents include Mg, Ca, K, PO and ascorbic acid, Fe, Zn, thiamine, niacin and riboflavin [311]. Other studies have also shown that the fruits of *P. amarus* are useful for treating tubercular ulcers, wounds, sores, scabies, and ring worm [19, 196].

It is widely distributed in all tropical and subtropical regions of the world. The exact geographic origin of *P. amarus* have not been found from paleobotanical studies of the plant. In several published research and review articles to date, *P. amarus* has been indexed with different names and has been confused with *Phyllanthus niruri.* A number of other species, including *P. amarus*, have been put under the name of *P. niruri* by Linnaeus and other early taxonomists. Webster included closely related genera *P. amarus*, under the sub-section *Swartiziani* of the section *Phyllanthus* while performing the taxonomic revision of the genus. *P. abnormis* that is endemic to the sandy areas in Texas and Florida in southern USA, is also said to be related to the herb *P. amarus*. Therefore *P. amarus* has been considered to likely originate in the Caribbean area of the southern United States as a vicarious species of *P. abnormis* and has further spread around the tropics by trading vessels [457]. *P. amarus* is indigenous to the rainforests of the Amazon and other tropical countries like India, China, the Bahamas, [258], Philippines [81]. It is a common pantropical weed that grows well in both moist, shady, and sunny places [75]. *P. amarus* is considered the most widely occurring *Phyllanthus* species in India and is distributed all over the country, ranging from the hotter parts from Punjab to Assam, spreading southwards to Travancore and further ascending the hills up to about 3000 ft. [87]. Figure 2 illustrates the herb *P. amarus*.

Several researchers across the globe, over the past decades, have studied and demonstrated the potential of *P. amarus* concerning its traditional uses and in terms of findings based on modern bioscientific research as well. Research on several aspects like pharmacognostic, ethnopharmacology, phytochemistry, pharmacology, clinical studies as well as molecular or transcriptome-based studies on this medicinal plant has not limited itself over the past

Fig. 2 *Phyllanthus amarus*

findings but has further gained momentum and widened its novel findings even at a faster pace. In the present review, the best possible attempt has been made to assess and compile detailed research on *P. amarus* over the several years to date to thoroughly study and get an elaborate overview of the medicinally significant plant.

Pharmacognostic study and ethnopharmacology of *P. amarus*

The genus *Phyllanthus* is one very significant group of plants that are traded as raw herbal drugs in India [449]. The diverse classes of compounds present in the genus *Phyllanthus* are attributed to its phytochemical diversity. The unique structural diversity that is found among the compounds of *Phyllanthus* as well as their strong bioactive nature makes the genus of great commercial value. Several herbal drug formulations prepared using species of *Phyllanthus* are available in the market in India. Hepex, Liv 52, Livomap, Liv D, Liv Plus, Vimliv, Nirocil, Livocin, Livcure, and Livol are some very popular herbal drug formulations for jaundice and other liver ailments in general. De and Datta (1990) conducted pharmacognostic study of *P. amarus* [100]. Various species of *Phyllanthus* are sold in India under the trade name Bhuiamlaki. The presence of all samples of *P. amarus*, *P. maderaspatensis,* and *P. fraternus* have been revealed by pharmacognostic studies of commercial 'Bhuiamlaki'. Further, pharmacognostic evaluation of *P. amarus* has also showed the presence of thin-walled epidermal cells. The study concludes that all the three species can be differentiated based on macro and microscopic characters along with physicochemical values, HPTLC fingerprint profile, and phyllanthin and hypophyllanthin were detected as marker components [192].

The genus *Phyllanthus* has long been reported for its varied activities like astringent, diuretic, and cathartic. The ethnopharmacology or traditional usefulness of *P. amarus* in multiple health problems has a long history of use in herbal systems of medicine in several tropical countries across the world where it grows. Its uses as Kaasahara (antitussive), Shwaasahara (antispasmodic, antidyspnoic), Kaphapittahara, Pipaasaaghna (which relieves Polydipsia), Raktapittahara (hemorrhage disease), Paanduhara (antianemic), Kaamalaahara (which cures jaundice), Kushthaghna (indicated in leprosy), Daahaghna (refrigerant, relieves burning sensation), Kshatakshayaghna (indicated in Trauma) and Mootrarogahara (which cures urinary disorders) have been shown by literature in the Ayurvedic system of medicine. The Spanish name of the herb 'chanca piedra' which translates to 'stone breaker' or 'shatter stone' was named by the Amazonian indigenous people for its effective use in eliminating gallstones and kidney stones for several generations used. The usage of *P. amarus* dates long back to the treatment of problems related to liver, kidney, bladder, and also diabetes, and intestinal parasites. Similarly, 'chanca piedra' in South America, has been used to eliminate gall bladder and kidney stones, and also to treat gall bladder and bronchial infections [124], cardiovascular problems [81], as well as a remedy for influenza around the world [126]. The Brazilian name 'quebra pedra' also converts to the meaning 'break stone'. Besides its primary role in removing kidney and gall stones, *P. amarus* in the Amazonian country is widely used for other ailments like blennorrhagia, carminative, colic, diabetes, digestive, diuretic, dropsy, dysentery, dyspepsia, emmenagogue, fever, flu, gonorrhea, itching, jaundice, laxative, malaria, proctitis, stomachache, tenesmus, tonic, appetizer, tumor, vaginitis, vermifuge [234, 387, 446]. This herb is also sold as fresh and dry plant material in the herb markets of Suriname (the North-Eastern part of South America). Decoctions of *P. amarus* are even used in herbal baths and after labor, cramps, asthma, uterus complaints and to treat stomachache [147, 248, 274, 382, 426]. Similar usage of this plant is employed worldwide by the various tribes across different countries like Aruba (used as a blood purifier also), Bahamas/Caribbean, Barbados (used as an abortifacient), Brazil, Cuba, Haiti, Indonesia, Jamaica, Malaya, Nigeria, Peru, Trinidad, United States, etc. for the above-mentioned diseases in addition to anti-inflammatory, antilithic, antispasmodic, antiviral, aperient, arthritis, cystitis, deobstruent, diaphoretic, gastrointestinal problems, gout, muscle relaxant, obesity, prostatitis, purgative, renal colic, renal problems, etc. [189]. Some other studies have also shown that the plant *P. amarus*, when boiled with the leaves, is considered to be a diuretic and is used in the treatment of menstrual disorders and skin disorders [147, 148, 425, 458] besides diabetes, dysentery, and hepatitis as already mentioned. The plant extracts are even used as blood

purifiers, for light malaria fevers and anemia. It also helps to release phlegm [147] and to combat fever [274]. This herb can be used for constipation also [428]. Several countries across the African continent have conducted research on *P. amarus* for studying its therapeutic effects on different ailments, according to its geographical distribution. For example, the antiplasmodial activity of various parts of the herb was evaluated for malaria treatment in three different areas in the Congo (Kisantu, Kimwenza, and the University of Kinshasa) [127]. Again, phytochemical analysis of the secondary metabolites of *P. amarus* from four geographical areas in the Democratic Republic of the Congo was performed [273]. Another recent research was conducted with leaf extracts of *P. amarus* collected from three different geographical zones in Nigeria for evaluating their effects on larva and adult of *Anopheles gambiae*, the causative agent of malaria [330]. A very recent article has reported the antidiabetic potential of *P. amarus* among the diverse flora of the Caribbean basin based on their pharmacological activity and the mechanism of action of their key active phytocomponents [254]. Similarly in India, several tribal groups across different parts of the

Table 1 Ethnomedicinal uses of *P. amarus* Schum. & Thonn. in India

Place	Local Name	Plant part used	Disease	References
Dharapuram Taluk, Tamil Nadu, India	Keelanelli	Whole plant	Migraine, Jaundice	[58]
Paliyar tribals in Theni district of Tamil Nadu, India	Keelanelli	Leaves	Jaundice	[157]
Eastern part of Rajasthan, India	Bhumiamla	Whole plant, leaves	Gonorrhea, syphilis, malaria skin diseases	[446]
Uttara kannada, Western Ghats, India	Nelli	Whole plant	Malaria	[211]
Eastern region of Shimoga district Karnataka, India	Nelanelli	Root juice	Jaundice	[361]
Dindigul District, Tamil Nadu, India	Kizhnelli	Leaves	Menstrual problem	[377]
Buldhana district, Maharashtra, India	Bhui-awala	Whole plant	Jaundice	[21]
North Andaman Island, India	Nallesari	Whole plant	Jaundice	[348]
Sivagangai district, Tamil Nadu, India	Keelaanelli	Leaves	Diabetes, Jaundice	[387]
Shimoga district of Karnataka, India	Nela nelli (Bhumy-amalaki)	Leaves	Jaundice, Chronic dysentery	[234]
Kattunaykas tribes of Mudumalai Wildlife Sanctuary, Nilgiris district Tamil Nadu, India	Kila nelli	Whole plant	Jaundice	[433]
Northern India	Bhui amla	Whole plant	Jaundice, aphrodisiac, dysentery	[184]
Kancheepuram district, Tamil Nadu, India	Keezhanelli	Leaves	Jaundice	[269]
Sitamata Wildlife Sanctuary of Chittorgarh and Udaipur district Rajasthan, India	Not stated	Leaves	Syphilis, gonorrhea, jaundice	[170]
Korba district, Chhattisgarh, India	Bhui amla	Whole plant	Jaundice, Liver problems	[427]

Table 2 Ethnomedicinal uses of *P. amarus* Schum. & Thonn. in other parts of the world

Place	Local name	Plant part used	Disease	References
Esan North East local govt. area of Edo State, Nigeria	Abenaghe	Leaves	Stomachache	[156]
Delta State Nigeria	Ibuko-oyeke	Leaves	Stomachache	[155]
Akwa Ibom State in Nigeria	Oyomokiso, aman keeden	Leaves	Malaria	[30]
South West Nigeria	Eyin olobe	Whole plant	Diabetes	[4]
West Africa	Hlinvi	Arial	Diabetes, fever, malaria	[17]
Semi-arid Northeasten Brazil	Quebra-pedra	Leaves	Kidney problems	[77]
Dangme West district of Ghana	Ofobi okpabi	Whole plant	Malaria	[52]
Surinamese migrants in Netherland	Fini bita	Whole plant	Stomach-ache, cleaning uterus, laxative, health promotion	[448]
Akha people in Thailand and China	Yu Jae	Leaves	Rashes, itches	[163]

country use this medicinal herb for several diseases as primary healthcare needs. For example, the whole plant of *P. amarus* is in use as an aphrodisiac, for dysentery, and in the treatment of jaundice by the tribal and adibasis of Maharashtra [146]. The ethnomedicinal uses of *P. amarus* by different tribes in India have been summarized in Table 1. Table 2 summarizes the ethnomedicinal uses of *P. amarus* by different tribes in other parts of the world.

Phytochemistry and analytical studies in *P. amarus*

Phytochemistry is the branch of chemistry that deals with the chemical nature of plant or plant products (chemistry of natural products). Many chemical constituents present in plants are therapeutically active or inactive like carbohydrates, triterpenoids, alkaloids, glycosides, tannins, flavonoids, essential oils, and other similar secondary metabolites. The different organic compounds that *P. amarus* elaborates include the secondary metabolite classes like lignans, flavonoids, alkaloids, hydrolyzable tannins (Ellagitannins), polyphenols, triterpenes, sterols, and volatile oil. These compounds of considerable medicinal importance complement the fact that the herb is a hub of a wide array of secondary metabolites present in its different parts, and have been discussed as follows.

Lignans

Lignans are a widespread class of phenylpropanoids derived from phenylalanine via dimerization of substituted cinnamic alcohols, known as monolignols to a dibenzylbutane skeleton, via the general phenylpropanoid pathway [99, 219]. The term 'lignan' was introduced by Haworth in 1936 [145]. This class of compounds is found in a wide variety of plant species [129]. Analogs of lignans have been commonly named sesquilignans and dilignans [440]. Lignans like phyllanthin (a bitter constituent) and hypophyllanthin (a non-bitter constituent) have been isolated from *P. amarus* [374], and are of considerable significance owing to its vast range of therapeutic properties viz. hepatoprotection, antitumor, antimitotic, antiviral properties [54, 76, 231, 278, 439] as well as antioxidant [123] activities. The highest amounts of phyllanthin (0.7% w/w) and hypophyllanthin (0.3% w/w) have been reported in leaves whereas, in the stem, these are present in minor quantities [388]. Various other lignans like niranthin, phyltetralin, nirtetralin, isonirtetralin, hinokinin, lintetralin, isolintetralin, demethylenedioxy-niranthin, 5-demethoxy-niranthin, etc. with significant therapeutic potentials reported in *P. amarus* along with other classes of secondary metabolites present have been summarized in Table 3.

Table 3 Different classes of secondary metabolites in *P. amarus*

Secondary metabolites class	Compound	Reference
Lignans	Phyllanthin, hypophyllanthin, niranthin, phyltetralin, nirtetralin, isonirtetralin, hinokinin, Lintetralin, isolintetralin, demethylenedioxy-niranthin, 5-demethoxy-niranthin	[2, 40, 42, 81, 83, 132, 154, 169, 173, 190, 230, 250, 255, 258, 260, 266, 336, 339, 372, 386, 388, 396, 405, 416, 472]
Flavonoids	Rutin, astragalin, kaempferol, quercetin, quercitrin, quercetin-3-O-glucoside	[40, 66, 132, 227, 258, 260, 275, 416, 421]
Alkaloids	Securinine, dihydrosecurinine, tetrahydrosecurinine, securinol, phyllanthine, allo-securine, nor-securinine, epibubbialine, isobubbialine, 4-methoxy-nor-securinine 4-methoxy dihydrosecurinine, 4-methoxytetrahydrosecurinine, 4 hydrosecurinine	[40, 66, 132, 152, 181, 260, 262, 393, 416]
Triterpenes	Phenazine and phenazine derivatives 2Z, 6Z, 10Z, 14E, 18E, 22E-farnesylfarnesol Lupeol, phyllanthenol, phyllanthenone, phyllantheol, Oleanolic acid, ursolic acid	[209, 394]
Sterols	Amarosterol A, amarosterol B	[22]
Volatile oil	Linalool, phytol	[28, 257, 325]
Ellagitannins (Hydrolysable tannin) Tannin precursors	Gallic acid, ellagic acid, gallocatechin	[42, 107, 124–126, 173]
Simple tannins	1, 6-digalloylglucopyranose, 4-O-galloylquinic acid	[125, 126]
Complex tannins	Geraniin, amariin, furosin, geraniinic acid B, amariinic acid, amarulone, repandusinic acid A, corilagin, isocorilagin, elaeocarpusin, phyllanthusiin A, B, C, and D, melatonin	[124] [125, 126] [416] [132] [40] [260, 66, 246, 255]

Flavonoids

Flavonoids are a class of plant secondary metabolites and are polyphenolic compounds. The different categories include flavanone, flavones, flavonols, isoflavones, catechins, chalcones, and their derivatives. Synthesis of flavonoids takes place through the phenylpropanoid pathway, transforming phenylalanine into 4-coumaroyl-CoA, that finally enters the flavonoid biosynthesis pathway. Chalcone synthase is the first enzyme specific to the flavonoid pathway that produces chalcone scaffolds, from which all flavonoids derive. It is known that the central pathway for flavonoid biosynthesis is conserved in plants. But depending on the species, different flavonoid subclasses are derived from a group of enzymes, such as isomerases, reductases, hydroxylases, and several Fe2 + /2-oxoglutarate-dependent dioxygenases that modifies the basic flavonoid skeleton [243]. The different flavonoids have diverse biological functions, like flower coloration, protection against ultraviolet (UV) radiation and phytopathogens, participation in stress responses and auxin transport, etc. Moreover, the beneficial functions of flavonoids in human health and their use for the prevention and treatment of different pathologies have also been well documented [18, 91, 150]. *P. amarus* owes its diverse bioactivities to this class of compounds as well. Some of the major flavonoids reported in this potent herb like rutin, astragalin, kaempferol, quercetin, etc. (Table 3) impart the antioxidant activities of *P. amarus*.

Alkaloids

Alkaloids are one of the most diverse groups of secondary metabolites found, having an array of structure types, biosynthetic pathways, and diverse pharmacological activities. Alkaloids are low molecular weight and cyclic nitrogenous compounds. The major source of alkaloids has been the flowering plants, the Angiospermae, where about 20% contain these constituents. Other than its involvement in plant defense against herbivores and pathogens, its wide range of pharmacological activities particularly in mammals like humans is notable since ancient times. *P. amarus* is also known to contain several alkaloids like securinine, epibubbialine, isobubbialine, etc. among its diverse class of secondary metabolites (Table 3) which are also responsible for the several reported medicinal properties of this herb.

Terpenes and terpenoids

Terpenes and terpenoids constitute a significant part of plant secondary metabolites and also are a large and diverse class of organic compounds. Terpenoids are similar to terpenes and are known as modified terpenes. On the other hand, some authors inversely use the term "terpenes" more broadly to include the terpenoids. Similar to the functions of other classes of plant secondary metabolites, terpenes and terpenoids also protect the plants producing them, by deterring herbivores and also attracting predators and parasites of herbivores [244]. This class of secondary metabolites thus play an important role in plant–insect, plant-pathogen, and plant-plant interactions [111, 334]. Further, they provide ample opportunities to address various human health and societal issues as well as have several applications both in the pharmaceutical and food industries. This class of compounds exhibit significant therapeutic potentials including anticancer, antiparasitic, antimicrobial, antiallergenic, antispasmodic, antihyperglycemic, anti-inflammatory, and immunomodulatory properties [105]. They are normally present in the vegetative tissues, flowers, and sometimes, roots [111], and are more commonly present in higher plants. *P. amarus* is among the several plant species, reported to have this class of phytoconstituents like lupeol, phyllanthenol, phyllanthenone, etc. (Table 3) which contributes to the diverse medicinal properties of the herb.

Studies on secondary metabolites isolation in *P. amarus*

The different phytochemical studies in *P. amarus* exhibiting the different classes of secondary metabolites reported to date have been isolated from the potent medicinal herb across the globe over the past several years employing different analytical techniques.

The flavonoids from different *Phyllanthus* species including *P. amarus* and also tannins from the same have been studied and analyzed [275, 434]. The MeOH eluate of the herb was chromatographed and studied to isolate and identify compounds of the tannin class like geraniin, ellagic acid, and gallic acid [434]. An acyclic triterpene was isolated and studied with its structure determination from hexane extract of the potent herb [394]. The structure and absolute stereochemistry of the alkaloid molecule ent-norsecurinine were confirmed by an X-ray analysis after its isolation from *P. amarus* [181]. The recovery of the two major lignans- phyllanthin and hypophyllanthin at about 98% was performed with the sensitive and precise procedure of high-performance liquid chromatographic (HPLC), from different parts of *P. amarus* plant [388]. For simultaneous determination of the bioactive lignans, phyllanthin, and hypophyllanthin from the dried whole plant powder of *P. amarus* like HPTLC method and a TLC—densitometric method were developed for its further estimation by other researchers [102, 378]. An isocratic reversed-phase (RP) HPLC procedure that showed high resolution (R = 1.9), accuracy, and reproducibility for the estimation of the two major lignans were also developed [264]. Further purification of the lignan phyllanthin by subjecting its fraction to silica gel column chromatography

was performed [80]. Even characterization employing mp, UV–Visible spectrophotometry, elemental analysis, FT-IR, 1H NMR, 13C NMR, and mass spectral analysis were carried out [202]. Other studies using *P. amarus* extracts for isolating, scanning, and quantifying phyllanthin and hypophyllanthin have been done by other research groups as well [107, 261, 431]. Another phytochemical investigation with methanolic extract of *P. amarus* revealed the presence of six bioactive lignans [isolintetralin (2,3-demethoxy-seco-isolintetralin diacetate), demethylenedioxy-niranthin, 5-demethoxy-niranthin, niranthin, phyllanthin and hypophyllanthin] and one triterpene (2Z, 6Z, 10Z, 14E, 18E, 22E-farnesil farnesol) that was performed by NMR characterization [230]. Further, a detailed study employing extraction, isolation, and characterization method optimized for the major lignan phyllanthin has been illustrated by Hamrapurkar et al., 2009 [138]. A reversed-phase hyphenated high-performance liquid chromatography–photodiode array-mass spectrometry (HPLC–PDA–MS) analytical method was developed for the determination of six therapeutically important lignans in *P. amarus* along with 3 other *Phyllanthus* species [386]. Isolation and characterization of the different classes of secondary metabolites viz. lignans, tannins and other bioactive molecules from this potent herb using different novel extraction methods and analytic techniques have been performed over the years [159, 161, 169, 281, 339]. Analysis of oils from *P. amarus* employing gas chromatography (GC) and gas chromatography coupled with mass spectrometry (GC/MS) revealed the presence of eighty-two identified compounds of which linalool (36.4%) and phytol (13.0%) were dominant [257]. Analytical techniques like High-Performance Liquid Chromatography (HPLC), liquid chromatography coupled to mass spectrometry (LC–MS) gas chromatography coupled to mass spectrometry (GC–MS), UPLC-QTOF-MS^{E}-based chemometric approach, UHPLC–MS/MS, HPLC-ESI-QTOF-MS/MS, NMR-based metabolomics, have been employed and standardized with further optimization in several research studies with *P. amarus* extracts. These studies were performed for qualitative and quantitative analyses of the varied biomolecules like lignans, tannins, terpenoids, phenols, etc. [208, 209, 250, 271, 340, 389, 400, 477]. Chromatographic fingerprint analysis was performed using HPLC combined with simultaneous quantification of the major lignans in one research. The study showed distinct profiles that were further used for the identification and authentication of three species of *Phyllanthus* [277]. Another study on *P. amarus* aimed to identify and quantify some biologically active compounds from the herb followed by the synthesis and characterization of silver nanoparticles [92]. Different methods such as UV–Vis spectrophotometric and HPLC–UV-MS for polyphenols analysis and LCMS methods for methoxylated flavonoids and phytosterols analysis were employed in this study. Also, the extract was further used to obtain silver nanoparticles (AgNPs) and thereby confirming that *P. amarus* is a source of biological compounds that can be used for nanoparticle synthesis, with potential health use. Chemical derivatization and analysis by GC–MS with *P. amarus* extract were performed to evaluate the antimicrobial activity of the lignan phyllanthin present in the herb [372]. A recent report on phytochemical screening, quantitative and gas chromatography-mass spectrometry (GC–MS) analyses carried out with ethanolic leaf extract of *P. amarus* revealed major bioactive constituents [28, 325]. Another green extraction and purification process for the rapid preparation of the tannin corilagin from *P. amarus* along with four other species of the same genus has been designed recently. The study used an aqueous ionic liquid coupled with preparative high-performance liquid chromatography (prep-HPLC) and precipitation [151]. GC–MS technique that offers a precise identification and quantitation of lignans found in different *Phyllanthus* spp. showed that *P. amarus* contains a high amount of lignans compared to other species used in the study [294]. Several such analytical techniques with this medicinal herb have been conducted over the years and research still being ongoing worldwide to identify different classes of biomolecules of therapeutic importance. In one recent study, the development and validation of a simple reversed-phase HPLC–PDA method for profiling the lignan classes viz. phyllanthin, hypophyllanthin, nirtetralin, and niranthin in extracts of *Phyllanthus* species including *P. amarus* was carried out in order to promote its commercial cultivation. The developed method in the study was aimed to be implemented that could be useful for quality control of herbal formulations containing plants from *Phyllanthus* species [336]. Leaf and root extracts of *P. amarus* were analyzed by another group of researchers, for identifying and quantifying its phytoconstituents which revealed the presence of three medicinally important bioactive compounds. These included 9-Octadecenoic acid that showed to be present at a percentage of an abundance of 92.23% and 82.46% in leaves and roots of the plant respectively, followed by n-Hexadecanoic acid and Tetradecanoic acid with their corresponding percentage of an abundance of 7.7% and 17.54% for leaves and root [46].

A detailed catalog of the various phytoconstituents reported in *P. amarus* over the past several decades has already been mentioned in Table 3.

Studies on *P. amarus* at molecular and transcriptome level

P. amarus, a potent medicinal herb has been explored very little at the molecular and transcriptome level. Species authentication/discrimination is an essential task in various areas in biology for correct species exploitation

regarding their purposes like ecology, evolution, forensics, food science, medical, and even herbal and cosmetic industries. A few reports addressed the genetic diversity of *P. amarus* for application in the cultivar identification using PCR and sequencing-based techniques viz. RFLP, RAPD, ISSR, SCAR, and AFLP [59, 171, 384]. Based on DNA dissociation kinetics and DNA barcoding, for the authentication of medicinal plant species, one research group applied DNA Barcoding—High Resolution Melting (Bar-HRM), which has proven to be a cost-effective and reliable method for the identification of closely related species in phytopharmaceuticals including *P. amarus* [324]. Application of DNA barcoding methodology, for authentication of *P. amarus* as well as its discrimination from other *Phyllanthus* species, has been reported in some recent studies as well [74, 194]. Besides, the establishment of an efficient transgenic system of *P. amarus* was performed by genetic transformation method using *Agrobacterium tumefaciens*, and shoot tips of full-grown plants were used as explants [60]. Recently, an efficient and easy protocol for in vitro propagation of the herb was also developed [409]. Despite its global medicinal importance, due to the lack of genomic or transcriptomic sequence resources for *P. amarus*, an attempt was made by one group of researchers to study the medicinal herb at the molecular and transcriptome level. Firstly, a cDNA library construction and EST analysis of *P. amarus* leaves were performed [79]. Further, high-throughput sequencing technology was employed to enhance a better understanding of this herb and provide comprehensive genomic information for future work [72]. *P. amarus* leaf transcriptome was sequenced using the Illumina Miseq platform and then de novo assembly followed by annotation and analysis were conducted. This was the first and only report of transcriptome sequencing of *P. amarus* using the NGS technique, that not only unraveled different genes involved in various secondary metabolic pathways attributing to the herb's medicinal importance but also the assembled, annotated, and analyzed data can be further used in its future genomics study thereby accelerating bhuiamlaki's therapeutic efficacy.

Bioactivities and pharmacological properties of *P. amarus*

Studies on bioactivities and pharmacological potentials of *P. amarus* have been conducted by several groups of researchers globally throughout the past few decades. This herb has been assigned several significant medicinal properties after rigorous research. These include hepatoprotective, antiviral, antioxidant, antimicrobial, antidiabetic, anti-inflammatory, antitumor, etc. among several other properties. Research on several studies related to its therapeutic importance has been summarized below.

(i) Hepatoprotective and anti-Hepatitis B properties of *P. amarus*

The hepatoprotective activity of *P. amarus* has long been reported. The valuable properties of this herb in hepatoprotection came forward and thus were recognized in the year 1985 by Syamasundara [411] and his co-workers, who showed the antihepatotoxic action of *P. amarus* using primary cultured rat hepatocytes. The hepatoprotective properties of the lignans phyllanthin, hypophyllanthin, and triacontanol on carbon-tetrachloride and galactosamine-induced cytotoxicity were demonstrated in primary cultured rat hepatocytes by the group [411]. Liver protecting potentials of *P. amarus* has also been shown by other research works [76, 422, 454]. Although clinical uses of *P. amarus* have been cited for over a century in the traditional (Ayurvedha and Siddha) literature, scientific studies on the same have been carried out only over the last 50 years. The effectiveness of *P. amarus* in ethanol-induced fatty liver, developed in rats, was observed on the administration of the herbal powder of this herb [438]. Dhir et al., in the year 1990, showed significant inhibition of the cytotoxic action caused by lead nitrate and aluminium sulphate, when the aqueous leaf extracts of *P. amarus* and *P. emblica*, were administered to mice for a week [108]. Antihepatotoxic activity of *Tinospora cordifolia* and *Ricinus communis* along with *P. amarus* extracts was shown by Reddy et al., 1993 [370]. Further, an in vitro study was conducted using isolated rat hepatocyte cultures to demonstrate the antihepatotoxicity potentials of *P. amarus* [175]. Hepatoprotection by *P. amarus* against carbon tetrachloride (CCl_4)-induced hepatotoxicity was also studied by other research groups [379, 451]. Besides, Prakash et al., also demonstrated that two *Phyllanthus* species viz. *P. urinaria, P. amarus*, but not *P. simplex*, reversed the elevated serum levels of transaminases (GOT and GPT) in rat liver, suggesting that these two species might have a protective action on the liver against carbon tetrachloride-induced hepatic damage [345]. The hepatoprotective potential of *P. amarus* was shown in other studies as well, including the study of the hepatoprotective mechanism of this plant [144, 459, 460], where the involvement of glutathione was evaluated by determining hepatic reduced glutathione. It was suggested that the hepatoprotective mechanism was partly due to the protective effect on the depletion of hepatic reduced glutathione and also its antioxidant activity, especially the radical scavenging and iron chelating activity. Similar studies of the hepatoprotective role of *P. amarus* fresh leaf protein extract, via its antioxidant properties against carbon tetrachloride-induced liver damage were also shown by Bhattacharjee and Sil [68]. Down the line, studies

on the hepatoprotective potential of this herb were continued by the works of other researchers [158, 182]. In vitro and in vivo studies to show the protective effects of aqueous extract from *P. amarus* on ethanol-induced rat hepatic injury were also performed by Pramyothin et al. [346]. Using different biochemical parameters and histopathological studies, the hepatoprotective effect of ethanolic extract from *P. amarus* was evaluated on aflatoxin B1-induced liver damage in mice [272]. Besides, using methanolic extract of *P. amarus* leaves, its hepatoprotective potentials were investigated against ethanol-induced oxidative damage in adult male Wistar albino rats by Faremi et al. [119]. Further, an effective and standardized combination therapy using ethanolic and aqueous extracts of *P. amarus* along with Silymarin was proposed by Yadav et al. [464], which exhibited higher liver protection in comparison to that of the aqueous or ethanolic extract against CCl_4-induced hepatotoxicity in rats. Several researchers have also shown the hepatoprotective potential of *P. amarus* owing to the presence of the significant lignan phyllanthin against CCl_4-induced hepatotoxicity in mice, HepG2 cell lines, or primary culture of rat hepatocytes over the past years [82, 198, 199, 202, 203]. Surya Narayanan et al., 2011 showed *P. amarus* as an effective anti-fibrotic agent, by analyzing the plant's effect on matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases (TIMPs) activity in alcohol and thermally oxidized polyunsaturated fatty acid (PUFA)-induced hepatic fibrosis using male albino Wistar rats for the study [410]. In a study conducted by Srirama et al. (2012) toxicity was chemically induced by tert-butyl hydroperoxide on HepG2 cell line and the protective effects of *Phyllanthus* and its related species were studied [404]. Methanolic and aqueous extracts made from seeds of *P. amarus* were studied for their hepatoprotective and nephroprotective activity under in vivo systems. The results confirmed the hepatoprotective nature of seeds. The results demonstrated that the methanolic extract of the seeds has a significant effect than aqueous extract when compared to silymarin and cystone, respectively and that the seeds of this plant possess a potent protective effect against thioacetamide-induced hepatic damage, and gentamycin-induced renal damage [57]. To make the extracts more available for systemic circulation, the technique of encapsulation versus non-encapsulation was studied on CCl_4-induced hepatotoxicity in male rats [104]. Results showed that an oral dose of nano emulsified ethanolic extract of *P. amarus* showed promising hepatoprotective activity than crude extract and the hydrophobic compounds dissolved better making dosage effective at a lower concentration. Another in vivo study showed that ellagitannins such as geraniin and amariin isolated from *P. amarus* were useful in restoring the ethanol-induced cytotoxicity, that was produced in liver slices of mice by reducing oxidative damage to biomolecules and also prevented apoptosis [229]. The study also showed that the ellagitannins altered Bax/BCl-2 ratio, thereby reducing liver damage. Furthermore, the hepatoprotective nature of *P. amarus* roots was studied in neonatal mice [237]. The protective mechanism of lignans from *P. amarus* against galactosamine/lipopolysaccharide-induced hepatitis has been shown by Bawankule et al., 2014 by in vivo and in silico studies [61]. Inhibition of CCl_4-mediated oxidative stress and hepatic fibrosis by phyllanthin, thereby highlighting the molecular mechanism responsible for the antifibrotic efficacy of the lignan present in *P. amarus*, was also demonstrated [201]. Recent studies have also revealed the therapeutic potential of *P. amarus* extracts in the treatment of liver diseases due to the presence of phyllanthin by inhibiting HepG2 cell proliferation, inducing apoptosis in HepG2 via caspase-3-dependent cell death mechanism, and protecting against CCl_4-induced hepatotoxicity [323]. Another study also revealed how phyllanthin was found to play a very promising role in treating liver fibrosis and thereby liver cirrhosis [200]. The anti-fibrotic effect was studied through signal transduction pathways and by down-regulating the TGF signaling pathway through ALK5 and Smad 2 and 3 inhibitions. Other studies on the hepatoprotective potential of *P. amarus* extract have been performed over the years [177,289, 335]. A hepatotoxic assessment of *P. amarus* leaf extract in Wistar rats was also studied [303]. Studies on in vivo protective effect of the lignan phyllanthin and downstream evaluation of synthesized phyllanthin nanoparticles (Phyll NP's) in carbon tetrachloride (CCl_4)-induced model of hepatic fibrosis were found to combat fibrosis and hepatotoxicity, and restore normalcy by reducing levels of liver marker enzymes and collagen levels in a dose-dependent manner [204]. The efficacy of a mixed herbal extracts product (MHEP) from different medicinal plants including *P. amarus*, to protect against the fatty liver hemorrhagic syndrome (FLHS) and its effect on the growth performance of a sample of 880-day-old broilers was investigated [239]. Research on the restorative potential of *P. amarus* leaf extract was carried out to demonstrate how it curtailed the toxic effects of CCl_4 and rifampicin on the liver and kidney respectively [305]. In vitro and in vivo studies along with chemical characterization were carried out for an in-depth hepatoprotective mechanistic study of the herb [117]. Phenolic-rich concentrate (PRC) of the herb has been shown to act as a therapeutic candidate in the management of high salt diet-driven immunological derangements and hepatotoxicity in a recent study [167]. Evaluation of *P. amarus* leaf meal to study the effects of lignans and flavonoids for hepato-nephroprotective potentials in broiler chickens was also performed [445]. Another recent study with P1EA and P1nB extracts from the endophytic fungi *Aspergillus niger* strain A6 (PALF-1) isolated from leaves of *P. amarus* was carried out to study the hepatoprotective as well as in vitro antioxidant effects in paracetamol-induced hepatotoxicity in rat

models [355]. Similar studies by the same group were conducted with another endophytic fungus *Nigrospora* sp. CMH2_13, isolated from leaves of *P. amarus* to screen the fungal fractions for hepatoprotective activity, followed by isolation of secondary metabolites from the endophytic fraction [354].

P. amarus along with hepatoprotective potentials exhibits its active involvement in inhibiting the hepatitis B virus. Several studies have shown the anti-hepatitis property of this herb for a long-time span. Both in vitro and in vivo studies with aqueous extract of the plant *P. amarus* were performed to study this property. Aqueous extract inhibited the endogenous DNA polymerase of hepatitis B virus by binding to the surface antigen of the virus in vitro. Whereas, a significant decrease in woodchuck hepatitis virus surface antigen, using *P. amarus* extracts, was observed in the case of in vivo assay, where WHV-carrier woodchucks (*Marmota monax*) were tested for antiviral activity [450]. The effect of *P. amarus* on chronic hepatitis B virus has been largely shown by Thyagarajan et al. [423, 424]. Initial studies demonstrated encouraging results of anti-hepatitis activity that showed *P. amarus* plant preparations for treating carriers of hepatitis B virus for 30 days. The active principles that were responsible for the same, were isolated by Thyagarajan et al., in 1988, and in the first clinical trial on chronic HBV carriers, HBsAg clearance in the *P. amarus* treated group was 59%, versus 4% in the placebo group [424], while the second open trial showed 20% HBsAg clearance and 63.6% loss of infectivity by HBeAg seroconversion [423]. Brook in the year 1988 also studied the effect of *P. amarus* on chronic carriers of hepatitis B virus [73]. *P. amarus* extract was again administered in the in vivo studies performed by Blumberg et al., in 1990 to show the prevention of Hepatitis B virus along with primary hepatocellular carcinoma [70]. In vivo effect of *P. amarus* on duck hepatitis B virus replication was also studied [290]. Further, the effects of *P. amarus* on hepatitis B virus (HBV) antigens and HBV-DNA was evaluated using initial ethanolic extract and subsequent fractions of *P. amarus* plants, out of which butanol extract was shown to be the most potent [253]. The following year, Shead et al. studied the effects of extracts of five Australian *Phyllanthus* species (*P. hirtellus, P. gunnii, P. gasstroemii, P. similis and P. tenellus*) along with other plant extracts and the antiviral drug foscarnet on duck hepatitis B virus (DHBV), as well as endogenous DNA polymerase (DNAp) activity were compared [390]. Yeh et al., in the year 1993 also suggested the effectiveness of aqueous *P. amarus* extract in the treatment of hepatitis B virus infection, by studying the effect of some active components of this herb on the cultured hepatoma cell line HepA2, which can suppress the HBsAg gene expression in human hepatoma cells and thus contributing the antiviral activity of *P. amarus* in vivo [470]. Extracts of the two traditional Indian herbs, *P. amarus*, and *P. maderaspatensis*, described by others as useful in the treatment of chronic hepatitis B virus infection, were studied for antiviral properties on duck hepatitis B virus infection [263]. Studies also showed that a number of species of the genus *Phyllanthus* (Euphorbiaceae) have been tested for their efficacy as antivirals, partly based on references to traditional usage for the treatment of diseases, possibly having a viral origin as hepatitis B [443]. Another research demonstrated the antiviral activity against chronic hepatitis B virus even by trials on human patients, by testing the effects of three different *Phyllanthus* extracts on the serologic status of 123 patients with chronic hepatitis B [455]. Also, experimentation by Jayaram and Thyagarajan in 1996 with a human hepatocellular carcinoma derived cell line named Alexander cell line, proved the anti-hepatitis B virus property of *P. amarus* at the cellular level, and further confirmed its beneficial use in the treatment of acute and chronic hepatitis B and healthy carriers of HBV [174]. Further, the mechanism of action of *P. amarus* in treating hepatitis B virus was defined, by Lee et al., in 1996 using HepG2 2.2.15 cells [214]. They showed how *P. amarus* inhibited hepatitis B virus polymerase activity, decreased episomal hepatitis B virus DNA content, and suppressed virus release into the culture medium. The antiviral potential of *P. amarus* against the hepatitis B virus was also studied at the molecular level by a specific mechanism involving interactions between HBV enhancer I and C/EBP transcription factors [328]. In acute viral hepatitis, a trial of *P. amarus* was performed to know whether the powders of *P. amarus* plants favorably influence the duration of the disease in patients when compared to placebo. The analysis showed that *P. amarus* powders did not significantly reduce the duration of jaundice in persons with virus B hepatitis [276]. To assess the efficacy and safety of the *Phyllanthus* genus for chronic hepatitis B virus (HBV) infection, a systematic review of randomized clinical trials was also performed [224, 225]. Inhibition of hepatocellular carcinoma by *P. amarus* extract administration to rat models has also been studied [183, 363]. The efficiency of *P. amarus* compound and interferon having a remarkable effect on chronic viral hepatitis B in the recovery of liver function and inhibition of the replication of HBV was shown when a comparative study of the two was performed with fifty-five patients with chronic viral hepatitis B [463]. Efficacy of the lignan niranthin present in *P. amarus* showed the best anti-HBsAg activity, while the most potent anti-HBeAg activity was observed with hinokinin, when different compounds from *P. amarus* and other *Phyllanthus* species were screened for anti-human hepatitis B virus in vitro using an HBV-producing cell line [153]. Further reports on clinical trials assessing the therapeutic effects of *Phyllanthus* on patients with hepatitis B virus were performed by many researchers [466, 474, 475]. Also, some randomized clinical trials were performed to evaluate the benefits and harms of *Phyllanthus* species compared with

antiviral drugs for patients with chronic HBV infection [226, 462]. Studies on homology modeling and molecular docking analysis of phytochemicals from the herb against Hepatitis B DNA Polymerase was carried out to promote the significant phytoconstituents as potential lead molecule for downstream studies [256]. Effects of herbal active compounds of *P. amarus* along with other plants in understanding the prevention and treatment of hepatocellular carcinoma (HCC) primarily caused by hepatitis B and C virus infection were studied [245]. The effectiveness of an ethanol extract of the herb was studied against hepatitis B viral (HBV) infection in human HepG2/C3A cells which showed that the ethanol fraction inhibited the growth of HBV-infected cells [222]. Recent works with *P. amarus* for examining its anti-HBV activity along with other Indonesian plants were conducted and the effect on viral entry was examined by determining levels of HBsAg expression in the supernatants of HBV-infected HepG2-NTCP cells by ELISA, for establishing the herb as a promising candidate for anti-HBV drug development [453]. In a recent clinical study, an evaluation of the herb's efficacy in alcoholic hepatitis was conducted with mild to moderately affected patients, after a 4-week administration of *P. amarus* extract was performed [401].

Besides hepatitis B virus, *P. amarus* extracts have been shown as a potent natural source in the inhibition of hepatitis C virus (HCV) replication [369]. The role of *P. amarus* in the protection of the liver against HCV was also studied, which strongly suggested that therapy with this herb increases antioxidants and reduces lipid peroxidation of hepatic cellular and intracellular membranes, and protects liver damage due to free radicals in hepatitis C [288]. In vitro studies to demonstrate the ethanol extract of the herb as good candidates for the development of anti-HCV drugs, were carried out followed by docking analysis to predict the interaction of the significant lignans against HCV receptor [452]. Another recent study demonstrating a structure-based approach to identify three structural congeners of phyllanthin as a novel, potent inhibitor of NS3 protease, a non-structural protein involved with the HCV viral replication and disease progression has been reported, thereby establishing the herbal plant *P. amarus* as a promising candidate for developing anti-HCV therapeutics to control HCV-induced liver diseases [371].

The different mechanisms reported on the hepatoprotective potential of *P. amarus* have been illustrated in Fig. 3

(ii) Antioxidant property of *P. amarus*

P. amarus besides its diverse function in hepatoprotection and other hepatic ailments also plays a major role in exhibiting antioxidant and anti-diabetic properties. Methanolic and aqueous extracts of *P. amarus* leaves and fruits showed inhibition of membrane lipid peroxidation (LPO), scavenging of 1,1-diphenyl-2picrylhydrazyl (DPPH) radical, and also inhibited reactive oxygen species (ROS) in vitro showing the antioxidant potential of the plant [144]. They also showed the antioxidant activity of the extracts in vivo by the inhibition of the carbon tetrachloride (CCl_4)—induced formation of lipid peroxides in the liver of rat models by pre-treatment with the plant extracts. In vitro antioxidant activities of five different *Phyllanthus* species with their methanol extracts were studied by Kumaran and Karunakaran [210]. The

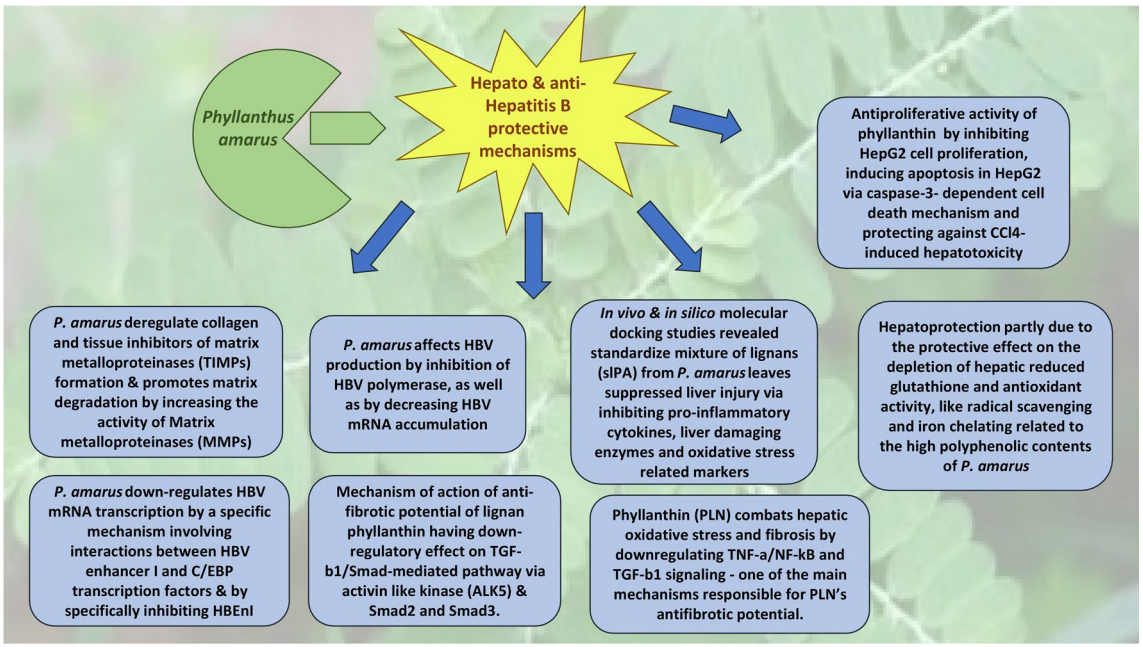

Fig. 3 Hepatitis-B and hepatoprotection mechanisms reported in *P. amarus*

different phytoconstituents present in *P. amarus* namely amariin, repandusinic acid and phyllanthusiin D showed higher antioxidant activity amongst the ellagitannins when compared to the flavonoids like rutin, and quercetin 3-Oglucoside for their free radicals scavenging ability in various systems including 2, 2-diphenyl-2- picrylhydrazyl (DPPH), 2,2-azobis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS)/ferrylmyoglobin, ferric reducing antioxidant power (FRAP) and also pulse radiolysis [227]. In addition, the ability of *P. amarus* to protect rat liver mitochondria against oxidative damage was also determined by them. Further, in vivo studies to demonstrate the antioxidant potential of *P. amarus* were performed to estimate the lipid peroxidation (LPO), vitamin C, uric acid, and reduced glutathione (GSH) in plasma of rats which were treated with aqueous extract of the herb. Also, evaluation of the antioxidant enzymes: Glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) were conducted [188]. In vitro oxidative toxicity induced by chromium (VI) in MDA-MB-435S human breast carcinoma cells was inhibited by *P. amarus* aqueous extract shown in a study. This high antioxidant potential of this potent medicinal plant was shown to be due to the presence of its phenolic constituents [135]. The antioxidant properties of 70% aqueous ethanol extract of roots of the herb were evaluated [236], where the ethyl acetate soluble fraction showed higher radical scavenging activity and further chemical characterization showed to contain gallic acid derivatives. In vitro antioxidant activity of aqueous extract of *P. amarus* leaf was also investigated together with its effect on oxidative stress and antioxidant enzymes levels in diabetic rat kidneys [132]. A study that was performed to evaluate the effects of *P. amarus* powder on oxidative stress, muscle damage, leukocyte counts, inflammation, and muscle soreness after high-intensity exercise, it was seen that *P. amarus* supplementation reduced oxidative stress and muscle soreness [373]. The antioxidant capacity along with findings of novel extraction methods on bioactive compounds from *P. amarus* was evaluated [281]. In-vitro antioxidant activities using methanolic extract of the whole plant of the herb have been performed by other groups of researchers [106]. Data from other research groups have shown that crude ethanolic leaf extract of *P. amarus* improved antioxidant defense capacity and invigorated the blood of experimental mice [37]. Again, the synergistic effect on the antioxidant activity of *P. amarus* along with other herbs on chicken muscle progenitors was also evaluated [353]. In another interesting research work that was performed under salt stress, where the antioxidant activity along with plant growth promotion were assessed from two salt-tolerant endophytic and phosphate solubilizing bacteria ACMS25 and PVMX4 isolated from *P. amarus,* identified as *Acinetobacter* sp. and *Bacillus* sp. based on 16srRNA sequencing. This study mainly aimed to introduce them as biofertilizer for the commercial cultivation of *P. amarus* [179]. In vitro studies were again conducted to show the great antioxidant potential as well as cytotoxic activities of *P. amarus* crude extracts. The study further targeted to show the potent medicinal herb as a promising source for downstream applications in the nutraceutical, medical, and pharmaceutical industries and also for the development of natural antioxidant products [282]. Nguyen et al. conducted another experiment where they applied microwave-assisted extraction (MAE) as an advanced technique for optimization of saponin yield and also to study antioxidant potential from *P. amarus* [280]. Antioxidant potential against oxidative stress along with the antihyperglycemic and hypolipidemic potential of aqueous extract of the herb has been studied [358]. Enhanced antioxidant capacity in case of plasmodiasis in experimental mice infested with *Plasmodium berghei*, solely or combined with vitamins A, B, and E by *P. amarus* seed extract was studied by Ojezele et al. [306]. Another research study conducted a phytochemical screening of *P. amarus* collected from Kerela region in India. The study showed the presence of different phytochemicals such as phenol, flavonoid, terpenoid, and saponin that were further screened for the evaluation of the herb's antioxidant and antimicrobial potentials [364]. Several such types of research to establish the antioxidant potential of this significant herb have been conducted across the globe over the years. Like, molecular mechanisms of antioxidative effects along with the hypoglycemic potential of *P. amarus* on streptozotocin-induced diabetic rats were studied [47]. Studies on the effect of *P. amarus* aqueous leaf extract on lipid peroxidation and some antioxidant factors in Wistar rats were performed [302]. Antioxidant activity along with total phenolic and flavonoid content from aqueous and methanolic extracts of different *Phyllanthus* species from Malaysia namely, *Phyllanthus urinaria, P. amarus* and *P. debilis* were also performed [473]. Assessment of the antioxidant potential of the herb was done in different parts across the globe like Vietnam [417], Malaysia, where the role of maslinic acid, a natural phytoalexin extracted from *P. amarus*, has been shown as a potent natural antioxidant [295]. A study was conducted with aqueous extracts of selected medicinal plants, including *P. amarus,* in Sri Lanka for comparison of antioxidant capacity. Results showed that *P. amarus* was found to possess a high antioxidant capacity compared to the other medicinal plants [456]. Similar research with selected Vietnamese plants along with three herbal commercial products was performed the following year [96]. To test the antioxidant potential either alone or in combination with other properties as well, is still being carried out worldwide. In vitro antioxidant and antimicrobial activity of *P. amarus* leaf extract including an evaluation of the herb's antifungal properties was also reported [69, 349]. Antioxidant activity and toxicological implications of the aqueous extract of *P. amarus* leaves in

female Wistar rats were also studied [296]. A few more research on *P. amarus* elaborating studies of its antioxidant potential evaluation [1, 314] have also been reported. One recent study to demonstrate the antioxidant potential evaluation along with the efficacy of terpenoid-rich fraction of *P. amarus* whole plant, in the amelioration of high salt diet-induced obesity was conducted [120]. Some more research reports focussing on quantification, antioxidant, and free radical scavenging potentials of *P.amarus* leaves have also been mentioned [110, 436]. Another recent study has showcased data that are expected to produce a combination formulation, including plants like *P. amarus*, *Euphorbia hirta,* and *Loranthus* sp. with very strong antioxidant activity that can be used as herbal medicines [197]. The therapeutic effect of ethyl acetate fraction of *P. amarus* leaf on hematological and biochemical parameters in albino rat with arsenic-induced toxicity was recently reported. The induced arsenic poisoning resulted in significant alterations in hematological indices thereby affecting the HGB, platelet, and WBC count as well as resulting in cholestasis showing increased bilirubin. However, amelioration of the effects of *P. amarus* extracts in this study was concluded to be due to either by ways of antioxidant activities as free radical scavengers or chelators of metal ions [435]. In another recent study, an evaluation of total antioxidant effects, total phenolics, and total flavonoids of fractions of ethanol extract of *P. amarus* leaves was conducted using column chromatography [465].

(iii) Antidiabetic or hypoglycemic activities of *P. amarus*

Insulin resistance is one of the common problems of the twenty-first century, and one of the common causes is the high consumption of refined carbohydrates. Management of both hypo and hyperglycemia is very important for controlling diabetes. Hypoglycemic, hypotensive, and diuretic effects of *P. amarus* on human subjects were assessed by Srividya and Periwal in the year 1995 [406]. A clinical study with 21 non-insulin-dependent diabetic patients treated with aqueous extract of *P. amarus* showed effective hypoglycemic activity of the plant [259]. Also, methanolic extract of *P. amarus* which was found to have potential antioxidant activity produced a significant ($P < 0.001$) reduction in blood sugar when administered for 15 days on alloxan-induced diabetic rats [368]. The antidiabetic and anti-lipidemic potentials of both aqueous leaf and seed extracts of *P. amarus* were further investigated [14]. In another study conducted by Lawson-Evi et al., 2011, the antidiabetic effects of aqueous and hydroalcoholic extract of *P. amarus* in the management of diabetes, were studied [212]. Diabetes was induced through both alloxan monohydrate and streptozotocin in rats' experimental model systems [187, 212]. The body weight gain, blood glucose level, serum insulin, total cholesterol, and triglycerides were evaluated [212] and protein oxidation and reduced glutathione was also estimated [187]. Further, for evaluating the effectiveness and mechanism(s) of action of aqueous leaf and seed extracts of *P. amarus*, the antihyperglycemic, antihyperlipidemic and cardioprotective potentials of the aqueous leaf and seed extract of *P. amarus* in type 2 Diabetes mellitus rat models were shown by Adeneye [16]. The traditional basis for the use of *P. amarus* as an antidiabetic agent with the pharmacological activities attributed to the presence of flavonoids and other phenolics contained in this plant, was also evaluated by using soft drink extract (SDE) of the herb, as well as histological changes in liver, kidney and pancreas were assessed [10]. Aqueous and organic extracts of the herb in inhibiting carbohydrate hydrolyzing enzymes, α-amylase, and α-glucosidase activity, were shown in a study by Mahomoodally and Muthoora [235]. They showed how the extract prepared from this plant could help mitigate hyperglycemia and the phenolic nature could help combat stress induced by hyperglycemia. The ethanolic leaf extract of *P. amarus* also possesses a potent hypoglycemic activity, and the possible mechanism may be the stimulation of β cells and subsequent release of insulin and activation of the insulin receptors—this was shown in the study by Shetti and Kaliwal [391], where the hypoglycemic activity in mice was comparable to that of the reference drug glibenclamide. A similar study for antidiabetic evaluation comparable with that of glibenclamide, along with in-vitro and in-vivo studies were conducted with polyherbal hydro-alcoholic extracts of *P. amarus* and other herbs [128]. Towards a better understanding of the molecular mechanism of this medicinal herb in managing diabetes mellitus, an evaluation of in vivo antidiabetic properties of two concentrations (250 and 500 mg/kg BW) of *P. amarus* via metabolomics approach in streptozotocin-induced obese-diabetic rats was done [251]. The use of an aqueous extract of *P. amarus* as adjuvant therapy for the prevention and management of diabetes was shown in research studies conducted with streptozotocin-induced diabetic male Wistar rats [47, 71, 350]. Evaluation of the two key enzymes viz. α-glucosidase and α-amylase involved in serum glucose regulation was performed in a study using 18 Vietnamese plants' extracts including *P. amarus* [429]. α-glucosidase inhibitors from aqueous extracts of *P. amarus* and *P. urinaria* were also identified in another study by the same group, demonstrating corilagin, repandusinic acid A, and mallotinin to be the potent inhibitors contributing significantly to the hypoglycaemic property of the herb [430]. In another study on the management of diabetes in Cameroon, an ethnopharmacological and ethnomedical data form was prepared and addressed to a total of 116 diabetic patients belonging to 58 tribes and living in several phytogeographic units. The objective of this study was to determine the diabetic patients who use herbal medicine and collect and identify the types of plants used and the type of diabetic patients using familial herbal treatment [432]. Further, in the following year, beneficial effects of aqueous extract of *P. amarus* were investigated on insulin resistance

as well as oxidative stress in high-fructose-fed male Wistar rats [358]. Again, a thorough investigation of aqueous extracts of four crude herbs possessing antidiabetic activity, including *P. amarus* was done for their organoleptic characters, physicochemical parameters, and microbiological standards for their quality and safety [398]. Evaluation of antibacterial and in vitro antidiabetic properties of *P. amarus* extract has also been reported [437]. Other studies down the years to show both hypoglycemic effects and comparative hypoglycemic effects of *P. amarus* leaf extract along with other tropical herbs on blood glucose levels of alloxan-induced diabetic guinea pigs have been evaluated by a group [38, 39]. A study of the antidiabetic properties and chemical composition of *P. amarus* along with another species *P. debilis* mostly used in Guadeloupe was performed for the first time in the region [247]. Another study where the combination of the herb along with the drug metformin to improve insulin resistance in obese rats was shown effective in treating diabetes [195]. One of the side effects of diabetes is diabetes-induced nerve damage where peripheral nerves are impaired with low conduction velocity and alterations in the behavior are seen. Srilatha and Reddy, 2019 have shown the neuroprotective role of *P. amarus* and esculentin on nerve conduction velocity and studied other parameters in diabetic rats [402]. In one study, out of the 37 medicinal plants selected from two Thai folk antidiabetic recipes, that were investigated for their potential anti-diabetic mechanisms via α-glucosidase and α-amylase inhibitory activities, ethanolic extracts of *P. amarus* along with some others, were observed to have the highest α- glucosidase inhibitory activity [420]. Inhibitory effects of the extracts of *P. amarus* on the activity of *α*-amylase, pepsin, and trypsin were studied by other researchers as well [447]. In vitro studies investigating the comparative anti glycemic properties and molecular docking of the methanolic extracts of dried leaves of *P. amarus* were performed in an attempt to show that methanolic crude extracts could be used in the prevention of diabetes secondary complications [327]. Recently, a complete study, including the fresh and dried aerial parts of *P. amarus* was performed using Guadeloupe's population's traditional extraction methods for evaluating the antidiabetic activities of the plant [246]. Another combination study using *P. amarus* and *Gymnema sylvestre* for the treatment of diabetes and its related long-term complications was reported [213]. In vitro studies using *P. amarus* extract for delaying or preventing complications of diabetes were also recently conducted and this study has been also previously mentioned for its antioxidant activity as well [110]. Very recently this year, the alpha-glucosidase activity of phytochemicals from *P. amarus* leaveswas studied via in-silico approaches [329].

(iv) Anti-HIV properties

The globally acknowledged and rising demand for a broader, safer as well as cheaper repertoire for the treatment of human immunodeficiency virus (HIV) infection cannot be ignored in scientific research. Considerable progress has also been achieved in research on natural products which can effectively inhibit HIV-1 replication. Aqueous extract of *P. amarus* inhibiting human immunodeficiency virus type-1 reverse transcriptase (HIV-1-RT) was shown by Ogata et al., in 1992 [304]. Also, many active compounds were isolated from traditionally used medicinal plants including *Phyllanthus* species like *P. amarus* who's aqueous as well as alcohol-based extracts potently inhibited HIV-1 replication in HeLa CD4 + cells [293]. Further water/alcohol extracts of *P. amarus* were shown to block HIV-1 attachment and the HIV-1 enzymes integrase, reverse transcriptase, and protease to different degrees, thereby preventing HIV infection and the isolated ellagitannins viz. geraniin and corilagin were shown to be the most potent mediators of these antiviral activities [292]. Their study supported the conclusion that *P. amarus* has inhibitory effects on HIV not only in vitro but also in vivo. Other research showing activity profiles of HIV-1 reverse transcriptase inhibitors from the herb has also been reported across the globe [115, 412]. In vitro studies using whole-plant extract of the herb have also been studied for its anti-HIV potential [136]. Traditional treatment practices for the management of HIV/AIDS in the Mpigi District of Uganda using *P. amarus* as one of the sources among diverse options have also been performed [298]. Another very recent research performed a study using fluorescence-based assay for screening new inhibitors from peptides that were extracted from 111 Asian medicinal plants, including the aerial parts of *P. amarus*. The HIV-1 reverse transcriptase (HIV-1 RT), which is responsible for the transcription of viral RNA genomes into DNA genomes, has become an important target for the treatment of patients with HIV infection. They targeted for development of potential HIV-1 reverse transcriptase (HIV-1 RT) inhibitors from the isolated peptides for the treatment of such patients. [383].

(v) Antigenotoxic, antimutagenic and anticancer potentials of *P. amarus*

Among the diverse pharmacological properties of *P. amarus*, the potential of this medicinal herb in exhibiting antigenotoxic, antimutagenic, and anticancer activities has also been studied extensively over the past decades. The role of crude extract of *P. amarus* in showing the antigenotoxic property was evaluated using the root meristem of *Vicia faba* L. by performing in vivo studies [133]. *P. amarus* extracts have been shown to be a potent inhibitor of the hepatocarcinogenesis induced by N-nitrosodiethylamine (NDEA) where none of the *P. amarus* extract-treated animals developed any tumors even 32 weeks after the NDEA administration, whereas all of the animals died due to tumor burden in the control group [183]. The anticarcinogenic activity of *P. amarus* extracts along with

extracts of *Emblica officinalis* and *Picrorrhiza kurroa* were further evaluated by showing significant inhibition of hepatocarcinogenesis induced by N-nitrosodiethylamine (NDEA) in a dose-dependent manner [176]. The effect of aqueous extract of *P. amarus* administration after induction of hepatocellular carcinoma (HCC) by N-nitrosodiethylamine (NDEA), was also studied in Wistar rats [363]. The antimutagenic and anticarcinogenic potentials of *P. amarus* were assessed using the bacterial preincubation mutation assay and an in vivo alkaline elution method for DNA single-strand breaks in hamster liver cells [403]. Potent anticarcinogenic activity against 20-methylcholanthrene (20-MC) induced sarcoma development was exhibited by an aqueous extract of *P. amarus* treatment. As a result, not only the survival of tumor harboring mice was increased, but also this treatment prolonged the life span of Dalton's Lymphoma Ascites (DLA) and Ehrlich Ascites Carcinoma (EAC) bearing mice, and reduced the volume of transplanted solid tumors [362]. The anti-mutagenic activity of methanolic extract of *P. amarus* was also tested in vitro as well as in vivo by another group of researchers [365]. The radioprotective effect of *P. amarus* extract along with its potential of increasing the antioxidant defense mechanism was shown in adult BALB/c mice [207]. Also, the protective effect of *P. amarus* extract against radiation-induced changes in the intestine and mouse chromosomal damage was evaluated [143]. The radioprotective activity of pure ellagitannins from *P. amarus* was also further studied using rat liver mitochondria and pBR322 plasmid DNA as an in vitro model system [228]. The chemoprotective activity of 75% methanolic extract of *P. amarus* was studied against cyclophosphamide (CTX) induced toxicity in mice [205]. They showed how *P. amarus* extract significantly reduced the myelosuppression and improved the WBC count, bone marrow cellularity as well as the number of maturing monocytes in mice. Chemopreventive activity of *P. amarus* extract was also studied with regard to N-methyl N'-nitro-N-nitrosoguanidine (MNNG) induced stomach cancer in Wistar rats [367]. Further, multidrug resistance (MDR) constitutes the major obstacle to the successful treatment of cancer. The possible cytotoxic and MDR reversing properties of the extract and compounds isolated from *P. amarus* were evaluated employing two human leukemia cell lines [218]. The inhibitory effects of the two lignans, phyllanthin and hypophyllanthin, were studied in different aspects. Using the in vitro model of human colon cancer Caco-2 cells, their role in the function of P-glycoprotein (P-gp) and multidrug resistance protein 2 (MRP2) was studied [407]. Also, the preventive and curative role of these lignans exhibiting antitumor activities against Ehrlich Ascites Carcinoma in Swiss albino mice has been reported [164]. Inhibition of carcinogenesis by an alcoholic extract of *P. amarus* by inhibiting cytochrome P450 (P450) enzymes both in vivo as well as in vitro, has also been shown [206]. Harikumar et al. showed that *P. amarus* inhibits cell growth and induces apoptosis in Dalton's lymphoma ascites cells through activation of caspase-3 and downregulation of Bcl-2 [142]. The ability of *P. amarus* to suppress virally induced cancers as well, has been further studied against friend murine leukemia virus (FMuLv)-induced erythroleukemia in BALB/c mice [141]. Hairy root extract of *P. amarus* has been shown to induce apoptotic cell death in human breast cancer cells [3]. To identify the genus *Phyllanthus* as a valuable candidate in the treatment of metastatic cancers, one study evaluated its potential using *P. amarus* as one of the candidates along with other species of the same genus on lung and breast carcinoma cells [216]. Furthermore, the anticancer potential of the lignans phyllanthin and hypophyllanthin against breast cancer has also been studied both by in vitro and in vivo methods [333]. The potential of *Phyllanthus* plant to inhibit tumor metastasis and angiogenesis through the suppression of MMP enzymes to halt the progression of cancer was studied by another group of researchers [413]. The anticlastogenic, antigenotoxic, and antimutagenic capability of *P. amarus* extract was performed in another study by Ahmad et al. [23]. The chromosomal aberrations were produced by Aflatoxin B1 in human lymphocyte culture and in vivo bone marrow cells of Albino mice. The frequencies of aberrations, cell growth kinetics, and total aberrant cells were studied and *P. amarus* extracts were found to have a dose and duration-dependent remedy. Phyllanthin and hypophyllanthin showed promising anticancer activity in a study where gold nanoparticles synthesized with *P. amarus* against MCF 7 breast cancer cell lines were conducted [352]. Another study used to determine the pathways utilized by four *Phyllanthus* species including *P. amarus*, indicated that ERK and hypoxia pathways are the most likely targets of the four *Phyllanthus* species for the inhibition of human breast cancer cells, viz. MCF-7 [215]. Another work to study the serum biochemical changes in azaserine-induced pancreatic cancer in Wister rats was conducted using both aqueous and alcoholic extract of the herb *P. amarus* [344]. The antitumor activities of *P. amarus* and its potential of herb-drug interactions with 5-Fluorouracil (5-FU), followed by 5-FU-induced perturbations in ribonucleotides and deoxyribonucleotides pool sizes in human hepatocellular carcinoma (HepG2) cells were reported [137]. Anti-proliferative activity of the medicinal plant *P. amarus* was also studied to show its anticancer activity by inhibiting cell division [172]. Another work showing the bio-guided fraction and isolation of the antitumor components from *P. amarus*, using different chromatographic methods like ^{1}H-NMR, ^{13}C-NMR, 2D-NMR, and mass spectrometric analyses, identified corilagin as the major active antitumor composition on hepatocellular carcinoma cells [476]. The role of dioscin, a polyphenolic component isolated from *P. amarus*, in suppressing lung cancer migration, and invasion in vitro by inhibiting the TGF-β1-induced epithelial-to-mesenchymal transition (EMT), an important cellular process that occurs during cancer development and progression, has a crucial role in metastasis by enhancing the motility

of tumor cells, was identified by a study [223]. Another study investigated the anticarcinogenic effect of 14 crude extracts from 7 medicinal plants (including *P. amarus* as one of them) and one isolated molecule on the survival and growth of selected cariogenic bacteria [268]. In the following year, another research showed that a phytomolecule isolated from *P. amarus* plant and used for the synthesis of vanadium oxide (V_2O_5) nanorods successfully, showed less cytotoxicity in comparison with standard drug, Methotrexate against breast cancer cell line MDA MB 231 and MCF 12 A human cell line, respectively [347]. Such research on the anticancer potential of the herb plant is still being carried out globally. In Malaysia, the herb locally known as Dukung Anak, one research isolated three lignans namely hypophyllanthin (from hexane crude), niranthin, and lintetralin (from ethanol crude), followed by its anticancer studies against HeLa cells and NIH/3T3 cells by MTT assays were performed to show the active effects [291]. Another in vitro study showed the potential of lignan enriched fraction of *P. amarus* to induce apoptotic cell death in human cervical cancer cells by activation of p53 and p21 against DNA damage, which was mainly due to the major lignan phyllanthin that showed strong irreversible affinities for viral E6 and MDM2 in an in silico analysis [338]. Further, other studies on pancreatic cancer cell lines [283], as well as human leukemic cells [356] with herb extracts, were also reported. The anticancer effects of *P. amarus* on HCT116 colorectal cancer cell lines were investigated. Some other reports of therapeutic effects of *P. amarus* extracts on dimethylhydrazine-induced colon carcinogenesis in balb/c mice [320], as well as the mutagenic properties of the herb [63] have also been shown. Studies on the anti-prostate cancer property of extracts of the herb have also been recently reported [1]. It was found that phyllanthin and gallic acid exhibited an apoptotic effect through the caspase-dependent signaling pathway. Some recent studies demonstrating this anticancer activity of *P. amarus* extracts showed that the phytoconstituents phyllanthin and gallic acid exhibited anti-proliferative and apoptotic effects on HCT 116 human colorectal cancer cells through the caspases-dependent pathway [255]. The anti-proliferative capacity of the combined extracts of *P. amarus* along with another plant *Paramignya trimera* against three pancreatic cancer cell lines (MiaPaCa2, BxPc3, and CFPAC1) was also studied [284]. In vitro anticancer activity using dimethylformamide leaf extract of *P. amarus* was tested against the Human colorectal adenocarcinoma (HCT 15) and Human breast cancer (T47D) cell lines, where the inhibitory effect on HCT 15 cell line was found to be greater than T47D cell line [332]. In another recent study, a novel strategy demonstrating the modified and treated titanium dioxide nanoparticles with three medicinal herbs including *P. amarus* were used for the determination of the anticancer nature against oral cancer cells [233].

(vi) Anti-inflammatory and antinociceptive properties

Several types of research have also been conducted over the past years to get an insight into the anti-inflammatory and analgesic properties of the medicinal herb *P. amarus*. For opening new possibilities for the development of new anti-allodynic drugs, the anti-oedematogenic and anti-allodynic effects of the hexanic extract, lignan-rich fraction, and purified lignans from *P. amarus*, in the inflammatory and neuropathic models of nociception were studied [191]. The anti-inflammatory potential of *P. amarus* by inhibition of iNOS, COX-2, and cytokines via the NF-kappaB pathway was shown by a research group [193]. Inhibition of experimental gastric lesions and inflammation by methanolic extract of *P. amarus* was also shown in another study [366]. The anti-inflammatory effect of the extracts, fractions, and purified lignans obtained from *P. amarus*, was also assessed and studied in carrageenan (Cg)-induced paw oedema by Kassuya et al. [189]. Further, Kassuya et al. [190] showed that the lignan niranthin from *P. amarus* exhibited anti-inflammatory and antiallodynic actions which were probably mediated through its direct antagonistic action on the platelet-activating factor (PAF) receptor binding sites. The hydroalcoholic extract (HE) from the genus *Phyllanthus* exhibited pronounced antinociception when assessed in chemical models of nociception, namely acetic acid-induced writhing, formalin and capsaicin-induced licking [380]. Because of its potent anti-inflammatory activity, one study was designed to evaluate its anti-arthritic activity using an aqueous extract of *P. amarus* [238]. Further down the line, anti-inflammatory and analgesic activities of *P. amarus* for pain-modulation and syndromes such as fibromyalgia were studied by several researchers [9, 84, 86, 93]. The chondroprotective potential of *P. amarus* extracts in experimentally induced cartilage degradation in the explants culture model to show its application for therapeutic use as an antiarthritic agent has also been shown to exhibit anti-inflammatory activity [343]. The isolated compounds and reference standards namely gallic acid, ellagic acid, corilagin, and geraniin, that were quantitatively analysed in the plant extracts of another study, showed a strong immunosuppressive effect. This could be further developed into leads useful for the development of immune-related disorders including inflammation [471]. Other studies have also showed the anti-inflammatory and gastric anti-ulcer activity of *P. amarus* extracts along with a study on improving kidney functions, kidney oxidative stress, inflammation, fibrosis, and apoptosis [131, 260]. Inhibitory effects of the major lignan phyllanthin and 80% ethanolic extract from *P. amarus* were investigated. It showed suppressive effects on the inflammatory process by mediating the release of inflammatory signaling molecules via the NF-κB, MAPKs, and PI3K-Akt signal-transducing pathways in lipopolysaccharide (LPS)-induced U937 human macrophages

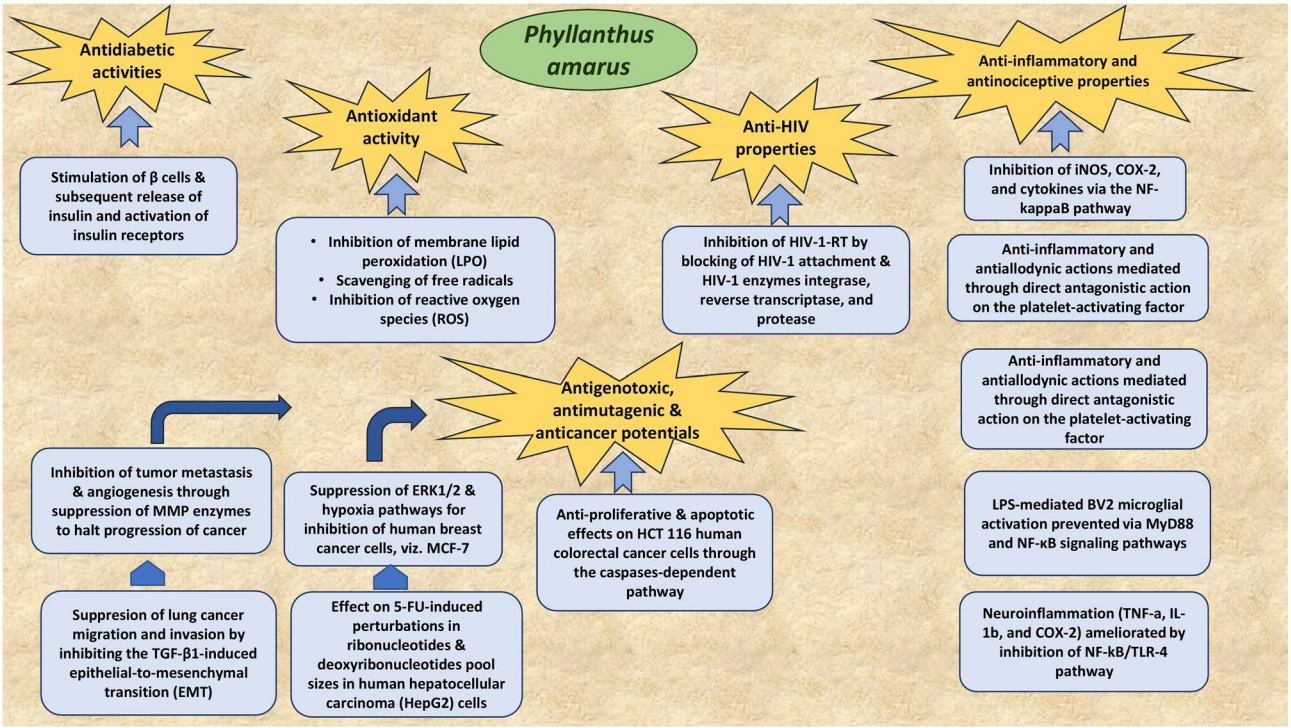

Fig. 4 Mechanisms reported to be involved in antioxidant, anti-HIV, antidiabetic, antigenotoxic, antimutagenic, anticancer, anti-inflammatory and antinociceptive potentials in *P. amarus*

[139, 140]. Another study has shown how the ellagitannin geraniin enhances the activation of the Wnt/β-catenin pathway, explaining how it promotes osteoblast proliferation and differentiation [221]. Again, the lignans phyllanthin and hypophyllanthin from *P. amarus* have been shown to ameliorate immune-inflammatory response in ovalbumin-induced asthma, a chronic airway immunoinflammatory disorder [461]. In vitro antiasthmatic activity of hexane extract of *P. amarus* has also been investigated [168]. The protective effect of the herb extracts against lipopolysaccharide (LPS)-induced neuroinflammation and cognitive impairment were studied in vitro since the effects of *P. amarus* in modulating immune responses in the central nervous system leading to protection against functional changes had remained unexplored [42]. One interesting study showing the evaluation of PHYLLPRO™, a standardized ethanol extract of *P. amarus* leaves in managing hangover, inflammation, and liver functions has also been reported [130]. Determination of changes in serum levels of inflammatory biomarkers and antioxidant levels among knee osteoarthritis patients after treatment with *P. amarus* by nanoparticle gel phonophoresis has been extensively studied [103, 342]. Ethanol extract of *P. amarus* in modulating anti-inflammatory responses in BV2 microglial cells with a subsequent neuroprotective action via MyD88 and NF-κB signaling pathways has been recently reported [166]. In vitro studies showing the antiepileptic potential of phyllanthin from the herb *P. amarus* thereby ameliorating neuroinflammation (TNF-a, IL-1b, and COX-2) by inhibition of NF-kB/TLR-4 pathway, have been also performed [414]. Very recently, the antiallergic activity of *P. amarus* extract and its compounds was determined by measuring the concentration of allergy markers released from rat basophilic leukemia (RBL-2H3) cells with ketotifen fumarate as the positive control, exhibiting its anti-inflammatory potential. It was shown that the lignan hypophyllanthin could potentially exhibit antiallergic activity by preventing the activation of the histamine 1 receptor or H1 receptor [2]. Another recent in vitro study with ethanol extracts of *P. amarus* has investigated its protective effect against high salt diet-induced oxidative stress, inflammation, and dyslipidemia [317].

Few other mechanisms of the different bioactivities of *P. amarus* have been depicted in Fig. 4

(vii) Anti-microbial and related properties of *P. amarus*

P. amarus has also been very effectively used against the common tropical infection malaria. In the treatment of malaria caused by *P. falciparum*, *P. amarus* in combination with other herbs was shown to be a potent anti-malarial drug [25]. The antifungal activity of *P. amarus* extracts was also studied against dermatophytic fungi *Microsporum gypseum* [20]. In vitro antiplasmodial activity of callus culture extracts and fractions from apical stems of this herb was shown by Cimanga et al. [89]. A study on the antimicrobial potentiality of *P. amarus* against drug-resistant pathogens was conducted and

shown by Mazumder et al. [249]. Also, the antimicrobial effects of *P. amarus* and *Piper guineense* on *Candida albicans* and *Streptococcus faecalis* were studied by Okigbo and Igwe [310]. Antiplasmodial effects of the aqueous extract of *P. amarus* against *Plasmodium berghei* in Swiss albino mice were shown by Dapper et al. [98]. Besides, *P. amarus* along with four other Euphorbiaceae members have been shown to exhibit larvicidal activity against *Aedes aegypti* and *Culex quinquefasciatus* establishing an ideal eco-friendly approach for the control of the dengue vector [359]. The antimicrobial potentials of *P. amarus* against multiple antibiotic-resistant bacteria were also evaluated by a group of researchers [12]. Ethyl oleate isolated from the methanolic extract of *P. amarus* showed pronounced antimicrobial activity and exhibited a broad spectrum of MICs [34]. The aqueous extract of the herb showed greater efficacy than its methanolic extract in treating malaria [27]. Antibacterial activity of the herb against urinary tract infection (UTI) causing bacterial pathogens has also been reported [381]. Quorum sensors play important role in bacterial pathogenesis. Hence, many plant extracts have been screened to attenuate bacterial pathogens [351]. The methanolic extracts of *P. amarus* could inhibit quorum sensing molecules present in *P. aeruginosa* PA101. It interfered with the swimming motility, pyocyanin production, and the lecA: lux expression. Hence, the compounds of *P. amarus* can be used as anti-pathogenic drugs. Antimicrobial activity of aqueous extract of *P. amarus* on some intestinal flora that is facultative anaerobes was also shown [56]. A more practical approach to synthesizing *P. amarus* extract was undertaken to help develop lead molecules against drug-resistant pathogens and was tested against fifteen multidrug-resistant strains of *P. aeruginosa* isolated from burn wards [395]. The green synthesis of CuO nanoparticles by using *P. amarus* extract was also found to possess strong antimicrobial activity against Gram-positive and Gram-negative MDR strains [5]. The antiplasmodial effect of ethanolic leaf extract of *P. amarus* on the markers of renal function was analyzed in *Plasmodium berghei*-infected mice [322]. *P. amarus* was found to have a beneficial effect in *Plasmodium*-infected mice. Extract and quinine suppressed *Plasmodium* effectively. Some antimicrobial studies of the plant were conducted with analgesic activity by Bhat et al. [67]. The ethanolic extract showed significant peripheral and central analgesic activity and showed a clear zone of inhibition against *Streptococcus* species. Several other types of research showing the antimicrobial properties of *P. amarus* against different pathogenic bacterial and fungal strains have also been reported in the following years [114, 318, 337, 397]. Antifungal and in vivo antiplasmodial properties of *P. amarus* extracts have also been reported [112, 116, 309]. Another study showed how the ethanol extract of *P. amarus* was formulated into herbal cream and ointment and evaluated using physicochemical, safety, and antimicrobial properties [26]. Similar other research on the antibacterial and antifungal activities with Bhuiamla extracts has been performed and reported [50, 385]. One investigation illustrated how the leaf extracts of *P. amarus* were used to synthesize silver nanoparticles (AgNPs) through an easy, rapid, and eco-friendly pathway and how the bio-synthesized AgNPs were shown to possess microbial activity against the selected pathogens and enhanced catalyst of the reduction of rhodamine B [31]. Several researchers across the globe further continued research with this herb exhibiting its antimicrobial activity against several strains of human pathogenic bacteria, fungi, and other microorganisms. In vitro antibacterial, prophylactic, and antiplasmodial activity studies with *P. amarus* extract have been conducted by different groups till now [299, 300, 307, 437]. Evaluation of the antimicrobial activity of the lignan phyllanthin from *P. amarus* extract and exhibiting inhibition of the NorA efflux pump of *Staphylococcus aureus* was conducted [372]. A study of the effects of five ethanol herbal extracts including Bhuiamla to show their potential in modulating immune responses and resistance to bacterial infection in striped catfish was also shown [287]. Another scientific research article, to address the issue of antibiotic resistance that has become a global concern, aimed to investigate the antibacterial effects of aqueous and methanolic extract of *P. amarus* on urinary tract pathogens [315]. Antibacterial activity of the herb against pathogens causing acute hepatopancreatic necrosis disease in white leg shrimp (*Litopenaeus vannamei*) in Vietnam [341] and against *Shigella dysenteriae* for treatment of bacterial dysentery in central Uganda [51] has also been reported. For therapeutically effective treatment against *Candida* infection, aqueous leaf extracts of *P. amarus* along with two other plants were tested for their antifungal efficacy [32]. The anticoccidial activity and similar antiplasmodial activity of *P. amarus* extracts, studied before, have also been evaluated [94, 313]. Another study aimed to produce scientific data on in vitro and in vivo efficacy of *P. amarus* along with *Uvaria chamae* and *Lantana camara* on multiresistant *Salmonella* spp isolated in Benin for the development of improved traditional medicine for the management of salmonellosis [217]. Antimicrobial properties of the herb extract of some other workers in the similar time frame have been mentioned already before in the antioxidant activity part [69, 96]. The antimicrobial sensitivity of ethanolic extracts of *P. amarus* on oral microorganisms [326] as well as in vitro study for evaluating the antimicrobial efficacy of *Tylophora indica*, *Curcuma longa*, and *Phyllanthus amarus* on *Enterococcus faecalis* biofilms formed on the tooth substrate were conducted [375]. Phytochemical analysis and antimicrobial potential of *P. amarus* extract on multidrug-resistant organisms associated with middle ear infection were carried out by another group [33]. The effect of *P. amarus* coating denture resin on *Candida* adhesion and its effect on human gingival fibroblast was executed using different *Candida* strains [418]. Some recent studies showed the adulticidal and cercaricidal activities of five Ghanaian medicinal plants including *P. amarus* both in vitro and in vivo for

providing baseline information that can be used to develop plant-based alternative commercial drugs against *S. mansoni* [6] and also from the herb collected from three different geographical zones in Nigeria and evaluated their effects on larva and adult of *Anopheles gambiae* [330]. Another investigation was carried out to evaluate the effect of *P. amarus* extract along with the effects of temperature, pH, on the *lipL32* gene expression in pathogenic *Leptospira* spp. that is responsible for causing leptospirosis, which is a worldwide infectious and zoonotic disease [469]. The impact of generic antimalarial like chloroquine (CLQ), and artesunate (ATS) or *P. amarus* seed extract and vitamin co-administration on the antioxidant status of experimental mice infested with *Plasmodium berghei* was performed and studied [306]. Similarly, an evaluation of *P. amarus* seed extract combined with vitamins was performed on the reproductive indices in *Plasmodium berghei*-infected mice treated with antimalarials [312]. Mycobactericidal effect of the herb [63], and in vivo antimalarial activity of the extracts of the plant against *Plasmodium berghei*-infected mice were also tested and reported [36]. One study has also shown the antibacterial potential of *P. amarus* along with two other medicinal plants in mitigating the bacteria *Salmonella typhimurium* causing typhoid fever [62]. Recent reports of in vitro antiplasmodial activity of *P. amarus* against *Plasmodium falciparum* and subsequent evaluation have also been found [43]. Leishmaniasis, a common tropical disease caused by the genus *Leishmania,* and the common carrier is sandfly. The most common method of treatment is the pentavalent antimonials which are associated with severe toxicity. Thus, plants and their herbal derivatives are the alternate ways to combat this disease. *P. amarus* is one of them and methanolic extracts of the leaves of the herb were used to study antileishmanial activity, phytotoxicity, and cytotoxicity [321]. Lignans identified from *P. amarus* extract like phyllanthin as well as niranthin were found to possess strong anti-leishmanial activity [44, 88]. Other lignans isolated from the hexane–ethyl acetate extract of leaves were tested against *Trypanosoma cruzi* intracellular amastigotes and *Leishmania amazonensis* promastigotes and was found to possess strong antileishmanial and antitrypanosomal activity [90]. Another study investigated the anti-leptospiral activity and isolated the potential anti-leptospiral constituents from the methanol extract of *P. amarus* after in vitro, in vivo, and in silico studies [78]. A recent study on a similar note showing in vitro anti-leptospiral activity of *P. amarus* extracts and their combinations with antibiotics have also been reported [165]. The antimalarial properties and preventive effects of *P. amarus* have continued to be explored to date. Effects on mitochondrial dysfunction by dichloromethane fraction of the herb were studied by another group recently and showed that it was well-tolerated without toxic effects [316]. Several other similar recent reports of the antibacterial or antimicrobial properties of *P. amarus* extracts by diverse groups from different parts of the world have been compiled and presented in this study [24, 41, 95, 180, 233, 252].

(viii) Other pharmacological properties of *P. amarus*

Besides the diverse therapeutic potentials exhibited by *P. amarus,* as already discussed, few works have also shown some other medicinal activities of this herb. The anti-diarrhoeal and gastrointestinal protective potentials of aqueous extract of leaves of *P. amarus* have been investigated in mice [301]. The aqueous crude extracts of *P. amarus* and *Euphorbia hirta* were administered to thirty-eight-week-old sexually mature male albino to determine the effects of these extracts on the male reproductive organs of these animals [7]. Chromatographic fractions obtained from *P. amarus* were tested for toxicity on the serum biochemistry of rats. The results revealed that some fractions of *P. amarus* had potentially deleterious effects on the blood and therefore caution should be exercised in the use of *P. amarus* as a medicinal plant [8]. The findings by Appiah-Opong et al. show a significant potential both for CYP-and GST-mediated herb-drug interactions of the Ghanaian medicinal plants investigated [49]. The methanol extract of *P. amarus* leaves showed oral antihyperuricemic activity in potassium oxonate- and uric acid-induced hyperuricemic rats [267]. Protective effect of the aqueous leaf and seed extract of *P. amarus* on gentamicin and acetaminophen-induced nephrotoxic rats were studied to show that *P. amarus* could constitute a lead to the discovery of a novel drug for the treatment of drug-induced nephrotoxicity [15]. Guha et al. showed that polyphenolic constituents of *P. amarus* aqueous extract mitigate oxidative stress-induced cellular degeneration and aging [134]. The modulating effects of phyllanthin and hypophyllanthin on vascular tension, used in the in vitro model of isolated rat aorta was studied by Inchoo et al., 2011 [162]. The anticonvulsant effect of *P. amarus* on maximal electroshock-induced seizures (MES) and pentylenetetrazole (PTZ) induced seizures in experimental animal models was investigated by Manikkoth et al. [240]. The cardiotonic activity of extracts of *P. amarus* and *P. fraternus* by improving the function of a hypodynamic heart was further evaluated [85]. Immunosuppressive effects of the standardized extract of *P. amarus* on cellular immune responses in Wistar-Kyoto rats were evaluated, showing that this herb may be useful for the improvement of immune-related disorders [160]. The efficacy of *P. amarus* extracts showing significant antiviral effects against white spot syndrome virus (WSSV) in freshwater crab, *Paratelphusa hydrodomous* (Herbst) has been shown [408]. An interesting study investigating *P. amarus* leaf extract as a corrosion inhibitor for mild steel using electrochemical impedance spectroscopy and potentiodynamic polarization technique for establishing the use of eco-friendly, green inhibitors was also reported [48]. Protective effects of the lignan phyllanthin from *P. amarus* against the progression of high-fat diet-induced metabolic disturbances like weight gain and adiposity were studied in mice [169]. Immuno-stimulating efficacy of aqueous extracts of *P. amarus*

leaves in positively modulating specific and nonspecific immune responses of *Oreochromis mossambicus* (Peters) thereby establishing the applicability of the herb in aquaculture was also shown [270]. *P. amarus* along with other herbal extracts were evaluated in a study to exhibit the activity of P-glycoprotein and Pregnane X receptor activation that may further exert herb-drug interactions [121]. The following year, a similar study by Fasinu et al. showing herb-drug interaction potential in the modulation of Cytochrome P450, P-glycoprotein, and Pregnane X receptor by *P. amarus* and other selected antimalarial herbs was conducted [122]. Several other kinds of research focussing on the bioactivities of the potential herb were also reported. In one study it was shown that among the crude extracts tested with different medicinal plants and marine seaweeds, methanol and aqueous extracts of *P. amarus* showed significant antiviral activity against Nuclear polyhedrosis virus (NPV) which is the most harmful virus responsible for the manifestation of grasserie disease in the larvae of silkworm, *Bombyx mori* thereby causing a huge economic loss in the sericulture industry [399]. Recently an in-silico study has demonstrated the potential of *P. amarus* along with *Andrographis paniculata* and *Zingiber officinale* as an inhibitor for the target protein of Nipah Virus (NiV) [360]. Other studies showed the evaluation of cardio-protective effects of *P. amarus* extracts against high-fructose (HF) diet-induced cardiac damage as well as studies on DOCA salt-induced left ventricle cardiac hypertrophy and endothelial dysfunction, both in rat models [357, 467]. Studies on reproductive parameters as well as gastroprotective potentials of the herb extracts were carried out in Wistar rats [53, 65]. One study to show the potential of *P. amarus* in the management of human schistosomiasis which is an important neglected tropical disease caused by blood flukes of the genus *Schistosoma* and is responsible for more than 280,000 deaths annually was reported, where an in vivo schistosomicidal activity evaluation of crude hexanic (HE) and ethanolic (EE) extracts obtained from *P. amarus* in mice infected with *Schistosoma mansoni* (BH strain) was done [101]. Another report on the efficacy of *P. amarus* against white spot syndrome virus (WSSV) was seen where molecular docking and simulation analysis was performed to show how the phytocompounds present in the herb were found to be the most suitable inhibitors for the antiviral treatment for WSSV infection [109]. Another in vitro study showing positive effects of the extracts of aerial parts of *P. amarus* on the male reproductive system of experimental rat models showed increased serum testosterone levels and epididymal sperm concentration supporting the use of the herb in fertility issues [55]. Interestingly, one study evaluated the insecticidal efficacy of essential oils from the leaves of *P. amarus* on *Periplaneta americana* (American cockroach), *Schistocerca americana* (American grasshopper), and *Anopheles gambiae* (African malaria mosquito) along with another plant *Stachytarpheta cayennensis* [312]. From this study, the results of the GC–MS analysis of essential oils from both plants revealed the presence of various active components viz. Decanoic acid, ethylester (Ethyl decanoate) 6.02%, Dodecanoic acid, ethylester (Ethyl dodecanoate) 11.26%, Tetradecanoic acid, ethylester (Ethyl tetradecanoate) 9.22%, Hexadecanoic acid, ethylester (Ethyl hexadecanoate) 10.16%, Phytol 28.52%, 9, 12, 15-Octadecatrienoic acid, rthylester (Ethyl linolenate) 11.34%, Stigmasta-7,25-dien 3-ol 7.95%, etc. that were likely responsible for the observed insecticidal properties. The primary phytochemical quality and secondary bioactive compounds of *P. amarus* were even shown to have the potency to sustainably enhance the survival, growth and nutritional quality of the prawn *Macrobrachium rosenbergii* [185, 186]. The modulatory effect of *P. amarus* and *Momordica charantia* leaves on some biomolecules linked with cardiac function in doxorubicin (DOX)-stressed rats was evaluated in a study that revealed a significant improvement in redox imbalance and other biomolecules associated with cardiac function, which was altered by DOX [376]. Bioactivity of different compounds isolated from *P. amarus* was also tested to show its potent immunosuppressive effects on different lineages of the innate immune system [472]. Extract of whole aerial parts of the herb was investigated for some specific and non-specific immune responses like in vivo leucocyte mobilization, delayed-type hypersensitivity (DTHR) response, and humoral antibody (HA) response in rats [35]. Anti-fertility activity in male albino rats was also studied [113]. In vitro studies using Swiss albino rats to evaluate the wound healing properties of *P. amarus* and *Diodia scandens* using fresh whole plant extracts were performed [308]. The potent herb has also been tested for its efficacy against dermal toxicity and has been shown to be highly safe for transdermal application for muscle injury and inflammation [232]. Works on the beneficial effects of *P. amarus* extract in lowering blood pressure, vascular activity, as well as cardiac hypertrophy, and endothelial dysfunction, are still being performed [64, 468]. The role of *P. amarus* leaf extracts in the management of female sexual inadequacies were investigated by evaluating the oestrogenic and uterine functioning indices of fluoxetine-treated female rats [297]. Effects of *P. amarus* extract on nonspecific immune responses, growth, and resistance to *Vibrio alginolyticus* in white shrimp *Litopenaeus vannamei* were investigated both in vitro and in vivo [279]. The potential of the therapeutic herb *P. amarus* along with *Psidium guajava* to modulate the immune mechanisms and disease resistance of striped catfish *Pangasianodon hypophthalmus*, both in single or combined dietary supply were investigated, which suggested positive synergistic effects on liver proteome profile related to immune system processes as well on the head kidney leukocytes of the striped catfish in another study [285, 286]. Selective ameliorative influence on the biochemical and hematological parameters in ibuprofen-induced nephrotoxic rats was studied with *P. amarus* extract [29]. Alkaloid leaf extracts of *P. amarus* along with *Andrographis paniculata* have been shown to serve as promising therapeutic candidates for the management of neurodegenerative disease [11]. A recent study showed an interesting potential of *P. amarus* apart from its therapeutic action, in

maintaining a good sensory quality of fish fillets and prolonging their shelf life up to 8 days under ice storage. The study mainly evaluated the effects of herbal extracts of *P. amarus* along with another plant *Euphorbia hirta*, using dip treatments, on the quality of striped catfish (*Pangasianodon hypophthalmus*) fillets [97]. Potential clinical applications of the herb in the management of anxiety using tannin-rich extract of *P. amarus* have been demonstrated recently [83]. Similar studies were performed to show the efficacy of *P. amarus* in remediating high salt diet-induced immunological and hepatic derangements [167]. Herbal supplements from three plants including *P. amarus* have been shown to improve reproductive characteristics by enhancing semen oxidative stability [178]. One more recent investigation of the therapeutic herb has shown that its aqueous extract accelerated the reflex maturation in neonates, and improved offspring memory while inducing no maternal or neonatal toxicity [45]. Effect of leaf flower treatment of the herb on kidney and uterus in sodium chloride-induced fibrotic rats were found to be potent to decrease the matrix extracellular in the kidney and uterus in one more study [331]. An assessment of the nutritive value of *P. amarus* leaves was conducted to show that the leaves are of high nutritional quality due to high crude protein, vitamin A, mineral contents especially potassium with the resultant phytochemicals, and that they can be utilized as a food supplement and even serve as feed additives in poultry production [319].

(ix) Study of *P. amarus* efficacy in combating Covid-19

The efficacy and potential of *P. amarus* in the inhibition of SARS-CoV-2 or Covid 19 has been reported by few studies since the last two years when the pandemic struck the world and created havoc. One study has screened 198 bioactive compounds from five selected medicinal plants including *P. amarus*, that were previously reported to be antiviral against SARS-CoV-2 protease and two co-receptors followed by molecular dynamics simulations. From the screened compounds, astragalin was shown to be a better inhibitor for the inactivation of COVID-19 and could be pursued as a potential drug candidate for this virus [13]. Another attempt was made to provide preliminary shreds of evidence for the interaction of 35 phytochemicals from two plants (*P. amarus* and *Andrographis paniculata* used in Ayurveda) with SARS-CoV-2 proteins (open & closed state S protein, 3CLpro, PLpro, and RdRp) through in silico docking analysis. The phytochemicals present in the extracts of both plants were shown to have a synergistic effect with action on multiple target sites of SARS-CoV-2 [149]. In silico screening against COVID-19 receptors has been carried out as an initial stage of drug discovery in a recent study by evaluating the activity of phyllanthin and hypophyllanthin isolated from *P. amarus* in inhibiting spike glycoprotein (6LZG) and main protease (5R7Y) which play as target receptors of COVID-19. In this study, both the lignans demonstrated to possess greater binding affinity towards the COVID-19 inhibition sites than their native ligand [242]. Yet another recent research aimed for an in silico study to identify phytochemicals from *P. amarus* and assess their anti-viral activity against the main protease ($3CL^{Pro}$/M^{Pro}) enzyme of the novel coronavirus. Out of the 190 compounds obtained from literature and docked against 3CLPro, 16 compounds showed a higher binding affinity with $3CL^{Pro}$ and the top two compounds being Myricitrin (CID: 5,352,000) and Quercetin-3-O-glucuronide (CID: 12,004,528) [265]. Thus quite a few research and analyses have been performed across the globe, which can be taken further for in vitro and in vivo studies to examine their efficacy and thereby pursue as a potential drug candidate for this virus.

The diverse therapeutic effects of the potent medicinal herb *P. amarus* have been represented schematically in Fig. 5.

Conclusion

The demands to standardize the therapeutic properties of *P. amarus* and their detailed clinical trials have led to elaborate scientific research on *P. amarus* by attracting

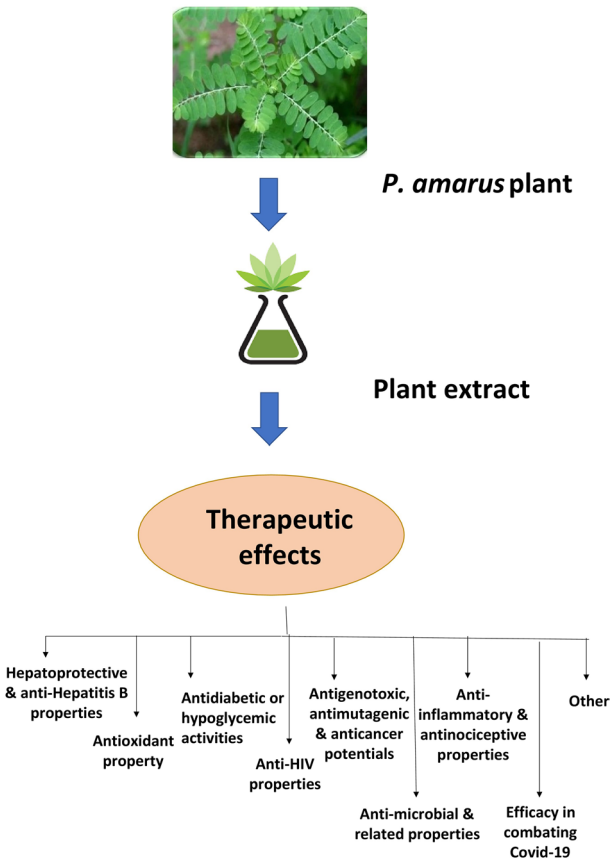

Fig. 5 Schematic representation of therapeutic potentials reported in *P. amarus*

researchers for many decades. The studies on this herb to date that have been compiled and summed up, to the best of our knowledge, suggest a huge biological potential of this plant. It is strongly believed that all the minute details and information on *P. amarus* as presented in this review, targeting every aspect might provide detailed evidence for the use of this potent medicinal plant in different diseases, and also be further explored in the future as a source of useful phytochemicals for the pharmaceutical industry.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13237-022-00409-z.

Acknowledgements The authors are grateful to the Director, CSIR-IICB, Kolkata for the help and support to conduct the research work. The authors would sincerely like to express their gratitude for an invitation to contribute to this special issue of the journal *Nucleus*.

Authors' Contribution ABMG conducted the primary research, drafted the manuscript, and also prepared the final version. AB conducted research on parts of the bioactivity of the study and helped to draft the manuscript. SC conceived the idea, supervised, critically revised the manuscript, and approved the final version.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Abankwa JK, Dotse E, Appiah-Opong R, Nyarko AK. Antioxidant and anti-prostate cancer activities of *Moringa oleifera*, *Phyllanthus amarus* and *Carica papaya*. HSI J. 2020;1(1):24–30. https://doi.org/10.4629/hsijournal.2020.6.1.1.24-30.
2. AbdRani NZ, Lam KW, Jalil J, Mohamad HF, Mat Ali MS, Husain K. Mechanistic studies of the antiallergic activity of *Phyllanthus amarus* Schum. & Thonn. and Its Compounds. Molecules. 2021;1:1. https://doi.org/10.3390/molecules26030695.
3. Abhyankar G, Suprasanna P, Pandey BN, Mishra KP, Rao KV, Reddy VD. Hairy root extract of *Phyllanthus amarus* induces apoptotic cell death in human breast cancer cells. Innov Food Sci Emerg Technol. 2010;11:526–32.
4. Abo KA, Fred-Jaiyesimi AA, Jaiyesimi AEA. Ethnobotanical studies of medicinal plants used in the management of diabetes mellitus in South Western Nigeria. J Ethnopharmacol. 2008;115:67–71.
5. Acharyulu NPS, Dubey RS, Swaminadham V, Kollu P, Kalyani RL, Pammi SVN. Green synthesis of CuO nanoparticles using *Phyllanthus amarus* leaf extract and their antibacterial activity against multidrug resistance bacteria. Int J Eng Res Technol. 2014;3(4):1.
6. Acheampong DO, Owusu-Adzorah N, Armah FA, Aninagyei E, Asiamah EA, Thomford AK, Anyan WK. Ethnopharmacological evaluation of schistosomicidal and cercaricidal activities of some selected medicinal plants from Ghana. Trop Med Health. 2020;48(1):1–10. https://doi.org/10.1186/s41182-020-00205-y.
7. Adedapo AA, Abatan MO, Akinloye AK, Idowu SO, Olorunsogo OO. Morphometric and histopathological studies on the effects of some chromatographic fractions of *Phyllanthus amarus* and *Euphorbia hirta* on the male reproductive organs of rats. J Vet Sci. 2003;4:181–5.
8. Adedapo AA, Abatan MO, Idowu SO, Olorunsogo OO. Toxic effects of chromatographic fractions of *Phyllanthus amarus* on the serum biochemistry of rats. Phytother Res. 2005;9:812–5. https://doi.org/10.1002/ptr.1721.
9. Adedapo AA, Ofuegbe SO. Anti-inflammatory and analgesic activities of soft drink leaf extract of *Phyllanthus amarus* in some laboratory animals. Br Biotechnol J. 2013;3:191–204.
10. Adedapo AA, Ofuegbe SO. The evaluation of the hypoglycemic effect of soft drink leaf extract of *Phyllanthus amarus* (Euphorbiaceae) in rats. J Basic Clin Physiol Pharmacol. 2014;25:47–57.
11. Adedayo BC, Ogunsuyi OB, Akinniyi ST, Oboh G. Effect of *Andrographis paniculata* and *Phyllanthus amarus* leaf extracts on selected biochemical indices in *Drosophila melanogaster* model of neurotoxicity. Drug Chem Toxicol. 2020;1:1–10. https://doi.org/10.1080/01480545.2019.1708377.
12. Adegoke AA, Iberi PA, Akinpelu DA, Aiyegoro OA, Mboto CI. Studies on phytochemical screening and antimicrobial potentials of *Phyllanthus amarus* against multiple antibiotic resistant bacteria. Int J Appl Res Nat Prod. 2010;3:6–12.
13. Adejoro IA, Babatunde DD, Tolufashe GF. Molecular docking and dynamic simulations of some medicinal plants compounds against SARS-CoV-2: an *in silico* study. J Taibah Univ Sci. 2020;14(1):1563–70. https://doi.org/10.1080/16583655.2020.1848049.
14. Adeneye AA, Amole OO, Adeneye AK. Hypoglycemic and hypercholesterolemia activities of aqueous leaf and seed extract of *Phyllanthus amarus* in mice. Fitoterapia. 2006;77:511–4.
15. Adeneye AA, Benebo AS. Protective effect of the aqueous leaf and seed extract of *Phyllanthus amarus* on gentamicin and acetaminophen-induced nephrotoxic rats. J Ethnopharmacol. 2008;118:318–23.
16. Adeneye AA. The leaf and seed aqueous extract of *Phyllanthus amarus* improves insulin resistance diabetes in experimental animal studies. J Ethnopharmacol. 2012;144:705–11.
17. Adjanohoun EJ, Ahyi MRA, Ake Assi L, Akpagana K, Chibon P, El-Haji A, Eyme J, Garba M, Gassita JN, Gbeassor M, Goudote E, Guinko S, Hodouto, KK, Houngnon P, Keita A, Keoula Y, Kluga-Ocloo WP, Lo I, Siamevi KM, Taffame KK. Contribution aux etudes ethnobotaniques et floristiques au Togo, first ed. Agence de Coopération Culturelle et Technique, première edition (ACCT), Paris; 1986.
18. Agati G, Azzarello E, Pollastri S, Tattini M. Flavonoids as antioxidants in plants: xlocation and functional significance. Plant Sci. 2012;196:67–76.
19. Agharkar SP. Medicinal plants of Bombay presidency. Jodhpur, India: Scientific Publ; 1991. p. 1–2.
20. Agrawal A, Srivastava S, Srivastava JN, Srivasava MM. Evaluation of inhibitory effect of the plant *Phyllanthus amarus* against dermatophytic fungi *Microsporum gypseum*. Biomed Environ Sci. 2004;17:359–65.
21. Ahirrao YA, Patil DA. Indigenous healthcare practices in Buldhana district (Maharashtra). Indian J Nat Prod Resour. 2010;1:85–8.
22. Ahmad B, Alam T. Components from whole plant of *Phyllanthus amarus* Linn. Indian J Chem - B Org Med Chem. 2003;42:1786–90.
23. Ahmad S, Bano S, Anwar S. Cancer ameliorating potential of *Phyllanthus amarus*: *In vivo* and *in vitro* studies against Aflatoxin B1 toxicity. Egypt J Med Hum Genet. 2015;16(4):343–53.
24. Aiwonegbe AE, Iyasele JU. Antimicrobial effects of methanolic extract of *Phyllanthus amarus* on selected clinical and environmental bacteria. DUJOPAS. 2021;7(1):224–31.

25. Ajaiyeoba EO, Falade CO, Fawole OI, Akinboye DO, Gbotosho GO, Bolaji OM, et al. Efficacy of herbal remedies used by herbalists in Oyo State Nigeria for treatment of *Plasmodium falciparum* infections - a survey and an observation. Afr J Med Med Sci. 2004;33:115–9.
26. Ajala TO, Femi-Oyewo MN, Odeku OA, Aina OO, Saba AB, Oridupa OO. The physicochemical, safety and antimicrobial properties of *Phyllanthus amarus* herbal cream and ointment. J Pharm Investig. 2016;46(2):169–78. https://doi.org/10.1007/s40005-015-0226-8.
27. Ajala TO, Igwilo CI, Oreagba IA, Odeku OA. The antiplasmodial effect of the extracts and formulated capsules of *Phyllanthus amarus* on *Plasmodium yoelii* infection in mice. Asian Pac J Trop Med. 2011;4(4):283–7.
28. Ajayi GO, Olorunrinu TJ, Shittu MA. Elucidation of bioactive compounds in hydroalcohol extract of *Phyllanthus amarus* Schum. and Thonn. leaf using GC-MS analysis. J Sci Innov Res. 2020;9:40–7.
29. Ajayi GO, Shittu MA, Olorunrinu TJ, Akinsanya MA, Olagunju JA. Influence of *Phyllanthus amarus* on biochemical and haematological status in rats with ibuprofen-induced nephrotoxicity. Sumerianz J Biotechnol. 2020;3(8):60–8.
30. Ajibesin KK, Ekpoa BA, Bala DN, Essien EE, Adesanya SA. Ethnobotanical survey of Akwa Ibom State of Nigeria. J Ethnopharmacol. 2008;115:387–408.
31. Ajitha B, Reddy YA, Jeon HJ, Ahn CW. Synthesis of silver nanoparticles in an eco-friendly way using *Phyllanthus amarus* leaf extract: antimicrobial and catalytic activity. Adv Powder Technol. 2018;29(1):86–93. https://doi.org/10.1016/j.apt.2017.10.015.
32. Akinjogunla OJ, Asamudo NU, Divine-Anthony O. Susceptibility of drug resistant *Candida* isolates to aqueous leaf extracts of *Phyllanthus amarus*, *Senna alata* and *Nymphaea lotus*. World J Appl Sci Technol. 2019;11(2):157–67.
33. Akinjogunla OJ, Umo AN, Okon MU, Akaka BC. *Nymphaea lotus* and *Phyllanthus amarus*: thin layer chromatography, alkaloidal fractions and antimicrobial activities on multidrug resistant organisms associated with middle ear infection. Niger J Pharm Appl Sci Res (NIJOPHASR). 2020;9(1):1–9.
34. Akin-Osanaiye CB, Gabriel AF, Alebiosu RA. Characterization and antimicrobial screening of ethyl oleate isolated from *Phyllanthus amarus* (Schum and Thonn). Ann Biol Res. 2011;2(2):298–305.
35. Akintola OB. Immunomodulatory activities of methanol extract of the whole aerial part of *Phyllantus niruri* L. Int J Biochem Biotechnol. 2019;8(9):001–6.
36. Akpo CO, Anie CO, Orhire V. In-vivo antimalarial activity of the aqueous leaf extract of *Phyllanthus amarus* Schum & Thonn. against *Plasmodium berghei* Infected Mice. East Afr Scholars J Med Sci. 2020;3(7):1–5. https://doi.org/10.36349/EASMS.2020.v03i07.01.
37. Akporowhe S, Onyesom I. *Phyllanthus amarus* augments the serum antioxidant capacity and invigorates the blood in experimental mice. Biochem Biophys Res Commun. 2016;9:15–8.
38. Akunneh-Wariso C, Aduema W. Comparative Hypoglycemic effects of aqueous leaf extracts of *Vernonia amygdalina, Ocimum gratissimum, Phyllanthus amarus, Gongronema latifolum, Piper nigrum and Solanum melongena* on Blood Glucose Level of Alloxan-Induced Diabetic Guinea Pigs. Res J Pharmacol Pharmacodyn. 2019;11(2):55–61. https://doi.org/10.5958/2321-5836.2019.00010.7.
39. Akunneh-Wariso C, Aduema W. The effects of the leaf extracts of *Vernonia amygdalina, Ocimum gratissimum* and *Phyllanthus amarus* on blood glucose level of alloxan-induced diabetic Guinea pigs. LOJ Med Sci. 2018; https://doi.org/10.32474/LOJMS.2018.02.000127
40. Al Zarzour RH, Ahmad M, Asmawi MZ, Kaur G, Saeed MAA, Al-Mansoub MA, Saghir SAM, Usman NS, Al-Dulaimi DW, Yam MF. *Phyllanthus niruri* standardized extract alleviates the progression of non-alcoholic fatty liver disease and decreases atherosclerotic risk in sprague-dawley rats. Nutrients. 2017;https://doi.org/10.3390/nu9070766
41. Alabi AO, Ifesan BO, Akosu NI. Opeyemi l Alabi. Chemical Composition and Antibacterial Activity of Extracts of *Cymbopogon citratus* (Lemon Grass) and *Phyllantus amarus* (Stone Breaker) Leaves. Journal of Medicine and Healthcare. 2021;3:176. https://doi.org/10.47363/JMHC/2021
42. Alagan A, Jantan I, Kumolosasi E, Ogawa S, Abdullah MA and Azmi N. Protective effects of *Phyllanthus amarus* against lipopolysaccharide-induced neuroinflammation and cognitive impairment in rats. Front Pharmacol 2019;https://doi.org/10.3389/fphar.2019.00632
43. Aliyu K, Mohammed Y, Abdullahi IN, Umar AA, Bashir F, Sani MN, Kabuga AI, Adamu AMY, Akande AO. *In vitro* antiplasmodial activity of *Phyllanthus amarus* against *Plasmodium falciparum* and evaluation of its acute toxicity effect in mouse model. Trop Parasitol. 2021;11(1):31–7.
44. Alkhaldi AAM, De Koning H, Bukhari SNA. Effects of some natural leads on *Trypanosoma* and *Leishmania* strains. Trop Biomed. 2019;36(2):373–8.
45. Alves M da Costa, Pereira DE, de Araújo Bidô RD, Freitas JC, Dos Santos CP, Soares JK. Effects of the aqueous extract of *Phyllanthus niruri* Linn during pregnancy and lactation on neurobehavioral parameters of rats' offspring. J Ethnopharmacol 2021;270:113862. https://doi.org/10.1016/j.jep.2021.113862
46. Ameen OA, Hamid AA, Yusuf Q, Njoku OG, Oseni TO, Jamiu W (2020) Quantitative and qualitative assessment of phytochemicals in methanolic extracts of hurricane weed (*Phyllanthus amarus* Schumach. &Thonn) Plant. J Appl Sci Environ Manag 2020;https://doi.org/10.4314/jasem.v25i2.4
47. Amina MD, Eugène AS, Machioud SM, Félix G, Rodrigue A, Madjid AA, Latifou L, Lamine B, Seri B, Khan NA. Molecular mechanisms of hypoglycemic and antioxidative effects of *Phyllanthus amarus* on streptozotocin-induced diabetic rats. J Endocrinol Diab. 2018;5(4):1–6. https://doi.org/10.15226/2374-6890/5/4/01112
48. Anupama KK, Ramya K, Joseph A. Electrochemical and computational aspects of surface interaction and corrosion inhibition of mild steel in hydrochloric acid by *Phyllanthus amarus* leaf extract (PAE). J Mol Liq 2016;216:146–55. https://doi.org/10.1016/j.molliq.2016.01.019
49. Appiah-Opong R, Commandeur JN, Axson C, Vermeulen NP. Interactions between cytochromes P450, glutathione S-transferases and Ghanaian medicinal plants. Food Chem Toxicol. 2008;46(12):3598–603.
50. Arpita S, Neeraj S. Antibacterial activity of Bhui amla (*Phyllanthus niruri*). Pharma Sci Monit (PSM). 2017;8(4):222–8.
51. Arthur M, Aliero AA, Odda J. Antibacterial activity of ethanol crude extracts of whole plant of the Ugandan *Phyllanthus amarus* Schumach. & Thonn against *Shigella dysenteriae*. Bact. Emp. 2019;2(2):33–6. https://doi.org/10.36547/be.2019.2.2.33-36
52. Asase A, Akwetey GA, Achel DG. Ethnopharmacological use of herbal remedies for the treatment of malaria in the Dangme West District of Ghana. J Ethnopharmacol. 2010;129:367–76.
53. Ataman JE, Sakpa CL. Effects of Ethanolic Leaf Extract of *Phyllanthus amarus* (Schum and Thonn) on ovarian morphology and reproductive parameters in wistar rats. African Scientist. 2017;18(4):245–51.
54. Ayres DC, Loike JD. Lignans. Chemical, biological and clinical properties. Cambridge University Press, Cambridge;1990.
55. Azubuike NC, Okwuosa CN, Onwukwe OS, Onyemelukwe AO, Ikele I, Achukwu PU. Effects of *Phyllanthus amarus* on

epididymal sperm characteristics, testosterone levels and histology of reproductive organs of male rats. Pharmacologyonline. 2018;3:57–67.
56. Babatunde SK, Abubakare AA, Abdulraheem YJ, Ajiboye EA. Antimicrobial activity of *Phyllanthus amarus* on some human intestinal facultatively anaerobic flora. Int J Med Biomed Res (IJMBR). 2014;3:52–7.
57. Bakhtiary SA, Iqbal MM, Ibrahim M. Hepatoprotective and nephroprotective activity of *Phyllanthus amarus* Schum & Thonn. seed extract. Ann Phytomed. 2012;1(2):97–104.
58. Balakrishnan V, Prema P, Ravindran KC, Philip RJ. Ethnobotanical studies among villagers from Dharapuram Taluk, Tamil Nadu, India. Glob J Pharmacol. 2009;3:8–14.
59. Bandyopadhyay S, Raychaudhuri SS. Development and comparison of RAPD, SCAR and AFLP markers for distinguishing some medicinally important species of the genus *Phyllanthus*. Plant Biosyst. 2013;147:12–20.
60. Banerjee A, Chattopadhyay S. Genetic transformation of a hepatoprotective plant, *Phyllanthus amarus*. In Vitro Cell Dev Biol-Plant 2009; 45:57–64. https://doi.org/10.1007/s11627-008-9160-z
61. Bawankule DU, Trivedi P, Pal A, Shanker K, Singh M, Sharma P, et al. Protective mechanism of lignans from *Phyllanthus amarus* against galactosamine/lipopolysaccharide-induced hepatitis: an *in-vivo* and *in-silico* studies. Curr Top Med Chem. 2014;14:1045–55.
62. Behera PP, Behera B, Mahalik G. Efficacy of *Nyctanthus arbour-tristis, Phyllanthus amarus* and *Cymbopogon citratus* used in the Traditional Treatment of Typhoid against *Salmonella typhimurium*. Indian J Nat Sci (IJONS). 2020;10(60):26341–5.
63. Bekoe EO, Kitcher C, Debrah P, Amoateng P, Donkor PO, Martinson S. A Study on *Phyllanthus amarus*; pharmacognostic, mycobactericidal and mutagenic properties. Pharmacogn J. 2020;12(6):1732–39. https://doi.org/10.5530/pj.2020.12.235
64. Bello I, Usman NS, Dewa A, Abubakar K, Aminu N, Asmawi MZ, Mahmud R. Blood pressure lowering effect and vascular activity of *Phyllanthus niruri* extract: the role of NO/cGMP signaling pathway and β-adrenoceptor mediated relaxation of isolated aortic rings. J Ethnopharmacol. 2020;250:112461. https://doi.org/10.1016/j.jep.2019.112461
65. Berezi E, Uwakwe A, Monago-Ighorodje C, Nwauche K. Gastroprotective potentials of aqueous leaf extracts of *Phyllanthus amarus* on ibuprofen-induced ulcer in Wistar rats. Int J Adv Res Biol Sci. 2017;4(10):138–46. https://doi.org/10.22192/ijarbs.2017.04.10.018.
66. Berezi EP, Mirinn E, Berezi P, Soroh AE. Comparative assessment, preliminary screening and GC- FID phytochemical analysis of aqueous and petroleum ether extracts of *Phyllanthus amarus* leaves. J Chem Soc Nigeria (JCSN). 2020;45:835–43.
67. Bhat SS, Hegde KS, Chandrashekhar S, Rao SN, Manikkoth S. Preclinical screening of *Phyllanthus amarus* ethanolic extract for its analgesic and antimicrobial activity. Pharmacogn Res. 2015;7(4):378.
68. Bhattacharjee R, Sil PC. Protein isolate from the herb, *Phyllanthus niruri* L (Euphorbiaceae), plays hepatoprotective role against carbon tetrachloride induced liver damage via its antioxidant properties. Food Chem Toxicol. 2007;45:817–26.
69. Biswas M, Ghosh P, Biswas S, Dutta A, Chatterjee S. Phytochemical analysis and determination of *In vitro* antioxidant and antimicrobial activity of *Phyllanthus amarus* leaves extracts. Int J Bot Stud. 2020;5(2):483–90.
70. Blumberg BS, Millman I, Venkates PS, Thyagarajan SP. Hepatitis B virus and primary hepatocellular carcinoma: treatment of HBV carriers with *Phyllanthus amarus*. Vaccine. 1990;8:S86-92.
71. Bongu SB, Sagree S, Gudapareddy V, Putakala M, Nukala S, Gujjala S, Bellamkonda R, Desireddy S. Protective role of aqueous extract of *Phyllanthus amarus* on oxidative stress in pancreas of streptozotocin induced diabetic male Wistar rats. J Exp Appl Anim Sci 2016;2:23–30. https://doi.org/10.20454/jeaas.2016.1087
72. Bose Mazumdar A, Chattopadhyay S. Sequencing, *De novo* Assembly, Functional Annotation and Analysis of *Phyllanthus amarus* Leaf Transcriptome Using the Illumina Platform. Front Plant Sci. 2016. https://doi.org/10.3389/fpls.2015.01199
73. Brook MG. Effect of *Phyllanthus amarus* on chronic carriers of Hepatitis B virus. Lancet. 1988;332:1017–8.
74. Buddhachat K, Paenkaew S, Sripairoj N, Gupta YM, Pradit W, Chomdej S. *et al.* Bar-cas12a, a novel and rapid method for plant species authentication in case of *Phyllanthus amarus* Schumach. & Thonn. Sci Rep. 2021;https://doi.org/10.1038/s41598-021-00006-1
75. Cabieses F. Apuntes de medicina traditional. La racionalizacion de lo irracional. Notes of traditional medicine. Consejo Nacional de Ciencia Technologia Concytec Lima-Peru;1993. pp. 414.
76. Calixto JB, Santos AR, Cechinel Filho V, Yunes RA. A review of the plants of the *Phyllanthus*: their chemistry, pharmacology, and therapeutic potential. Med Res Rev. 1998;18:225–58.
77. Cartaxo SL, de Almeida Souza MM, de Albuquerque UP. Medicinal plants with bioprospecting potential used in semi-arid Northeastern Brazil. J Ethnopharmacol. 2010;131:326–42.
78. Chandan S, Umesha S, Prasad KS, Balamurugan V, Chandrashekar S, Kumar SS, Ramu R, Shirahatti PS, Syed A, Elgorban AM. Potential antileptospiral constituents from *Phyllanthus amarus*. Pharmacogn Mag. 2020;16:S371–8.
79. Chattopadhyay S, Bose Mazumdar Ghosh A. Establishment of cDNA library and EST analysis from leaves of *Phyllanthus amarus*. Int J Biochem Res Rev. 2014; 4:1–15. https://doi.org/10.9734/IJBCRR/2014/5262.
80. Chaudhuri PK, Bagchi G, Srivastava R, Kumar S. Procedure for the extraction and isolation of phyllanthin from the plant *Phyllanthus amarus.* Ger. Offen. 2001. 6 pp. CODEN: GWXXBX DE 10014674 A1 20011031.
81. Chevallier A. Encyclopedia of herbal medicine: natural health. 2nd ed. USA: Dorling Kindersley Book; 2000. p. 336.
82. Chirdchupunseree H, Pramyothin P. Protective activity of phyllanthin in ethanol-treated primary culture of rat hepatocytes. J Ethnopharmacol. 2010;128:172–6.
83. Chopade AR, Pol RP, Patil PA, Dharanguttikar VR, Naikwade NS, Dias RJ, Mali SN. An insight into the anxiolytic effects of lignans (Phyllanthin and Hypophyllanthin) and Tannin (Corilagin) rich extracts of *Phyllanthus amarus*: an *in-silico* and *in-vivo* approaches. Comb Chem High Throughput Screen. 2021;24(3):415–22. https://doi.org/10.2174/1386207323666200605150915.
84. Chopade AR, Sayyad FJ. Antifibromyalgic activity of standardized extracts of *Phyllanthus amarus* and *Phyllanthus fraternus* in acidic saline induced chronic muscle pain. Biomed Aging Pathol. 2014;4:123–30.
85. Chopade AR, Sayyad FJ. Evaluation of cardiovascular effects and cardiotonic activity of *Phyllanthus amarus* and *Phyllanthus fraternus*. J Pharm BioSci (JPBS). 2013;1:19–25.
86. Chopade AR, Sayyad FJ. Pain modulation by lignans (phyllanthin and hypophyllanthin) and tannin (corilagin) rich extracts of *Phyllanthus amarus* in carrageenan-induced thermal and mechanical chronic muscle hyperalgesia. Phytother Res. 2015;29:1202–10.
87. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian Medicinal Plants. Council of Scientific and Industrial Research, New Delhi, India; 1956. pp. 191.

88. Chowdhury S, Mukherjee T, Mukhopadhyay R, Mukherjee B, Sengupta S, Chattopadhyay S, Jaisankar P, Roy S, Majumder HK. The lignan niranthin poisons *Leishmania donovani* topoisomerase IB and favours a Th1 immune response in mice. EMBO Mol Med. 2012;4(10):1126–43. https://doi.org/10.1002/emmm.201201316.
89. Cimanga RK, Tona L, Luyindula N, Mesia K, Lusakibanza M, Musuamba CT, et al. *In vitro* antiplasmodial activity of callus culture extracts and fractions from fresh apical stems of *Phyllanthus niruri* L. (Euphorbiaceae): part 2. J Ethnopharmacol. 2004;95:399–404.
90. Conrado GG, Grazzia N, Adriana da Silva S, Franco CH, Moraes CB, Gadelha FR, Miguel DC, Garcia VL. Prospecting and Identifying *Phyllanthus amarus* Lignans with Antileishmanial and Antitrypanosomal Activity. Planta Med. 2020;(11):782–9. https://doi.org/10.1055/a-1179-1003
91. Cook NC, Samman S. Review: flavonoids-chemistry, metabolism, cardioprotective effects and dietary sources. J Nutr Biochem. 1996;7:66–76.
92. Corciovă A, Mircea C, Tuchiluş C, Cioancă O, Burlec A-F, Ivănescu B, Vlase L, Gheldiu A-M, Fifere A, Lungoci A-L, Hăncianu M. Phenolic and sterolic profile of a *Phyllanthus amarus* extract and characterization of newly synthesized silver nanoparticles. Farmacia. 2018;https://doi.org/10.31925/farmacia.2018.5.13
93. Couto AG, Kassuya CA, Calixto JB, Petrovick PR. Anti-inflammatory, antiallodynic effects and quantitative analysis of gallic acid in spray dried powders from *Phyllanthus niruri* leaves, stems, roots and whole plant. Rev Bras Farmacogn. 2013;23:124–31.
94. Dakpogan HB, Houndonougbo VP, Pomalegni C, Ahounou JE, Chrysostome C. Evaluation of the effect of *Phyllanthus amarus, Jatropha curcas* and *Piliostigma thonningii* on experimental chicken coccidiosis. J Anim Plant Sci. 2019;42(2):7269–78.
95. Danjuma L, Bashir SM, Dogara MM, Tsakuwa RA. Therapeutic potentials of biosynthesized silver nanoparticles from *Phyllanthus amarus* leaf against resistant clinical bacterial isolates. JIRMEPS. 2021;16(1):1–9.
96. Dao Le Anh N, Tran Minh P, Caroline D, Joëlle Q-L, Bui Thi Buu H, Le Thi B, Truong QN, Bui Thi Bich H, Do Thi Thanh H, Nguyen Thanh P, Patrick K, Marie-Louise S. Screening and comparative study of *in vitro* antioxidant and antimicrobial activities of ethanolic extracts of selected Vietnamese plants. Int J Food Prop 2020;23:1:481–96. https://doi.org/10.1080/10942912.2020.1737541
97. Dao N Le A, Phu TM, Douny C, Quetin-Leclercq J, Hue BT, Bach LT, Quynh Nhu T, Thi Bich Hang B, Thi Thanh Huong D, Thanh Phuong N, Kestemont P. Effects of *Phyllanthus amarus* and *Euphorbia hirta* dip treatments on the protection of striped catfish (*Pangasianodon hypophthalmus*) fillets against spoilage during ice storage. J Aquat Food Prod Technol 2021;30(10):1218–34. https://doi.org/10.1080/10498850.2021.1987606
98. Dapper DV, Aziagba BN, Ebong OO. Antiplasmodial effects of the aqueous extract of *Phyllanthus amarus* Schumach and Thonn against *Plasmodium berghei* in Swiss albino mice. Niger J Physiol Sci. 2007;22:19–25.
99. Davin LB, Lewis NG. Phenylpropanoid metabolism: biosynthesis of monolignols, lignans and neolignans, lignins and suberins. In: Stafford HA, Ibrahim RK, editors. Phenolic metabolism in plants. Plenum Press: New York; 1992. p. 325–75.
100. De B, Datta PC. Pharmacognostic evaluation of *Phyllanthus amarus*. Int J Crude Drug Res. 1990;28:81–8.
101. de Oliveira CN, Frezza TF, Garcia VL, Figueira GM, Mendes TM, Allegretti SM. *Schistosoma mansoni*: *In vivo* evaluation of *Phyllanthus amarus* hexanic and ethanolic extracts. Exp. Parasitol. 2017;183:56–63. https://doi.org/10.1016/j.exppara.2017.10.008
102. Deb S, Mandal SK. TLC-densitometric determination of phyllanthin and hypophyllanthin in *Phyllanthus amarus* (bhumiamalaki) and in polyherbal formulation. Indian Drugs. 1996;33:415–6.
103. Decha P, Kanokwan K, Jiraporn T, Pichaya J, Pisittawoot A. Phonopheresis associated with nanoparticle gel from *Phyllanthus amarus* relieves pain by reducing oxidative stress and proinflammatory markers in adults with knee osteoarthritis. Chin J Integr Med. 2019;25(9):691–5. https://doi.org/10.1007/s11655-019-3202-8.
104. Deepa V, Sridhar R, Goparaju A, Reddy PN, Murthy PB. Nanoemulsified ethanolic extract of *Phyllanthus amarus* Schum & Thonn ameliorates CCl_4 induced hepatotoxicity in Wistar rats. Indian J Exp Biol. 2012;50(11):785–94.
105. Demain AL, Fang A. The natural functions of secondary metabolites. Adv Biochem Eng Biotechnol. 2000;69:1–39.
106. Devi S, Kumar D, Kumar M. *In-Vitro* antioxidant activities of methanolic extract of whole plant of *Phyllanthus amarus* (Euphorbiaceae). Int J Botany Stud. 2016;1(3):30–2.
107. Dhalwal K, Birandar YS, Rajani M. High performance thin layer chromatography densitometric method for simultaneous quantitation of phyllanthin, hypophyllanthin, gallic acid and ellagic acid in *Phyllanthus amarus*. J AOAC Int. 2006;89:619–23.
108. Dhir H, Roy AK, Sharma A, Talukder G. Protection afforded by aqueous extracts of *Phyllanthus* species against cytotoxicity induced by lead and aluminium salts. Phytother Res. 1990;4:172–6.
109. Dinesh S, Sudharsana S, Mohanapriya A, Itami T, Sudhakaran R. Molecular docking and simulation studies of *Phyllanthus amarus* phytocompounds against structural and nucleocapsid proteins of white spot syndrome virus. 3 Biotech 2017;7:353.
110. Dinesha R, Chikkanna D, Joshi V. Metal ion chelation and antiglycation properties of polysaccharides of *Phyllanthus amarus* plant. GSC Biol Pharm Sci. 2021;15(3):349–53. https://doi.org/10.30574/gscbps.2021.15.03.0190.
111. Dudareva N, Pichersky E, Gershenzon J. Biochemistry of plant volatiles. Plant Physiol. 2004;135:1893–902.
112. Edith OO, Helen EK, Israel OO. *In-vivo* antiplasmodial activity of ethanolic extract of *Cassia alata* and *Phyllanthus amarus*. NJSE. 2016;14:1.
113. Ekpo PB, Edu NE, Umoyen AJ, Thomas TL, Abraham SO. Effect of *Phyllanthus amarus* on Some Reproductive Indices of Male Albino Rats. J Appl Life Sci Int. 2019;20(1):1–8. https://doi.org/10.9734/JALSI/2019/v20i130076.
114. Elamvaluthi M, Saravanan S, Sathyanarayanan PC. Optimization of *in vitro* regeneration of *Phyllanthus amarus* and its antibacterial potential. JAIR. 2016;5(4):54–7.
115. Eldeen IMS, Seow EM, Abdullah R, Sulaiman SF. *In vitro* antibacterial, antioxidant, total phenolic contents and anti-HIV-1 reverse transcriptase activities of extracts of seven *Phyllanthus* sp. S. Afr. J. Bot. 2011;77:75–9. https://doi.org/10.1016/j.sajb.2010.05.009.
116. Ene AC, Egbosi NC, Obika CJ, Ibegbulem CO, Ujowundu CO, Alisi CS. *In vivo* antiplasmodial activity of ethanol and aqueous extracts of *Uvaria chamae* and *Phyllanthus amarus* Plants. Futo J Ser. 2016;2(2):83–97.
117. Ezzat MI, Okba MM, Ahmed SH, El-Banna HA, Prince A, Mohamed SO, Ezzat SM. In-depth hepatoprotective mechanistic study of *Phyllanthus niruri: In vitro* and *in vivo* studies and its chemical characterization. PLoS ONE. 2020;15(1):e0226185. https://doi.org/10.1371/journal.pone.0226185.
118. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect. 2001;109(suppl 1):69–75.

119. Faremi TY, Suru SM, Fafunso MA, Obioha UE. Hepatoprotective potentials of *Phyllanthus amarus* against ethanol induced oxidative stress in rats. Food Chem Toxicol. 2008;46:2658–64.
120. Fasan TI, Olorunnisola OS, Adetutu A, Ajilore BS. Evaluation of Antioxidant Potential and Efficacy of Terpenoid Rich Fraction of *Phyllanthus Amarus* (Schum and Thonn) Whole Plant in the Amelioration of High Salt Diet Induced Obesity. Res Sq. 2021;https://doi.org/10.21203/rs.3.rs-562700/v1.
121. Fasinu PS, Manda VK, Dale OR, Egiebor NO, Walker LA, Khan S. Evaluation of the influence of selected herbal extracts on the activity of p-glycoprotein and pregnane X receptor activation. Planta Med. 2016;82(05):PB13. https://doi.org/10.1055/s-0036-1578661.
122. Fasinu PS, Manda VK, Dale OR, Egiebor NO, Walker LA, Khan SI. Modulation of cytochrome P450, P-glycoprotein and pregnane X receptor by selected antimalarial herbs—implication for herb-drug interaction. Molecules. 2017;22(12):2049. https://doi.org/10.3390/molecules22122049.
123. Fauré M, Lissi E, Torres R, Videla LA. Antioxidant activities of lignans and flavonoids. Phytochemistry. 1990;29:3773–5.
124. Foo LY, Wong H. Phyllanthusiin D, an unusual hydrolysable tannin from *Phyllanthus amarus*. Phytochemistry. 1992;31:711–3.
125. Foo LY. Amarinic acid and related ellagitannins from *Phyllanthus amarus*. Phytochemistry. 1995;39:217–24.
126. Foo LY. Amarulone, a novel cyclic hydrolyzable tannin from *Phyllanthus amarus*. Nat Prod Lett. 1993;3:45–52.
127. Franccedil oise BV. Antiplasmodial activity of various parts of *Phyllanthus niruri* according to its geographical distribution. Afr J Pharm Pharmacol. 2009;3(12):598–601.
128. Francis BT, Sudha S. Antidiabetic effect of polyherbal extract in streptozotocin induced diabetic rats. World J Pharm Res 2016;5(10):659–73. https://doi.org/10.20959/wjpr201610-7074.
129. Fuss E. Lignans in plant cell and organ cultures: an overview. Phytochem Rev. 2003;2:307–20.
130. George A, Udani JK, Yusof A. Effects of *Phyllanthus amarus* PHYLLPRO^{TM} leaves on hangover symptoms: a randomized, double-blind, placebo-controlled crossover study. Pharm Biol. 2019;57(1):145–53. https://doi.org/10.1080/13880209.2019.1585460.
131. Giribabu N, Karim K, Kilari EK, Salleh N. *Phyllanthus niruri* leaves aqueous extract improves kidney functions, ameliorates kidney oxidative stress, inflammation, fibrosis and apoptosis and enhances kidney cell proliferation in adult male rats with diabetes mellitus. J Ethnopharmacol. 2017;205:123–37. https://doi.org/10.1016/j.jep.2017.05.002.
132. Giribabu N, Rao PV, Kumar KP, Muniandy S, Rekha SS, Salleh N. Aqueous extract of *Phyllanthus niruri* leaves displays *in vitro* antioxidant activity and prevents the elevation of oxidative stress in the kidney of streptozotocin-induced diabetic male rats. Evid Based Complement Alternat Med. 2014; 2014:834815; https://doi.org/10.1155/2014/834815.
133. Gowrishanker B, Vivekanandan OS. *In vivo* studies of a crude extract of *Phyllanthus amarus* L. in modifying the genotoxicity induced in *Vicia faba* L. by tannery effluents. Mutat Res - Genet Toxicol Environ Mutagen. 1994;322:185–192.
134. Guha G, Mandal T, Rajkumar V, Kumar RA. Antimycin A-induced mitochondrial apoptotic cascade is mitigated by phenolic constituents of *Phyllanthus amarus* aqueous extract in Hep3B cells. Food Chem Toxicol. 2010;48:3449–57.
135. Guha G, Rajkumar V, Kumar RA, Mathew L. Aqueous extract of *Phyllanthus amarus* inhibits chromium (VI)-induced toxicity in MDA-MB-435S cells. Food Chem Toxicol. 2010;48:396–401.
136. Gujjeti RP, Mamidala E. *In vitro* cytotoxic and anti-HIV activity of *Phyllanthus niruri* whole plant extracts. Int J Pharma Bio Sci. 2015;6(2): B-487-B-93.
137. Guo JR, Chen QQ, Lam CW, Wang CY, Xu FG, Liu BM, Zhang W. Effect of *Phyllanthus amarus* extract on 5-fluorouracil-induced perturbations in ribonucleotide and deoxyribonucleotide pools in HepG2 cell line. Molecules. 2016;21(9):1254. https://doi.org/10.3390/molecules21091254
138. Hamrapurkar P, Phale M, Pawar S. Extraction, isolation and characterization of phyllanthin from *Phyllanthus amarus* with preliminary phytochemical evaluation of the crude extract. Nat Prod: Indian J. 2009;5:120–4.
139. Harikrishnan H, Jantan I, Haque MA, Kumolosasi E. Anti-inflammatory effects of *Phyllanthus amarus* Schum. & Thonn. through inhibition of NF-κB, MAPK, and PI3K-Akt signaling pathways in LPS-induced human macrophages. BMC Complement Altern Med 2018a;18(1):1–13. https://doi.org/10.1186/s12906-018-2289-3
140. Harikrishnan H, Jantan I, Haque MA, Kumolosasi E. Phyllanthin from *Phyllanthus amarus* inhibits LPS-induced proinflammatory responses in U937 macrophages via downregulation of NF-κB/MAPK/PI3K-Akt signaling pathways. Phytother Res. 2018;32(12):2510–9. https://doi.org/10.1002/ptr.6190
141. Harikumar KB, Kuttan G, Kuttan R. Inhibition of viral carcinogenesis by *Phyllanthus amarus*. Integr Cancer Ther. 2009;8:254–60.
142. Harikumar KB, Kuttan G, Kuttan R. *Phyllanthus amarus* inhibits cell growth and induces apoptosis in Dalton's lymphoma ascites cells through activation of caspase-3 and downregulation of Bcl-2. Integr Cancer Ther. 2009;8:190–4.
143. Harikumar KB, Kuttan R. An extract of *Phyllanthus amarus* protects mouse chromosomes and intestine from radiation induced damages. J Radiat Res. 2007;48:469–76.
144. Harish R, Shivanandappa T. Antioxidant activity and hepatoprotective potential of *Phyllanthus niruri*. Food Chem. 2006;95:180–5.
145. Haworth RD. Natural resins. Annu Rep Prog Chem. 1936;33:266–79.
146. Hemadri K, Rao SS. Jaundice: tribal medicine. Anc Sci Life. 1984;3(4):209–12.
147. Heyde H. Medicijn planten in Suriname (Den dresi wiwiri foe Sranan). Medicinal Plants in Suriname. Uitg. Stichting Gezondheidsplanten Informaite (SGI) Paramaribo; 1990. pp. 157.
148. Heyde H. Surinaamse planten als volksmedicijn. Surinamese plants as folk medicine. GRANMA-MK, Paramaribo-Suriname; 1968. pp. 33.
149. Hiremath S, Kumar HD, Nandan M, Mantesh M, Shankarappa KS, Venkataravanappa V, Basha CR, Reddy CN. *In silico* docking analysis revealed the potential of phytochemicals present in *Phyllanthus amarus* and *Andrographis paniculata*, used in Ayurveda medicine in inhibiting SARS-CoV-2. 3 Biotech. 2021;11(2):1–8. https://doi.org/10.1007/s13205-020-02578-7.
150. Hollman PC, Katan MB. Dietary Flavonoids: Intake, Health Effects and Bioavailability. Food Chem Toxicol. 1999;37:937–42.
151. Hou X, Chenga Z, Wang J. Preparative purification of corilagin from *Phyllanthus* by combining ionic liquid extraction, prep-HPLC, and precipitation. Anal Methods. 2020;https://doi.org/10.1039/D0AY00860E
152. Houghton PJ, Woldemariama TZ, Siobhan OS, Thyagarajan SP. Two securinega type alkaloids from *Phyllanthus amarus.* Phytochemistry. 1996;43:715–17. https://doi.org/10.2174/2210315509666190405100745.
153. Huang RL, Huang YL, Ou JC, Chen CC, Hsu FL, Chang C. Screening of 25 compounds isolated from *Phyllanthus* species for anti-human hepatitis B virus *in vitro*. Phytother Res. 2003;17:449–53.
154. Huang YL, Chen CC, and Ou JC. Isolintetralin: a new lignan from *Phyllanthus niruri*. Planta Med. 1992;https://doi.org/10.1055/s-2006-961520.

155. Idu M, Ejale A, Timothy O, Comor AO. Common medicinal plants sold in some local markets in Warri, Delta State. Nigeria Plant Arch. 2008;8:557–61.
156. Idu M, Timothy O, Oghinan OM. Plants used for ethnomedicine in Esan North East local government area of Edo State in Nigeria. Ethnobotany. 2008;20:85–90.
157. Ignacimuthu S, Ayyanar M, Sankarasivaraman K. Ethnobotanical study of medicinal plants used by Paliyar tribals in Theni district of Tamil Nadu. India Fitoterapia. 2008;79:562–8.
158. Igwe CU, Nwaogu LA, Ujuwondu CO. Assessment of the hepatic effects, phytochemical and proximate compositions of *Phyllanthus amarus*. Afr J Biotechnol. 2007;6:728–31.
159. Ilangkovan M, Jantan I, Bukhari SN. Phyllanthin from *Phyllanthus amarus* inhibits cellular and humoral immune responses in Balb/C mice. Phytomedicine. 2016;23:1441–50.
160. Ilangkovan M, Jantan I, Mesaik MA, Bukhari SN. Immunosuppressive effects of the standardized extract of *Phyllanthus amarus* on cellular immune responses in Wistar-Kyoto rats. Drug Des Devel Ther. 2015;9:4917–30.
161. Ilangkovan M, Jantan I, Mesaik MA, Bukhari SN. Inhibitory Effects of the Standardized Extract of *Phyllanthus amarus* on Cellular and Humoral Immune Responses in Balb/C Mice. Phytother Res. 2016;30:1330–8.
162. Inchoo M, Chirdchupunseree H, Pramyothin P, Jianmongkol S. Endothelium-independent effects of phyllanthin and hypophyllanthin on vascular tension. Fitoterapia. 2011;82:1231–6.
163. Inta A, Shengji P, Balslev H, Wangpakapattanawong P, Trisonthi C. A comparative study on medicinal plants used in Akha's traditional medicine in China and Thailand, cultural coherence or ecological divergence? J Ethnopharmacol. 2008;116:508–17.
164. Islam A, Selvan T, Mazumder UK, Gupta M, Ghosal S. Antitumour effect of phyllanthin and hypophyllanthin from *Phyllanthus amarus* against Ehrlich Ascites Carcinoma in mice. Pharmacologyonline. 2008;2:796–807.
165. Ismail CAM, Deris ZZ, Bakar RA, Ismail N. *In Vitro* Anti-Leptospiral Activity of *Phyllanthus amarus* Extracts and Their Combinations with Antibiotics. Int. J. Environ. Res. Public Health. 2021;18:2834. https://doi.org/10.3390/ijerph18062834.
166. Ismail EN, Jantan I, Vidyadaran S, Jamal JA, Azmi N. *Phyllanthus amarus* prevents LPS-mediated BV2 microglial activation via MyD88 and NF-κB signaling pathways. BMC Complement Med Ther. 2020;20(1):1–3. https://doi.org/10.1186/s12906-020-02961-0.
167. Israel FT, Olorunnisola OS, Adetutu A, Ajilore BS. Hepatic and Immuno-Remediating Potential of Phenolic Rich Concentrate of *Phyllanthus amarus* (Schum & Thonn) Whole Plant in Acute High Salt Diet Assaulted Animal Model. Int J Sci Res Biol Sci (IJSRBS). 2021;8(4):67–73.
168. Iyekowa O, Oyelakin O, Edjere O. GC-MS Analysis and Antiasthmatic Activity of Hexane Extract of *Phyllanthus amarus* (Chanca piedra) L. Guinea Pig Malays J Chem. 2019;21(1):96–103.
169. Jagtap S, Khare P, Mangal P, Kondepudi KK, Bishnoi M, Bhutani KK. Protective effects of phyllanthin, a lignan from *Phyllanthus amarus*, against progression of high fat diet induced metabolic disturbances in mice. RSC Adv. 2016;6:58343–53.
170. Jain A, Katewa SS, Galav PK, Sharma P. Medicinal plant diversity of Sitamata wildlife sanctuary, Rajasthan. India J Ethnopharmacol. 2005;102:143–57.
171. Jain N, Shasany AK, Sundaresan V, Rajkumar S, Darokar MP, Bagchi GD, et al. Molecular diversity in *Phyllanthus amarus* assessed through RAPD analysis. Curr Sci. 2003;85:1454–8.
172. Jain P, Singh P, Sharma HP. Anti-proliferative activity of some medicinal plants. Int J Pharmacol Pharm Sci. 2016;3(2):46–52.
173. Jantan I, Ilangkovan M, and Mohamad HF. Correlation between the major components of *Phyllanthus amarus* and *Phyllanthus urinaria* and their inhibitory effects on phagocytic activity of human neutrophils. BMC Complement Alternat Med. 2014;https://doi.org/10.1186/1472-6882-14-429.
174. Jayaram S, Thyagarajan SP. Inhibition of HBsAg secretion from Alexander cell line by *Phyllanthus amarus*. Indian J Pathol Microbiol. 1996;39(211–15):214o.
175. Jayaram S, Udaya Shankar K, Rajendran P, Thyagarajan SP. Antihepatotoxicity potentials of *Phyllanthus amarus*: An *in vitro* study using isolated rat hepatocyte cultures. Indian J Med Microbiol. 1994;12:248–51.
176. Jeena KJ, Joy KL, Kuttan R. Effect of *Emblica officinalis*, *Phyllanthus amarus* and *Picrorrhiza kurroa* on N-nitrosodiethylamine induced hepatocarcinogenesis. Cancer Lett. 1999;136:11–6.
177. Jia R, Du JL, Cao LP, Liu YJ, Xu P, Yin GJ. Protective action of the phyllanthin against carbon tetrachloride-induced hepatocyte damage in *Cyprinus carpio*. In Vitro Cell Dev Biol Anim. 2016;https://doi.org/10.1007/s11626-015-9946-3.
178. Jimoh OA, Oyeyemi WA, Okin-Aminu HO, Oyeyemi BF. Reproductive characteristics, semen quality, seminal oxidative status, steroid hormones, sperm production efficiency of rabbits fed herbal supplements. Theriogenology. 2021;168:41–9. https://doi.org/10.1016/j.theriogenology.2021.03.020.
179. Joe MM, Devaraj S, Benson A, Sa T. Isolation of phosphate solubilizing endophytic bacteria from *Phyllanthus amarus* Schum & Thonn: Evaluation of plant growth promotion and antioxidant activity under salt stress. J Appl Res Med Aromat Plants. 2016;3(2):71–7. https://doi.org/10.1016/j.jarmap.2016.02.003.
180. Joseph J, Deborah K, Raghavi R, Mary Shamya A, Aruni W. Green synthesis of silver nanoparticles using *Phyllanthus amarus* Seeds and their antibacterial activity assessment. Biomed Biotechnol Res J. 2021;5(1):35–8.
181. Joshi BS, Gawad DH, Pelletier SW, Kartha G, and Bhandary K. Isolation and structure (x-Ray analysis) of ent-norsecurinine, an alkaloid from. *Phyllanthus niruri.* J. Nat. Prod. 1986;https://doi.org/10.1021/np50046a009.
182. Joshi CS, Priya ES. β - Glucuronidase inhibitory effect of phenolic constituents from *Phyllanthus amarus*. Pharm Biol. 2007;45:363–5.
183. Joy KL, Kuttan R. Inhibition by *Phyllanthus amarus* of hepatocarcinogenesis induced by N-Nitrosodiethylamine. J Clin Biochem Nutr. 1998;24:133–9.
184. Kala CP, Dhyani PP, Sajwan BS. Developing the medicinal plants sector in Northern India: challenges and opportunities. J Ethnobiol Ethnomed. 2006;2:1–15.
185. Kalaiselvi VC, Saravana B, Kalpana R, Rajkumar G, Satgurunathan T. *Phyllanthus amarus* enriched *Artemia nauplii* enhanced survival, growth and nutritional quality of early post-larvae of the prawn *Macrobrachium rosenbergii*. Clin Nutr Metab. 2018;5:1–15. https://doi.org/10.15761/CNM.1000110.
186. Kalaiselvi VC, Satgurunathan T, Kalpana R, Manjula T. Influence of Ethanolic Extract of *Phyllanthus amarus* on the Growth of the Prawn *Macrobrachium rosenbergii* Post-Larvae. Sumerianz J Biotechnol. 2019;2(1):1–10.
187. Karuna R, Bharathi VG, Reddy SS, Ramesh B, Saralakumari D. Protective effects of *Phyllanthus amarus* aqueous extract against renal oxidative stress in Streptozotocin-induced diabetic rats. Indian J Pharmacol. 2011;43(4):414.
188. Karuna R, Reddy SS, Baskar R, Saralakumari D. Antioxidant potential of aqueous extract of *Phyllanthus amarus* in rats. Indian J Pharmacol. 2009;41:64–7.
189. Kassuya CA, Leite DF, de Melo LV, Rehder VL, Calixto JB. Anti-inflammatory properties of extracts, fractions and lignans isolated from *Phyllanthus amarus*. Planta Med. 2005;71:721–6.
190. Kassuya CA, Silvestre AA, Menezes-de-Lima O Jr, Marotta DM, Rehder VL, Calixto JB. Antiinflammatory and antiallodynic actions of the lignan niranthin isolated from *Phyllanthus*

amarus. Evidence for interaction with platelet activating factor receptor. Eur J Pharmacol. 2006;546:182–8.
191. Kassuya CA, Silvestre AA, Rehder VL, Calixto JB. Anti-allodynic and antioedematogenic properties of the extract and lignans from *Phyllanthus amarus* in models of persistent inflammatory and neuropathic pain. Eur J Pharmacol. 2003;478:145–53.
192. Khatoon S, Rai V, Singh Rawat AK, Mehrotra S. Comparative pharmacognostic studies of three *Phyllanthus* species. J Ethnopharmacol. 2006;104:79–86.
193. Kiemer AK, Hartung T, Huber C, Vollmar AM. *Phyllanthus amarus* has anti-inflammatory potential by inhibition of iNOS, COX-2, and cytokines via the NF-kappaB pathway. J Hepatol. 2003;38:289–97.
194. Kiran KR, Swathy PS, Paul B, Prasada KS, Rao MR, Joshi MB, Rai PS, Satyamoorthy K, Muthusamy A. Untargeted metabolomics and DNA barcoding for discrimination of *Phyllanthus* species. J Ethnopharmacol. 2021;273: 113928.
195. Kosnayani AS, Hidayat AK, Darmana E, Riwanto I, Hadisaputro S. Effective combination of *Phyllanthus niruri* Linn and metformin to improve insulin resistance in obese rats. Int J Innov Creat Chang. 2019;9(1):167–76.
196. Krishnamurty, T. Minor forest products of India. 1993;Oxford and IBH Publ, Co. Pvt. Ltd. New Delhi.
197. Kristiani EB, Kasmiyati S. The Combination of *Phyllanthus niruri*, *Euphorbia hirta*, and *Loranthus* sp as a Source of Antioxidant Agents. Biosaintifika: Journal of Biology & Biology Education. 2021;13(2):201–11.
198. Krithika A, Verma RRJ. Mitigation of carbon tetrachloride induced damage by *Phyllanthus amarus* in liver of mice. Acta Pol Pharm - Drug Research. 2009;66:439–45.
199. Krithika AR, Verma RJ. Ameliorative potential of *Phyllanthus amarus* against carbon tetrachloride induced hepatotoxicity. Acta Pol Pharm – Drug Res 2009a;66:579–83.
200. Krithika R, Jyothilakshmi V, Prashantha K, Verma RJ. Mechanism of protective effect of phyllanthin against carbon tetrachloride-induced hepatotoxicity and experimental liver fibrosis in mice. Toxicol Mech Methods. 2015;https://doi.org/10.3109/15376516.2015.1077361.
201. Krithika R, Jyothilakshmi V, Verma RJ. Phyllanthin inhibits CCl_4-mediated oxidative stress and hepatic fibrosis by down-regulating TNF-α/ NF-Kb and pro-fibrotic factor TGF-β1 mediated inflammatory signaling. Toxicol Ind Health. 2014;32:953–60.
202. Krithika R, Mohankumar R, Verma RJ, Shrivastav PS, Mohamad IL, Gunasekaran P, Narasimhan S. Isolation, characterization and antioxidative effect of phyllanthin against CCl_4-induced toxicity in HepG2 cell line. Chem Biol Interact. 2009;181:351–8.
203. Krithika R, Verma RJ, Shrivastav PS, Suguna L. Phyllanthin of Standardized *Phyllanthus amarus* Extract Attenuates Liver Oxidative Stress in Mice and Exerts Cytoprotective Activity on Human Hepatoma Cell Line. J Clin Exp Hepatol. 2011;https://doi.org/10.1016/S0973-6883(11)60123-0.
204. Krithika R, Vhora I, Verma RJ. Preparation, toxicity analysis and *in vivo* protective effect of phyllanthin-loaded PLGA nanoparticles against CCl_4-induced hepatic fibrosis. J Drug Deliv Sci Technol. 2019;51:364–71. https://doi.org/10.1016/J.JDDST.2019.03.019.
205. Kumar KBH, Kuttan R. Chemoprotective activity of an extract of *Phyllanthus amarus* against cyclophosphamide induced toxicity in mice. Phytomedicine. 2005;12:494–500.
206. Kumar KBH, Kuttan R. Inhibition of drug metabolizing enzymes (Cytochrome P450) *in vitro* as well as *in vivo* by *Phyllanthus amarus* Schum & Thonn. Biol Pharm Bull. 2006;29:1310–3.
207. Kumar KBH, Kuttan R. Protective effect of an extract of *Phyllanthus amarus* against radiation-induced damage in mice. J Radiat Res. 2004;45:133–9.
208. Kumar S, Singh A, Bajpai V, Singh B, Kumar B. Development of a UHPLC-MS/MS method for the quantitation of bioactive compounds in *Phyllanthus* species and its herbal formulations. J. Sep. Sci. 2017a;https://doi.org/10.1002/jssc.201601361.
209. Kumar S, Singh A, Kumar B. Identification and characterization of phenolics and terpenoids from ethanolic extracts of *Phyllanthus* species by HPLC-ESI-QTOF-MS/MS. J Pharm Anal. 2017. https://doi.org/10.1016/j.jpha.2017.01.005.
210. Kumaran A, Karunakaran RJ. *In vitro* antioxidant activities of methanol extracts of five *Phyllanthus* species from India. LWT - Food Sci Technol. 2007;40:344–52.
211. Kuppusamy C, Murugan K. *In vitro* antimalarial activity of traditionally used Western Ghats plants from India and their interactions with chloroquine against chloroquine-resistant *Plasmodium falciparum*. Parasitol Res. 2010;107:1351–64.
212. Lawson-Evi P, Eklu-Gadegbeku K, Agbonon A, Aklikokou K, Creppy E, Gbeassor M. Antidiabetic activity of *Phyllanthus amarus* Schum and Thonn (Euphorbiaceae) on alloxan induced diabetes in male Wistar rats. J Appl Sci. 2011;11(16):2968–73.
213. Le TM, Nguyen CD, Ha AC. Combination of *Phyllanthus amarus* Schum. & Thonn. and *Gymnema sylvestre* R. Br. for treatment of diabetes and its long-term complications. Fine Chem Technol. 2021;16(3):232–40. https://doi.org/10.3262/2410-6593-2021-16-3-232-240.
214. Lee C-D, Ott M, Thyagarajan SP, Shafritz DA, Burk RD, Gupta S. *Phyllanthus amarus* down-regulates hepatitis B virus mRNA transcription and replication. Eur J Clin Invest (EJCI). 1996;26:1069–76.
215. Lee SH, Jaganath IB, Atiya N, Manikam R, Sekaran SD. Suppression of ERK1/2 and hypoxia pathways by four *Phyllanthus* species inhibits metastasis of human breast cancer cells. J Food Drug Anal. 2016;24(4):855–65. https://doi.org/10.1016/j.jfda.2016.03.010.
216. Lee SH, Jaganath IB, Wang SM, Sekaran SD. Antimetastatic Effects of *Phyllanthus* on Human Lung (A549) and Breast (MCF-7) Cancer Cell Lines. PLoS One. 2011;6(6): e20994. https://doi.org/10.1371/journal.pone.0020994.
217. Legba B, Dougnon V, Chabi Y. et al. Evaluation of *in-vivo* anti-*Salmonella* activity of *Uvaria chamae, Lantana camara* and *Phyllanthus amarus* used in Benin, West Africa. BMC Vet Res. 2020;16:49. https://doi.org/10.1186/s12917-020-2266-1.
218. Leite DF, Kassuya CA, Mazzuco TL, Silvestre A, de Melo LV, Rehder VL, et al. The cytotoxic effect and the multidrug resistance reversing action of lignans from *Phyllanthus amarus*. Planta Med. 2006;72:1353–8.
219. Lewis NG, Yamamoto E. Lignin: occurrence, biogenesis and biodegradation. Annu Rev Plant Physiol Plant Mol Biol. 1990;41:455–96.
220. Lewis WH, Elvin-Lewis PF. A text book of medicinal botany: Plants a ecting Man's Health. Wiley, 2nd Edition: A Wiley-Inter Science Publication; 1977.
221. Li K, Zhang X, He B, Yang R, Zhang Y, Shen Z, Chen P, Du W. Geraniin promotes osteoblast proliferation and differentiation via the activation of Wnt/β-catenin pathway. Biomed Pharmacother. 2018;99:319–24. https://doi.org/10.1016/j.biopha.2018.01.040.
222. Li Y, Li X, Wang J, Kuang Y, Qi M. Anti-hepatitis B viral activity of *Phyllanthus niruri* L (Phyllanthaceae) in HepG2/C3A and SK-HEP-1 cells. Trop J Pharm Res 2017;16:1873–79. https://doi.org/10.4314/TJPR.V16I8.17.
223. Lim WC, Kim H, Kim YJ, Choi KC, Lee IH, Lee KH, Kim MK, Ko H. Dioscin suppresses TGF-β1-induced epithelial-mesenchymal transition and suppresses A549 lung cancer migration and invasion. Bioorg Med Chem Lett. 2017;27(15):3342–8. https://doi.org/10.1016/j.bmcl.2017.06.014.

224. Liu J, Lin H, McIntosh H. Genus *Phyllanthus* for chronic hepatitis B virus infection: a systematic review. J Viral Hepat. 2001;8:358–66.
225. Liu J, McIntosh H, Lin H. Chinese medicinal herbs for chronic hepatitis B: a systematic review. Liver. 2001;21:280–6.
226. Liu S, Wei W, Shi K, Cao X, Zhou M, Liu Z. *In vitro* and *in vivo* antihepatitis B virus activities of the lignan niranthin isolated from *Phyllanthus niruri* L. J Ethnopharmacol. 2014;155:1061–7.
227. Londhe JS, Devasagayam PAT, Foo LY, Ghaskadbi SS. Antioxidant activity of some polyphenol constituents of the medicinal plant *Phyllanthus amarus* Linn. Redox Rep. 2008;13:199–207.
228. Londhe JS, Devasagayam PAT, Foo LY, Ghaskadbi SS. Radioprotective properties of polyphenols from *Phyllanthus amarus* Linn. J Radiat Res. 2009;50:303–9.
229. Londhe JS, Devasagayam TP, Foo LY, Shastry P, Ghaskadbi SS. Geraniin and amariin, ellagitannins from *Phyllanthus amarus*, protect liver cells against ethanol induced cytotoxicity. Fitoterapia. 2012;83(8):1562–8.
230. Maciel M, Cunha A, Dantas F, Kaiser C. NMR characterization of bioactive lignans from *Phyllanthus amarus* Schum and Thonn. J Magn Reson Imaging. 2007;6:76–82.
231. MacRae WD, Towers GHN. Biological activities of lignans. Phytochemistry. 1984;23:1207–20.
232. Maharan S, Muchimapura S, Wattanathorn J, Thukhummee W, Thong-Un T, Wannanon P. Dermal toxicity studies of an herbal cream contained *Zingiber officinale* Roscoe and *Phyllanthus amarus* extracts in Sprague-Dawley rats. J Med Assoc Thai. 2019;102(4):52–63.
233. Maheswari P, Harish S, Ponnusamy S, Muthamizhchelvan C. A novel strategy of nanosized herbal *Plectranthus amboinicus, Phyllanthus niruri* and *Euphorbia hirta* treated TiO_2 nanoparticles for antibacterial and anticancer activities. Bioprocess Biosyst Eng. 2021;2:1–24. https://doi.org/10.1007/s00449-020-02491-6.
234. Mahishi P, Srinivasa BH, Shivanna MB. Medicinal plant wealth of local communities in some villages in Shimoga District of Karnataka. India J Ethnopharmacol. 2005;98:307–12.
235. Mahomoodally MF, Muthoora DD. Kinetic of inhibition of carbohydrate-hydrolysing enzymes, antioxidant activity and polyphenolic content of *Phyllanthus amarus* Schum. & Thonn. (Phyllanthaceae). J Herb Med. 2014;4:208–23.
236. Maity S, Chatterjee S, Variyar PS, Sharma A, Adhikari S, Mazumder S. Evaluation of antioxidant activity and characterization of phenolic constituents of *Phyllanthus amarus* root. J Agric Food Chem. 2013;61(14):3443–50.
237. Maity S, Nag N, Chatterjee S, et al. Bilirubin clearance and antioxidant activities of ethanol extract of *Phyllanthus amarus* root in phenylhydrazine-induced neonatal jaundice in mice. J Physiol Biochem. 2013. https://doi.org/10.1007/s13105-013-0234-y.
238. Mali SM, Sinnathambi A, Kapase CU, Bodhankar SL, Mahadik KR. The anti-arthritic activity of standardized extract of *Phyllanthus amarus* in Freund's complete adjuvant-induced arthritis. Biomed Aging Pathol. 2011;1:185–90. https://doi.org/10.1016/j.biomag.2011.09.004.
239. Malisorn M, Akkaramadhurakul P-O, Songserm T, Wannachart S, Paraksa N. Effects of dietary mixed herbal extracted product supplementation on fatty liver hemorrhagic syndrome protection and productive performances of broilers. Agr. Nat. Resour. 2020;54(5): 485–90. https://doi.org/10.34044/j.anres.2020.54.5.04.
240. Manikkoth S, Deepa B, Joy AE, Rao SN. Anticonvulsant activity of *Phyllanthus amarus* in experimental animal models. Int J Appl Biol Pharm. 2011;2:144–9.
241. Mao X, Wu L-F, Guo H-L, Chen W-J, Cui Y-P, Qi Q, et al. The genus *Phyllanthus*: An ethnopharmacological, phytochemical, and pharmacological review. Evid Based Complement Alternat Med. 2016;7584952.
242. Marhaeny HD, Widyawaruyanti A, Widiandani T, Hafid AF, Wahyuni TS. Phyllanthin and hypophyllanthin, the isolated compounds of *Phyllanthus niruri* inhibit protein receptor of corona virus (COVID-19) through *in silico* approach. J Basic Clin Physiol Pharmacol. 2021;32(4):809–15. https://doi.org/10.1515/jbcpp-2020-0473.
243. Martens S, Preuss A, Matern U. Multifunctional flavonoid dioxygenases: flavonols and anthocyanin biosynthesis in *Arabidopsis thaliana* L. Phytochemistry. 2010;71:1040–9.
244. Martin DM, Gershenzon J, Bohlmann J. Induction of volatile terpene biosynthesis and diurnal emission by methyl jasmonate in foliage of Norway spruce. Plant Physiol. 2003;132:1586–99.
245. Mathew S, Faheem M, Suhail M, Fatima K, Archunan G, Begum N, et al. Updates on traditional medicinal plants for hepatocellular carcinoma. Pharmacogn J. 2016;8(3):203–14.
246. Matou M, Bercion S, Marianne-Pepin T, Haddad P, Merciris P. Phenolic profiles and biological properties of traditional *Phyllanthus amarus* aqueous extracts used for diabetes. J Funct Foods. 2021. https://doi.org/10.1016/j.jff.2021.104571.
247. Matou M, Merciris P, Haddad P, Sanchez M, Herbette G, Marianne-Pepin T, Bercion S. Study of antidiabetic properties and chemical composition of two *Phyllanthus* species usually consumed by Guadeloupean. InCaribbean Science and Innovation Meeting. 2019.
248. May AI. Surinaams Kruidenboek. Sranan Oso Dresi. Surinamese Book of Herbs. Uitgeverij Vaco, Paramaribo-Suriname; 1982. pp. 80.
249. Mazumder A, Mahato A, Mazumder R. Antimicrobial potentiality of *Phyllanthus amarus* against drug resistant pathogens. Nat Prod Res. 2006;20:323–6.
250. Mediani A, Abas F, Maulidiani M, Khatib A, Tan CP, Ismail IS, Shaari K, Ismail A. Characterization of metabolite profile in *Phyllanthus niruri* and correlation with bioactivity elucidated by nuclear magnetic resonance-based metabolomics. Molecules. 2017. https://doi.org/10.3390/molecules22060902.
251. Mediani A, Abas F, Maulidiani M, Khatib A, Tan CP, Ismail IS, Shaari K, Ismail A, Lajis NH. Metabolic and biochemical changes in streptozotocin induced obese-diabetic rats treated with *Phyllanthus niruri* extract. J Pharm Biomed Anal. 2016;128:302–12. https://doi.org/10.1016/j.jpba.2016.06.003.
252. Meena J, Sharma RA, Rolania R. Climate based comparative study of antibacterial activity of selected extracts of *Phyllanthus amarus* Schum. & Thonn. IJMCER. 2021;10(4):58–64.
253. Mehrotra R, Rawat S, Kulshreshtha DK, Goyal P, Patnaik GK, Dhawan BN. *In vitro* effect of *Phyllanthus amarus* on hepatitis B virus. Indian J Med Res. 1991;93:71–3.
254. Méril-Mamert V, Ponce-Mora A, Sylvestre M, Lawrence G, Bejarano E, Cebrián-Torrejón G. Antidiabetic potential of plants from the Caribbean basin. Plants. 2022;11:1360. https://doi.org/10.3390/plants11101360.
255. Mohamed SIA, Jantan I, Nafiah MA, Seyed MA, Chan KM. Lignans and Polyphenols of *Phyllanthus amarus* Schumach and Thonn Induce Apoptosis in HCT116 Human Colon Cancer Cells through Caspases-Dependent Pathway. Curr Pharm Biotechnol 2021;22(2):262–73. https://doi.org/10.2174/1389201021666200612173029.
256. Mohan M, James P, Valsalan R, Nazeem PA. Molecular docking studies of phytochemicals from *Phyllanthus niruri* against Hepatitis B DNA Polymerase. Bioinformation. 2015;11(9):426–31. https://doi.org/10.6026/97320630011426.
257. Moronkola DO, Ogunwande IA, Oyewole IO, Baser KHC, Ozek T, Ozek G. Studies on the volatile oils of *Momordica charantia* L. (Cucurbitaceae) and *Phyllanthus amarus* Sch. et Thonn (Euphorbiaceae). J. Essent. Oil Res. 2009;21:393–99.

258. Morton JF. Atlas of Medicinal Plants of Middle America. Library of Congress cataloging in Publication Data. Thomas books; 1981. pp. 1420.
259. Moshi MJ, Lutale JJ, Rimoy GH, Abass ZG, Josiah RM, Swai AB. The effect of *Phyllanthus amarus* aqueous extract on blood glucose in non-insulin dependent diabetic patients. Phytother Res. 2001;15:577–80.
260. Mostofa R, Ahmed S, Begum MM, Rahman MS, Begum T, Ahmed SU, Tuhin RH, Das M, Hossain A, Sharma M, Begum R. Evaluation of anti-inflammatory and gastric anti-ulcer activity of *Phyllanthus niruri* L. (Euphorbiaceae) leaves in experimental rats. BMC Compl. Alternative Med. 2017; https://doi.org/10.1186/s12906-017-1771-7
261. Mukherjee PK, Wahile A, Kumar V, Rai S, Mukherjee K, Saha BP. Marker profiling of botanicals used for hepatoprotection in Indian system of medicine. Drug Inf. 2006;40:131–9.
262. Mulchandani NB, and Hassarajani SA. 4-Methoxy-norsecurinine, a new alkaloid from *Phyllanthus niruri.* Planta Med. 1984; https://doi.org/10.1055/s-2007-969635
263. Munshi A, Mehrotra R, Ramesh R, Panda SK. Evaluation of antihepadnavirus activity of *Phyllanthus amarus* and *Phyllanthus maderaspatensis* in duck hepatitis B virus carrier Pekin ducks. J Med Virol. 1993;41:275–81.
264. Murali B, Amit A, Anand MS, Dinesh TK, Samiulla DS. An improved HPLC method for estimation of phyllanthin and hypophyllanthin in *Phyllanthus amarus*. J Nat Remedies. 2001;1:55–9.
265. Murthy TK, Joshi T, Gunnan S, Kulkarni N, Priyanka V, Kumar SB, Gowrishankar BS. *In silico* analysis of *Phyllanthus amarus* phytochemicals as potent drugs against SARS-CoV-2 main protease. Curr Res Green Sustain Chem (CRGSC). 2021;4:100159. https://doi.org/10.1016/j.crgsc.2021.100159
266. Murugaiyah V, Chan KL. Analysis of lignans from *Phyllanthus niruri* L. in plasma using a simple HPLC method with fluorescence detection and its application in a pharmacokinetic study. J. Chromatogr. B. 2007; https://doi.org/10.1016/j.jchromb.2007.01.014
267. Murugaiyah V, Chan KL. Antihyperuricemic lignans from the leaves of *Phyllanthus niruri*. Planta Med. 2006;72:1262–7.
268. Mutheeswaran S, Kumar PS, Yuvaraj P, Duraipandiyan V, Al-Dhabi NA, Balakrishna K, Ignacimuthu S. Screening of some medicinal plants for anticariogenic activity: An investigation on bioactive constituents from *Jatropha gossypifolia* (L.) root. Biocatal. Agric. Biotechnol. 2017;10:161–6. https://doi.org/10.1016/j.bcab.2017.03.006
269. Muthu C, Ayyanar M, Raja N, Ignacimuthu S. Medicinal plants used by traditional healers in Kancheepuram District of Tamil Nadu. India J Ethnobiol Ethnomed. 2006;2:1–10.
270. Muthulakshmi M, Subramani PA, Michael RD. Immunostimulatory effect of the aqueous leaf extract of *Phyllanthus niruri* on the specific and nonspecific immune responses of *Oreochromis mossambicus* Peters. Iran J Vet Res (IJVR). 2016;17(3):200–2.
271. Muthusamy A, Sanjay ER, Nagendra Prasad HN, Radhakrishna Rao M, Manjunath Joshi B, Padmalatha Rai S, Satyamoorthy K. Quantitative Analysis of *Phyllanthus* Species for Bioactive Molecules Using High-Pressure Liquid Chromatography and Liquid Chromatography–Mass Spectrometry. Proc Natl Acad Sci India Sect B. 2017;https://doi.org/10.1007/s40011-017-0839-y.
272. Naaz F, Javed S, Abdin MZ. Hepatoprotective effect of ethanolic extract of *Phyllanthus amarus* Schum. et Thonn. on aflatoxin B1-induced liver damage in mice. J Ethnopharmacol 2007;113:503–09.
273. Nakweti RK, Ndiku SL, Doumas P, Kanyanga RC, Ndofunsu AD, Otono FB, Jay-Allemand C. Phytochemical analysis of *Phyllanthus niruri* L. (Phyllanthaceae) extracts collected in four geographical areas in the Democratic Republic of the Congo. Afr J Plant Sci. 2013;7(1):9–20.
274. Nanden AT. Medicinale planten: tips en simpele recepten voor eengoede gezondheid. In: Medicinal Plants and Simple Recipes for a Good Health. Paramaribo-Suriname; 1998. pp. 18.
275. Nara TK, Glyeye J, Lavergne de Cerval E, Stanislan E. Flavonoids of *Phyllanthus niruri* L., *Phyllanthus urinaria* L., *Phyllanthus orbiculatus* L. c. rich. Plants Med Phytother. 1977;11:82–6.
276. Narendranathan M, Remla A, Mini PC, Satheesh P. A trial of *Phyllanthus amarus* in acute viral hepatitis. Trop Gastroenterol. 1999;20:164–6.
277. Nasrulloh R, Rafi M, Wahyuni WT, Shimma S, & Heryanto R. HPLC fingerprint and simultaneous quantitative analysis of phyllanthin and hypophyllanthin for identification and authentication of *Phyllanthus niruri* from related species. Rev Bras Farmacogn. 2018.https://doi.org/10.1016/J.BJP.2018.04.014.
278. Negi AS, Kumar JK, Luqman S, Shanker K, Gupta MM, Khanuja SP. Recent advances in plant hepatoprotectives: a chemical and biological profile of some important leads. Med Res Rev. 2008;28:746–72.
279. Ngo HVT, Huang HT, Lee PT, Liao ZH, Chen HY, Nan FH. Effects of *Phyllanthus amarus* extract on nonspecific immune responses, growth, and resistance to *Vibrio alginolyticus* in white shrimp *Litopenaeus vannamei*. Fish Shellfish Immunol. 2020;107:1–8. https://doi.org/10.1016/j.fsi.2020.09.016.
280. Nguyen VT, Bowyer MC, Van Altena IA, Scarlett CJ. Microwave-assisted extraction as an advanced technique for optimization of saponin yield and antioxidant potential from *Phyllanthus amarus*. Sep Sci Technol. 2017;52(17):2721–31. https://doi.org/10.1080/01496395.2017.1374972.
281. Nguyen VT, Pham HNT, Bowyer MC, van Altena IA, Scarlett CJ. Influence of solvents and novel extraction methods on bioactive compounds and antioxidant capacity of *Phyllanthus amarus*. Chem Pap. 2016;70:556–66. https://doi.org/10.1515/chempap-2015-0240.
282. Nguyen VT, Sakoff JA, Scarlett CJ. Physicochemical properties, antioxidant and cytotoxic activities of crude extracts and fractions from *Phyllanthus amarus*. Medicines. 2017;4(2):42. https://doi.org/10.3390/medicines4020042.
283. Nguyen VT, Scarlett CJ. Cytotoxic activity of extracts and fractions from *Paramignya trimera* root and *Phyllanthus amarus* against pancreatic cancer cell lines. J Can Res Ther. 2019;15:245–9. https://doi.org/10.4103/jcrt.JCRT_85_18.
284. Nguyen VT. Antiproliferative capacity of combined extracts from *Paramignya trimera* and *Phyllanthus amarus* against cancer cell lines. J Can Res Ther. 2021;17(2):471–76. https://doi.org/10.4103/jcrt.JCRT_14_19
285. Nhu TQ, Bich Hang BT, Cornet V, Oger M, Bach LT, Anh Dao NL, Thanh Huong DT, Quetin-Leclercq J, Scippo M-L, Phuong NT and Kestemont P. Single or Combined Dietary Supply of *Psidium guajava* and *Phyllanthus amarus* Extracts Differentially Modulate Immune Responses and Liver Proteome in Striped Catfish (*Pangasianodon hyphophthalmus*). Front. Immunol. 2020;11:797. https://doi.org/10.3389/fimmu.2020.00797
286. Nhu TQ, Dam NP, Hang BT, Hue BT, Scippo ML, Phuong NT, Quetin-Leclercq J, Kestemont P. Immunomodulatory potential of extracts, fractions and pure compounds from *Phyllanthus amarus* and *Psidium guajava* on striped catfish (*Pangasianodon hypophthalmus*) head kidney leukocytes. Fish Shellfish Immunol. 2020a;104:289–303. https://doi.org/10.1016/j.fsi.2020.05.051.
287. Nhu TQ, Hang BT, Hue BT, Quetin-Leclercq J, Scippo ML, Phuong NT, Kestemont P. Plant extract-based diets differently modulate immune responses and resistance to bacterial infection in striped catfish (*Pangasianodon hypophthalmus*). Fish Shellfish Immunol. 2019;92:913–24. https://doi.org/10.1016/j.fsi.2019.07.025400o

288. Nikam PS, Nikam SV, Sontakke AV, Khanwelkar CC. Role of *Phyllanthus amarus* treatment in Hepatitis-C. Biomed Res. 2011;22:319–22.
289. Nipanikar SU, Chitlange SS, Nagore D. Pharmacological Evaluation of Hepatoprotective Activity of AHPL/AYTAB/0613 Tablet in Carbon Tetrachloride-, Ethanol-, and Paracetamol-Induced Hepatotoxicity Models in Wistar Albino Rats. Pharmacognosy Res. 2017;https://doi.org/10.4103/pr.pr_44_17.
290. Niu J, Wang Y, Qiao M, Gowans E, Edwards P, Thyagarajan SP, et al. Effect of *Phyllanthus amarus* on duck hepatitis B virus replication *in vivo*. J Med Virol. 1990;32:212–8.
291. Noor NA, Nafiah MA, Tuan Johari SA, Hasnan MH, Tan SP, Liew SY, Supratman U. Anticancer Effect of Hypophyllanthin, Niranthin and Lintetralin from *Phyllanthus amarus* on HeLa Cells And NIH/3T3 Cells. Int J Recent Technol Eng (IJRTE). 2019;8(2S7):106–10. https://doi.org/10.35940/ijrte.B1024.0782S719.
292. Notka F, Meier GR, Wagner R. Concerted inhibitory activities of *Phyllanthus amarus* on HIV replication *in vitro* and *ex vivo*. Antiviral Res. 2004;64:93–102.
293. Notka F, Meier GR, Wagner R. Inhibition of wild type human immunodeficiency virus and reverse transcriptase inhibitor-resistant variants by *Phyllanthus amarus*. Antiviral Res. 2003;58:175–86.
294. Novellino KVA, Bernardo SR, Tappin MRR, Alves R de B. das N, da Silva DB, da Silva MJ, Vieira RF, Behrens M das DD, & Moreira D de L. Phyllanthin and hypophyllanthin determination by gas chromatography-mass spectrometry of six stone-breaker species from different regions of Brazil. J Med Plant Res. 2020;14(4):175–184.
295. Nur NM, Ahmed W, Jamshed F, Al-jasabi SA. The role of maslinic acid, a natural phytoalexin extracted from *Phyllanthus amarus* in the reduction of phenytoin-induced hepatic 8-hydroxydeoxyguanosine in DNA of Balb/c mice. Int Medical J. 2018;25(1):57–8.
296. Nurudeen QO, Salimon SS, Falana MB, Oweh OT, Abubakar IB. Antioxidant activity and toxicological implications of the aqueous extract of *Phyllanthus amarus* (Euphorbiaceae) leaves in female Wistar rats. Pac J Med Sci. 2020;21(1):29–40.
297. Nurudeen QO, Yakubu MT. Aqueous extract of *Phyllanthus amarus* Schum & Thonn leaves attenuated the alterations in fluoxetine-induced anti-oestrogenic activity in female wistar rats. Trop J Nat Prod Res. 2020;4(7):310–14. https://doi.org/10.26538/tjnpr/v4i7.10.
298. Nyamukuru A, Tabuti JR, Lamorde M, Kato B, Sekagya Y, Aduma PR. Medicinal plants and traditional treatment practices used in the management of HIV/AIDS clients in Mpigi District. Uganda J Herb Med. 2017;7:51–8. https://doi.org/10.1016/j.hermed.2016.10.001.
299. Odda J, Aliero AA, Waako P, Obua C, JD Kabasa. Microbiological analysis and total aflatoxins levels from shoot powder of *Phyllanthus amarus* (Schum. and Thonn) from Tororo, Uganda. NRMJ 2018a;2(5):75–84. https://doi.org/10.21608/NRMJ.2018.17863
300. Odda J, Waako P, Obua C, Kabasa JD. *In Vivo* antiplasmodial activity and safety of the aqueous ethanolic shoot extracts of *Phyllanthus amarus* Schum. and Thonn. Ijppr Human 2018;12(3):265–80.
301. Odetola AA, Akojenu SM. Anti-diarrhoeal and gastro-intestinal potentials of the aqueous extract of *Phyllanthus amarus* (Euphorbiaceae). Afr J Med Med Sci. 2000;29:119–22.
302. Oduola T, Kakako SL, Tajudeen M, Aiyelabegan F, Olayinka OS, Isah LO. Effect of intake of *Phyllanthus amarus* aqueous leaf extract on lipid peroxidation and some antioxidant factors in wistar rats. J Pharmacogn Phytochem. 2018;7(4):2660–6.
303. Oduola T, Muhammad AA, Aiyelabegan F, Tajudeen M, Okalawon SO. Hepatotoxic Assessment of *Phyllanthus amarus* leaf Extract in Wistar Rats. Eur J Med Plants. 2018;23(4): 1–11. https://doi.org/10.9734/EJMP/2018/41238
304. Ogata T, Higuchi H, Mochida S, Matsumoto H, Kato A, Endo T, et al. HIV-1 reverse transcriptase inhibitor from *Phyllanthus niruri*. AIDS Res Hum Retrovir. 1992;8:1937–44.
305. Ogunmoyole T, Mutiyat A, Idowu S, Daramola O. *Phyllanthus amarus* extract restored deranged biochemical parameters in rat model of hepatotoxicity and nephrotoxicity. Heliyon. 2020;6:e05670. https://doi.org/10.1016/j.heliyon.2020.e05670.
306. Ojezele MO, Moke EG, Onyesom I. Impact of generic antimalarial or *Phyllanthus amarus* and vitamin co-administration on antioxidant status of experimental mice infested with *Plasmodium berghei*. Beni-Suef Univ J Basic Appl Sci. 2017;6(3):260–5. https://doi.org/10.1016/j.bjbas.2017.04.008.
307. Ojo S, Falode JA, Adeoye AO, Ojerinde AO, Uzairue LI, Olowokere VO, Normo JI. Prophylactic activity and haematological changes in Swiss Albino Rats. Project: Drug Discov Altern Med Res. 2018;5(1):62–79.
308. Ojo SK, Sunmonu GT, Ukhureigbe OM, Fabulous-Fabowale TA. Wound healing potentials of *Diodia scandens* and *Phyllanthus amarus* leaf extracts on Swiss albino rats. Med Plants - Int J Phytomed Relat Ind 2019;11(4):440–3. https://doi.org/10.5958/0975-6892.2019.00058.3
309. Okey EN, Asuqwo IE. Phytochemical screening and antifungal activities of five plant species. Trop Plant Res. 2016;3(1):48–51.
310. Okigbo RN, Igwe DI. Antimicrobial effects of *Piper guineense* "Uziza" and *Phyllanthus amarus* "Ebe-benizo" on *Candida albicans* and *Streptococcus faecalis*. Acta Microbiol Immunol Hung. 2007;54:353–66.
311. Okiki PA, Olatunji BP, Adebimpe ASE, Comfort O. A comparative study of nutritional and phytochemical composition of *Phyllanthus amarus* leaf and seed. Am Eurasian J Toxicol Sci. 2015;7:321–7.
312. Okonkwo CO, Onyeji CM. Insecticidal potentials and chemical composition of essential oils from the leaves of *Phyllanthus amarus* and *Stachytarpheta cayennensis* in Nigeria. Int J Biochem Res Rev. 2018;22(3):1–16. https://doi.org/10.9734/IJBCRR/2018/42315
313. Okpako I, Onyesom I. Antiplasmodial activity of the ethanolic extract and flavonoid fraction of the stem of *Phyllanthus amarus* in experimental mice. Afr Sci. 2020;20(4):175–80.
314. Olabiyi FA, Aboua YG, Popoola OK, Monsees TK, Oguntibeju OO. Evaluation of antioxidant, antityrosinase activities and cytotoxic effects of *Phyllanthus amarus* extracts. Nat Prod J. 2020;10(2):130–8. https://doi.org/10.2174/2210315509666190405100745
315. Oladosu SA, Coker AO, Nwaokorie F. Antibacterial effects of *Phyllanthus amarus* on urinary tract pathogens. Int Clin Pathol J. 2019;7(1):1–10. https://doi.org/10.15406/icpjl.2019.07.00191.
316. Olanlokun JO, Babarinde CO, Olorunsogo OO. Antimalarial properties and preventive effects on mitochondrial dysfunction by extract and fractions of *Phyllanthus amarus* (Schum. and Thonn) in *Plasmodium berghei*-infected mice. J Basic Clin Physiol Pharmacol. 2021;32(3):255–66.
317. Olorunnisola OS, Fadahunsi OS, Adegbola PI, Ajilore BS, Ajayi FA, Olaniyan LW. *Phyllanthus amarus* attenuated derangement in renal-cardiac function, redox status, lipid profile and reduced TNF-α, interleukins-2, 6 and 8 in high salt diet fed rats. Heliyon. 2021;7(10):e08106. https://doi.org/10.1016/j.heliyon.2021.e08106
318. Oluboyo BO, Oluboyo AO, Kalu SO. Inhibitory effects of *Phyllanthus amarus* extracts on the growth of some pathogenic

microorganisms. Afr. J. Cln. Exper. Microbiol. 2016;17(3):166–72. https://doi.org/10.4314/ajcem.v17i3.2.
319. Olufayo OO, Tayo GO, Olumide MD, Akintunde AO. Assessment of the nutritive value of *Phyllanthus niruri* Linn. (stone-breaker) leaves. Nigerian J. Anim. Sci. 2021;23(3):108–15.
320. Omoregie FO, Eriyamremu GE, Kapur S. Therapeutic Effects of Aqueous and Ethanolic Extracts of *Phyllanthus amarus* on 1, 2 Dimethylhydrazine Induced Colon Carcinogenesis in Balb/C Mice. Int. J. Biochem. Res. Rev. 2020;31:36–43. https://doi.org/10.9734/IJBCRR/2020/v29i730206.
321. Onocha PA, Ali MS. Antileishmaniasis, phytotoxicity and cytotoxicity of Nigerian Euphorbiaceous Plants 2: *Phyllanthus amarus* and *Phyllanthus muellerianus* extracts. Afr Sci. 2010;11:79–83.
322. Onyesom I, Onumaechi IF, Ehiwario J, Dagana R. Antiplasmodial activity of *Phyllanthus amarus* preserves renal function in *Plasmodium berghei* infected mice. Eur J Med Plants. 2015;109–116.
323. Ooi KL, Loh SI, Sattar MA, Muhammad TST, Sulaiman SF. Cytotoxic, caspase-3 induction and *in vivo* hepatoprotective effects of phyllanthin, a major constituent of *Phyllanthus niruri*. J Funct Foods. 2015;14:236–43.
324. Osathanunkul M, Suwannapoom C, Osathanunkul K, Madesis P, de Boer HJ. Evaluation of DNA barcoding coupled high resolution melting for discrimination of closely related species in phytopharmaceuticals. Phytomedicine. 2016;23(2):156–65.
325. Oshomoh EO, Uzama-Avenbuan O. Quantitative Phytochemical Composition and Bioactive Constituents of Ethanolic Extract of *Phyllanthus amarus* (schum. et thonn) Leaves. Eur J Eng Res Sci (EJERS). 2020;https://doi.org/10.24018/ejfood.2020.2.4.59.
326. Oshomoh EO, Uzama-Avenbuan O, Ayanru D. Assessment of the Antimicrobial Sensitivity of Ethanolic Extracts of *Phyllanthus amarus* (Schum. et Thonn) Leaves on Oral Microorganisms. Nipes J. Sci. Technol. Res. 2020;2(3):96–102. https://doi.org/10.37933/nipes/2.3.2020.10.
327. Oso BJ, Olaoye IF. Comparative *in vitro* studies of antiglycemic potentials and molecular docking of *Ageratum conyzoides* L. and *Phyllanthus amarus* L. methanolic extracts. SN Appl Sci. 2020;2(4):629. https://doi.org/10.1007/s42452-020-2275-5.
328. Ott M, Thyagarajan SP, Gupta S. *Phyllanthus amarus* suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. Eur J Clin Invest (EJCI). 1997;27:908–15.
329. Oyebamiji AK, Soetan EA, Akintelu SA, Ayeleso AO, Mukwevho E. Alpha-glucosidase Activity of Phytochemicals from *Phyllanthus amarus* Leaves via *In-silico* Approaches. Pharmacol Res-Mod Chin Med. 2022;25: 100054.
330. Ozioko KU, Okoye CI, Okafor FC, Obiezue RN. *Anopheles gambiae* larvicidal and adulticidal potential of *Phyllanthus amarus* (Schumach and Thonn, 1827) obtained from different localities of Nigeria. Asian Pac J Trop Med. 2021;14(1):27–33.
331. Pahmi K, Sidratullah M. Effect of Leaf flower (*Phyllanthus niruri* Linn.) treatment on kidney and uterus in sodium chloride-induced fibrotic rats. Bioscientia Medicina: Journal of Biomedicine and Translational Research. 2021;5(3):263–7. https://doi.org/10.32539/bsm.v5i3.187
332. Pammi SS, Giri A. *In vitro* cytotoxic activity of *Phyllanthus amarus* Schum. & Thonn. World J Biol Pharm Health Sci (WJBPHS). 2021;6(2):34–42. https://doi.org/10.30574/wjbphs.2021.6.2.0050
333. Parvathaneni M, Battu GR, Gray AI, Gummalla P. Investigation of anticancer potential of hypophyllanthin and phyllanthin against breast cancer by *in vitro* and *in vivo* methods. Asian Pac J Trop Dis. 2014;4:S71–6.
334. Paschold A, Halitschke R, Baldwin IT. Using 'mute' plants to translate volatile signals. Plant J. 2006;45:275–91.
335. Patel HR, Patel N, Patel J, Patel P, Patel A. Phytochemical evaluation and exploration of the hepatoprotective activity of 5 different formulations in CCL_4 induced albino RATS. Int J Pharmacol. 2016;https://doi.org/10.14419/ijpt.v4i1.5962.
336. Patel J, Nagar PS, Pal K, Singh R, Dhanani T, Patel V, Srivastava S, Kumar S. Comparative profiling of four lignans (Phyllanthin, Hypophyllanthin, Nirtetralin, and Niranthin) in nine *Phyllanthus* species from India using a validated reversed phase HPLC-PDA detection method. J AOAC Int. 2021;https://doi.org/10.1093/jaoacint/qsaa133.
337. Pathmavathi M, Thamizhiniyan P. Antimicrobial activity of various extracts of *Plectranthus ambionicus* and *Phyllanthus amarus*. J Appl Adv Res 2016;1:29–35. https://doi.org/10.21839/JAAR.2016.V1I2.22.
338. Paul S, Patra D, Kundu R. Lignan enriched fraction (LRF) of *Phyllanthus amarus* promotes apoptotic cell death in human cervical cancer cells *in vitro*. Sci Rep. 2019;9:14950. https://doi.org/10.1038/s41598-019-51480-7.
339. Pereira RG, Garcia VL, Rodrigues MVN, Martínez J. Extraction of lignans from *Phyllanthus amarus* Schum. & Thonn using pressurized liquids and low pressure methods. Sep Purif Technol. 2016;158:204–11.
340. Pereira RG, Nakamura RN, Rodrigues MV, Osorio-Tobón JF, Garcia VL, & Martínez J. Supercritical fluid extraction of phyllanthin and niranthin from *Phyllanthus amarus* Schum. & Thonn. J Supercrit Fluids. 2017;127:23–32.
341. Phuong TV, Hai Yen PT, Linh NQ. Antibacterial activity of extracts from dried and fresh herbal plant (*Phyllanthus amarus*) against pathogens causing acute hepatopancreatic necrosis disease (Ahpnd) in white leg shrimp (*Litopenaeus vannamei*) at Thua Thien Hue Province, Vietnam. Asp Biomed Clin Case Rep. 2019;2(3):120–28. https://doi.org/10.36502/2019/ASJBCCR.6173.
342. Pinkaew D, Kiattisin K, Wonglangka K, Awoot P. Phonophoresis of *Phyllanthus amarus* nanoparticle gel improves functional capacity in individuals with knee osteoarthritis: A randomized controlled trial. J Bodyw Mov Ther. 2020;24(1):15–8. https://doi.org/10.1016/j.jbmt.2019.04.013.
343. Pradit W, Chomdej S, Nganvongpanit K, Ongchai S. Chondroprotective potential of *Phyllanthus amarus* Schum. & Thonn. in experimentally induced cartilage degradation in the explants culture model. In Vitro Cell. Dev. Biol. Animal. 2015;51(4):336–44. https://doi.org/10.1007/s11626-014-9846-y.
344. Prajapati AS, Raval SK, Sarvaiya V, Varia TN. Chemoprotective activity of *Phyllanthus amarus* and serum biochemical changes in azaserine induced pancreatic cancer in wistar rats. Indian Vet J. 2016;93(5):79–81.
345. Prakash A, Satyan KS, Wahi SP, Singh RP. Comparative hepatoprotective activity of three *Phyllanthus* species, *P. urinaria*, *P. niruri* and *P. simplex*, on carbon tetrachloride induced liver injury in the rat. Phytother Res. 1995;9: 594–96.
346. Pramyothin P, Ngamtin C, Poungshompoo S, Chaichantipyuth C. Hepatoprotective activity of *Phyllanthus amarus* Schum. et. Thonn. extract in ethanol treated rats: *In vitro* and *in vivo* studies. J. Ethnopharmacol. 2007;114:169–73.
347. Prasad KS, Shivamallu C, Shruthi G, Prasad M. A Novel and One-pot Green Synthesis of Vanadium Oxide Nanorods Using a Phytomolecule Isolated from *Phyllanthus amarus*. ChemistrySelect. 2018;3(13):3860–5. https://doi.org/10.1002/slct.201800653.
348. Prasad PR, Reddy CS, Raja SH, Dutt CBS. Folklore medicinal plants of North Andaman Islian. India Fitoterapia. 2008;79:458–64.
349. Preeja RP, Arivarasu L, Rajeshkumar S. Antimicrobial and antioxidant activity of *Phyllanthus niruri* mediated silver nanoparticles. Plant Cell Biotechnol Mol Biol. 2020;21(29–30):30–7.

350. Priscilla EI, Chukwuemeka OE, Pauline OU, Adamma AR, Kalu AA, Athanatius OO, Victor O. The Effect of *P. amarus* Leaf Extract on The Electrolyte Profile Levels of Alloxan-Induced Diabetic Wistar Rat. Adv. Biores. 2018;9(4):78–82. https://doi.org/10.15515/abr.0976-4585.9.4.7882.
351. Priya K, Yin WF, Chan KG. Anti-quorum sensing activity of the traditional Chinese herb, *Phyllanthus amarus*. Sensors. 2013;13(11):14558–69.
352. Priya MK, Iyer PR. Anticancer studies of the synthesized gold nanoparticles against MCF 7 breast cancer cell lines. Appl Nanosci. 2015;5(4):443–8.
353. Priya S, Mangala Gowri A, Sujatha G, Gnanalaksshmi KS, Baskaran D (2016) Chicken muscle derived progenitors as a source for testing free radical scavenging activity. Adv Biomed Pharma. 2016;205–11. https://doi.org/10.19046/abp.v03i04.04.
354. Puri SK, Habbu PV, Kulkarni PV, Joshi AB, Kulkarni VH, Dixit SR. Hepatoprotective activity and constituents of *Nigrospora* sp. CMH2_13: An endophytic fungus isolated from leaves of *Phyllanthus amarus* Schum. and Thonn. Ann Phytomed. 2020;9(2):239–46. https://doi.org/10.21276/ap.2020.9.2.22.
355. Puri SK, Habbu PV, Kulkarni PV, Kulkarni VH. Hepatoprotective potential of endophytic *Aspergillus niger* strain A6 fractions isolated from *Phyllanthus amarus* Schum and Thonn. J Pharm Sci. 2021;11(2):21–31.
356. Puspita NA, Alhebshi H. The effect of *Phyllanthus niruri* L extracts on human leukemic cell proliferation and apoptosis induction. Indones J Pharm. 2019;30(4):241–51. https://doi.org/10.14499/indonesianjpharm30iss4pp241.
357. Putakala M, Gujjala S, Nukala S, Bongu SB, Chintakunta N, Desireddy S. Cardioprotective effect of *Phyllanthus amarus* against high fructose diet induced myocardial and aortic stress in rat model. Biomed. Pharmacother. 2017;95:1359–68. https://doi.org/10.1016/j.biopha.2017.09.054.
358. Putakala M, Gujjala S, Nukala S, Desireddy S. Beneficial effects of *Phyllanthus amarus* against high fructose diet induced insulin resistance and hepatic oxidative stress in male wistar rats. Appl Biochem Biotechnol. 2017; 183(3):744–64. https://doi.org/10.1007/s12010-017-2461-0.
359. Rahuman AA, Gopalakrishnan G, Venkatesan P, Geetha K. Larvicidal activity of some Euphorbiaceae plant extracts against *Aedes aegypti* and *Culex quinquefasciatus* (Diptera: Culicidae). Parasitol Res. 2008;102:867–73.
360. Raja T, Ravikumar P, Srinivasan MR, Vijayarani K, Kumanan K. Identification of potential novel inhibitors for nipah virus—an *in-silico* Approach. Int J Curr Microbiol App Sci 2020;9(9):3377–90. https://doi.org/10.20546/ijcmas.2020.909.420.
361. Rajakumar N, Shivanna MB. Ethno-medicinal application of plants in the eastern region of Shimoga district, Karnataka. India J Ethnopharmacol. 2009;126:64–73.
362. Rajeshkumar NV, Joy KL, Kuttan G, Ramsewak RS, Nair MG, Kuttan R. Antitumour and anticarcinogenic activity of *Phyllanthus amarus* extract. J Ethnopharmacol. 2002;81:17–22.
363. Rajeshkumar NV, Kuttan R. *Phyllanthus amarus* extract administration increases the life span of rats with hepatocellular carcinoma. J Ethnopharmacol. 2000;73:215–9.
364. Ramandeep K, Nahid A, Neelabh C, Navneet K. Phytochemical screening of *Phyllanthus niruri* collected from Kerala region and its antioxidant and antimicrobial potentials. J Pharm Sci Res. 2017;9(8):1312.
365. Raphael KR, Ajith TA, Joseph S, Kuttan R. Anti-mutagenic activity of *Phyllanthus amarus* Schum & Thonn *in vitro* as well as *in vivo*. Teratog carcinog mutagen. 2002;22:285–91.
366. Raphael KR, Kuttan R. Inhibition of experimental gastric lesion and inflammation by *Phyllanthus amarus* extract. J Ethnopharmacol. 2003;87:193–7.
367. Raphael KR, Sabu M, Kumar KH, Kuttan R. Inhibition of N-Methyl N'- nitro-N-nitrosoguanidine (MNNG) induced gastric carcinogenesis by *Phyllanthus amarus* extract. Asian Pac J Cancer Prev. 2006;7:299–302.
368. Raphael KR, Sabu MC, Kuttan R. Hypoglycemic effect of methanol extract of *Phyllanthus amarus* Schum & Thonn. on alloxan induced diabetes mellitus in rats and its relation with antioxidant potential. Indian J Exp Biol. 2002a;40:905–09.
369. Ravikumar YS, Ray U, Nandhitha M, Perween A, Naika HR, Khanna N, Das S. Inhibition of hepatitis C virus replication by herbal extract: *Phyllanthus amarus* as potent natural source. Virus Res. 2011;158:89–97.
370. Reddy BP, Murthy VN, Venkateshwarulu V, Kokate CK, Rambhau D. Antihepatotoxic activity of *Phyllanthus niruri, Tinospora cordifolia* and *Ricinus communis*. Indian Drugs. 1993;30:338–41.
371. Reddy U, Tandon H, Pradhan MK, Adhikesavan H, Srinivasan N, Das S, Jayaraman N. Potent HCV NS3 Protease Inhibition by a Water-Soluble Phyllanthin Congener. ACS omega. 2020;5(20):11553–562. https://doi.org/10.1021/acsomega.0c00786.
372. Ribeiro AMB, Sousa JN de, Costa LM, Oliveira FA de Alcântara, Santos RC dos, Nunes AS Silva, Silva WO da, Cordeiro PJM, Neto José de Sousa L, Siqueira-Júni JP de, Kaatz GW, Barreto HM, Oliveira AP de. Antimicrobial activity of *Phyllanthus amarus* Schumach. & Thonn and inhibition of the NorA efflux pump of *Staphylococcus aureus* by Phyllanthin, Microb Pathog. 2019;https://doi.org/10.1016/j.micpath.2019.03.012
373. Roengrit T, Wannanon P, Prasertsri P, Kanpetta Y, Sripanidkulchai B, Leelayuwat N. Antioxidant and anti-nociceptive effects of *Phyllanthus amarus* on improving exercise recovery in sedentary men: a randomized crossover (double-blind) design. J Int Soc Sports Nutr. 2014;11:9.
374. Row LR, Satyanarayana P, Subba Rao GSR. Crystalline constituents of Euphorbiaceae—the synthesis and absolute configuration of phyllanthin. Tetrahedron. 1967;23:1915.
375. Sainudeen S, Nair VS, Zarbah M, Abdulla AM, Najeeb CM, Ganapathy S. Can Herbal Extracts Serve as Antibacterial Root Canal Irrigating Solutions? Antimicrobial Efficacy of *Tylophora indica*, *Curcumin longa*, *Phyllanthus amarus*, and Sodium Hypochlorite on *Enterococcus faecalis* Biofilms Formed on Tooth Substrate: *In Vitro* Study. J Pharm Bioallied Sci. 2020;12(1):S423–S429. https://doi.org/10.4103/jpbs.JPBS_127_20
376. Saliu JA, Oyeleye SI, Olasehinde TA, Oboh G. Modulatory effects of stonebreaker (*Phyllanthus amarus*) and bitter gourd (*Momordica charantia*) on enzymes linked with cardiac function in heart tissue of doxorubicin-stressed rats. Drug Chem Toxicol. 2019;10:1–9. https://doi.org/10.1080/01480545.2019.1700271.
377. Samuel JK, Andrews B. Traditional medicinal plant wealth of Pachalur and Periyur hamlets Dindigul District, Tamil Nadu. Indian J Tradit Knowl. 2010;9:264–70.
378. Sane RT, Chawla JL, Kuber VV. Studies on *Phyllanthus amarus*. Part I Indian Drugs. 1997;34:580–4.
379. Sane RT, Kuber VV, Mary SC, Menon S. Hepatoprotection by *Phyllanthus amarus* and *P. debelis* in CCl_4 induced liver dysfunction. Curr Sci. 1995;68:1242–46.
380. Santos AR, De Campos RO, Miguel OG, Filho VC, Siani AC, Yunes RA, Calixto JB. Antinociceptive properties of extracts of new species of plants of the genus *Phyllanthus* (Euphorbiaceae). J Ethnopharmacol. 2000;72:229–38.
381. Saranraj P, Sivasakthivelan P. Screening of antibacterial activity of the medicinal plant *Phyllanthus amarus* against urinary tract infection causing bacterial pathogens. Appl J Hyg (AJH). 2012;1:19–24.

382. Sedoc N. Afro-Surinaamse natuurgeneeswijzen. Bevattende meer dan tweehonderd meest gebruikelijke geneeskrachtige kruiden. African–Surinamese natural cures, containing more than two hundred most useful healing/curative herbs; 1992. pp. 224.
383. Seetaha S, Hannongbua S, Rattanasrisomporn J, Choowongkomon K. Novel peptides with HIV-1 reverse transcriptase inhibitory activity derived from the fruits of *Quercus infectoria*. Chem Biol Drug Des. 2021;97(1):157–66. https://doi.org/10.1111/cbdd.13770.
384. Senapati SK, Aparajita S, Rout GR. Identification of species diagnostic inter simple sequence repeat markers for ten *Phyllanthus* species. Z Naturforsch C. 2011;66:167–72.
385. Senjobi CT, Ettu AO, Otujo CO. Antibacterial and antifungal activities of leaf extracts of *Phyllanthus amarus* Schum and Thonn. J Pharmacogn Phytotherapy. 2017;9(1):6–10. https://doi.org/10.5897/JPP2013.0261.
386. Shanker K, Singh M, Srivastava V, Verma R, Gupta A, Gupta M. Simultaneous analysis of six bioactive lignans in *Phyllanthus* species by reversed phase hyphenated high performance liquid chromatographic technique. Acta Chromatogr. 2011;23:321–37.
387. Shanmugam S, Manikandan K, Rajendran K. Ethnomedicinal survey of medicinal plants used for the treatment of diabetes and jaundice among the villagers of Sivagangai District, Tamilnadu. Ethnobot Leaflets. 2009;13:189–94.
388. Sharma A, Singh RT, Anand S. Estimation of phyllanthin and hypophyllanthin by high performance liquid chromatography in *Phyllanthus amarus*. Phytochem Anal. 1993;4:226–9.
389. Shazlyana MF, MSA Syed, Mohamad MEN. Chromatographic Characterization of Hypophyllantin and Phyllantin in Methanolic Extracts from Three Common *Phyllanthus* Species in Malaysia. Planta Med. 2017;4(S 01):S1-S202.
390. Shead A, Vickery K, Pajkos A, Medhurst R, Freiman J, Dixon R, Cossart Y. Effects of *Phyllanthus* plant extracts on duck hepatitis B virus *in vitro* and *in vivo*. Antivir Res. 1992;18:127–38.
391. Shetti A, Kaliwal BB. Hypoglycemic activity of ethanolic leaf extract of *Phyllanthus amarus* in alloxan induced diabetic mice. Eur J Exp Biol. 2015;5:26–9.
392. Shi Q, Li L, Huo C, Zhang M, Wang Y. Study on natural medicinal chemistry and new drug development. Zhongcaoyao¼ Chin Tradit Herb Drugs. 2010;41(10):1583–89.
393. Singh AK, Pandey M, Singh S, Singh AK, Singh U. Antifungal activity of securinine against some plant pathogenic fungi. Mycobiology. 2008;36:99–101.
394. Singh B, Agrawal PK, Thakur RS. An acyclic triterpene from *Phyllanthus niruri*. Phytochemistry. 1989. https://doi.org/10.1016/S0031-9422(00)97901-9.
395. Singh K, Panghal M, Kadyan S, Chaudhary U, Yadav JP. Green silver nanoparticles of *Phyllanthus amarus*: as an antibacterial agent against multi drug resistant clinical isolates of *Pseudomonas aeruginosa*. J Nanobiotechnol. 2014;12(1):1–9.
396. Singh M, Tiwari N, Shanker K, Verma RK, Gupta AK, Gupta MM. Two new lignans from *Phyllanthus amarus*. J Asian Nat Prod Res. 2009;11:562–8.
397. Singh RP, Pal A, Pal K. Antimicrobial activity of *Phyllanthus niruri* against different human pathogenic bacterial strains. World J Pharm Res. 2016;5(3):1093–8.
398. Singh S, Chauhan MG, Kaur B, Kumar B, Gulati M, Singh SK. Characterization, organoleptic evaluation and standardization of aqueous extracts of antidiabetic herbs *Trigonella foenum, Allium sativum, Aloe vera, Phyllanthus niruri*. J Pharm Res. 2017;11(11):1370–5.
399. Somu C, Paulchamy R, Moorthy SM, Sundaram J. Antiviral activity of selected medicinal plants and marine seaweeds on the grasserie infected larvae of silkworm, *Bombyx mori.* Arch Phytopathol Pflanzenschutz. 2017;50(17–18):850–67. https://doi.org/10.1080/03235408.2017.1401700.
400. Sousa AD, Maia IV, Ribeiro PRV, Canuto KM, Zocolo GJ, Brito E Sousa de. UPLC-QTOF-MSE-based chemometric approach driving the choice of the best extraction process for *Phyllanthus niruri.* Sep Sci Technol. 2017;52(10):1696–1706.
401. Sowjanya K, Girish C, Bammigatti C, Prasanna Lakshmi NC. Efficacy of *Phyllanthus niruri* on improving liver functions in patients with alcoholic hepatitis: a double-blind randomized controlled trial. Indian J Pharmacol. 2021;53:448–56. https://doi.org/10.4103/ijp.IJP_540_20
402. Srilatha K, Reddy KP. Sciatic Nerve Structural and Functional Recovery with Extract of *Phyllanthus amarus* and Esculetin in STZ-Induced Hyperglycemic Rats. Ann Neurosci. 2019;26(3–4):17–29. https://doi.org/10.1177/0972753120911840
403. Sripanidkulchai B, Tattawasart U, Laupatarakasem P, Vinitketkumneun U, Sripanidkulchai K, Furihata C, Matsushima T. Antimutagenic and anticarcinogenic effects of *Phyllanthus amarus*. Phytomedicine. 2002;9:26–32.
404. Srirama R, Deepak HB, Senthilkumar U, Ravikanth G, Gurumurthy BR, Shivanna MB, Chandrasekaran CV, Agarwal A, Shaanker RU. Hepatoprotective activity of Indian *Phyllanthus*. Pharm Biol. 2012;50(8):948–53.
405. Srivastava V, Singh M, Malasoni R, Shanker K, Verma RK, Gupta MM, Gupta AK, Khanuja SPS. Separation and quantification of lignans in *Phyllanthus* species by a simple chiral densitometric method. J Sep Sci. 2008;31:2338.
406. Srividya N, Periwal S. Diuretic, hypotensive and hypoglycaemic effect of *Phyllanthus amarus*. Indian J Exp Biol. 1995;33:861–4.
407. Sukhaphiroma N, Vardhanabhutib N, Chirdchupunsereea H, Pramyothina P, Jianmongkola S. Phyllanthin and hypophyllanthin inhibit function of P-gp but not MRP2 in Caco-2 cells. J Pharm Pharmacol. 2012;65:292–9.
408. Sundaram D, Kesavan K, Kumaravel H, Mohammed RF, Tohru M, Toshiaki I, Raja S. Protective efficacy of active compounds from *Phyllanthus amarus* against white spot syndrome virus in freshwater crab (*Paratelphusa hydrodomous*). Aquac Res. 2016;47(7): 2061–7. https://doi.org/10.1111/are.12660
409. Suraya AA, Misran A, Hakiman M. The efficient and easy micropropagation protocol of *Phyllanthus niruri*. Plants. 2021. https://doi.org/10.3390/plants10102141.
410. Surya Narayanan B, Latha P, Rukkumani R. Protective effects of *Phyllanthus amarus* on fibrotic markers during alcohol and polyunsaturated fatty acid induced toxicity. Toxicol Mech Methods. 2011;21:48–52.
411. Syamasundara KV, Singh B, Thakur RS, Husain A, Yoshinobu K, Hiroshi H. Antihepatotoxic principles of *Phyllanthus niruri* herbs. J Ethnopharmacol. 1985;14:41–4.
412. Tai BH, Nhut ND, Nhiem NX, Tung NH, Quang TH, Luyen BTT, Huong TT, Wilson J, Beutler JA, Cuong NM, Kim YH. Evaluation of the RNase H inhibitory properties of Vietnamese medicinal plant extracts and natural compounds. Pharm Biol. 2011;49:1046–51. https://doi.org/10.3109/13880209.2011.563316
413. Tang YQ, Jaganath IB, Manikam R, Sekaran SD. *Phyllanthus* spp. Exerts anti-angiogenic and anti-metastatic effects through inhibition on Matrix Metalloproteinase Enzymes. Nutr Cancer. 2015;67:783–95.
414. Tao Z, Chun-Yan H, Hua P, Bin-Bin Y, Xiaoping T. Phyllathin from *Phyllanthus amarus* ameliorates epileptic convulsion and kindling associated post-Ictal depression in mice via inhibition of NF-κB/TLR-4 pathway. Dose-Response. 2020;18(3):1–12. https://doi.org/10.1177/1559325820946914.
415. Taylor L. The healing power of rainforest herbs: a guide to understanding and using herbal medicines. Square One Publishers. Cornell University; 2005. pp. 519.

416. Thakur I, Devi PU, Bigoniya P. Protection against radiation clastogenecity in mouse bone marrow by *Phyllanthus niruri*. Indian J Exp Biol. 2011;49:704–10.
417. Thao NT, Nhan TT, Ni HT, Thien TV, Ngan NT. Obtaining the extract containing rich content of phenolic compounds from diep ha chau (*Phyllanthus amarus*) grown in phu yen province for medication purposes. J Tech Educ Sci. 2018;48:51–6.
418. Thaweboon S, Thaweboon B, Srichan R. Effect of *Phyllanthus amarus* Coating Denture Resin on *Candida* Adhesion and its Effect on Human Gingival Fibroblast. Key Eng. Mater. 2020;853:36–40. https://doi.org/10.4028/www.scientific.net/KEM.853.36.
419. The Wealth of India; A dictionary of Indian raw materials and industrial product. Vol. 8. Council of Scientific and Industrial Research, New Delhi, India; 2003. pp. 34–6.
420. Thengyai S, Thiantongin P, Sontimuang C, Ovatlarnporn C, Puttarak P. α-Glucosidase and α-amylase inhibitory activities of medicinal plants in Thai antidiabetic recipes and bioactive compounds from *Vitex glabrata* R. Br Stem Bark J Herb Med. 2020;19: 100302. https://doi.org/10.1016/j.hermed.2019.100302.
421. Thyagarajan S, Jayaram S. Natural history of *Phyllanthus amarus* in the treatment of hepatitis B. Indian J Med Microbiol. 1992;10:64–80.
422. Thyagarajan SP, Jayaram S, Gopalakrishnan V, Hari R, Jeyakumar P, Sripathi MS. Herbal medicines for liver diseases in India. J Gastroenterol Hepatol. 2002;17:S370–6.
423. Thyagarajan SP, Jayaram S, Valliammai T, Madanagopalan N, Pal VG, Jayaraman K. *Phyllanthus amarus* and hepatitis B. Lancet. 1990;336:949–50.
424. Thyagarajan SP, Subramanian S, Thirunalasundari T, Venkateswaran PS, Blumberg BS. Effect of *Phyllanthus amarus* on chronic carriers of hepatitis B virus. Lancet. 1988;332:764–6.
425. Tirimana ASL. Medicinal plants of suriname. Uses and chemical constituents. Chemical Laboratory, Ministry of Agriculture, Animal Husbandry and Fisheries, Suriname; 1987. pp. 92.
426. Titjari. Famiri-encyclopedia Foe da Natoera Dresi-Fasi. Gezinskruidenboek van de Natuurgeneeswijzen. Natuurgeneeswijzen uit het zonnige Suriname. Family herb book of natural cures. Natural cures of sunny Suriname, Amsterdam; 1985. pp. 419.
427. Tiwari SK. Diversity and Socioeconomic Importance Of Different Medicinal Plants in Korba Chhattisgarh India. Frontiers in Science and Technology in India. 2021;50–5.
428. Tjong A, Young G. Het gebruik van medicinale planten door de Javaanse bevolkingsgroep in Suriname. The Use of Medicinal Plants by the Javanese Community in Suriname. Instituut voor de Opleiding van Leraren, Paramarib; 1989. pp. 196.
429. Trinh BT, Staerk D, Jäger AK. Screening for potential α-glucosidase and α-amylase inhibitory constituents from selected Vietnamese plants used to treat type 2 diabetes. J Ethnopharmacol. 2016;186:189–95. https://doi.org/10.1016/j.jep.2016.03.060.
430. Trinh BT, Staerk D, Jäger AK. α-Glucosidase inhibitors from *Phyllanthus amarus* and *Phyllanthus urinaria*. Planta Med. 2016a;82(S01):P849. https://doi.org/10.1055/s-0036-1596863.
431. Tripathi AK, Verma RK, Gupta AK, Gupta MM, Khanuja SPS. Quantitative determination of phyllanthin and hypophyllanthin in *Phyllanthus* species by high-performance thin layer chromatography. Phytochem Anal. 2006;17:394–7.
432. Tsabang N, Ngah N, Estella FT, Agbor GA. Herbal medicine and treatment of diabetes in Africa: case study in Cameroon. Diabetes Case Rep. 2016;1(2):112. https://doi.org/10.4172/2572-5629.1000112
433. Udayan PS, Tushar KV, George S, Balachandran I. Ethnomedicinal information from Kattunaykas tribes of Mudumalai Wildlife sanctuary, Nilgiris district, Tamil Nadu. Indian J Tradit Knowl. 2007;6:574–8.
434. Ueno H, Horie S, Nishi Y, Shagawa H, Kawasaki M, Suzuki S, et al. Chemical and pharmaceutical studies on medicinal plants in Paraguay, Geraniin, an angio-tensin-converting enzyme inhibitor from "'Paraparai Mi",'*Phyllanthus niruri*. J Nat Prod. 1988;51:1. https://doi.org/10.1021/np50056a033.
435. Ujah FO, Yusuf Y. Mohammad M, Vera E. Audu-War. Effect of Ethyl Acetate Fraction of *P. amarus* Leaf on Hematological and Biochemical Parameters in Albino Rat with Arsenic Induced Toxicity. Asian J. Pharm. Res. Dev. 2021a;9(3):11–15. https://doi.org/10.22270/ajprd.v9i3973
436. Ujah OF, Mohammad YY, Dewua CM. Quantification, antioxidant and free radical scavenging potentials of polyphenols from crude extracts of *Phyllanthus amarus* leaves. ChemSearch J. 2021;12(1):97–107.
437. Ukwubile CA, Odugu JA. Evaluation of antibacterial and in vitro antidiabetic activities of *Phyllanthus amarus* Linn. (phyllanthaceae) leaf ethanol extract. J Bacteriol Mycol. 2018;6(4):254–6. https://doi.org/10.15406/jbmoa.2018.06.00214.
438. Umarini D, Devaki T, Govindaraju P, Shanmugasundaram KR. Ethanol induced metabolic alterations and the effect of *Phyllanthus niruri* in their reversal. Anc Sci Life. 1985;4:174.
439. Umezawa T, Shimada M. Enantiomeric composition of (-)-pinoresinol, (+)- matairesinol and (+)-wikstromol isolated from *Wikstroemia sikokiana*. Mokuzai Gakkaishi. 1996;42:180–5.
440. Umezawa T. Chemistry of extractives. In Hon DN-S & Shiraishi N (eds) Wood and Cellulosic Chemistry 2nd Ed. revised and expanded Marcel Dekker, New York; 2000. pp. 213–41.
441. Unander DW, Webster GL, Blumberg BS. Records of usage or assays in *Phyllanthus* (Euphorbiaceae) I. Subgenera *Isocladus, Kirganelia, Cicca* and *Emblica*. J Ethnopharmacol. 1990;30:233–64.
442. Unander DW, Webster GL, Blumberg BS. Usage and bioassays in *Phyllanthus* (Euphorbiaceae): a compilation III. The subgenera *Eriococcus, Conami, Gomphidium, Botryan thus, Xylophylla* and *Phyllan thodendron*, and a complete list of the species cited in the three-part series. J. Ethnopharmacol. 1992;36:103–12.
443. Unander DW, Webster GL, Blumberg BS. Usage and bioassays in *Phyllanthus* (Euphorbiaceae). IV. Clustering of antiviral uses and other effects. J Ethnopharmacol. 1995;45:1–18.
444. Unander DW, Webster GL, Blumberg BS. Uses and bioassays in *Phyllanthus* (Euphorbiaceae): a compilation II. The subgenus *Phyllanthus*. J Ethnopharmacol. 1991;34:97–133.
445. Unigwe CR, Esan OO, Enibe F, Igwe KK, Igwe IR, Ajayi JO, Koleosho SA, Shobowale OM, Balogun FA. Evaluation of *Phyllanthus amarus* leaf meal for hepato-nephro-protective potentials in broiler chickens. J Vet Biomed Sci. 2021;3(1):126–35.
446. Upadhyay B, Parveen AK, Dhaker AK. Ethnomedicinal and ethnopharmaco statistical studies of Eastern Rajasthan. India J Ethnopharmacol. 2010;29:64–86.
447. Uthayakumar C, Rupert S. Evaluation of the inhibitory effect of a medicinal herb *Phyllanthus amarus* on the activity of α-amylase, pepsin and trypsin. Adv Enzyme Res (AER). 2020;8:1–18. https://doi.org/10.4236/aer.2020.81001.
448. Van Andel T, Westers P. Why Surinamese migrants in the Netherlands continue to use medicinal herbs from their home country. J Ethnopharmacol. 2010;127:694–701.
449. Ved DK, Goraya GS. Demand and Supply of Medicinal Plants in India. Bishen Singh Mahendra Pal Singh. Bangalore, India: FRLHT; 2008.
450. Venkateswaran PS, Millman I, Blumberg BS. Effects of an extract from *Phyllanthus niruri* on hepatitis B and woodchuck

hepatitis viruses: *In vitro* and *in vivo* studies. PNAS USA. 1987;84:1274–8.
451. Visweswaram D, Rao PR, Satyanarayana S. A noninvasive method for screening hepatoprotective drugs against carbon tetrachloride-induced hepatotoxicity. Indian J Pharmacol. 1994;26:301–3.
452. Wahyuni TS, Azmi D, Permanasari AA, Adianti M, Tumewu L, Widiandani T, Utsubo CA, Widyawaruyanti A, Hafid AF, Hotta H. Anti-viral activity of *Phyllanthus niruri* against hepatitis c virus. Malays Appl Biol. 2019;48(3):105–11.
453. Wahyuni TS, Permanasari AA, Widyawaruyanti A, Hotta H, Aoki-Utsubo C, Hafid AF. Antiviral activity of indonesian medicinal plants against hepatitis B virus. Pharmacogn J. 2020;12(5):1108–14. https://doi.org/10.5530/pj.2020.12.157.
454. Wang BE. Treatment of chronic liver diseases with traditional Chinese medicine. J Gastroenterol Hepatol Supplement 2000;E67–70.
455. Wang M, Cheng H, Li Y, Meng L, Zhao G, Mai K. Herbs of the genus *Phyllanthus* in the treatment of chronic hepatitis B: observations with three preparations from different geographic sites. J Lab Clin Med. 1995;126:350–2.
456. Wanigasekera WM, Joganathan A, Pethiyagoda R, Yatiwella LN, Attanayake HM. Comparison of antioxidant activity, Phenolic and Flavonoid contents of selected medicinal plants in Sri Lanka. Ceylon J Sci. 2019;48(2):155–62. https://doi.org/10.4038/cjs.v48i2.7619.
457. Webster GL. A monographic study of the West Indian species of *Phyllanthus*. J Arnold Arbor. 1957;38:51–80, 170–78, 295–373.
458. Wessels Boer JG, Hekking WHA, Schulz JP. Fa joe kan tak'mi no moi. Inleiding in de flora en vegetatie van Suriname; Deel I en II. Why do say that I am not beautiful. Introduction to the Flora and Vegetation of Suriname; Part I and II. Natuurgids serie B No. 4, Stinasu, Paramaribo;1976.
459. Wongnawa M, Thaina P, Bumrungwong N, Nitiruangjarat A, Muso A, Prasartthong V. Congress on Medicinal and Aromatic Plants – Vol. 6: Traditional Medicine and Nutraceuticals. ISHS Acta Horticulturae 2005;680, III WOCMAP.
460. Wongnawa M, Thaina P, Bumrungwong N, Rattanapirun P, Nitiruangjaras A, Muso A, Prasartthong V. The protective potential and possible mechanism of *Phyllanthus amarus* Schum. & Thonn. aqueous extract on paracetamol-induced hepatotoxicity in rats. Songklanakarin J Sci Technol. 2006;28:551–61.
461. Wu W, Li Y, Jiao Z, Zhang L, Wang X, Qin R. Phyllanthin and hypophyllanthin from *Phyllanthus amarus* ameliorates immune-inflammatory response in ovalbumin-induced asthma: role of IgE, Nrf2, iNOs, TNF-α, and IL's. Immunopharmacol Immunotoxicol. 2019;41(1):55–67. https://doi.org/10.1080/08923973.2018.1545788
462. Xia Y, Luo H, Liu JP, Gluud C. *Phyllanthus* species versus antiviral drugs for chronic hepatitis B virus infection. Cochrane Database of Systematic Reviews (CDSR). 2013;Issue 4. Art. No.: CD009004.
463. Xin-Hua W, Chang-Qing L, Xing-Bo G, Lin-Chun F. A comparative study of *Phyllanthus amarus* compound and interferon in the treatment of chronic viral hepatitis B. Southeast Asian J. Trop. Med. Public Health. 2001; 140–42.
464. Yadav NP, Pal A, Shanker K, Bawankule DU, Gupta AK, Darokar MP, Khanuja SP. Synergistic effect of silymarin and standardized extract of *Phyllanthus amarus* against CCl_4-induced hepatotoxicity in *Rattus norvegicus*. Phytomedicine. 2008;15:1053–61.
465. Yakubu OE, Abu MS, Akighir J, Onuche JI, Arabi A. Comparative determination of total antioxidant effects of ethanol extract of *Phyllanthus amarus* leaves. Asian J Nat Prod Biochem. 2022;8;20(1).
466. Yan J, Liu XQ, Du M, Chen LY. Therapeutic effect observation interferon alpha and *Phyllanthus* capsule for chronic hepatitis B. J Clin Hepatol. 2008;11:37–8.
467. Yao AN, Rasul Z, Najmanová I, Kamagaté M, Said A, Chabert P, Auger C, Die-Kakou H, Schini-Kerth V. Beneficial effect of *Phyllanthus amarus* (Euphorbiaceae) on DOCA-salt-induced left ventricle cardiac hypertrophy and endothelial dysfunction in rats. Biochem Pharmacol. 2017;139:112–3.
468. Yao N'Guessan Alain, Niazi ZR, Najmanová I, Kamagaté M, Said A, Chabert P, Auger C, Die-Kakou H, Schini-Kerth V. Preventive beneficial effect of an aqueous extract of *Phyllanthus amarus* Schum. and Thonn. (Euphorbiaceae) on DOCA-salt–induced hypertension, cardiac hypertrophy and dysfunction, and endothelial dysfunction in rats. J Cardiovasc Pharmacol. 2020;75(6):573–83.
469. Yasouri SR, Doudi M, Ghane M, Naghavi NS, Rezaei A. The Effect of Environmental Stresses on lipL32 Gene Expression in Pathogenic *Leptospira* spp. through Real-Time PCR. Pol J Microbiol. 2020;69(3):301–10. https://doi.org/10.33073/pjm-2020-033
470. Yeh SF, Hong CY, Huang YL, Liu TY, Choo KB, Chou CK. Effect of an extract from *Phyllanthus amarus* on hepatitis B surface antigen gene expression in human hepatoma cells. Antivir Res. 1993;20:185–92.
471. Yuandani IJ, Ilangkovan M, Husain K, Chan KM. Inhibitory effects of compounds from *Phyllanthus amarus* on nitric oxide production, lymphocyte proliferation, and cytokine release from phagocytes. Drug Des Devel Ther. 2016;10:1935.
472. Yuandani, Jantan I, and Husain K. Phyltetralin, 1,7,8-trihydroxy 2-naphtaldehyde, ethyl 8-hydroxy-8-methyl-tridecanoate and 1-triacontanol from *Phyllanthus amarus* Schumach. & Thonn. inhibit phagocytic activity of human leucocytes. J Pharm Pharmacol, 2019; https://doi.org/10.1111/jphp.13139.
473. Zain SN, Omar WA. Antioxidant activity, total phenolic content and total flavonoid content of water and methanol extracts of *Phyllanthus* species from Malaysia. Pharmacogn J. 2018;10(4):677–81. https://doi.org/10.5530/pj.2018.4.111.
474. Zhang HF, Zhu SX, Dong Y, Xu ZQ, Chen DW, Jia WZ, et al. The effect and safety assessment of *Phyllanthus* capsule and adefovir dipivoxil tablet for chronic hepatitis B. Shandong Med J. 2009;49:60.
475. Zhang MJ, Dong P, Yong J, Teng J, Li ZX. Therapeutic effect observation of *Phyllanthus* for patients with chronic hepatitis B. J Ningxia Med Coll. 2006;28:451.
476. Zheng ZZ, Chen LH, Liu SS, Deng Y, Zheng GH, Gu Y, Ming YL. Bioguided Fraction and Isolation of the Antitumor Components from *Phyllanthus niruri* L. Biomed Res Int. 2016;9729275:1–7. https://doi.org/10.1155/2016/9729275.
477. Zubair MF, Atolani O, Ibrahim SO, Adebisi OO, Hamid AA, and Sowunmi RA. Chemical constituents and antimicrobial properties of *Phyllanthus amarus* (Schum & Thonn). Bayero J Pure Appl Sci 2017;10:238–246. https://doi.org/10.4314/bajopas.v10i1.35.