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Review Article

In silico Insights Into the Medicinal Potential of *Phyllanthus amarus*: Phytoconstituents and Therapeutic Applications

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ABSTRACT

Phyllanthus amarus is a globally distributed herb. Over the 3000 years, it has been used as traditional medicine. This plant is articulated in different languages differently like in Hindi- Bhuyiavla, Jangli amla, Marathi- Bhuivali, Bihari- Muikoa, Sanskrit- Bhumyaamlaki, etc. It is an herb that can grow between 30 and 75 cm tall annually. Worldwide, *Phyllanthus amarus* is a plant widely distributed in tropical and subtropical areas. In Indian Ayurveda, the *Phyllanthus amarus* is used as a traditional medicine. It treats various diseases such as cough, diuretics, menstrual problems, stomach, kidney, etc. Scientific research said that *Phyllanthus amarus* exhibits potency against multiple diseases including diabetes, arthritis, inflammation, convulsion, neuroactive, hepatoprotective, nephroprotective, vasoconstriction, etc. *Phyllanthus amarus* has several secondary metabolites such as tannin, flavonoid, saponin, alkaloids, terpenoids, lignans, sterols, and volatile oils. Aqueous and non-aqueous extraction of *Phyllanthus amarus* and isolation of chemical compounds such as securinine, phyllanthine, rutin, quercitrin, amariin, geraniin, hypophyllanthins, isonirtetralin, amarosterol-A, phytol, phenazine, ursolic-acid, isolintetralin, etc. These compounds are responsible for pharmacological activity such as anti-cancer, antibacterial, analgesic, antifungal, antioxidant, antiviral, contraceptive, anti-inflammatory, etc. On the other hand, molecular docking is a potent computational process for studying molecular interactions from the drug discovery perspective. It is applied to forecast the orientation in which small drug molecules will bind to their protein targets, predicting their affinity and activity.

Keywords: Medicinal potential, Molecular docking, *Phyllanthus amarus*, Phytoconstituent,

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INTRODUCTION

Phyllanthus amarus is one of the most significant categories of plants traded in India as a rudimentary homemade cure. It has roughly a thousand species, distributed throughout tropical and subtropical regions. For almost three millennia, *Phyllanthus amarus* has been used in traditional medicine. It is crucial to advancing environmentally friendly medications. 53 species, 23 of which are endemic, of the roughly 1000 species in the genus Phyllanthus have been found in India.[1] Because of its cultural and medicinal significance, this species has a variety of regionally specific colloquial names (Table 1). These names demonstrate how well-known it is worldwide as a useful medical herb. It is small-leafed, grows 30 to 40 cm high, and produces yellow flowers with five white petals and a sharp apical anther on a green capsule-shaped stem. The fruit comprises smooth, fruiting pedicels and green capsules. The seeds are rugose lengthwise simultaneously.[2] It has been used for many years to cure various illnesses, such as leprosy, malignancy, ulcers, hypertension, bronchitis, and malaria. *Phyllanthus amarus* is widely used as a therapeutic plant that has become well-known worldwide.[3] They are dispersed across the Indian subcontinent, with the south having the highest concentrations. Thirteen herbs, three trees, and 37 shrubs make up the 53 species of Phyllanthus. Many bioactive substances, including lignans like phyllanthin, have been isolated from *P. amarus* through phytochemical research.[4,5] Various extraction techniques have been used to separate its bioactive components for therapeutic application (Table 2). Phytochemical research has isolated many bioactive substances, including lignans, flavonoids, and alkaloids, and their chemical structures from *P. amarus* (Table 3).

Taxonomical classification

Bhumi Amla, or Bhuiamlaki, is part of the kingdom Plantae. It belongs to the family Euphorbiaceae, specifically the genus Phyllanthus, of which *Phyllanthus niruri* is the species. The visual representation of a *Phyllanthus amarus* plant has been incorporated to illustrate morphological characteristics (Figure 1).[1-4]

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Pharmacological activities

Anti-diabetic

The leaves of *Phyllanthus amarus* are used in diabetes. Extraction of alkaloids from *Phyllanthus amarus* leaves can potentially treat diabetes.[4] The water-based extract of the aerial parts of *Phyllanthus amarus* was prepared through infusion. This extract contains various polyphenols, including phenolic acids, tannins, flavonoids, and lignans, which have demonstrated anti-diabetic properties. These compounds help inhibit glucose uptake by affecting the glucose-6-phosphatase enzyme. The polyphenolic composition was analyzed using reverse-phase UPLC-DAD-MS.[6] Ethanol extraction of the *Phyllanthus amarus* by Soxhlet and formation of nanoparticles (leaf extract added into silver nitrate and then centrifuged) indicates the nanoparticles of Phyllanthus treat diabetes.[7]

Anti-arthritic

Water extract of *Phyllanthus amarus* (phyllanthin and hypophyllanthin) can potentially treat arthritis. The extract was assessed regarding mechanical withdrawal threshold, pain threshold, paw volume, and joint diameter.[8] The entire plant of *Phyllanthus amarus* was extracted via EtOH. The lignans and phenolics are major compounds. They assessed biochemical change and hepatological change, suggesting that the Oral application of the extract *Phyllanthus amarus* has the potential to treat arthritis. Standardization of the extract by HPLC, LC-MS/MS.[9] Extraction of *Phyllanthus amarus* plant and formation of nanoparticle gel phonophoresis. Demonstrate knee pain (osteoarthritis). Lessens the level of the inflammatory biomarker and increases anti-oxidant capacity.[10]

Anti-inflammatory

Ethanolic extraction of the entire plant of *Phyllanthus amarus* is used in anti-inflammatory. It restrains NF-κB, MAPK, and P13K-AkT signaling pathways. It inhibits the emission of cytokines or other inflammatory-inducing mediators. Extract downregulates the TLR4 and MyD88 signaling pathways. Extract use suppresses the inflammation. Analysis HPLC, LC/MS.[11]

Anti-convulsion

Phyllanthus amarus leaf and stem extract, ethanolic, and aqueous (70 mg/kg, P.O.) by Soxhlet can potentially treat convulsion. Acute toxicity was performed. It evaluated anti-convulsant activity on maximal electroshock seizure (phenytoin 25 mg/kg I.P.) and pentylene tetrazole-induced convulsion (Sodium valproate 75 mg/kg I.P.).[12] CH_3OH extract of the branch region of *Phyllanthus amarus* after Phyllathin separated and phyllanthin was characterized by MS, HPTLC, ESI-MS/MS, and LC/MS. The brain's Na^+ K^+ATPase, GABA, Glutamate, Dopamine, and oxide-nitrosative levels are restored upon treatment with *Phyllanthus amarus*. Phyllanthin has an anti-convulsive impact.[13]

Diuretic activity

The ethanolic fraction of *Phyllanthus amarus* indicates diuretic properties and *Phyllanthus amarus* hydro extract stimulates the elimination of water and Na+ through the urine and supports diuretic prostaglandins. Its use for hypertension, the dose for urinary excretion is 5 to 80 mg/kg, and the reference drug is Furosemide (5 mg/kg).[14] The healing potential that its ethanol-based leaf extracts have on renal and hepatic assaults caused by rifampicin and CCl_4, respectively. Extract restores deranged biochemical parameters. The extract attenuates the toxicity of CCl_4 and rifampicin in the kidney and liver. Following silymarin treatment, all measured biochemical indices returned to comparable levels. Histopathology examination confirms the curative effect of *Phyllanthus amarus* on damaged liver and kidney cells. An alternate that may be used to treat hepatic and renal diseases is *Phyllanthus amarus*.[15]

Neuroactive effect

Water-based leaf extract of *Phyllanthus amarus* and *Momordica charantia* used in various pharmacological actions. Rat pretreated with the extract of both plants (200 and 400 mg/kg bwt.) for fourteen days. After that, on the final day, Doxorubicin was administered (15 mg/kg bwt. I.P.). The extract restored Nootripoic-related enzyme activities, and cognitive behavior, and improved the anti-oxidant biomarkers altered by Doxorubicin. The Responses were scrutinized by using two tests, the Y-maze test and the Morris test, characterization of the extract by using HPLC.[16] Low amounts of arsenic can cause neurological harm, Ethanolic extract from leaves of *Phyllanthus amarus* assesses the neurotoxicity. The extract reduced acetylcholinesterase activity in the central nervous system, boosted dopamine and serotonin levels, and elevated the brain's superoxide dismutase or catalase activity. The decrease in lipid peroxidase. So, it concludes that *Phyllanthus amarus* demonstrates a preventive function against neurotoxicity caused by arsenic.[17] The *Phyllanthus amarus* whole plant's 80% ethanolic extract is used in neuroinflammation. Corilagin, Phyllanthin, Isonirtetralin, ellagic acid, niranthin, and geraniin phyltetralin, were identified. Through oral route administration of *Phyllanthus amarus* extract (100, 200, 400 mg/kg) and Ibuprofen (IBF-40 mg/kg) for 14 to 28 days. So, it concludes that it is used in neuroinflammation.[18]

Hepatoprotective activity

By using gradient elution using a solvent combination of hexane and ethyl acetate in silica gel column chromatography, the lignin (phyllanthin) found in this species of plant was extracted from the *Phyllanthus amarus* aerial parts ethanol: water. *Phyllanthus amarus* extract and phyllanthin showed a greater antioxidative and hepatoprotective effect when examining the effect of Hepatoma HepG2 cell line toxicity enhanced by CCL_4, and these effects were obtained in high yields (1.23%). The ability of P to scavenge free radicals. The DPPH assay was used to investigate phyllanthin and

amarus extract. Cell viability was significantly reduced after being treated with CCl_4. Furthermore, the toxin treatment-induced (LPO) led to a considerable drop in Glutathione (GSH) levels as well as the spillage of enzymes like Lactate Dehydrogenase (LDH) or Alanine Transaminase (ALT).In a concentration-dependent manner, phyllanthin adequately mitigated the alteration caused by CCl_4, albeit to a lesser degree than *Phyllanthus amarus* extract. *Phyllanthus amarus* extract/phyllanthin combined with the toxin significantly enhanced cellular sustainability, inhibited enzyme release, decreased lipid peroxidation, and enhanced glutathione.[19] *Phyllanthus amarus* is used in hepatotoxicity and nephrotoxicity, and ethanolic extract from leaves of *Phyllanthus amarus* treats hepatotoxicity.[15] *Phyllanthus amarus* dry leaves and stems are extracted first in methanol and then H_2O. The extracts tested at a 50 µg/mL concentration for hepatoprotective efficacy against toxicity induced in HepG2 cells by t-butyl hydroperoxide-BH cells, phyllanthin, and hypophyllanthin (lignans) are present in *Phyllanthus amarus* show hepatoprotective activity.[20]

Anti-cancer activity

The extraction of the leaf using dimethylformamide of *Phyllanthus amarus*. Some compounds present in the leaf show anti-cancer activity. The (HCT15) human colorectal adenocarcinoma cancerous cell line and the human cell line for breast cancer (T47D) have been utilized to test the leaf extract. The active compound (ligan) in the extract blocks cancer cell propagation effectively. In which the MTT assay measures cell viability and the Trypan blue dye method is used for cell viability assessment.[21] In cancer therapy, *Phyllanthus amarus* whole plant methanolic extract is applied. Worldwide, women get cervical cancer at the fourth-highest rate. Lignans present in *Phyllanthus amarus*, Lignan-Rich Friction (LRF) of *Phyllanthus amarus* used in cervical cancer. LRF-induced ROS, DNA, and Apoptosis in cancer cells.[22] Non-aqueous extract of the entire plant of *Phyllanthus amarus* obtained by Soxhlet extractor. Which involved an *in vivo* investigation of albino mouse bone marrow cells and an *in vitro* study of human lymphocytes. The extract of *Phyllanthus amarus* reduced chromosomal aberrations and sister chromatid exchanges. In which the extract reduces the mutagenicity and genotoxicity. The anticarcinogenic activity was shown against sarcoma and carcinoma in mice. The chi-square test for cell growth kinetics and t-test (student two-tailed) is used to determine statistical significance.[23] These compounds are used in breast cancer. The study's *in vitro* outcomes are evaluated using the MTT assay against the cell lines MCF-7 and MDA-MB-231, and its *in vivo* results were assessed using Sprague-Dawley rats that had been given, Breast cancer brought on by N-methyl-N-nitrosourea.[24]

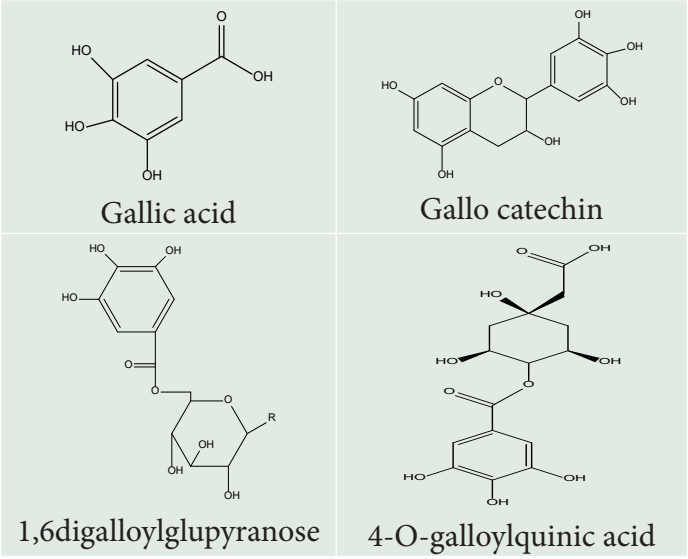
Effect on the reproductive system

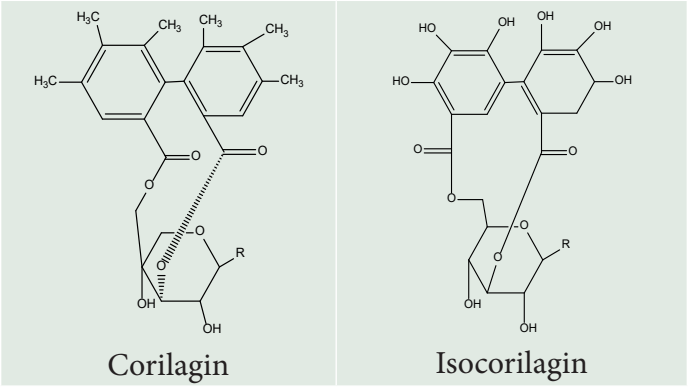
The entire *Phyllanthus amarus* plant is extracted with methanol, which significantly alters sperm viability, motility, count, and abnormalities of the sperm head. It also results in decreased mean weight of the testes and epididymis. In a mammalian model using male albino rats, it was observed that *Phyllanthus amarus* exhibits dose-dependent effects on male fertility, reducing reproductive capability as the dosage increases.[25] Aqueous extraction of the leaf of *Phyllanthus amarus* testing for pregnancy and implantation. In rats, the extract accelerates the process of implantation but leads to abortions. The extract of *Phyllanthus amarus* may potentially alleviate the challenges associated with childbirth.[26]

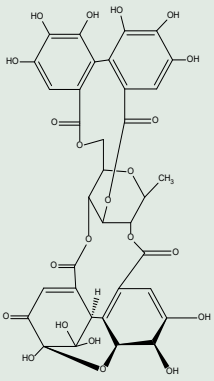
Structure of phytoconstituents that are present in *Phyllanthus amarus*

Tannins

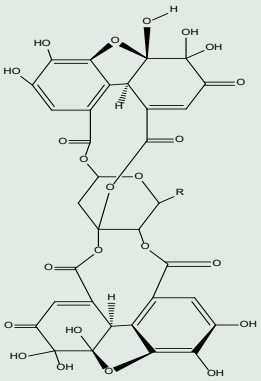
Polyphenolic compounds; they are complex and water-soluble. It is divided into two categories, non-hydrolyzable and hydrolyzable tannins. It is present in various plant sources, such as nuts, fruits, and vegetables. They are recognized for their anti-fibrotic, anti-microbial qualities and anti-inflammatory.[3,27-29,32,35,37,48]



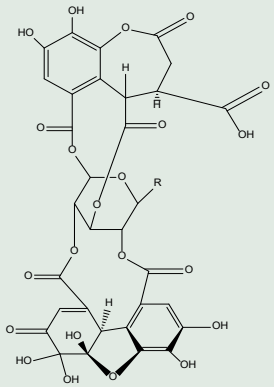




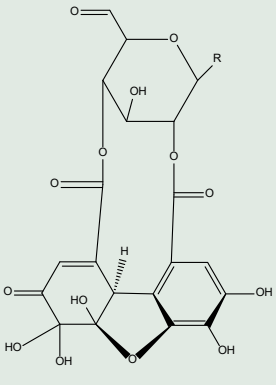
Geraniin



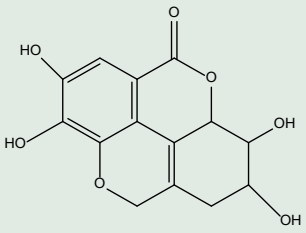
Amariin



Amarulone



Furosin

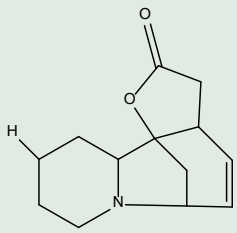


Ellagic acid

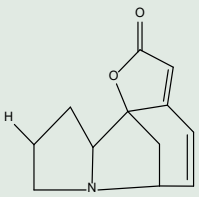
Some chemical Structure of tannins that is present in Phyllanthus amarus

Alkaloids

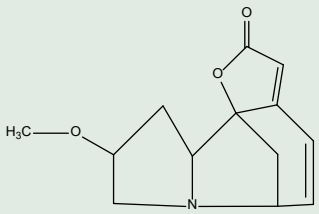
Plants containing secondary metabolites are a significant source of alkaloids, bioactive compounds characterized by nitrogen. Known for their remarkable biological properties, alkaloids are often considered essential active ingredients in traditional Chinese herbal medicine. With advancements in natural product isolation techniques and innovative analytical methods, alkaloid chemistry has seen substantial progress in recent years.[45,46]



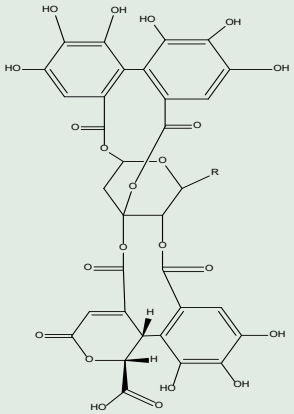
securinine



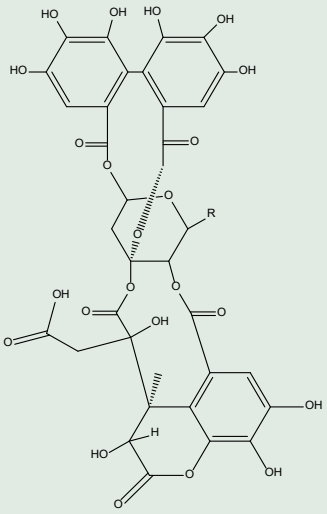
Nor-securinine



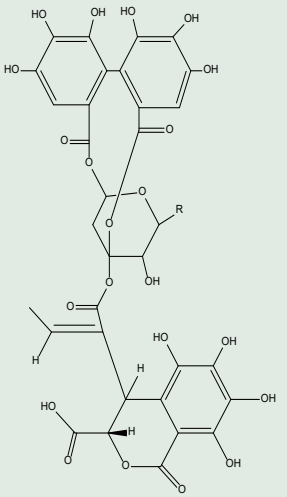
4-methoxy-nor-securinine



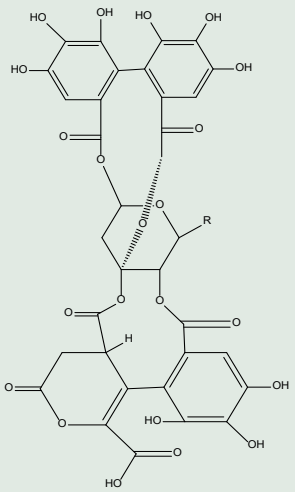
Geraniinic acid B



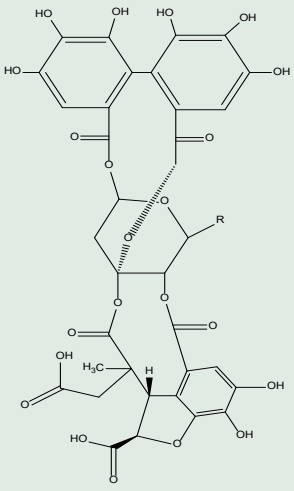
Amariinic acid



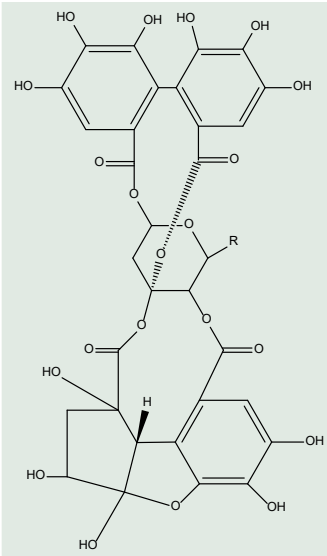
Repandusinic acid A

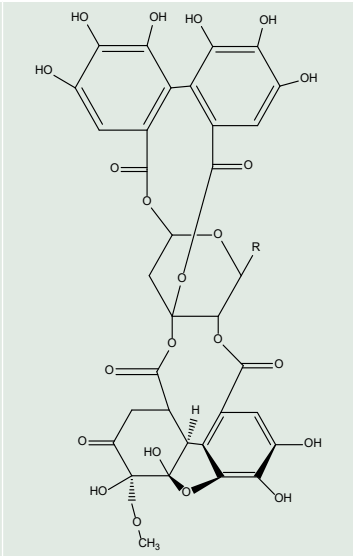


Phyllanthusiin A



Phyllanthusiin B


Phyllanthusiin C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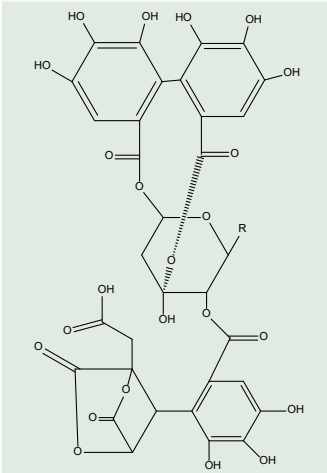
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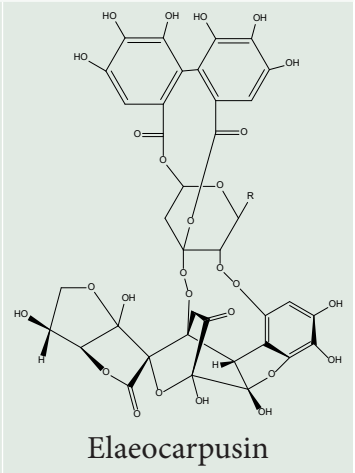
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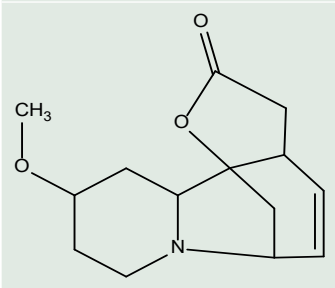
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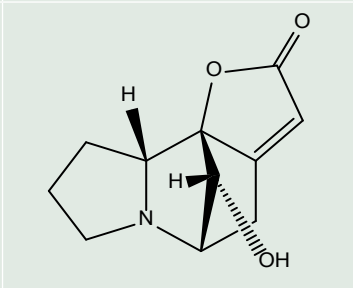
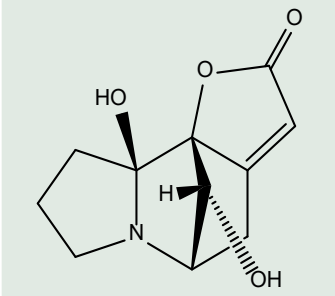

Isobubbialine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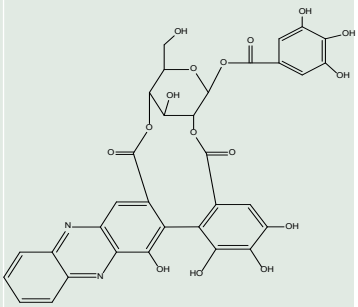
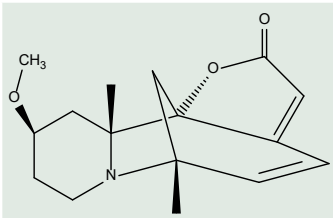
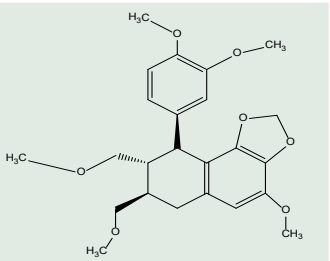

Phenazine

Some chemical Structure of alkaloids that is present in *Phyllanthus amarus*

Lignans

Over the years, food chemists and nutrition researchers have become interested in phenolic compounds in phytochemicals known as lignans. Lignans are extensively distributed secondary metabolites of vascular plants in the kingdom of plants. They are thought to have various physiological effects. These belong to the class of secondary plant metabolites called phenolic compounds. Combining at the β and β' carbons, two phenylpropanoid C6-C3 units can form additional ether, lactone, or carbon bonds.[49]


Phyllanthin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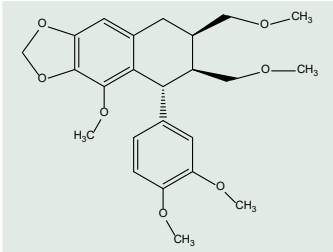
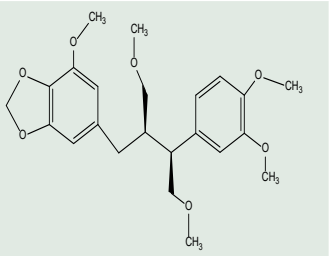

Nirtetralin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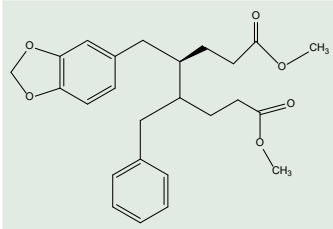
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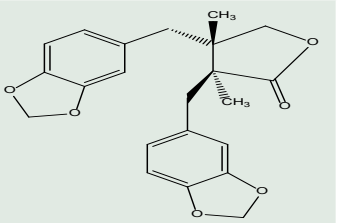
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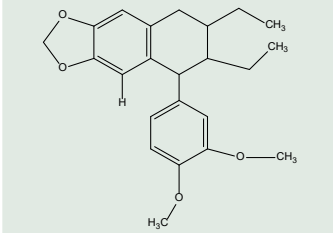
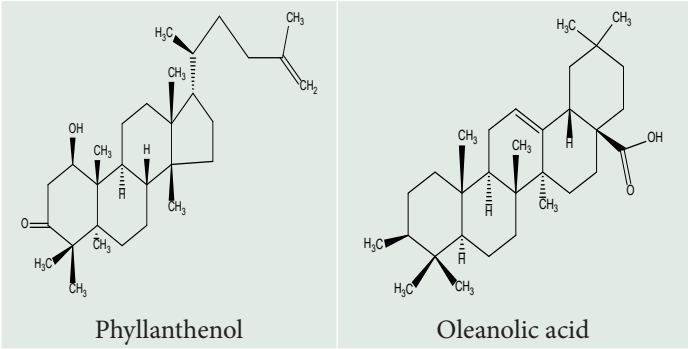

Isonirtertralin

Some Chemical Structure of Lignans that are present in *Phyllanthus amarus*

Triterpene

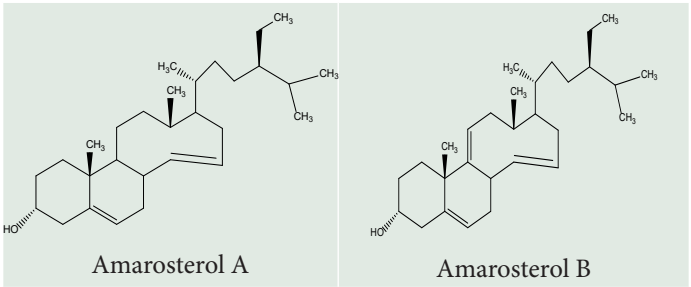
Terpenoids are a diverse class of natural products formed from the precursor 5C derived compounds Dimethylallyl diphosphate (DMAPP) and its isomer Isopentenyl diphosphate (IPP), These precursors are condensed various terpenes like hemiterpene (Consist of isoprene unit), Sesquiterpenes (contain three isoprene units), Diterpenes (comprise four isoprene unit) Sesterterpenes (Consist of five isoprene units), Triterpenes (comprise of six isoprene unit), Tetraterpenes (consist of eight isoprene unit), Polyterpenes (Consists long chains of isoprene units).[52]



Some chemical Structures of triterpene are present in *Phyllanthus amarus*

Steroids

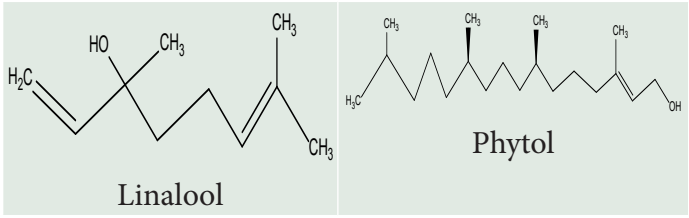
Fundamental biomolecules that contribute to various physiological functions and are integral to drug development. Their stable structural framework and vital pharmacological properties make them indispensable in the pursuit of new therapeutic compounds.[39] Steroids are naturally occurring metabolites of isoprene molecules with a high biological activity level. They are classified as isoprenoid lipids.[43]



Some chemical Structures of steroids are present in *Phyllanthus amarus*

Volatile oil

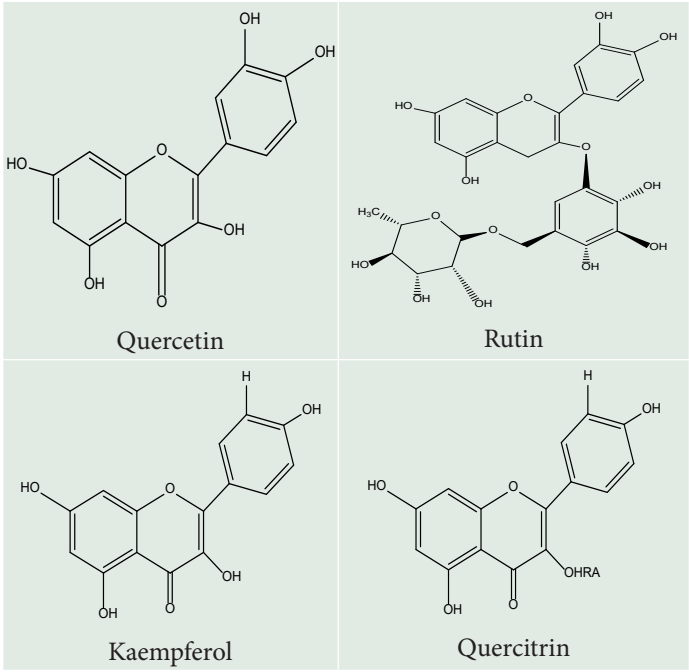
Essential oil refers to a product made from raw vegetable materials using steam or water distillation, or from the extraction process of citrus fruit's epicarp. That is, solely by physical means (ISO 9235, 1997). Essential Oils (EOs) are concentrated hydrophobic liquids recognized for their aromatic characteristics and bioactive components. They are derived from different parts of plants.[51,61]



Some chemical Structures of volatile oil are present in *Phyllanthus amarus*

Flavonoid

Flavonoids constitute some of the most significant non-nitrogenous plant pigments. It has red or blue/yellow coloration in fruits, buds, shoots, petals, leaves, and petals, giving flowers their color. The purpose of this coloring is to draw pollinators to the flowers. The symbiotic nitrogen fixation mechanism involves flavonoids UV filtration, and flower coloration in certain plant species. subclass of flavonoids, Flavonol, Flavones, Flavonones, Flavanol, Anthocyanidins, and Isoflavones.[47] Plant polyphenolic chemical compounds, known as flavonoids are a broad group that demonstrates high bioactivity and have been related to anti-microbial, anti-inflammatory, even anti-cancer, etc.[50]



Some chemical Structures of flavonoids are present in *Phyllanthus amarus*

Docking

Phyllanthus amarus is well-known for its therapeutic qualities, containing potential benefits against diabetes. Molecular docking or molecular dynamics simulations could have been utilized to simulate the atomic-level interaction between the compounds and the glucosidase enzyme. Compound 1 [(1 S,19 R,21 S,22 R,23 R)-6,7,8,11,12,13,22,23-octa hydroxy-3,16-dioxo-2,17,20-trioxatetracyclo [17.3.1.0 4,9.0 10,15] tricosa-4,6,8,10,12,14-hexaen21-yl 3,4,5-trihydroxybenzoate demonstrate a larger ability to suppress α-glucosidase than metformin and other chemical compound isolated leaves of *Phyllanthus amarus*, that have been studied.[55] Amarulone emerges as a promising malaria drug candidate due to its stable complex with Plasmodium falciparum lactate dehydrogenase. *Phyllanthus amarus* has been employed in determining potential antiplasmodial medication candidates using molecular dynamics and computer simulations. Strong inhibitory effects on important Plasmodium falciparum drug targets are demonstrated by *Phyllanthus amarus* compounds, especially amarulone, indicating the possibility of these compounds as novel anti-malarial drugs. According to molecular dynamics simulations, the Amarulone-1u5c complex showed the greatest stability, suggesting it may be a good candidate for an anti-malarial medication.[56] *Phyllanthus amarus* exhibits a strong binding affinity to the major protease of SARS-CoV-2 by *in silico* techniques, indicating their potential for use as antiviral medications.The study examined 190 phytoconstituents from *Phyllanthus amarus* using molecular docking against the SARS-CoV-2 primary protease, or 16 compounds with high binding affinities were found. The protein's stability-ligand complexes were examined using molecular dynamics simulations, showing significant interactions and binding site changes. Using MM-PBSA (Molecular Mechanics Poisson-Boltzmann Surface Area) computations, the binding free energies of the top compounds were ascertained, providing insight into the thermodynamics of protein-ligand interactions. The two compounds with the highest binding affinities, myricitrin, and quercetin-3-O-glucuronide, are present *in vitro* and *in vivo* research to assess their effectiveness against COVID-19.[57] Methanolic extract of *Phyllanthus amarus* used for Alzheimer's disease. The AutoDock Vina tool in PyRx 0.8 was employed for molecular docking studies to anticipate the binding interactions between the Acetylcholinesterase (AChE) enzyme and the phytoconstituents of *Phyllanthus amarus*. The docking technique was verified by aligning co-crystallized and re-docking ligands, determining the RMSD (Root Mean Square Deviation) assessment, and it within an acceptable range. The compounds that assessed the highest affinity with the AChE enzyme were amarosterol A, hinokinin, stigmasterol, ellagic acid, and β-sitosterol. This suggests that these molecules may have the ability to block the enzyme.[58] The phytochemicals isolated from *Phyllanthus amarus* demonstrate better docking scores against Neuraminidase than Oseltamivir, indicating that may be useful as antiviral medication candidates. Patchdock software was utilized for protein ligand-based molecular docking, while PyMol was employed for macromolecule visualization.[59] *Phyllanthus amarus* yielded methyl labda-5(6),11(12),14(15)-triene-17-oate, a diterpenoid with potential antifungal and antihypertensive

Table 1: The vernacular name of *Phyllanthus amarus* in different places.[1,27,30,31,38]

Sl. No.	Language	Another name for *Phyllanthus amarus*
1	Kanada	Kirunelli, Nela-nelli
2	Marathi	Bhuivali
3	Hindi	Jangli, Amla, Bhuyiavla
4	Bengali	Sadahazurmani, Bhuiamla
5	Netherland	Fini bita
6	Bihari	Muikoa, Kantara, Pirikantaru
7	America	Yerba da la nina, Hurricane weed, Chanca piedra
8	English	Gulf leaf flower, Black catnip, Stonebreaker, Shatterstone, Child pick-a-back, Carry Me seed, Hurricane weed, Gale of wind.
9	Malayalam	Kilanelli, Kizhkkayinelli
10	Sanskrit	Thamalaki, Bhumyaamlaki, Bhoodhatree
11	North, Central, and South American names	Egg women, Quinine weed, Gale-of-(the)-wind, Quinine creole, Yerba da la Nina, Chanca piedra, Carry-messed, Flor quebra-pedra, Black catnip, Djari-bita, Fini-bita, Escondida, Hurricane weed, Seed-under-leaf
12	Spanish	Yerba magica (Cuba)
13	French	Pordre de plomb (Ivory cost)
14	African names	Hinlinew (West Africa), Bounou (Ivory coast), Bomagua kene (Ivory coast), Ahlivi (Mina-togo), Mokichinento (Korokoro-East Africa), Tsekulemegbe (Ouatchi-togo), Bounou Honlin (Ivory coast)
15	Tamil	Keelanelli (Keezhanelli)
16	Gujarati	Bhonya ammali
17	Rajasthani	Gugario
18	German	Weisse blattblume
19	Telugu	Nela uirika, Nelavusari
20	Nigeria	Eyin Olobe, Pick-a-back
21	Brazil	Quebra-pedra
22	Oriya	Bhuiaola, Badianala

Table 2: A plant part of *Phyllanthus amarus* and its extraction with the potential.

Disease	Chemical	Plant part	References
Hepatoprotective	Aqueous/Ethanol	Leaves/Aerial	[19]
Anti-carcinogenic	Non-aqueous	Whole plant	[23,24,42]
Anti-bacterial	Methanol/Hexane/Water	Aerial	[3,33]
Anti-viral	Aqueous	Root	[34]
Anti-inflammatory	Methanol/Aqueous	Whole plant	[1,11]
Anti-oxidant	Methanol/Aqueous	Aerial/Whole plant	[1,27]
Anti-diabetic	Methanol/Ethanol	Leaves	[4,7]
Anti-venom	Methanol	Whole plant	[32]
Reproductive	Aqueous/Methanol	Whole plant/Leaf	[25,26]
Lithiasis	Aqueous	Whole plant	[44]
Nephroprotective	Aqueous	Leaves	[45]
Anti-plasmodial	Ethanol/Aqueous	Whole plant	[3]
Cardiovascular	Aqueous	Leaves	[3]
Jaundice	Aqueous	Leaf/Root/Whole plant	[1,27]
Anti-amnesic	Aqueous	Leaves	[3]
Gastroprotective	Methanol	Leaves/Steam	[3]
Anti-ulcer	Ethanol/AQueous	Leaves	[3]
Anti-fungal	Chloroform	Aerial	[1,27]
Analgesic	Aqueous	Leaves	[3]
Anti-allodynic	Hexane	Aerial	[1,27]
Aphrodisiac	Aqueous/Ethanol	Leaves	[1,27]
Anti-convulsion	Aqueous/Ethanol	Leaves/Aerial	[12,13]
Anti-cancer	Non-Aqueous/Aqueous	Leaves/Whole plant	[23,24,41]

Figure 1: *Phyllanthus amarus*-A herb known for its traditional medicinal application.

Table 3: Phytoconstituents are present in *Phyllanthus amarus*.[1,3,5,27,28,32,36,37]

Secondary metabolite	Definition	Phytoconstituents
Flavonoids	Flavonoids are polyphenolic compounds with low molecular weight, flavonoids are found in fruits, stems, roots, etc.[47]	Astragalin, Kaempferol, Quercertin, Rutin, Quercitrin, Quercetin-3-O-glucoside.
Tannins-simple, complex	Tannins are polyphenolic compounds, they are complex and water-soluble. It is divided into two categories, non-hydrolysable and hydrolysable tannins.[29,48]	Melatonin, Amarulone, Elaeocarpusin A, B, C, Amariin,1,6 digalloyglucopyranose phyllanthusin D, Amarulonr, Geraniin, Corilagin, furosin, Corilagin, Geraniin, 4-ogalloylquinic acid, Amariinic acid, Repandusinic acid A, Phyllanthusiin, Geraniinic acid B, Isocorilagin.
Sterols	Sterols are a category of natural organic compounds within the isoprenoid class and possess various vital roles across all eukaryotic organisms.[39]	Amarosterol B, Amarosterol A.
Lignans	Plants consist of an extensive variety of low molecular weight polyphenols called lignans. It is derived from a combination of two phenylpropanoids.[49]	Hypophyllanthin, Niranthin, Phyllanthin, Isonirtetralin, Nirtetralin,5-dimethoxy-niranthin, Lintetralin, Phyltetralin, Hinokinin, Demethylenedioxy-niranthin, Isolintetralin.
Volatile oil	Volatile or essential oils are driven to plants with high vaporization rates.[51]	Phytol, Linalool.
Triterpenes	Based on their biosynthesis pathways and structural characteristics terpenoids are classified into natural product categories.[52]	Phyllanthenol, Phenazine derivative 6Z,10Z,14E,2Z,18E,22E, Farnesyl, Farnesol, phyllanthenone, Lupeol, Phyllantheol, Ursolic acid, Phenazine, Oleanolic acid.
Alkaloids	Natural organic compounds are called alkaloids, the nitrogen atom present and contributes to their alkaline nature, influencing their medicinal effect.[46,53]	Securinine, 4-methoxy-nor-securinine, Tetrahydrosecurinine, 4-methoxy dihydrosecurinine, Phyllanthine, Epibubbialin e,4-methoxytetrahydrosecurinine, Isobubbialine, 4-hydrosecurinine, Allo-securine, Nor-securinine.

properties. Isolation and characterization of diterpenoid by IR, MASS,1H NMR,13C NMR. Using Pass cheminformatics software and Molinspiration, *in silico* investigations predict bioactivity, generate bioactivity scores, and analyze molecular and pharmacokinetic features, methyl labda-5(6),11(12), 14(15)-triene-17-oate showing a molecular composition of C21H34O2 and potential antifungal activity.[60] White Spot Syndrome Virus (WSSV) may resist phytocompounds from *Phyllanthus amarus*, providing a natural substitute for pharmaceuticals. And the treatments for white spot illness in shrimp cultivation may include 2H-1-benzopyran-6-ol,3,4-dihydro-2,5,7,8-tetramethyl-2(4,8,12trimethyltridecyl)-acetate and 1,4-benzenediamine, N, N 0-diphenyl. According to computational studies, These chemical substances could be turned into secure antiviral drugs to combat the White spot syndrome virus, reducing the number of aquaculture deaths and associated financial losses. The target protein is VP26 VP28 VP110 (Envelop protein) VP664 (nucleocapsid protein) of white spot syndrome virus. The Autodock 4.2 program was used in this study's molecular docking to simulate ligand-protein interaction. Select their preferred binding locations, a grid box has to be set up over the entire protein. To calculate partial charges, Kollman and Gasteiger-Marsili charges have been calculated for the ligands and the protein, respectively. The ligands attached to the proteins were generated as conformers using the Lamarckian genetic process, where the conformer with the lowest binding energy was chosen as stable molecular dynamics and simulations confirmed that antiviral therapies for White spot syndrome virus infection are stable and effective.[61] SARS-CoV-2 may be suppressed by *Phyllanthus amarus* and *Andrographis paniculata* phytochemicals from these two plants, exploring their interaction with SARS-CoV-2 proteins through docking analysis substances from *Phyllanthus amarus*, including flavonoids (kaempferol, astragalin, quercetin-3-O-glucoside, quercetin) and tannins (corilagin, geraniin, furosin), demonstrated a notable affinity for binding the viral proteins. These phytochemicals were selected for their potential interaction with various SARS-CoV-2 proteins including S protein, 3CLpro, PLpro, and RdRp.[62] By inhibiting H1 receptor activation, *Phyllanthus amarus* extract and compound hypophyllanthin demonstrate antiallergic potential.

Evaluating antiallergic activity using molecular docking and the histamine 1 receptor binding assay. Evaluation methods included measuring allergy marker release from RBL-2H3 cells, testing the Histamine 1 Receptor (H_1R) in a competition radioligand binding experiment, and evaluating binding interactions using molecular docking.RBL-2H3 cells were used for bioassays after reaching passages 3 to 5, with ketotifen furmate as a suitable control for antiallergic activity Analytical validation for HPLC quantification involved assessing linearity, the accuracy of the method is ensured by the Limits of Detection (LOD) and Quantification (LOQ) for standards. As demonstrated by molecular docking, Hypophyllanthin had a favorable binding in the H1 receptor binding site, which may indicate a mechanism behind its antiallergic action.[63]

Phytochemical analysis of *Phyllanthus amarus*

Chemical test for alkaloid-When different reagents are used like Potassium bismuth iodide, the Dragendorff reagent, results in a reddish-brown precipitate. Wagner's reagent, which is made of potassium iodide and iodine, likewise produces a reddish-brown precipitate. The precipitate produced by Hager's reagent, which contains picric acid, is yellow. Finally, a cream-colored precipitate is formed by potassium mercuric iodide, also known as Mayer's reagent.[64,65]

A chemical test for Flavonoids found flavonoids in the plant extract, some of the aqueous filtrate was mixed with 5 mL of diluted ammonia solution, and then concentrated H_2SO_4 was added. Each extract's appearance of a yellow hue suggested the presence of flavonoids. The coloring test is a popular technique for determining if these chemicals are present in plant extracts.

Chemical test for Tannins

When 2 mL of the plant extract solution is mixed with 5% ferric chloride, a deep blue color is observed. Adding a few drops of lead acetate to 2 mL of the extract solution results in a white precipitate. Similarly, adding a few drops of gelatin solution also produces a white precipitate. When a few drops of potassium dichromate are added, a red precipitate forms. The addition of a few drops of dilute nitric acid changes the color from red to yellow. Finally, when 4 mL of the extract solution is combined with 4 mL of 10% ammonia solution, an emulsion is formed.

Chemical test for Triterpenoids and Steroids

Liebermann Burchard test (LB test)

When 2 mL of the plant extract is treated with Chloroform ($CHCl_3$) and acetic anhydride, followed by heating and cooling, and finally adding 2 drops of Sulfuric Acid (H_2SO_4), the color changes from red to green.

Salkowski tests that 2 mL of the plant extract is mixed with 2 mL of Chloroform ($CHCl_3$) and Sulfuric Acid (H_2SO_4), followed by heating and cooling, and a red color is observed.

Liebermann test 2 mL of the plant extract is treated with Chloroform ($CHCl_3$) and acetic anhydride, followed by heating, cooling, and the addition of 2 drops of Sulfuric Acid (H_2SO_4), a blue color is observed.

CONCLUSION

Many researchers have been intrigued by *Phyllanthus amarus* for several decades for its potent pharmacological activities. *Phyllanthus amarus* is a valuable plant with enormous biological and therapeutic activity. It comprises several naturally occurring substances that can possess activity against various illnesses. Although there are numerous significant uses for treatment, it has a variety of traditional uses that vary by nation. Chemical and pharmacological studies have demonstrated that the plant extract exhibits a variety of pharmacological impacts. This review summarizes the distribution, vernacular names, extraction, pharmacological activity, phytoconstituents, and structure associated with this plant. On the other hand, Molecular docking analyses demonstrated that the chemicals adhered to the active site. It underscores the significance of utilizing natural substances in pursuing new drugs, particularly highlighting the potential of phytochemicals sourced from *Phyllanthus amarus*.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

UPLC-DAD-MS: Ultra Performance Liquid Chromatography-Diode Array Detector-Mass Spectrometry; **HPLC:** High-Performance Liquid Chromatography; **LC-MS/MS:** Liquid Chromatography-Tandem Mass Spectrometry; **CCL_4:** Carbon Tetrachloride; **NF-κB:** Nuclear Factor-kappa B; **MAPK:** Mitogen Activated Protein Kinase; **PI3K-Akt:** Phosphatidylinositol 3-Kinase/Akt; **MyD88:** Myeloid Differentiation Primary Response 88; **TLR4:** Toll-like Receptor 4; **CH3OH:** Methanol; **MS:** Mass Spectrometry; **HPTLC:** High-Performance Thin Layer Chromatography; **ESI-MS/MS:** Electrospray Ionization Tandem Mass Spectrometry; **LC/MS:** Liquid Chromatography-Mass Spectrometry; **Na^+ K^+ ATPase:** Sodium Potassium Adenosine Triphosphatase; **GABA:** Gamma-Aminobutyric Acid; **P.O:** Per Oral (Oral Administration); **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **CCl_4:** Carbon Tetrachloride.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ayushi Varshney: Writing-original draft. Shashi Bhooshan Tiwari: Supervision, Conceptualization. Pawan Kumar Gupta: Editing and supervision. Prashant Kumar: Validation.

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