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Revisiting the Emerging Pharmacological Perspectives of *Nyctanthes arbor-tristis*

Review Article

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Abstract

A mythical plant indigenous to the southern Asian area known as *Nyctanthes arbor-tristis* (Oleaceae) is highly valued for its therapeutic properties in Ayurveda. The plant contains a number of Phytoconstituents, and almost every part of the plant has pharmacological properties. In order to identify therapeutic potential and gaps requiring more study, the current review includes an ethnopharmacological evaluation that focuses on data on the chemical components, pharmacological activities, and toxicity. In India most significant use of *N. arbor-tristis* for the treatment of intractable sciatica, arthritis, and intermittent fevers. The plant's crude extracts and isolated components have pharmacological activity against inflammation, malaria, viral infection, leishmaniasis, and as an immunostimulant. Iridoid glucosides, including Arbortristoside A, B, and C from the seeds, are a prominent family of physiologically active substances that have anticancer, anti-leishmania, anti-inflammatory, anti-allergic, immunomodulatory, and antiviral properties. It has been stated that the leaves' calceolarioside A, 4-hydroxyhexahydrobenzofuran-7one, and β-sitosterol are each effective against leishmaniasis, cancer, and inflammation, respectively. While arbortristoside-A isolated from the seeds had an LD_{50} of 0.5 g/kg, the crude extracts were determined to be safe with an LD_{50} of 16 gm/kg.The majority of the time, in-vitro or occasionally in-vivo models offer some evidence, particularly when it comes to the treatment of inflammatory illnesses like arthritis, fevers associated with malaria, and protozoan infections, particularly leishmaniasis. The sole clinical trial discovered only used crude extract to treat malaria. For crude extracts or pure chemicals, more thorough safety data must also be collected on cardiotoxicity, immunotoxicity and acute and subacute toxicity.

Key Words: *Nyctanthes arbor-tristis,* Pharmacological actions, Therapeutics, Chemical constituents, Bioprospection, Ethnopharmacology.

Introduction

Synonyms and taxonomy Oleaceae bushes or tiny trees with delicate white hairs and sharply quadrangular juvenile branches are called *Nyctanthes arbor-tristis* L. The leaves are opposite, ovate, rough, and covered with short, stiff hairs. The margins are either whole or have a few, big, noticeable teeth. The bases are rounded or slightly cuneate, and the major nerves are clearly visible beneath. Axillary, single, or in terminal short trichotomous cymes describe the inflorescence. The blooms, which are produced in clusters of two to seven together, have a nice aroma and a white corolla with five to eight lobes and an orange-red core. Individual flowers begin to open around twilight and close at morning. Fruits are compressed, orbicular, and in capsule form. Orbicular and flattened seeds are present. (1)

The geographical distribution of the plant, *N. arbor-tristis L.*, is said to range from northern Pakistan and southern Nepal through northern India and southeast to Thailand, according to reports from the Germplasm Resources Information Network, Flora of Pakistan, and Agro Forestry Tree Database. It is a tiny tree or shrub with flaky grey bark that can grow up to 10 meters. It is believed that *N. arbor-tristis* L. has a variety of therapeutic uses for people. In India, Indonesia (Java), and Malaysia, *N. arbor-tristis* blossoms are used to induce menstruation, and the bitter leaves are used as a laxative, cholagogue, diuretic, and diaphoretic.The plant has opposite, simple, 6–12 cm long, and 2–6.5 cm wide leaves. Children with roundworms and threadworms are treated with leaf juice to get rid of them. The leaf juice is also used as a diuretic and to treat piles, chronic fever, malarial fever, stubborn sciatica, rheumatism, and loss of appetite. When combined with honey and table salt, fresh leaf juice has been proposed as a safe purgative for newborns. It works as a diuretic and diaphoretic in the form of infusion in dosages of two ounces for rheumatism and fever. The seed powder is used as an

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anthelmintic, for alopecia, and to treat scalp scurvy. Bronchitis and snakebites are treated with the bark.The tribal people of central India utilize various parts of the *N. arbor-tristis* to treat wounds, ulcers, diarrhea, cough, and hiccups. Scabies and other skin conditions are treated using the inflorescence. The herb has been employed as an anthelmintic in Nepal. In Indian traditional medicine, *N. arbor-tristis* is also known to have antiallergic, immunotoxic, purgative, antihistaminic, ulcerogenic, and antibacterial properties in addition to the ones already listed. As an expectorant and for bilious fevers are two more applications. Some senior Buddhist monks from Sri Lanka take the hot floral infusion as a sedative. In Myanmar, a dose of 3-6 g of dry herb or a decoction of 300-500 ml is used orally to treat diabetes.Crushed fresh leaves are also used topically to wounds and sores to lessen inflammation. The Indian Jayantia tribes that live in the vicinity of Myanmar utilize the flower and honey as an antispasmodic and the leaf juice as an oral anthelmintic. The plant's blooms have historically been used to cure piles and a variety of skin conditions because they are useful as carminative, stomachic, anti-bilious, astringent, hair tonics, and expectorant. Bronchitis and snake bites are both treated with the bark. (2)

According to scientific investigations, the herb has been used traditionally to treat a wide range of diseases. It was thought that there was a need for a comprehensive examination of the gaps in scientific investigations tying phytochemical profiles, pharmacological studies, or toxicity studies to the conventional claims.

Materials and methods

The current evaluation makes an effort to compile all the full text material that is currently accessible, database like PubMed and Scopus were reviewed concluding both the medicinal value of plants and the gaps that require research intervention.

Review of Literature

Pharmacological perspectives of Nyctanthes arbor-tristis L.

Anthelmintic

Natural therapies should be considered again because the currently prescribed anthelmintic medications, such as albendazole and praziquantel, have certain drawbacks. Moderate anthelmintic efficacy in a dose-dependent suppression of spontaneous movement in adult earthworms has been demonstrated by hydroalcoholic extracts from the leaves of *N. arbor-tristis* at 0.1 percent to 1 percent, and the activity is equivalently powerful to standard medication. For a 1 percent extract, the paralytic effect was noticed at 0.4407 min, and death occurred at 1.1507 min. Albendazole revealed paralysis at 0.3247 min and mortality at 0.4267 min at the same dose. In addition to aqueous and hydroalcoholic extracts, fresh juice has also been mentioned for the same effect.On *Pheretimaposthuma*, alcohol and aqueous extracts from the bark of *N. arbor-tristis* were tested at concentrations of 20 mg/kg, 40 mg/kg, and 60 mg/kg depending on the worms' paralysis or death times. The outcomes were similar to those of albendazole. Additionally, because worms are killed faster by the alcoholic extract than by albendazole, it is more effective. The research on anthelmintic action is in its very early stages because the only helminth taken into account in the experiments listed above was the earthworm.Studies using other important human models, such as *Haemonchusconcortus*, *Ascarida spp.*, *Ascaris sp.*, *Caenorhabditis elegans*, *Fasciola sp.*, *Taenia sp.*, *Hymenolepsis sp.*, and *Strongylus sp.* should be taken into consideration. It may be said that there is a lot of room to evaluate how this plant affects anthelmintic action. (3)

Antiallergic

The ability of several plant extracts and secondary metabolites to lower eosinophilia and/or eosinophil recruitment suggests that these substances might be used as therapeutic alternatives to allopathic anti-histaminics. Three studies on Nyctanthes, all from the same group, found that a 50 percent alcoholic extract of the plant's flower, root, seed, and leaf significantly inhibited PCA at 50 mg/kg in both mice and rats. This means that Nyctanthes has the same ability to prevent anaphylaxis in the skin as the widely used medication disodium cromoglycate (DSCG).Additionally, when Arbortristoside-A and Arbortristoside-C, which were isolated from the seed, were tested at 25 mg/kg and 50 mg/kg, they significantly inhibited PCA at these concentrations and significantly protected against the degranulation of mast cells brought on by compound at 10 mg/kg thanks to their activity in stabilizing mast cells in comparison to DSCG. Thus, when administered orally to rats, both substances showed notable anti-PCA and mast cell stabilizing effect, although DSCG is poorly absorbed. Additionally, the plant's bark was examined for its potential anti-histaminic properties.The bark of *N. arbor-tristis* was examined in petroleum ether, chloroform, ethyl acetate, ethanol, and aqueous extracts. Of these, petroleum ether extract at 50 mg/kg and 100 mg/kg demonstrated the greatest protection against mast cell degranulation by clonidine and resisted contraction (bronchodilation) induced by histamine better than other extracts, which they proposed may be due to β-sitosterol. The foregoing study by several organizations appears to demonstrate the extracts' capacity to suppress histamine release at levels within acceptable bounds. Despite the fact that none of these works have toxicity assessments, other reports of toxicity in comparable extracts point to a much safer level. (4)

Anticancer

Currently available anti-cancer medications have a natural origin for more than 60% of the time. It is believed that dietary flavonoids and other polyphenols from healing plants play a significant role as chemopreventive agents. There hasn't been much research done on *N. arbor-tristis*' anticancer abilities. However, it has been shown that the iridoid glycosides Arbortristoside A and B, at 2.5 mg/kg in mice, exhibit

anticancer action against methylcholanthrene-induced fibrosarcoma. At 20 mg/kg, a benzofuran derivative called 4-hydroxy hexahydrobenzofuran-7-one that was extracted from the leaves suppressed the development of Ehrlich ascites carcinoma cells by 43.27 percent without having any harmful effects. (5)

Antidiabetic

There are several different types of hypoglycemic medications, both new and old, including biguanides and sulphonylureasthat can be used to treat diabetes. However, none of these drugs are recommended because to their harmful side effects, which can sometimes result in a reduction in responsiveness after lengthy usage towards the conclusion of the activity. Despite being said to have anti-diabetic properties, *N. arbor-tristis* lacks considerable scientific support because the claims have not been thoroughly investigated. When given orally to rats that had been made diabetic by alloxan, a methanolic extract of the root at a dose of 500 mg/kg was shown to be successful in reversing the symptoms. In rats, the extract was determined to be safe when administered orally up to 3000 mg/kg.Another study determined that a high fructose diet developed insulin resistance in rats, and that chloroform extract from leaves at concentrations of 50 mg/kg, 100 mg/kg, and 200 mg/kg substantially lowered blood glucose and insulin levels. The safety and efficacy of the extract, however, were not proven. In a related study, the same dose of a chloroform extract from the flower and leaves, given over a period of 27 days to STZ-induced diabetic rats, significantly decreased levels of lipid peroxidation, liver enzymes, aspartate aminotransferase (SGOT), alanine transaminase (SGPT), alkaline phosphatase (ALKP), cholesterol, and triglyceride, demonstrating a potent hypocholesterol Alkaloids and flavanoids have been detected, according to the qualitative tests.In a research using rats with diabetes caused by streptozotocin (STZ), blood levels of superoxide dismutase, catalase, and glutathione peroxidase were considerably raised by a 50 percent ethanolic extract from the leaves at doses of 100 and 200 mg/kg. By decreasing the liver's production of thio-barbituric acid reducing substances (TBARS), the extract also prevented lipid peroxidation. With these data on hypoglycemic potential, it appears that there is room for thorough research employing different plant components against diverse models for antidiabetic testing. (6)

Antiinflammatory

Ayurvedic doctors have treated intractable sciatica and arthritis using the plant's leaves. Different types of its leaf juices have been recommended for treating acute, chronic, as well as intermittent fevers. Intriguingly, researchers used rat models of immunological and non-immunogenic inflammation caused by various phlogistic agents, including carrageenin, formalin, histamine, 5-hydroxytryptamine hyaluronidase, and Freund's adjuvant, to report the presence of anti-inflammatory activity in the water soluble portion of an ethanol (absolute) extract of the plant's leaves. The dosages under consideration ranged from 1 gm/kg bd.wt. to 8 gm/kg bd.wt. The water soluble component of the ethanolic extract has been discovered to provide considerable anti-nociceptive effects similar to aspirin but not analgesia similar to morphine.The same fraction's toxicity experiments at five dosages ranging from 2.0 g/kg to 32 g/kg showed that the fatal dose (LD_{50}) was 16 g/kg. Furthermore, when being administered orally to rats for six days straight at dosages ranging from 0.5 g/kg to 8.0 g/kg, the same fraction likewise shown antipyretic efficacy but also clearly manifested stomach ulcers. Studies on the orange tubular calyx's extracted carotenoid and ethanol (absolute) extract showed considerable antiinflammatory effect at 200 mg/kg in carageenan-induced rat paw edema. The ethanolic extract's LD_{50} was established to be 1500 mg/kg.Studies revealed that oral administration of the water soluble fraction of the ethanolic extract of leaves at a dose of 100 mg/kg in arthritic mice consistently reduced host plasma levels of tumour necrosis factor (TNF-a) and interferon (IFN-g) in arthritic and soluble protein A (SpA)-treated Balb/c mice, without affecting the levels of immunoglobulin-G (IgG) and immunoglobulin-M (IgM), indicating the potential for its use in the In a different investigation, it was shown that pre treating animals exposed to silica with leaf extract at a dose of 50 mg dramatically reduced the amount of TNF-alpha that accumulated in the mice's broncheoalveolar lavage (BAL) fluid.In a related investigation, mice with Freund's complete adjuvant-induced arthritis were treated with 25 mg/kg bd.wt of the water-soluble component of the ethanolic extract of leaf and fruit. This showed that the extract may operate as a modulator of the balance between pro- and anti-inflammatory cytokines. The extracts were given an acute oral NOAEL (no observed adverse effect level) of 2000 mg/kg. Arbortristoside-A, an iridoid glycoside isolated from the ethanolic extract of seeds, was shown to have considerable (50 and 75 mg/kg) and dose-dependent anti-inflammatory and antinociceptive activity. They hypothesized that this effect may be caused by the prostaglandins' inhibitory action. The substance's LD_{50} was determined to be 500 mg/kg.According to a recent study, a leaf extract in petroleum ether at a dose of 50 mg/kg combined with b-sitosterol isolated from the extract significantly reduced mouse pain in hot plate and acetic acid-induced writhing tests when compared to standard medications pentazocine at a dose of 10 mg/kg and paracetamol at a dose of 50 mg/kg, and at the same dose significantly reduced inflammation when compared to ibuprofen at a dose From the aforementioned studies, it can be inferred that the majority of research has focused on the ethanolic extract's water-soluble fraction for anti-inflammatory efficacy. Concerningly, the trial doses ranged from 0.5 g/kg to 8 g/kg. The studied extract and the separated Arbortristoside A are both harmless, according to the toxicity studies.Additionally, there is room to investigate the origins of related biological activities, and bioactivity-guided fractionation may produce active fractions or molecules with respectable biological activity. (7)

Antileishmanial

Leishmaniasis is a common tropical illness that, if neglected, can be lethal. Pentavalent antimonials are among the first-line treatments that are advised, although all of them have financial restrictions and particular toxicity when administered parenterally. Arbortristoside-A, Arbortristoside-B, Arbortristoside-C, and 6-β-hydoxyloganin (iridoid glucosides extracted from seeds) demonstrated high order of activity against *Leishmania donovani* amastigotes in vitro between 30 mg/ml and 100 mg/ml and *in vivo* at 10 mg/kg and 100 mg/kg as a result of biological activity from Nyctanthes. Analyzing naturally occurring chemicals generated from plants is one of the most promising methods for discovering new anti-leishmanial agents.In this effort, bioactivity-guided fractionation resulted in the successful isolation of calceolarioside A from the methanolic extract of *N. arbor-tristis* leaves, which displayed an IC_{50} of 20 mg/ml. The in-vivo efficacy was observed at a dose of 20 mg/kg in terms of reduced hepatic and splenic parasite burden in a well-established model of *L.donovani* in golden ham Inhibitors of trypanothione reductase, a validated therapeutic target enzyme of the *Leishmania* parasite, were initially identified in iridoid glucosides isolated from seed kernels. The compounds had considerable inhibitory action with IC_{50} values ranging from 2.29 mM to 4.74 mM. It is stated that, in keeping with the previous investigation, these iridoid glucosides significantly inhibited the proliferation of intracellular amastigotes.With an IC_{50} of 3.264mM - 9 mM, the compounds thus demonstrated suppression of the development of *L.donovani* promastigotes and axenic amastigotes. As previously documented, these substances had a considerable impact on the parasite's redox equilibrium, leading to an increase in reactive oxygen species as a result of trypanothione reductase inhibition. As a result, the elevated reactive oxygen species causes oxidative stress, cell membrane damage, and *Leishmania* parasite death. The iridoid glucosides at 4mM and 100 mM demonstrated 90 percent -95 percent and 50 percent -71 percent viability, respectively, and are safe and can thus be utilized for human administration, according to cytotoxicity experiments on HEK 293 and mouse macrophages.It should be noted that the given research has been done during the last ten years, with a focus on chemicals extracted from leaves and seeds whose in vitro cytotoxicity results in safety. *L.donovani* has been the subject of well-organized investigations, although bioactivity on *L. major*, *L.amazonensis*, *L. infantum*, and *L. aethiopica* might point to the uniqueness of the molecules isolated from *N. arbor-tristis*. (8)

Antimalarial

A new antimalarial medicine is clearly needed after laboratory tests indicated the development of resistance to nearly all antiplasmodial medications now available. Researchers have identified *N.arbor-tristis* as active with stem bark, leaf, root, seed, and flowers. Fresh leaf juice was described as the first scientific proof that *Plasmodium falciparum* was resistant to chloroquine. According to reports, the plant is used by tribal people in Orissa to make a decoction of seven leaves that is combined with honey and consumed for three to four days to treat malaria. Only at 100 mg/ml does a 50 percent ethanolic extract of the root and seed show in vitro action. However, leaf extract has antimalarial efficacy against *P. falciparum* and *P.berghei* both in vitro and in vivo (NK65).Inhibitory concentrations (IC50) of 54 mg/ml and 38 mg/ml, respectively, have been observed for the alcohol-based extract of fruit and leaf against chloroquine-susceptible strains of the human malaria parasite *P. falciparum*. An activity-guided fractionation of an ethanol extract of flowers produced rengylone and its acetate derivative, two cyclohexylethanoides with antiplasmodial activity and IC50 values of 2.1 mg/ml and 4.6 mg/ml against *P. falciparum*, respectively. By administering a fresh paste made from five fresh *N. arbor-tristis* leaves orally three times per day for 7days to 10 days, it has been reported to have a therapeutic effect (76.17 percent) in the treatment of malaria. This finding also raises the possibility of creating a standardized formulation.125 patients (15–70 years old, excluding pregnant women) who tested positive for *P. vivax*, *P. falciparum*, or both participated in the clinical study. No more antipyretics or antimalarials were administered. Tepid sponging and a cold water enema were used in cases of severe fever. According to traditional ayurvedic literature, patients were daily checked for fever and rigors as well as the severity of 35 malaria-related signs and symptoms. When making counts at the time of admission and on the third and seventh days after treatment, blood smears were taken into consideration for parasite identification. For individuals whose clinical condition had improved but who had no parasite count after 7 days, the medication was maintained.Both the early and late full groups as well as the early partial group of treatment response categories demonstrated parasite eradication. As a result, 76.7 percent of patients experienced the therapeutic response. Studies from the Indian state of Orissa, once more, have revealed the effectiveness of freshly squeezed leaf juice in the treatment of malaria-like illnesses. The only plant studied on which the ethnopharmacological usage has been clinically confirmed, albeit in a limited way, is Nyctanthes. The findings described above imply that at greater baseline parasitemia, the typical dose of *N. arbor-tristis* Linn may not always be sufficient. For future research to be able to correlate the treatment response with the level of parasitaemia, a standardized formulation as well as a set flexible dose regimen is required.Since each piece of labor has been completed individually, the leaf and fruit may be examined for comprehensive chemical and biological activity using the currently available scientifically certified lead. (9)

Antimicrobial

The antibacterial potential of Nyctanthes and several other ethnomedicinal plants has been investigated. It has been claimed that the juice of fresh leaves has antibacterial properties. Escherichia coli was discovered to be resistant to the antibacterial action of

this plant's flower petals. The Gram positive bacteria *Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus*, *B. megaterium*, *Sarcina lutea*, and *Streptococuus sp*. as well as the Gram negative bacteria *Shigella dysentriae*, *Escherichia coli*, *S. boydii*, *S.shiga*, *Pseudomonas aeruginosa*, and *S.sonnei* can be killed by the ethanolic extracts of the leaves. It has been discovered that the ethanolic extract of the stem and leaves is effective against *S. aureus*, *C. albicans*, and *S. epidermidis*, whereas the aqueous extract of the leaves is only somewhat effective against Pseudomonas testosteroni. The leaves' methanol and aqueous extracts have bactericidal effects on *B. subtilis*, *E. coli*, and *S. aureus*. The methanolic extract of the leaves was also shown to be effective against bacterial strains that were multi-drug resistant, including *S. epidermis*, *S. aureus*, *Salmonella paratyphi*, and *S. typhi*.A disc diffusion assay was used to test the effectiveness of root bark extracts (Petroleum ether, chloroform, ethanolic, and aqueous extracts) against *B. subtilis*, *E. coli*, *S. aureus*, *Pseudomonas aeruginosa*, and *S. faecalis* at concentrations ranging from 10 mg/ml to 60 mg/ml. The aqueous, methanolic, and ethanolic extracts demonstrated bactericidal efficacy against medically significant Gram positive and Gram negative strains in-vitro at dosages ranging from 10 mg to 40 mg, according to a research that was somewhat better structured. The erythrosine B dye exclusion test-based cell viability assay findings showed that all of the extracts were most viable at 100 mg.In a thorough investigation, dried leaf, flower, fruit, and seed extracts that showed a considerable amount of activity against Gram positive bacteria in comparison to Gram negative by preliminary antibacterial assay were extracted using ethyl acetate and chloroform. Additionally, they underlined that the action is more evident when plant material is ingested in fresh form and that combining extracts that have been dried did not produce any synergistic effects.The stem bark extract has also been reported to be effective against yeast (*C. albicans*), mold (*Aspergillus niger*), and both types of bacteria in a different early investigation. They suggested as well that chloroform extract from the plant's stem bark be used instead of petroleum ether and ethanolic extracts, which were proven to merely have antibacterial action. A disc diffusion experiment using 200 ml of crude extract was used to test the activity of an aqueous extract against pathogenic and non-pathogenic bacteria as well as one yeast, *C.krusei*, in the sole report from the bark of this plant.In a recent study, chloroform and ethyl acetate extracts of fresh leaf, seeds and fruits have shown significant antibacterial activity against *Klebsiella pneumonia*, *S. aureus*, and *E. coli*while the dried extracts of chloroform and ethyl acetate show significant antibacterial activity against Pseudomonas aeruginosa through disc diffusion assay. With respect to anti-viral activity, only two reports from ethanolic extract, n-butanol fraction and Arbortristoside A and C isolated from the seed of the plant were traced against Encephalomyocarditis virus and Semlinki forest virus both in vitro and in vivo. Further, it has also been mentioned that Arbortristoside B, D and E were not active against these viruses.When analyzing the antibacterial activity described in the literature, it can be shown that none of the research used the broth dilution method to determine the minimum inhibitory concentration (MIC), which provides a definitive assessment of the activity. There are very few reports on the antibacterial properties of pure molecules or bioactivity-guided fractions, which might be the topic of further research. Any promising lead can also be examined in particular in vivo models of bacterial or fungal infection. The lack of antiviral literature calls for at least a preliminary test against different virus families. (10)

Antioxidant

Strong antioxidants are produced by plants, and the anti-oxidant activity of classes of chemicals that help scavenge the free radicals primarily responsible for the pathophysiology might be connected to the use of Nyctanthes leaves as a decoction in Ayurveda treatment for various diseases. Using bovine brain phospholipid liposomes, the initial research assessed the impact of the methanolic extract from the leaves of Nyctanthes on free radical-induced lipid peroxidation and discovered excellent activity with an IC50 value of 20 mg/ml.The DPPH radical, hydroxyl radical scavenging activity, and lipid peroxidation prevention properties of the plant's aqueous extracts have previously been reported; however, the total flavonoid and phenolic content was found to be very low, which was correlated to be the lowest antioxidant activity in comparison to other leafy vegetables. Through tests including the hydrogen peroxide scavenging assay, reducing power assay, di-phenyl picryl hydrazyl (DPPH) radical scavenging assay, and total antioxidant assay, studies have shown that ethanolic extracts of the plant's leaves and stem are a possible source of antioxidants. According to a study on the antioxidant activity of aqueous extract from the flower and its components, the calyx is the most effective in scavenging DPPH radicals, followed by the flower and the petals. Another investigation on the fractionated alcoholic extract of leaves revealed that butanol (95.22 percent) was the most effective antioxidant at 100 mg/ml, followed by ethyl acetate (84.63 percent), petroleum ether (82.04 percent), and ascorbic acid (93.88 percent) at 10 mg/ml. DPPH, hydroxyl and superoxide radicals as well as H2O2 scavenging tests were used in a research to demonstrate the excellent antioxidant activity of an ethyl acetate extract from leaves that is acetone soluble. The fractions have been evaluated and shown to be equivalent to well-known antioxidants such a-tocopherol, BHT, and mannitol. Gamma ray-induced DNA damage and Fe(II)-induced liposome lipid peroxidation were used as further proof. Interestingly, aqueous extracts of the flowers demonstrated significant levels of enzymatic antioxidants, whereas methanolic extracts of the flowers revealed high phenolic content and antioxidant activity. With an IC50 value of 63.67 mg/ml and 61.97 mg/ml, respectively, methanol extract and the flavonoid fraction of the leaves demonstrated DPPH scavenging activity and high ferric reducing activity. When the antioxidant

activity is considered collectively, it can be said that leaf, stem, and flower extracts containing phenolics and flavonoids are what cause the antioxidant activity, which was generally seen in extracts produced solvents of lower polarity. According to the research on aqueous extract (greater polarity), the antioxidant activity was decreased. (11)

Antitrypanosomal

Trypanosomiasis, a major source of misery in sub-Saharan Africa caused by intracellular parasites of the trypanosome species *Trypanosoma cruzei* and *Trypanosoma brucei*, is similar to other protozoan disorders. Under *in-vitro* circumstances, a crude 50 percent ethanol extract of *N. arbor-tristis* leaves demonstrated trypanocidal action at 1000 mg/ml. Through extending mouse longevity, *in-vivo* experiments showed that the extract has anti-trypanosomal properties at dosages of 300 mg/kg and 1000 mg/kg. The medicine was stopped, though, and the experiment animals perished. (12)

Central nervous system

With the Sanskrit words medhya, which means intelligence or cognition, and rasayana, which means rejuvenation, some plants have long been categorized as medhyarasayanas in the Indian medical system. A few research teams have attempted to track the plant's impact on the central nervous system, despite the fact that it has not been mentioned in the treatment of disorders connected to the central nervous system. According to studies, the plant's leaves' aqueous extract can counteract malathion's impact on acetylcholine esterase activity, which is crucial for the metabolism of acetylcholine.The water-soluble component of the alcoholic extract of the leaves had no impact on the righting reflex in a different research, but at dosages of 4.0 g/kg and 8.0 g/kg, it greatly increased the duration that pentobarbitone remained in the body while it was asleep. The extract considerably decreased CAR activity at similar dosages, according to tests for sedative action. The sedative potential of a hot floral infusion has also been tested for sedative effect in rats in a different study. Surprisingly, female rats were not affected by the infusion's mild dose-dependent (3.7 mg/kg to 18.7 mg/kg) conscious sedative effect. Even after subchronic sessions, the infusion was well tolerated and exhibited no overt symptoms of dependency.Similar research on the 600 mg/kg dosage of ethanolic extracts of flowers, leaves, barks, andseeds shows a considerable dose-dependent extension of the onset and duration of sleep, which may be brought on by lowered dopamine and elevated serotonin levels. At dosages of 500 mg/kg, 1000 mg/kg, and 1500 mg/kg, the ethanolic and aqueous extracts of Nyctanthes leaves have an anti-convulsant action against MES-induced seizures, but they also cause drowsiness and motor deficits. Although the precise ingredients or the mechanism behind the ethanolic extract's superior performance against the most intense electroshock could not be determined. The extracts' LD_{50} was discovered to be 45000 mg/kg. In a separate investigation, mice treated with 250 mg/kg and 500 mg/kg of the hydroalcoholic extract of the leaves shown strong antidepressant efficacy.Additionally, the same research has noted that the same extract at the same dosage possesses anti-aggressive properties. The central nervous system effects of *N. arbor-tristis* can be summarized as sedative and this fact should be taken into account when the plant is utilized to treat various conditions. When researching other pharmacological processes, researchers should also plan their studies with the important effects of the extracts on the central nervous system in mind. (13)

Diuretics

Natural products have recently concentrated on scientific and clinical research for novel diuretic medications that are mostly supported by actual usage. The majority of these compounds have shown meaningful benefits in animal models, albeit the mechanisms of action have received little attention. In terms of Nyctanthes' diuretic properties, hot floral infusions of the plant at dosages ranging from 3.7 mg/kg to 18.7 mg/kg significantly decreased urine output and retained K+ ions in the body in rats when compared to furosemide at 13 mg/kg. A considerable, quick yet long-lasting diuresis was induced by the floral infusion in a dose-dependent manner. Additionally, the flower infusion significantly reduced the amounts of Na^+ and K^+ in the urine and slightly but significantly increased its alkalinity.However, neither the Na^+/K^+ ratio nor the urine specific gravity were significantly impacted by the infusion. Additionally, subchronic administration of the infusion in rats shows that it is safe. Through measurement of variables including urine volume and electrolyte excretion, similar data have also been reported on the ethanolic extract of the leaves, seeds, and flower at dosages ranging from 200 mg/kg to 600 mg/kg. The extract was also determined to be safe at 2 g/kg in an acute toxicity investigation. Overall, it can be said that the flowers have a promising future as a reliable, affordable diuretic. (14)

Hepatoprotective

The treatment of liver illnesses has become one of the biggest challenges in twentieth-century medicine. The liver has a large capacity for regeneration, and damage is typically severe before it becomes apparent. Based on conventional wisdom, *N. arbor-tristis* has also been tested for its hepatoprotective properties. Early research on the effects of carbon tetrachloride on the liver found that leaf extracts, both alcoholic and aqueous, were efficient in lowering the raised levels of enzymes. The possibility of blocking P_{450}-mediated CCl_4 bioactivation through the selective suppression of reactive oxygen species by the ethanolic extract at 1 g/kg is indicated in a further expansion of the work.In a separate experiment, rats treated with methanolic extracts of leaves after being given 1 g/kg of acetaminophen recovered by preventing the level of glutathione. At 500 mg/kg, the plant's leaves' ethanolic and aqueous extract was proven to be efficient as a hepatoprotective in rats with liver damage brought on by galactosamine. Nyctanthesin, which is found in the

plant's leaves and seeds, was identified by researchers as having potential hepatoprotective properties. Hepatoprotective activity investigations have been conducted using early conventional models. The first findings in certain models of phalloidin-induced liver damage or drug-induced hepatotoxicity (Isoniazid, Rifampicin, Ethambutol, etc.) appear to have room for future expansion. (15)

Immunomodulatory

Some medicinal plants are thought to strengthen the body's innate immune system, which is thought to increase natural resistance or the body's ability to fight off infections. The modulation of immune response with the help of different bioactive in order to alleviate certain diseases is an active area of interest. A rise in the humoral and delayed type hypersensitivity response to the macrophage migration index (MMI) and sheep red blood cells (SRBC) were indicators of immunostimulant activity in a 50 percent ethanolic extract from seeds and a 50 percent ethanolic extract from leaves and flowers in the aqueous fraction.In addition, a prophylactic treatment with ethanol (50 percent) extracts of the seed at 50 mg/kg, the root at 25 mg/kg, and arbortristoside-A and arbortristoside-C at 5 mg/kg significantly protected Swiss mice against systemic infection with Candida albicans. This protection was a result of the potentiation of immunostimulant activity, which was demonstrated by an increase in humoral and delayed type hypersensitivity (DTH) response to In treated or untreated mice exposed to malathion, aqueous extract of the leaves was found to potentiate the immune systems by increasing humoral, cell-mediated immune, numerical values of immunocytes, and functions of phagocytes. This was found to counteract the immunotoxic effect of chemical pesticides. When challenged with SRBC and heat-killed *Salmonella* antigens, the ethanolic extract from leaves, at dosages ranging from 50 mg/kg to 200 mg/kg, not only stimulated the cell-mediated immune response but also enhanced the humoral immune response. In a study different from mammalian system, it was found that feed supplemented with chloroform extract of the seed at 0.1% and 1% level provide disease resistance of tilapia, *Oreochromis mossambicus* against live virulent Aeromonas hydrophila by stimulating non-specific immune response by significantly enhancing non-specific immune response such as alternate complement haemolytic (ACH_{50}) activities, serum lysozyme, reactive nitrogen intermediate (RNI), cellular reactive oxygen species (ROS), and myeloperoxidase production confirmed the presence of methoxylated flavonoids quercetin-3,3'-dimethoxy-7'-rhamnoglucopyranose and polyacetylene from the ethanolic extract of leaves, acting as an immunoprophylactic in finfish aquaculture, and correlated the activity with the improvement in mice's immune status by raising the amount of the antioxidant polyacetylene in phagocytic index of white blood cell count, reticuloendothelial system (RES), spleen leukocyte count, spleen weight, antibody secreting cells in spleen, haemagglutination antibody titre, IgG titre, and delayed type hypersensitivity reaction when challenged with TT and reduction in active systemic anaphylactic reaction at 0.25 g/kg and 0.5 g/kg of extracts, respectively. According to every data on the immune system, the plant contains immunostimulating qualities. The extracts may be able to reverse immunosuppressing action, according to the research on antagonistic pesticide activity, and they are also effective in aquatic environments. (16)

Larvicidal

The hunt for natural sources of vector control measures has arisen as a result of complex issues with the chemical insecticides used to eradicate the vectors that transmit different tropical illnesses. Some employees have also tried Nyctanthes for these purposes. With LC50 values of 25.67-72.60 ppm and 73.31-99.02 ppm, respectively, it has been determined that the chloroform extract and its isolated component NCS-2 from Nyctanthes flowers are larvicidal against the common filarial vector, *Culex quinquefasciatus*. Additionally, it was shown that late instar larvae were more resistant to the extract than early instar larvae. Additionally, *N. arbor-tristis* leaves have larvicidal properties.The LC_{50} values of the leaves of *N. arbor-tristis* against malarialspecies like *Anopheles stephensi*, *Aedes aegypti*, and *C.quinquefasciatus* were 518.2 ppm, 303.2 ppm, and 420.2 ppm, respectively. The *N. arbor-tristis* flower extracts in methanol and chloroform also exhibited larvicidal efficacy against *A.stephensi* larvae, with LC_{50} values of 244.4 ppm and 747.7 ppm, respectively. In a research on the toxicological characteristics of several medicinal plants, the petroleum ether extract of leaves from *N. arbor-tristis* had a larvicidal activity (LC_{50} values) of 185 ppm against *A.stephensi*. With LC_{50} values of 114.5 mg/l and 260.72 mg/l, the crude dichloromethane extract of leaves outperforms the other studied extracts in terms of larvicidal efficacy against *A. aegypti* and *A.stephensi*.According to all four investigations, the leaves and flowers have larvicidal action and may provide effective natural vector control methods. However, it's also important to take into account the safety research on aquatic life. (17)

Conclusion

In certain cases, the early research of biomedical investigations on metabolic disorders including inflammation, allergies, diabetes, diuresis, hepatoprotection, or immunomodulation has been useful in demonstrating the relationship between biological activity and chemical ingredient nature with toxicity. In accordance with the aforementioned observation, research on infectious diseases like malaria, trypanosomiasis, leishmaniasis are caused by microbial pathogens has revealed that the activities are more pronounced in crude extracts than in pure molecules, with generally encouraging toxicological data. The development of combination therapies including therapeutic entities susceptible to the development of resistance may be one of the future

paths since the bioactivity guided fractionation studies in the majority of illnesses have shown lower effectiveness. Further evidence for the therapeutic claims would come from investigations on the mechanisms of action. A high-level analysis of the examined literature reveals a gap in the body of research that requires filling in order to support claims made by the conventional medical system. In addition to piles and gynecological research, some of the validation studies, such as antiviral, ophthalmic issues, bronchitis, and antidotes to snake venom, have not been covered. The biological activities of some research, such as those connected to intestinal worms through anthelmintic activity, gout through analgesic and antiinflammatory activity, and anxiety and restlessness through CNS modulatory activity, are, however, only indirectly related to these investigations.

Conflict of interest

No conflict of interest declared.

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