

A review Study of the Chemical Constituents and Pharmacological Activities of *Alstonia scholaris* linn

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Abstract— The Indian medical systems hold promise for the genus *Alstonia*. Different types of *Alstonia*, primarily *Alstonia scholaris*, have been used by the various ethnic communities in India to treat various human illnesses. A historically significant medicinal herb is *Alstonia scholaris*. The Indian subcontinent and Southeast Asian nations are the native habitats of this evergreen tree. The plant is used in conventional, Ayurveda, Unani, homeopathic, Sidhha/Tamil, and other alternative medical systems to treat a variety of illnesses, including asthma, malaria, fever, dysentery, diarrhea, epilepsy, skin conditions, and snakebites, among others. Alkaloids make up the majority of reported phytochemicals. In this review, reports on pharmacological and phytochemical varieties of *A. scholaris* are compiled.

Keywords— *Alstonia scholaris*, Apocynaceae, Phytochemistry, Pharmacology, Alkaloids.

I. INTRODUCTION

Herbal medicines are in great demand in developed as well as developing countries for primary healthcare because of their wide biological and medicinal actions, higher safety margins, and lesser costs [1-2]. Various medicinal plants have been used for years in daily life to treat diseases all over the world. Moreover, there happens an enormous diversity in the phytochemicals derived from plants [3]. In order to survive in different environments, the morphological characters of widely distributed plant species often vary considerably. Leaves are exposed to aerial conditions more than any other plant organs, and the changes in their characters have been interpreted as adaptations to specific environments [4]. Studies on the use of plant extracts for monitoring disease have shown the importance of natural chemicals (phytochemicals) as possible sources of non-phytotoxic and easily biodegradable, alternative fungicides and antibiotics [5-6].

One such plant, *Alstonia scholaris*, requests the attention of the researchers worldwide for its pharmacological activities ranging from antimalarial to anticancer activities. *Alstonia scholaris* Linn. R.Br. belongs to the family Apocynaceae [7], and grows throughout India, in deciduous

and evergreen forests, and also in plains. The Apocynaceae family contains about 250 genera and 2500 species of tropical trees, shrubs, and vines. This family is known for plants that have very high biological activities and medicinal properties. The genus *Alstonia* finds a prominent place in different Indian systems of medicine for their pharmacological activities [8]. The different ethnic societies in India have used different species of *Alstonia* in the treatment of various human ailments as they have proven their pharmacological activities [9]. The important plants of the genus *Alstonia* include *Alstonia scholaris*, *Alstonia boonei*, *Alstonia congensis*, and *Alstonia macrophylla* which have been demonstrated to be useful in various diseases [10].

The plant is widely found in India in the sub-Himalayan area from the Yamuna eastward ascending to 3000 feet above sea level, and abundantly found in West Bengal and South India [11]. It has wide occurrence also in the Asia-Pacific region from India, and Sri Lanka through mainland South-East Asia and Southern China, throughout Malaysia to northern Australia, and the Solomon Islands. The timber is a non-durable hardwood, suitable for light indoor construction purposes, pulp and paper production. The wood has been used for school blackboards, hence the name 'scholaris'. The bark is official in the Indian, British, and French Pharmacopoeias.

A. Systematic Position

Kingdom: Plantae
Order: Gentianales
Family: Apocynaceae
Tribe: Plumeriae
Subtribe: Alstoniinae
Genus: *Alstonia*
Species: *Alstonia scholaris*

B. Botanical description

Alstonia scholaris is a large, buttressed evergreen tree, 6–10 m in height; bark rough, gray–white, yellowish inside, and exudes bitter latex when injures. The leaves are thick, dark green, in whorls of 4–8, obovate to oblanceolate, 5–15_2–6 cm², narrow at the base, entire, coriaceous, rounded



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or bluntly acuminate at apex, shining overhead, pale beneath; petioles 6–12 mm long. Flowers are compressed, umbellately branched, pubescent, paniced cymes; bracts leafy; bracteoles minute; pedicels are very short. Calyx 1.5–2 mm long, pubescent; teeth oblong, ciliate. Corolla is greenish white, pubescent outside; lobes ovate–obtuse, spreadingly, 2–3 mm long. Ovaries are distinct, follicles slender, terrate, 20–50 cm long, and pendulous. (Fig. 1).

Seeds are oblong, 6–8 mm long, and flattened with a tuft of brownish hair at either end [12]. In India, the flowering period is from December to March and fruiting is from May to July. It is widely dispersed in dried forests of India especially in Western Himalayas, Western Ghats, and in the Southern region [13].

The plant is a large evergreen tree up to 17 to 20 m in height with a straight often fluted and buttressed bole, about 110 cm in diameter. The bark is grayish brown, rough, lenticellate abounding in bitter, white milky latex; leaves 4–7 in a whorl, coriaceous, elliptic-oblong, pale beneath; flowers small, greenish white, numerous in umbellate panicles, corolla tube short, very strongly scented; fruits follicles, 30 – 60 cm long; seeds papillose with brownish hair at each end [14–15]. The fruits are a pair of follicles, linear, 20–50 cm long, glabrous, and narrowly winged on one suture (Fig. 2). Seeds are oblong, 5–6 mm long, brown tomatoes, and with long brown hair. It is flowering–fruiting season is during the months of September to December [16]. It is commonly established in the Andaman and Nicobar Islands of India and native to Malaysia, now introduced into different parts of India and frequently set in gardens [17].



Fig. 1. *Alstonia scholaris* flowering twig with bark and root (inset).



Fig. 2. *Alstonia macrophylla* flowering twig with bark and root (inset).

C. Chemical constituents

The various species of *Alstonia* are highly rich in alkaloids, steroids, triterpenoids, and phenolic compounds. Numerous alkaloids that have been reported in the *Alstonia venenata* R.Br. are minovincinine, 19-Epi(+)-echitoveniline, echitovenidine, echitoveniline, echitoserpidine, echitovenaldine, 11-methoxyechitoveniline, 11-methoxyechitovenidine, echitoserpine, alstovenine, 16-epialstovenine, venenatine, venoxidine, 16-epivenenatine, stigmasterol, reserpine, venenatine picrate, isovenenatine, kopsinine, venenatic acid, norvenenatic acid, venenatyl alcohol, tetrahydrovenenatine chloride, 7-chloro-7H-venenatine [18].

Alstonia scholaris Linn. is known to be a rich source of alkaloids and there is interest among the researcher to use this for therapeutic purposes. Amongst the chemical modules present in medicinal plant species, alkaloids stand as a class of major importance in the development of new drugs because alkaloids possess a great variety of chemical configurations and have been identified as responsible for the pharmacological properties of medicinal plants. However, of the large variety of alkaloids (about 180 alkaloids) isolated, so far only a few have been assessed for biological

activities [19]. Almost all the parts of the plant (bark, flower, root) are found to contain active principles. The species *A. scholaris* is used in the commercial formulation of Ayush 64 [20]. The bark of this plant comprises alkaloid ditamine and echitamine, echitenine, echicaoutchin, an amorphous yellow mass, echicerin in acicular crystals, echitin in crystallized scales, echitein in rhombic prisms (a crystallisable acid) and echiretin an amorphous substance, resembling an alkaloid, fatty acid, and fatty resinous elements. An uncrystallisable bitter principle called ditain was isolated and ascribed to the febrifuge properties of the drug [21]. Among the other constituents, Isookanin-7- α -l-rhamnopyranoside, a new flavanone glycoside [21] and Alstonoside, a secoiridoid glucoside have been recorded. Iridoids, coumarins, flavonoids, leucoanthocyanins, reducing sugars, simple phenolics, steroids, saponins and tannins were also found in the plant [22]. Presence of agr-amyrin, bgr-amyrin, lupeol acetate, venenative, rhazine and yohimbine have been noted [23]. Linalool, cis- and trans-linalool oxides (furanoid and pyranoid), α -terpineol, 2-phenylethyl acetate and terpinen-4-ol [24] and steroids [25] are among the other phytoconstituents of the species. Atta-ur-Rahman *et al* reported the isolation of an anilinoacrylate alkaloid, scholaricine, from the leaves of *Alstonia scholaris* to which structure 2-(demethylschoarine) has been suggested [26–27]. They also reported the isolation of 19, 20-dihydrocondylocarpine alkaloid from the leaves of *Alstonia scholaris* [28]. Atta-ur-Rahman *et al* also isolated 19, 20-Z-Vallesamine and 19, 20-E-Vallesamine from *Alstonia scholaris* [29]. Lagunamine (19-hydroxytubotaiwine), angustilobine B acid and losbanine (6,7-seco-6-norangustilobine B) were obtained from the leaves of Philippine *A. scholaris*, together with tubotaiwine, its oxide and 6,7- seco-angustilobine B by Tatsuo Yamauchi *et al*

[30]. 17-OAcetylochitamine was isolated from the bark of the plant along with echitamine [30].

II. BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

A- Antimalarial activity

Several studies confirmed that alkaloids have excellent antiplasmodial potential. *Alstonia scholaris* is rich in alkaloid content; however, despite this fact, its antimalarial potential is less explored. There are only two reports, which confirmed the antimalarial potential of *Alstonia scholaris* [31-32]. In both studies, the methanol extract of *Alstonia scholaris* bark was more promising. Nevertheless, the detected antiplasmodium activity of *Alstonia scholaris* was less pronounced as compared to *Alstonia macrophylla*.

B- Antimicrobial activity

Goyal *et al* [33] reported the antimicrobial property of the plant constituents of *A. scholaris* (alkanes, alkanols and sterols). Khan *et al* [34] estimated the antibacterial activity of the petrol, dichloromethane, ethyl acetate, and butanol fractions of crude methanolic extracts of the leaves, stem, and root barks of *Alstonia scholaris*, and reported that butanol fraction exhibited a broader spectrum of antibacterial activity.

C- Anti-depressant activity

C. Pradeep Kumar *et al.*, subjected the ethanolic extract of *Alstonia venenata* R.Br. stem bark for phytochemical examination and LD50. It was found that ethanolic extract contained reducing sugars, proteins, amino acids, flavonoids, phenolic compounds and tannins. Phenolic compounds and flavonoids were responsible for anti-depressant activities. The extract was confirmed for its lethal effect up to the dose level of 1000 mg/kg and no mortality was observed in mice. The management of extract at doses of 50 mg/kg, and 100 mg/kg, by oral administration, produced a significant ($P < 0.05-0.01$) anti-depressant effect in mice by tail suspension test and forced swim test of 50 mg/kg by oral administration [35].

D- Antidiarrhoeal activity

The antidiarrhoeal effects of the aqueous and the alcoholic bark extracts of *A. scholaris* in mice were reported by Patil *et al* [36].

E- Antioxidant activity

Antioxidants are the constituents that counteract the excess free radicals, reactive oxygen species (ROS), and nitric oxide (NO); and nullified their pathological effects [37-38]. Plants are an excellent source of natural antioxidants that reduce the risk of certain diseases such as cancer, heart diseases and stroke [38]. There is no report on in vivo antioxidant potential of *Alstonia scholaris*. By this time in vitro radical scavenging and antioxidant activity were reported to crude alcoholic extracts of stem bark, leaves, flower and fruit of *Alstonia scholaris* [39]. James *et al.* [40] reported that the methanol extracts of the flower had higher antioxidant activity than the fruit. The observed radical scavenging and antioxidant potential of leaves was ascribed to their phenolic and flavonoid content, and of flower and fruit extracts to their flavonoid content [39].

F- Anticancer activity

Methanol extracts of root barks of *Alstonia macrophylla*, *A. glaucescens*, and *A. scholaris*, collected from Thailand, have been assessed for cytotoxic activity against two human lung cancer cell lines, MOR-P (adenocarcinoma) and COR-L23 (large cell carcinoma), using the SRB assay. Pleiocarpamine, O-methylmacralstonine and macralstonine were all considerably less active than villalstonine [41].

G- Anti-fungal activity

T. Vaidyanatha iyer *et al.*, reported the anti-fungal activity of *Alstonia venenata* R.Br. Various plant parts like leaves, stem-bark, root-bark, flowers and fruits were extracted with a variety of solvents ranging from non-polar to polar and screened for bioactivity. Butanol and methanol extracts of all the parts alone were selected for anti-fungal testing [42].

H- Antidiabetic and antihyperlipidemic activity

The aqueous extract of *Alstonia scholaris* significantly reduced elevated blood glucose levels in streptozotocin (STZ) diabetic rats without showing any hypoglycemic effect in normal rats. The antidiabetic effect of the extract could be due to increased use of glucose by peripheral tissues, improved sensitivity of target tissues for insulin or it may be due to improved metabolic regulation of glucose. *Alstonia scholaris* bark significantly reduced serum triglyceride levels in STZ diabetic rats support its long term use not only for better control of blood glucose but also for normalization of disturbances in lipid metabolism which may inhibit further predisposition of the patients to cardiovascular complications [43].

I- Antipyretic activity

Pyrexia or fever is the body's natural protection to create an environment where infectious agents or damaged tissue cannot survive [44]. Thus far, antipyretic potential of *Alstonia macrophylla* leaf extract and its fraction have been studied [44]. Antipyretic activities of methanol extract of *Alstonia macrophylla* leaf (at doses 200 and 300 mg/kg, p.o.) and its n-butanol fraction fractions (at dose 50 mg/kg, p.o.) having β -sitosterol, ursolic acid and β -sitosterol glucoside were studied on normal body temperature and yeast induced pyrexia in Wistar albino rats. All extracts and portions showed a significant antipyretic effect in a dose dependent manner compared to standard antipyretic drug paracetamol. Nevertheless, the observed antipyretic effect was more pronounced, when the two fractions were administered together, i.e. produced an additive effect in combination [44]. The ethanolic extract of *A. scholaris* does exhibit significant dose-dependent antipyretic and anti-ulcer activity. The bioactivity-guided phytochemical screening of ethanolic extract of *A. scholaris* revealed the presence of flavonoids, tannins, and triterpenoids, which may be responsible for the antipyretic effect and can be further fractionated and investigated for their role and utility in any of the antipyretic mechanisms [45].

J- Hepatoprotective activity

The hepatoprotective effect of *Alstonia scholaris* R. Br. Liver injuries induced by carbon tetrachloride (CCl₄), e-

Dgalactosamine, acetaminophen, and ethanol were examined by Lin *et al* through serum-biochemical and histopathological examinations. All serological and histopathological effects of *A. scholaris* were compared with those of *Bupleurum chinense*, which has been reported previously as treatment criteria of hepatitis. A tendency was also shown to prevent cell necrosis and inflammatory cell infiltration caused by e-Dgalactosamine in histopathological examination [46].

K- Anti-fertility activity

The antifertility effect of *Alstonia scholaris* bark extract in male rats was estimated by Gupta *et al* [23]. Male Wistar rats were given oral (200 mg/kg) bark extract of *Alstonia scholaris* for 60 days. This did not cause body weight loss, while the weights of testes, epididymis, seminal vesicle and ventral prostate were significantly reduced. The production of step- 19 spermatids was reduced by 79.6% in treated rats. The populations of preleptotene and pachytene spermatocytes was reduced by 61.9% and 60.1%, respectively. Spermatogonia and Sertoli cell population were also affected. There was a reduction in seminiferous tubule and Leydig cell nuclear area, sperm count, motility, protein and sialic acid content of the testes, epididymis, seminal vesicle and ventral prostate. *Alstonia scholaris* bark extract had a significant antifertility effect in male rats. Gupta *et al* reported the antifertility effect of lupeol acetate isolated from benzene extract of *Alstonia scholaris* in male albino rats, which further augmented their findings [47].

L- Radioprotective effect

It has been found that ionizing radiation improved the formation of reactive oxygen species that attack DNA leading to cell death. The radioprotective effect of bark of *Alstonia scholaris* is well studied in both pre and post treatment regimes. It was found that pretreated hydro-alcoholic extract of bark of *Alstonia scholaris* to irradiated animals leads to a significant increase in erythrocytes, hematocrit, and hemoglobin values, and considerably lower lipid peroxidation levels [23]. In the post treatment study, it has been also found that aqueous bark extracts of *Alstonia scholaris* restores radiation-induced biochemical alterations in mice [48].

M- Anti-epileptic activity

C.Pradeep Kumar *et al.*, reported the ethanolic extract of *Alstonia venenata* R.Br. stem bark has anti-epileptic activity. It was exposed for phytochemical investigation and LD50. It was found that ethanolic extract contained reducing sugars, proteins, amino acids, flavonoids, phenolic compounds and tannins. Phenolic composites and flavonoids were responsible for anti-epileptic activities. Significantly ($P < 0.05$ - 0.01) produced anti-epileptic effect in mice at 100mg/kg compared to 50mg/kg by oral administration by using the method pentylenetetrazole induced model. It was decided that, the ethanolic extract of stem bark of *Alstonia venenata* R.Br. Possessed anti-epileptic activities. During acute toxicity study, no mortality was observed up to high dose of 1000mg/kg body weight. It was not possible to elucidate the actual mechanism through which *Alstonia venenata* R.Br. exerts its effects [35].

N- CNS activity

CNS activity of leaves *Alstonia macrophylla* was shown against its traditional use as a decoction to reduce mental tension and disturbance as well as to induce sleep [49]. CNS activity of methanol extract and major nonpolar nbutanol fractions A, B and C of *Alstonia macrophylla* leaves were studied in mice and rats through general behavior profiles, analgesic activities and exploratory behaviors. The results showed that *Alstonia macrophylla* appears to have a moderate to strong degree of antipsychotic activity [49].

O- Antiprotozoal activity

The antiprotozoal potential of bark methanolic and aqueous extracts was assessed *Leishmania donovani* and *Trypanosoma brucei* along with other 42 plant species [50]. The findings of this study confirmed antiprotozoal potential of *Alstonia macrophylla*.

P- Immunostimulating effect

The Immunostimulating effect of *Alstonia scholaris* bark extracts was studied in BALB/c mouse. The aqueous extract at 50 mg/kg.b.w. enhanced phagocytic activity of immunosuppressed mice significantly ($p < 0.01$). At 50 and 100 mg/kg b.w. the extract prevents the decline of immune system induced by prednisone. The aqueous extract at 100 mg/kg b.w. increased lytic activity of peritoneal exudate cells against *Escherichia coli* significantly ($P < 0.05$). The aqueous extract at 50 mg/kg b.w. induced the cellular immune response while at 100 mg/kg.b.w. inhibited the delayed type of hypersensitivity reaction [51].

III. CONCLUSIONS

An ethnopharmacological approach is needed for thorough analysis of plants used in traditional medicine. The most modern strategies for isolation and characterization pharmacological research have sparked interest in plants as potential sources for novel medicines. The plant *Alstonia scholaris* has a wide range of pharmacological activities, and many of its isolated compounds have not been studied for their pharmacological activity. It therefore seems worthwhile to scientifically validate the pharmacological properties of *Alstonia scholaris* constituents, which will support the plant's long history of use by tribal people as a medicine.

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