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Pharmacological activities of *Alstonia scholaris* linn. (Apocynaceae) - A Review

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ABSTRACT
Many herbal remedies have been employed in various medical systems for the treatment and management of different diseases. The plant *Alstonia scholaris* has been used in different system of traditional medication for the treatment of diseases and ailments of human beings. It is reported to contain various alkaloids, flavonoids and phenolic acids. It has been reported as antimicrobial, antiamoebic, antidiarrhoeal, antiplasmodial, hepatoprotective, immunomodulatory, anti-cancer, antiasthmatic, free radical scavenging, antioxidant, analgesic, anti-inflammatory, anti-ulcer, anti-fertility and wound healing activities. There are also reports available for the traditional use of this plant for its cardiotonic, anti-diabetic and anti-arthritic properties. Many isolated constituents from *Alstonia scholaris* lack the reports of pharmacological activities, which support its further pharmacological studies.
Keywords: *Alstonia scholaris,* Pharmacology, Traditional Uses, Review

INTRODUCTION
Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years and have served humans well as valuable components of medicines, seasonings, beverages, cosmetics and dyes. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness. In recent times, focus on plant research has increased all over the world and a large body of evidence has collected to show immense potential of medicinal plants used in various traditional systems. Today, we are witnessing a great deal of public interest in the use of herbal remedies. Further more many western drugs had their origin in plant extract. There are many herbs, which are predominantly used to treat cardiovascular problems, liver disorders, central nervous system, digestive and metabolic disorders. Given their potential to produce significant therapeutic effect, they can be useful as drug or supplement in the treatment / management of various diseases. Herbal drugs or medicinal plants, their extracts and their isolated compound(s) have demonstrated spectrum of biological activities. Such have been used and continued to be used as medicine in folklore or food supplement for various disorders. Ethnopharmacological studies on such herbs/medicinally important plants continue to interest investigators throughout the world.

One such plant, *Alstonia scholaris*, invites attention of the researchers worldwide for its pharmacological activities ranging from antimalarial to anticancer activities. *Alstonia scholaris* Linn. *R.Br*. belongs to family Apocynaceae (1), grows throughout India, in deciduous and evergreen forests, also in plains. The plant is widely found in India in sub Himalayan region from the Yamuna eastward ascending to 3000 feet above sea level, abundantly found in West Bengal and South India (2). It has wide occurrence also in the Asia-Pacific region from India, Sri Lanka through mainland South-East Asia and Southern China, throughout Malaysia to northern Australia and 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.

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. 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 (1, 2).

The synonyms of the plant include *Echites scholaris* L. *Echites pala* Ham., *Tabernaemontana alternifolia* Burm. The plant is also known as Alipauen, Andarayan, Bita, Dalipauen, Dirita, Dita, Ditaa, Dilupaon, Lava, Lipauen, Oplai, Pasuit, Pulai, Tanitan, Tangitang, Milky pine, White chesse wood, Devil tree, Shaitan wood, Saittan ka jat, Hale, Satween, Elilappalai, Saptaparna, Phalagaruda through out the world. The bark, leaves and milky exudates of *Alstonia scholaris* are used in India (1 – 3).

PHYTOCHEMISTRY
Alstonia scholaris Linn. is known to be a rich source of alkaloids and there is interest among the scientist to use this for therapeutic purposes. Amongst the chemical classes present in medicinal plant species, alkaloids stand as a class

Taxonomical Classification of Alstonia scholaris Linn. R.Br.

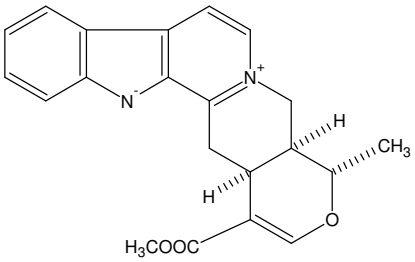
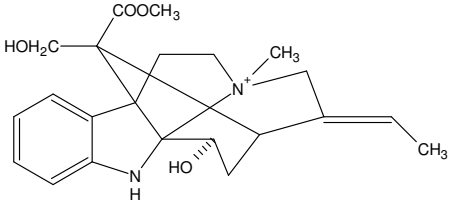
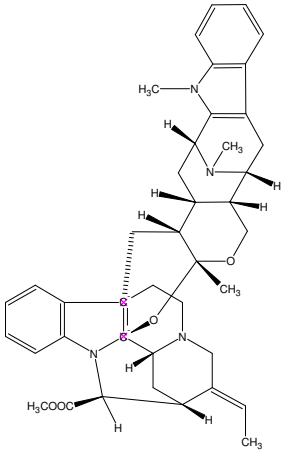
Taxonomy	***Alstonia scholaris***
Kingdom	*Plantae, Planta*
Subkingdom	*Tracheobionta, vascular plants;*
Division	*Magnoliophyta, Flowering plants;*
Class	*Magnoliopsida, Dicotyledon*
Subclass	*Asteridae*
Order	*Gentianales*
Family	*Apocynaceae*
Brief History	*The plant was named by Robert Brown in 1811, after Charles Alston (1685 – 1760), Professor of Botany at Edinburgh from 1716 – 1760. The type species Alstonia scholaris (L.) R. Br., was originally named as Echites scholaris by Linnaeus in 1767. The wood from this tree can be used to make blackboards for schools, and thus came the name 'blackboard tree' to the Taiwanese; hence the name scholaris.*

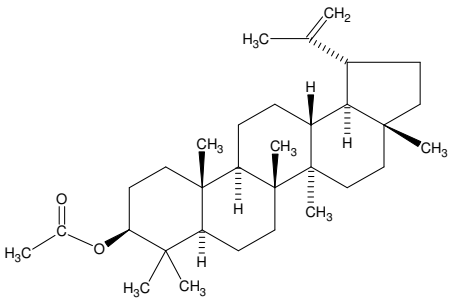
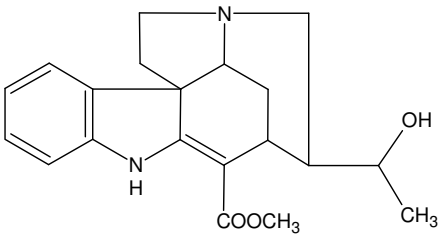
Traditional uses of Alstonia scholaris Linn. R.Br., (1 – 3)

Part	Constituents	Traditional Uses
Bark	Ditamine, echitamine, echitenine, echicaoutchin, echicerin, echitin, echitein, echiretin, ditain, ditamine, losbanine, 6,7-seco angustilobine B, N^b-demethyl echitmaine, 17-O-acetyl echitamine, picraline deacetyl, lupeol and β - sitosterol.	Stimulant, carminative, stomachic, bitter tonic, astringent, aphrodisiac, expectorant, febrifuge, alterative and antiperiodic. **Bark in Ayurveda** – febrifuge, alterative, tonic and gastrointestinal sedative. **Infusion, Tincture** - galactogogue **Fresh bark extract in milk** – leprosy, dyspepsia. **Amritashtakapachana –** valuable in debility, after effects of fever, chronic diarrhoea, dysentery and catarrhal fever. **Decoction (Pachan)** – After effects of Malaria, distinct drop in fever. **Philippines –** Fever and dysentery **Cambodia –** Astringent, antidysenteric and emmenogogue. Chronic plaudism with enlargement of spleen and liver. **Unani:** Ingredient of 'Kashim'. **Homoeopathy:** Malarial fever, anaemia, indigestion, general debility and other stomach ailments. **Ayush – 64:** Microfilaraemia **Ethanolic extract of Stem bark:** Antileishmanial activity.
Milky Juice or latex of Bark	caoutchouc and resins	Dental caries, pimple, pyorrhea. Applied to ulcers and rheumatic pains. Mixed with oil and dropped into ears, relieves earache.
Tender Leaves	picrinine, nareline, akuammidine, picralinal,akuammigine, betulin, ursolic acid, β - sitosterol, flavonoids, phenolic acids, scholarine.	Roasted, pulverized and made to a poultice which is used as a local stimulant to unhealthy ulcers. Administered to women after confinement, used in snake – bite and scorpion bite.

Leaves	Alschomine, isoalschomine, tubotaiwine, N^b-oxide, lagunamine, N^b – methyl scholaricine,pseudo-akkuammigine N^b oxide, akuammidine, N^a-methyl burnamine, picraline, picrinine, picrarinal, areline, angustilobine B acid, 6, 7 seco angustilobine B, losbanine, vallesamine, vallesamine N^b oxide, 6, 7 seco-19, 20 α-epoxy angustilobine B.	Anti–ulcer, anti-rheumatic, asthma. **Tribal use:** Anti –rheumatic, anti- diabetic (Tribals of Western Ghats)
Flower	Picrinine, strictamine, tetrahydroalstonine, n-hexacosane, lupeol, β-amyrin, palmitic acid, ursolic acid	Asthma, respiratory troubles.
Root	Picraline diacetyl	Enlarged liver with pain.

Pharmacological activities of isolated compounds from Alstonia scholaris Linn.

Name	Structure	Pharmacological activity
Alstonine		Antimalarial activity (39), Anxiolytic activity (40), schizophrenia (41-43), antipsychotic (44) and anticancer (45) activities.
Echitamine chloride		Anticancer activity in S–180, regression of tumour growth, fibrosarcoma (35 – 38).
Villalstonine		Antiamoebic, antiplasmodial activity against K1 strain of Plasmodium falciparum (18), In vitro anticancer activity against human lung cancer cell lines MOR-P and COR-L23 (21).

Lupeol acetate		Antifertility effect on male Wistar rats (31).
Scholaricine		---

of major importance in the development of new drugs because alkaloids possess a great variety of chemical structures and have been identified as responsible for pharmacological properties of medicinal plants. However, of the large variety of the alkaloids (about 180 alkaloids) isolated, so far only few have been assessed for biological activities (4). Almost all the parts of plant (bark, flower, root) are found to contain active principles. The species *A.scholaris* is used in commercial formulation Ayush 64 (3). The bark of this plant contains 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, a fatty acid and fatty resinous substances. An uncrystallisable bitter principle called ditain was isolated and ascribed the febrifuge properties of the drug (2).

Dung *et al* extracted the fresh plant material with hexane, hydrodistilled the combined extracts in slight and wet residue and analyzed by a high-resolution GC and GC/MS. The principal constituents were reported to be linalool (35.7 %), cis and trans linalool oxides, alpha-terpineol and terpinen-4-ol (5).

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 (6, 7). They also reported the isolation of 19, 20-dihydrocondylocarpine alkaloid from the leaves of *Alstonia scholaris* (8). Atta-ur-Rahman *et al* also isolated 19, 20-Z- Vallesamine and 19, 20-E- Vallesamine from *Alstonia scholaris* (9). Lagunamine (19-hydroxytubotaiwine), angustilobine B acid and losbanine (6,7-seco-6-nor-angustilobine 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* (10). 17-O-Acetylechitamine was isolated from the bark of the plant along with echitamine (10).

Macabeo *et al* reported the isolation and structural elucidation (MS and NMR) of first seco-uleine alkaloids, manilamine (18-hydroxy-19,20-dehydro-7,21-seco-uleine) and N^4-methyl angustilobine B) from the (pH 5) alkaloid extract of Philippine *Alstonia scholaris* leaves together with the known indole alkaloids 19,20-(E)-vallesamine, angustilobine B N^4-oxide, 20(S)-tubotaiwine and 6,7-seco-angustilobine B (11).

Tatsuo Yamauchi *et al* isolated several alkaloids from the leaves of *A. scholaris*. 19-epischolaricine, N^b-methylscholaricine, N^a-methylburnamine and vallesamine N^b oxide were isolated and their structures were determined by spectral and chemical methods. They reported that the leaves of plants from Taiwan and Thailand showed similar alkaloid patterns, with picrinine, nareline and alschomine as the major alkaloids (12).

Indole alkaloids, nareline ethyl ether, 5-epi-nareline ethyl ether and scholarine-N^4-ioxide, in addition to nareline methyl ether, picrinine and scholaricine were isolated form the leaf extract of *A. scholaris* by Toh-Seok Kam *et al* (13).Another indole alkaloid, alstonamine and a sitsrikine type indole alkaloid, rhazimanine, were also isolated from the leaves of *A. scholaris* by Atta-ur-Rahman *et al* (14).

PHARMACOLOGY

Traditional Uses

The bark is bitter, astringent, acrid, thermogenic, digestive, laxative, anthelmintic, febrifuge, antipyretic, depurative, galactogogue, stomachic, cardiotonic and tonic. It is useful in fever, malarial fever, abdominal disorders, diarrhoea, dysentery, dyspepsia, leprosy, skin diseases, pruritus, tumours, chronic and foul ulcers, asthma, bronchitis, cardiopathy, helminthiasis, agalactia and debility. The milky exudate is bitter and is good for ulcers, vitiated conditions of *vata* and otalgia (1,2).

The preparation infusion, 1 to 2 ozs., of tincture, 1 to 2 drachms diluted in water and of ditanin 5 to 10 grains given two or three times a day and an extract is prepared from the fresh bark and given in milk in cases of leprosy. It is also used as an anthelmintic (2).

Milky juice is applied to ulcers and to rheumatic pains; mixed with oil and dropped into ear it relieves earache. Tincture of the bark acts in certain cases as a powerful galactogogue.

Juice of the leaves with that of fresh ginger-root or zedoary is administered to women after confinement. The drug is also used in cases of snake-bite (2). The active constituents of the plant include antimalarials, CNS depressants, anticancers, antituberculosis, antidysentrics and galactopoietics (1 – 3).

Scientifically Validated uses

Antimicrobial activity

Goyal *et al* (15) reported the antimicrobial property of the plant constituents of *A. scholaris* (alkanes, alkanols and sterols). Khan *et al* (16) evaluated the antibacterial activity of the petrol, dichloromethane, ethyl acetate, butanol fractions of crude methanolic extracts of the leaves, stem and root barks of *Alstonia scholaris* and reported that butanol fraction exhibited broader spectrum of antibacterial activity.

Antidiarrhoeal activity

The antidiarrhoeal effects of the aqueous and the alcoholic bark extracts of *A. scholaris* in mice were reported by Patil *et al* (17).

Antiplasmodial activity

Keawpradub *et al* evaluated the antiplasmodial activity of the methanolic extracts of various parts of *A. scholaris* which was tested against multidrug-resistant K1 strain of *Plasmodium falciparum* cultured in 73 human erythrocytes. Pronounced antiplasmodial activity was exhibited. The indole alkaloids were isolated from the active extract and were subsequently tested against the K1 strain of *P. falciparum*. They reported pronounced antiplasmodial activity mainly among the bis-indole alkaloids, particularly villalstonine and macrocarpamine with IC_{50} values of 0.27 and 0.36 µM, respectively (18).

Ironically Gandhi and Vinayak have reported that the petroleum ether extract and methanol extract of the bark of *Alstonia scholaris* were found to be devoid of antiamalarial activity in mice infected with *Plasmodium berghei*. However, they have noticed a dose-dependent improvement of conditions and delayed mortality amongst animals receiving methanol extract of *A. scholaris* (19). Reports state that *A. scholaris* has little or no demonstrable action in malaria induced in monkeys and naturally occurring in human patients. It cannot, therefore, be recommended as a substitute for quinine and other cinchona alkaloids (2).

Hepatoprotective activity

The hepatoprotective effect of *Alstonia scholaris R. Br.* on liver injuries induced by carbon tetrachloride (CCl_4), Ƀ-D-galactosamine, acetaminophen and ethanol was investigated by Lin *et al* by serum-biochemical and histopathological examinations. All serological and histopathological effects of *A. scholaris* were comparative with those of *Bupleurum chinense*, which has been reported previously as treatment criteria of hepatitis. A tendency was also shown to inhibit cell necrosis and inflammatory cell infiltration caused by Ƀ-D-galactosamine in histopathological examination (20).

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 (21).

Antimutagenic activity

Lim *et al* reported the antimutagenic effect of *Alstonia scholaris* in micronucleus test in mice. Methylmethanesulfonate, mitomycin C and dimethylnitrosamine are genotoxic to bone marrow cells, since they fragment the chromatin material leading to the formation of micronucleated polychromatic erythrocytes in bone marrow cells of experimental mice. Expressions from *Alstonia scholaris L.* reduced the induction of micronucleated polychromatic erythrocytes by methylmethanesulfonate, mitomycin C and dimethylnitrosamine indicating that the plant has antimutagenic effect (22).

The radiosensitizing effect of alkaloid fraction of *Alstonia scholaris* (ASERS 5 µg/mL) was evaluated by Jagetia *et al* in various neoplastic cell lines, namely: HeLa, HePG2, HL60, MCF-7, and KB exposed to 0, 0.5, 1, 2, 3, and 4 Gy of gamma-radiation. The ASERS pretreatment increased the effect of radiation which was evidenced by enhanced cell killing when compared with the concurrent phosphate-buffered saline (PBS) treated irradiation group. Their study demonstrated that ASERS treatment enhanced the effect of radiation and disease-free survival of the mice (23).

They have also observed the alterations in the neoplastic activity of cyclophosphamide (CPA) by the extract of *Alstonia scholaris* (ASE) in mice transplanted with Ehrlich ascites carcinoma (EAC). Administration of *Alstonia scholaris* (120 mg/kg) 6 h before the administration of 25 mg/kg of CPA resulted in a greater tumor remission, drastic decline in the glutathione levels and increased the lipid peroxidation considerably when compared with drug alone (24).

Jagetia *et al* studied the chemopreventive effect of various doses of hydroalcoholic extract of *Alstonia scholaris* (ASE) on the benzo(a)pyrene (BaP) induced fore stomach carcinoma in female mice. The pre or post-treatment of mice with 4 mg/ml ASE also significantly reduced the frequency of BaP-induced MN in the splenocytes of treated animals (25).

Jagetia *et al* (26) also reported the seasonal variation as well as cytotoxicity of different fractions of *Alstonia scholaris* R. Br. (ASE) against HeLa cells. The exposure of HeLa cells to different extracts prepared from the stem bark collected in monsoon, winter and summer seasons resulted in a dose dependent increase in the cell killing effect of ASE and they observed the highest cell killing effect for the extract prepared from the summer collections. They have also observed that treatment of HeLa cells with different doses of various fractions of the *Alstonia scholaris* extract viz. residue in the order of (ASERS), steroidal (ASEST), chloroform (ASECH), petroleum ether (ASEPE), diethyl ether (ASEDE), ethyl acetate (ASEEA), n-butanol (ASENB), aqueous (ASEAQ) and echitamine chloride (ECL) also resulted in a dose dependent decline in the cell viability, where the cytotoxicity declined in the order of ASERS > ASE > ASECH >ECL > ASEEA > ASEDE > ASEPE > ASENB > ASEAQ > ASEST. Their study demonstrated that the extract prepared from the summer collection and the fractions containing the alkaloids were highly effective in cell killing.

Teratogenicity:

The teratogenic effect of hydroalcoholic extract of *Alstonia scholaris* (ASE) was studied in the pregnant Swiss albino mice by Jagetia *et al* (27) on Day 11 of gestation. The litters were monitored regularly for mortality, growth retardation, congenital malformations, and appearance of physiological markers up to 7 weeks post-parturition (p.p.). The administration of 60, 120, 180, and 240 mg/kg ASE to the pregnant mice on day 11 did not induce mortality, congenital malformations, or alter the normal growth patterns. A further increase in the herbal extract dose up to 360 or 480 mg/kg resulted in a dose dependent increase in the mortality, growth retardation, and congenital malformations, characterized mainly by bent tails and syndactyly. The administration of higher doses (360 or 480 mg) of ASE also caused a significant delay in the morphological parameters such as fur development, eye opening, pinna detachment, and vaginal opening. The incisor eruption and testes descend were found to be delayed in litters born to the mothers treated with 240-480 mg/kg ASE. The study indicated clearly that ASE treatment caused teratogenic effect only at doses above 240 mg/kg. Lower doses had no developmental toxicity.

Immunomodulatory activity

The immunostimulating effect of *Alstonia scholaris* bark extracts was studied in BALB/c mouse by Iwo *et al* (28). The aqueous extract at 100 mg/kg b.w. increased lytic activity of peritoneal exudate cells against *Escherichia coli*. At the doses of 50 and 100 mg/kg b.w., the aqueous extract had no effect on primary antibody level. 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 (28).

Antiasthmatic activity

Bronchodilatory activity of the ethanol extract of *Alstonia scholaris* leaves in anaesthetized rats was reported by Channa *et al* (29). *In vitro* preparations of guinea-pig trachea did not confirm this property, indicating that bronchodilation is not due to the direct tracheal smooth muscle relaxation. The vasodilatory activity of the extract was reported to be independent of adrenergic or muscarinic receptors or prostaglandins but was mainly via endothelial-derived relaxing factor, nitric oxide. The extract inhibited the spontaneous movements of rabbit jejunum and contractile effects of acetylcholine and histamine on guinea-pig ileum. Additionally, the extract caused marked reduction of barium chloride-, potassium chloride- and calcium chloride-induced contraction on guinea-pig ileum and pulmonary artery, implying a direct interference of plant extract with the influx of calcium ions into cells. However, the extract had no detectable effect on mobilization of intracellular calcium. These results coupled with the in vivo effects of ethanol extract reveal that the *Alstonia scholaris* leaves possess broncho-vasodilatory activity mediated presumably by prostaglandins, calcium antagonism and endothelium-derived relaxing factor(s).

Anti-fertility activity

The antifertility effect of *Alstonia scholaris* bark extract in male rats was evaluated by Gupta *et al* (30). Male Wistar rats were given with oral (200 mg/kg) bark extract of *Alstonia scholaris* 60 days. This did not cause body weight loss, while the weights of testes, epididymes, seminal vesicle and ventral prostate were significantly reduced. The production of step-19 spermatids was reduced by 79.6% in treated rats. The population of preleptotene and pachytene spermatocytes was decreased by 61.9% and 60.1%, respectively. Spermatogonia and Sertoli cell population were also affected. There was a decrease in seminiferous tubule and Leydig cell nuclear area, sperm count, motility, protein and sialic acid content of the testes, epididymes, 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 (31).

Free Radical Scavenging Activity

Jagetia *et al* evaluated the plant extracts of 17 commonly used Indian medicinal plants for their possible regulatory effect on nitric oxide (NO) levels using sodium nitroprusside as a NO donor in vitro. The potency of scavenging activity was reported to be as follows: *Alstonia scholaris* > Cynodon dactylon > Morinda citrifolia > Tylophora indica > Tectona grandis > Aegle marmelos (leaf) > Momordica charantia > Phyllanthus niruri > Ocimum sanctum > Tinospora cordifolia (hexane extract) = Coleus ambonicus > Vitex negundo (alcoholic) > T. cordifolia (dichloromethane extract) > T. cordifolia (methanol extract) > Ipomoea digitata > V. negundo (aqueous) > Boerhaavia diffusa > Eugenia jambolana (seed) > T. cordifolia (aqueous extract) > V. negundo (dichloromethane/methanol extract) > Gingko biloba > Picrorrhiza kurroa > A. marmelos (fruit) > Santalum album > E. jambolana (leaf). All the extracts evaluated exhibited a dose-dependent NO scavenging activity. The A. *scholaris* bark showed its greatest NO scavenging effect of 81.86% at 250 microg/mL, as compared with *G. biloba*, where 54.9% scavenging was observed at a similar concentration (32).

Wound healing activity

Wound healing activity of the ethanol and aqueous extracts of *Alstonia scholaris* was tested against excision, incision and dead space wound models (33). The wound healing was assessed by the rate of wound contraction, period of epithelialisation, skin breaking strength, granulation strength, dry granulation tissue weight, hydroxyproline, collagen and histopathology of granulation tissue. Malondialdehyde level was also estimated to evaluate the extent of lipid peroxidation. The extracts promoted wound healing significantly in all the wound models studied. Increased rate of wound contraction, skin breaking strength, granulation strength, dry granulation tissue weight, hydroxyproline and collagen, decrease in the period for epithelialisation and increased collagenation in histopathological section were

observed with extracts treated groups. The extracts also significantly decreased the levels of lipid peroxidation.

Analgesic and anti-inflammatory activities

The effect of ethanolic extract of leaves of *alstonia scholaris* was evaluated in experimental models of pain and inflammation (34). the leaf extract at 200 and 400 mg/kg showed significant decrease in acetic acid induced writhings in mice with a maximum of 65.76 % at 400 mg/kg. in hot plate method, the percentage of pain inhibition was found to be 73.90 % and 79.56 % with 200, 400 mg/kg of extract. there was a significant inhibition in carrageenan induced paw edema with 200 and 400 mg/kg of the extract.

Anti-ulcer activity

The ethanolic extract of leaves of *Alstonia scholaris* was evaluated for anti-ulcer activity (34) by pyloric ligation method. The animals treated with the extract did not show ulcer, whereas the ulcer score was found to be significantly high ($p<0.01$) in rats administered diclofenac sodium.

Anthelmintic activity

Anthelmintic activity of the alcoholic extract of *Alstonia scholaris* was investigated using *Ascardia galli*. Glucose uptake, glycogen content, lactic acid production, gross motility and acetylcholine esterase (AchE) activity of the worms were estimated after the incubation. There was a significant inhibition of glucose uptake and decrease in glycogen content of the worms with *Alstonia scholaris*. There was a significant increase in lactic acid content and decrease in gross motility which indicates that the extract affects the energy generating mechanism of the parasite. The significant increase in lactic acid content suggests the inhibition of ATP production or accumulation of lactic acid. The extract had significant anthelmintic activity and the possible mechanism of action may be by inhibition of energy metabolism (unpublished data of the author).

Antioxidant activity

The effect of ethanolic extract of *Alstonia scholaris* Linn. (Apocynaceae) on various *in vitro* antioxidant parameters was evaluated. Ethanolic extract of *Alstonia scholaris* had significant ($DPPH^{\cdot}$) free radical scavenging, metal ion chelating, hydrogen peroxide scavenging, superoxide anion radical scavenging and ferric thiocyanate reducing activities. Ethanolic extract of *Alstonia scholaris* Linn. was found to prevents lipid peroxidation and radicalic chain reactions. The results observed were comparable to that of BHA, BHT, l-ascorbic acid and α-tocopherol (unpublished data of the author).

PHARMACOLOGICAL ACTIVITIES OF ISOLATED CONSTITUENTS

Echitamine Chloride:

Saraswathi *et al* reported that echitamine chloride (EC), an indole alkaloid, extracted from the bark of *Alstonia scholaris* has got highly promising anticancer effect. The effect of this drug on the microsomal drug detoxifying system was studied in sarcoma-180 induced mice. When given subcutaneously at a dosage of 5 mg/kg body weight, it was able to alter the impaired drug detoxifying system which was observed in the sarcoma-180 bearing mice (35).

Further, echitamine chloride was also found to affect both cellular and mitochondrial respiration, leading to reduction of the cellular energy pool and thereby resulting in the loss of viability of S-180 cells (36).

They have also reported the enhancement of the cytotoxic effects of echitamine chloride by vitamin A on *in vitro* Ehrlich ascites carcinoma cell culture. They report a tumoricidal action by a free radical dependent mechanism similar to that of adiramycin, mitomycin – C and bleomycin (37).

Saraswathi *et al* (38) screened for the anticancer effects of echitamine chloride on methylcholanthrene-induced fibrosarcoma, which exhibited significant regression in tumor growth. The altered activities of plasma and liver transaminases and gamma-glutamyl transpeptidase and lipid peroxidation in fibrosarcoma have been corrected to near normal after echitamine chloride treatment. The decreased liver glutathione content and the lowered activities of glutathione peroxidase, superoxide dismutase and catalase have also been reversed to near normals after echitamine chloride treatment.

Alstonine:

The indole alkaloid alstonine has been identified as the major component of a plant-based remedy. In a preliminary evaluation done by Wright *et al*, alstonine demonstrated *in vivo* antimalarial activity (39).

It is used in Nigeria to treat mental illnesses by traditional psychiatrists. Although it is certainly difficult to compare the very concept of mental disorders in different cultures, the traditional use of alstonine is remarkably compatible with its profile in experimental animals. Even though alstonine in mice models shows a psychopharmacological profile closer to the newer atypical antipsychotic agents, it also shows important differences. Meldrum and Ozawa *et al* reported that alstonine possesses clear anxiolytic activity (40), mediated by $5\text{-}HT_{2A/2C}$ serotonin receptors, suggesting effectiveness against negative symptoms of schizophrenia; It interferes with the glutamate system in a manner consistent with resulting beneficial effects for schizophrenia (41 – 43).

According to the study of Costa-Campos *et al*, alstonine lacks the pro-convulsant property (44) common to many antipsychotics, a considerable advantage for chronic use in general and epileptic schizophrenic patients in particular. The lack of direct effects on dopaminergic system suggests lack of significant extra pyramidal effects, the major drawback of many antipsychotic agents.

Beljanski and Beljanski reported about the anticancer activity (45) of alstonine which successfully treated a relatively important proportion of BALB/C mice inoculated with transplantable YC8 lymphoma ascites cells as well as Swiss mice bearing Ehrlich ascites carcinoma cells. Development of some solid tumours was only partially prevented by alstonine.

Beljanski also reported the capacity of alstonine to distinguish cancer DNA from the healthy tissue DNA (46). It inhibits DNA *in vitro* synthesis when DNA from different cancerous tissues or cells is used as template. The reported inhibitory effect of alstonine is due to its capacity to form an alkaloid-cancer DNA complex.

CONCLUSION

Plants, which are used in traditional medicine, require detailed investigation with ethnopharmacological approach. The recently developed isolation, characterization techniques and pharmacological testing have led to interest in plants as a source of new drugs. The plant *Alstonia scholaris* has a wide array of pharmacological activities and many isolated compounds of *Alstonia scholaris* lack study on their pharmacological activity and therefore seems worthwhile to scientifically validate the pharmacological properties of constituents of *Alstonia scholaris,* which will substantiate the use of this plant over centuries for medicinal purposes by tribal people.

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