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OVERVIEW OF TRADITIONAL, PHYTOCHEMICAL, AND PHARMACOLOGICAL USES OF PULAI (*ALSTONIA SCHOLARIS*)

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ABSTRACT

Many herbal medicines have been used in various medical systems for the treatment and management of various diseases. Pulai plant (*Alstonia scholaris*) has been used in various traditional treatment systems to treat various diseases in humans. Phytochomically, this plant has been reported to contain various alkaloids, flavonoids, and phenolic acids. Pharmacologically this plant has been reported as an antimicrobial, antiamoebic, antidiarrheal, antiplasmodial, hepatoprotective, immunomodulatory, anticancer, antiasthmatic, free radical scavenging, antioxidant, analgesic, anti-inflammatory, anti-ulcer, anti-fertility, anti-fertility, and anti-wound healing activities. There are also reports available for this plant's traditional uses because of its cardiotonic, antidiabetic, and anti-rheumatic properties. Many isolated constituents of *Alstonia scholaris* have reports of pharmacological activity, which supports further pharmacological studies.

KEYWORDS: *Alstonia scholaris*, Traditional Use, Phytochemistry, Pharmacology.

INTRODUCTION

Pulai is the name of a tree with the botanical name *Alstonia scholaris*. This tree is from a type of tree plant that lives on the islands of Java and Sumatra. This tree is also known locally as pule, corkwood, lame, lamo, and jelutung. The wood's quality is not too hard and is not preferred for building materials because the wood is smoothly curved when it is damp but is widely used to make household appliances out of wood and carvings and sculptures. This tree is widely used for greening because its leaves are shiny green, lush, and wide to the side, giving coolness (Figure 1). The skin is used as a raw material for medicine. efficacious for treating strep throat and others.[1]

Figure 1. Pulai tree.[2]

Pulai trees can reach 40 m in height. The leaves are shiny green with pale lower leaves. The leaves line up with three to ten leaves and petioles along the 3 cm length (Figure 2).

Figure 2. Pulai leaves.[3]

The flowers bloom in October and have a fragrant aroma (Figure 3). Pulai seeds are oblong shaped and have hair. The bark has no odor but has a very bitter taste, with quite a lot of sap. The stem is dark green. Pule blossoms are a type of compound flowers, with ovoid petals, yellowish-white. The fruit of this plant is ribbon-shaped, white, with a length of 20 - 50 mm. Small white seeds with a length of 1.5 - 2 cm. The root of the so-called plant anchor is tap-shaped and brown.

Figure 3. Pulai flower.[4]

Scientific classification[1]

Kingdom: Plantae

Clade: Tracheophytes

Clade: Angiosperms

Clade: Eudicots

Clade: Asterids

Order: Gentianales

Family: Apocynaceae

Genus: Alstonia

Species: *A. scholaris*

Binomial name: *Alstonia scholaris* L. R. Br.

Synonym: *Echites scholaris* L.

This plant was named Robert Brown in 1811, after Charles Alston (1685-1760), Professor of Botany, in Edinburgh from 1716-1760. The species of *Alstonia scholaris* (L.) R. Br. was initially named *Echites scholaris* by Linnaeus in 1767. Wood from this tree can be used to make blackboards for schools, and thus the name 'chalkboard tree' appears for Taiwanese; hence the name *scholaris*.[5]

Evergreen trees are widely planted throughout India and are also found in China, Africa, Southeast Asia, Latin America, and Australia. This bark is well-known in Hindu medicine for centuries as a tonic, alterative, useful for fever and skin diseases, chronic diarrhea medicine, and advanced stages of dysentery, valued as a heat-lowering drug, and used in the treatment of gout, rheumatism, in recovery after illness and exhausting fever. In China, this is widely used to treat respiratory diseases like cough, asthma, sputum, and COPD. On the island of Luzon, the bark is valued by the natives as the most potent tonic and heat-reducing drug and is used as a decoction for a long time for severe, intermittent, and remittance fevers. In

Nigeria, the bark is widely used as an antipyretic in malaria, and sometimes, along with leaves and roots, in external applications for rheumatic pain. In Ghana, bark decoction is given after delivery to help remove the placenta. The bark contains triterpenes: β-amyrine and lupeol; and indole alkaloids: echitamine or designed as the main alkaloids, alstoscholarisines H-J, echitamidine, and lactone ditamine. Methanol bark extracts produce adaptogenic effects in mice, improve cognitive function and memory, and show vigorous antioxidant activity. Petroleum ether and methanol extracts did not have antimalarial activity against P. falciparum (in vitro) and P. berghei (in vivo); Methanol extract, however, delayed death and improved the physical condition of the treated rats. Spasmolytic activity in isolated preparations is proposed due to calcium channel blockade, and bronchovasodilatoric activity is thought to be due to prostaglandins, calcium antagonism, and NO release.[28]

DATA COLLECTION

In compiling this review article, the technique used is to use literature studies by finding sources or literature in the form of primary data or the form of official books and international journals in the last 20 years (2000-2020). Also, in making this review article then search for data using online media with keywords is Alstonia scholaris, phytochemicals, and pharmacology. Search for the primary references used in this review article through trusted websites such as Mendeley, ScienceDirect, NCBI, ResearchGate, Google Scholar, and other published and trusted journals.

TRADITIONAL USE

Alstonia scholaris is an important traditional medicinal plant. This tree is a plant native to the Indian subcontinent and Southeast Asian countries. This plant is used in traditional alternative medicine systems, Ayurvedic, Unani, Homeopathy, and Siddha/Tamil against various diseases such as asthma, malaria, fever, dysentery, diarrhea, epilepsy, skin diseases, snake bites, and other.[6]

Alstonia scholaris Linn., popularly known as "Saptaparni" or the tree of Satan, is used as a well-known drug for the treatment of various types of disorders in the Ayurvedic, Homoeopathic and Folklore treatment systems in India. *Alstonia scholaris* is mainly used to treat diarrhea and malaria, as a tonic, heat-lowering drug, emmenagog, anti-choleric, and susceptible.[7]

Alstonia scholaris (L.) R. Br. and *Alstonia macrophylla* Wall. ex G. Don is two important medicinal plant species (Family: Apocynaceae). In India, the use of *Alstonia scholaris* therapy has been described in a codified and not codified drug system for malaria, jaundice, digestive problems, cancer, and many other diseases. Another species, *Alstonia macrophylla*, has been used in conventional medicine in Thailand, Malaysia, and the Philippines as a general tonic, aphrodisiac, anticholinergic, antidysenteric, antipyretic, emmenagogic, and susceptible agent.[8]

Tribal and non-tribal indigenous communities in the coastal district of Karnataka use *Alstonia scholaris* (L.) R. Br. for the treatment of various diseases such as fever, asthma, vaginal discharge, eczema, digestive disorders, and curing spider bites. Annual health-related rituals, mass drinking bitter juice or decoction of tree bark in the new moon (Amavasya), the 'aati' month of the traditional 'Tulu' calendar, which coincides with the rainy season, followed in the study area, mainly by rural families. The underlying belief is that this drink keeps away all diseases and ensures prosperity. The recorded ethnomedicinal use and traditional practice of drinking bitter juice seem to be scientifically meaningful when interpreted based on the ayurvedic background and various curative properties derived from this plant, many of which have been confirmed by reported pharmaco-chemical studies. Showed that the toxicity of bark extract was minimal during the rainy season and the maximum active principle concentration in skin juice collected on certain new moon days. This study further justifies the time of the annual medication program described. Also, some Tulu-speaking indigenous communities consider this tree as a reincarnation of a mythological demon named Bali and worship its branches during the Deepavali festival days, in his honor. As such, *A. scholaris* appears as a plant with excellent ethnobotany significance in the study area.[25]

The study was conducted to document ethnomedicinal plants used against jaundice by tribes in the Morigaon district in Assam, India. An ethnomedicinal field study was conducted from June 2016 - July 2017. Information was collected using a semi-structured questionnaire about traditional knowledge of medicinal plants used against jaundice by the tribes in the Morigaon district in Assam. Documented data were evaluated using quantitative ethnobotany indexes of loyalty (FL), Value Use (UV), and Family Use Value (FUV). A total of 39 plant species, including 36 genera and 27 families, have each been mentioned from ethnobotanical investigations. A total of 53 informants aged 20 - 75 years were interviewed to record ethnomedicinal data. Lamiaceae is a dominant family. Among the plant parts, the leaves are

used most often. Among the 39 species of medicinal plants that are recognized mostly plant. Plant species that have the highest use value are *Drymaria cordata*, followed by *Xylosma longifolia* and *Achyranthes aspera*, *Aegle marmelos*, *Alstonia scholaris*, and *Justicia gendarussa*. The level of loyalty is 100% for *Achyranthes aspera, Cheilocostus speciosus, Clerodendrum infortunatum, Justicia gendarussa, Lawsonia inermis, Coffea benghalensis*, and *Saccharum officinarum.* The tribes in the Morigaon district still rely on herbal therapy to cure jaundice. *Coffea benghalensis* has never been reported as a jaundice cure from Northeast India. Further research is needed to investigate the effectiveness of phytochemistry and pharmacology of plant species that can be the basis for the isolation and development of several new active phytotherapeutic compounds in the future.[26]

PHYTOCHEMICAL REVIEW

The first seco-uleine alkaloids, manilamine (1) (18-hydroxy-19,20-dihydro-7,21-seco-uleine) and N-methyl angustilobine B (2) were isolated from extracts of alkaloids (pH 5) of *Alstonia scholaris* leaves Philippines together with known indole alkaloids 19,20-(E)-vallesamine (3), angustilobine BN-oxide (4), 20(S)-tubotaiwine (5), and 6.7-secoangustilobine B (6). The structure of the alkaloids was determined by MS and NMR experiments.[9]

A pair of geometric isomeric indole monoterpenoid alkaloids with a skeletal arrangement and two additional carbons, named (19,20) E-alstoscholarine (1) and (19,20) Z-alstoscholarine (2), were obtained from *Alstonia scholaris* leaf extracts (Figure 4). Their structure is explained based on spectroscopic methods and then confirmed by X-ray crystal diffraction. The biogenesis of these compounds is also proposed.[10]

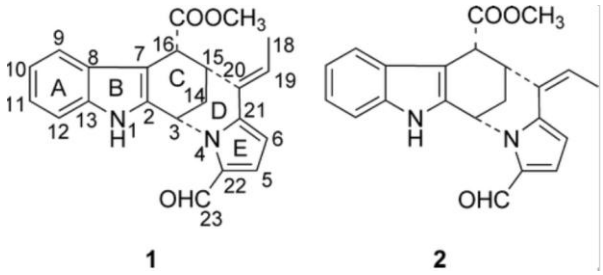

Figure 4. Structure (19,20)-E-alstoscholarine (1) and (19,20)-Z-alstoscholarine (2).

An unprecedented alkaloid like a cage, scholarisine A, was isolated from the leaves of *Alstonia scholaris*. Its structure was determined based on 1D and 2D NMR, FTIR, UV, and high-resolution mass spectroscopy data (Figure 5). These alkaloids may originate from picrinine through oxygenation, rearrangement, and lactonization.[11]

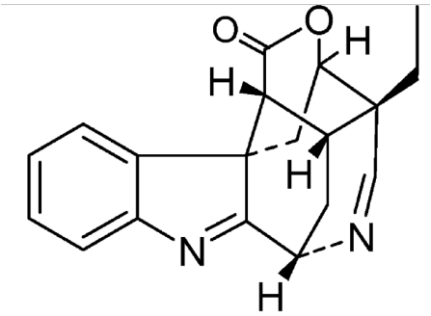

Figure 5. Alkaloid structure: scholarisine A.[11]

2,3-Secofernane triterpenoid, alstonic acid A (1), and B (2), isolated from the leaves of Alstonia scholaris together with indole alkaloids, N1-methoxymethyl picrinine (3). Their structure was formed from MS and NMR spectroscopic analysis and was confirmed by single-crystal X-ray diffraction analysis (Figure 6).[12]

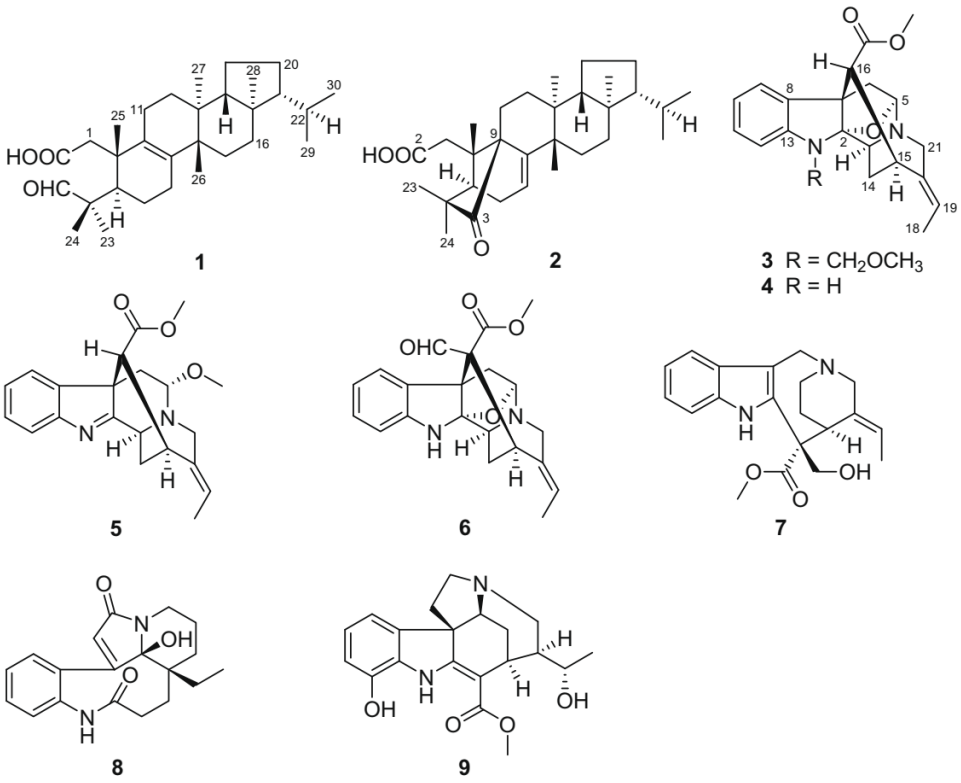

Figure 6. Structure of compounds 1 - 9 isolated from *A. scholaris*.[12]

Six new monoterpenoid indole alkaloids, scholarisine B-G (1-6), and 15 known analogs (7-21) are isolated from the bark of Alstonia scholaris. Their structure is determined by 1D and 2D NMR spectra and MS analysis. Single-crystal X-rays further support structure 1.[13]

Pulai (*Alstonia scholaris* R.Br), Apocynaceae family is one of the forest plants that function as a traditional medicine to treat fever, malaria, cough with phlegm, diarrhea, diabetes,

cholesterol-lowering, intestinal worms, acute rheumatism, ulcers, and hypertension. The total phenol content is 51.50 mg GAE/g extract, while the total flavonoid content is 0.35 mg QE/g extract.[14]

Alstoniascholarines T (1) and U (2), two novel monoterpenoid indole alkaloids from *Alstonia scholaris*, allow unexpected deuteration through activation of the CH sp2 bond without any catalyst below room temperature (Figure 7). Structurally, alkaloids 1 represent the rare in dry strychnan nor-C17, and compound 2 has a highly modified strychnan skeleton with a new furan ring between C-16/19. This finding presents a detailed description of natural products with self-activation and deuteration of sp2 CH itself, which can explain the CH functionalization that is blocked by expensive metal catalysts and rather harsh reaction conditions.[31]

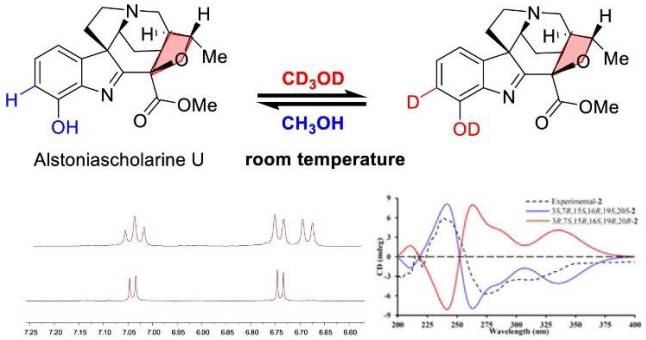

Figure 7. Activation of the CH sp2 bond without any catalyst at room temperature.[31]

Alstonia scholaris (L.) R. Br (Apocynaceae), a tropical tree originating from the Indian subcontinent, Australasia, and the Malay Peninsula, is well documented in Traditional Chinese Medicine and Ayurveda to cure fever and pain inflammation, cancer, breathing, and disorders skin. Nearly 169 alkaloids have been reported along with iridoids, coumarins, flavonoids, and steroids from this plant. Data analysis reveals that there are requirements for turning existing knowledge into finished products. For example, straminamine isolated from this plant has shown the same antiviral activity as acyclovir. However, discovering the new potent antiviral indole alkaloids will require the study of the relationship of structural activity with the natural analogs of these compounds. In conclusion, although there are more than 100 patents and various *A. scholaris* pharmacological activities, only one product has reached the market. The report establishes a gap between existing knowledge and the requirements for commercialization of *A. scholaris* derivative products.[32]

Scholarinine A (1), an indole alkaloid such as a new N-type cage, is isolated from branches and leaves of *Alstonia scholaris*. Structurally, (1) is displayed by a unique 6/5/6/5/5/6 carbocyclic skeleton, which has a new imidazolidine ring E. Structure 1 is determined by extensive spectroscopic analysis and X-ray crystallography (Figure 8). Biological studies show that compound 1 is a Ca-Ca-T type calcium channel blocker with an IC value of 4.28μM. Also, 1 promotes neurite growth from nerve growth factor (NGF) mediated by PC12 cells at ten μM.[33]

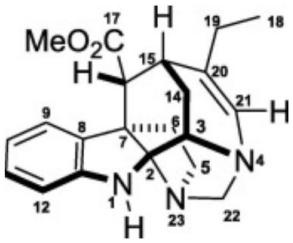

Figure 8. Structure of scholarinine A (1).[33]

PHARMACOLOGICAL REVIEW

Antibacterial

Crude methanol extracts of leaves stem and bark of *Alstonia scholaris* and *Leea tetramera* in the partition (benzene, dichloromethane, ethyl acetate, butanol) provide fractions that show a better and broader spectrum of antibacterial activity. Especially the butanol fraction of *A. scholaris* and root bark *L. tetramera.* No active fraction of the fungi tested.[15]

The antibacterial activity of *Alstonia scholaris* R.Br. has also been investigated. Antibacterial activity was tested against both Gram-positive and Gram-negative organisms. The methanol extract of this plant leaf showed broad-spectrum antibacterial activity against the organism tested. Maximum activity is shown against *Bacillus subtilis* followed by *Escherichia coli* and *Staphylococcus aureus*. Chloroform and acetone extracts showed lower activity, whereas petroleum ether extract showed no inhibition.[16]

Antidiabetic

α-Glucosidase inhibitors are used in the treatment of insulin-dependent diabetes mellitus. Researchers have tried to isolate α-glucosidase inhibitors from 24 samples of traditional Thai medicinal plants. Inhibitory activity of α-glucosidase is found in aqueous methanol extract of dried Devil leaves (*Alstonia scholaris*). The active ingredients against α-glucosidase, made from rat small intestine acetone powder, were isolated and identified. The structure of this

isolated compound was found to be quercetin 3-O-β-D-xylopyranosyl (1‴ → 2″)-β-D-galactopyranoside and (-) - lyoniresinol 3-O-β-D-glucopyranoside based on chemical and spectral evidence. The latter shows inhibitory activity against sucrase and maltase with IC values of 1.95 and 1.43 mM, respectively, whereas the previous one only inhibited maltase with IC values of 1.96 mM. These preliminary observations will provide a basis for further examining the suitability of *Alstonia scholaris* as a drug supplement that contributes to the treatment and prevention of diabetes.[17]

Alstonia scholaris is commonly known as the Devil tree belonging to the Apocynaceae family. *Alstonia scholaris* species are used as medicines for the treatment of various diseases. This research was carried out to develop environmentally friendly, inexpensive, and effective procedures for the synthesis of green Silver Nanoparticles (AgNPs) from aqueous extracts of *Alstonia scholaris* leaves (ASAE) and evaluate their antidiabetic activity in vitro. The addition of ASAE to $AgNO_3$ (1 mM) solution continued to be stirred at 60 ^oC resulting in the formation of *Alstonia scholaris* extract containing Nanoparticles (ASAENP). Various procedures characterized by synthesized nanoparticles. UV-Visible spectroscopy shows peak absorption at 440 nm, which is present in ASAE and AgNO3. FTIR spectroscopy revealed peak absorption from various functional groups involved in the formation of ASAENP. Scanning Electron Microscopy (SEM) revealed an average size ranging from 72.9 nm to 144.9 nm with an average size of 115.95 nm and round. The particle size was determined, and its size was found 263.3 nm. ASAENP stability was determined by Zeta Potential, which was found to be -61.3 mV & Electrophoresis. Mobility average found - 0,000474 cm^2/Vs. Successfully marked ASAENPs are evaluated for their in-vitro antidiabetic activities such as alpha-amylase activity and alpha-glucosidase activity. Acarbose is used as a standard.[24]

Anti-inflammatory and analgesic

Alkaloid fraction of *Alstonia scholaris* leaves, three main alkaloids, picrinine, vallesamine, and scholaricine, can produce peripheral anti-inflammatory and analgesic effects based on several in vivo tests. In in vitro tests, alkaloids show inhibition of inflammatory mediators (COX-1, COX-2, and 5-LOX), consistent with the results in animal models. Additionally, dual COX-2/5-LOX inhibitors found in experiments, such as 16-formyl-5α-methoxystrictamine, picralinal, and tubotaiwine, may be further valuable attention.[18]

Since ancient times, *Alstonia scholaris*, commonly known as the devil tree or chalkboard tree, has been used to treat many human diseases. This plant is used in Ayurvedic, Unani, and

Siddha/Tamil alternative medicine systems. Literature shows that *Alstonia scholaris* is useful in treating malaria, stomach disorders, dyspepsia, leprosy, skin diseases, tumors, chronic and foul ulcers, asthma, bronchitis, and other. By this ethnobotanical practice, the anti-inflammatory activity of methanol extracts and various bioactive fractions of Saptparn (*Alstonia scholaris*, Apocynaceae) was tested. The anti-inflammatory activity of the extract and its various fractions was evaluated using the carrageenan-induced mouse foot edema method to determine the acute phase of inflammation. Indomethacin is used as a reference drug. Pharmacological (anti-inflammatory) studies show methanol extract (200 mg/kg) significantly inhibits carrageenan rat paw edema compared with edema inhibition by standard drug Indomethacin (10 mg/kg). Maximum inhibition of mouse foot edema was observed with plant methanol extract (400 mg/kg) at the end of the 4th hour compared with the control group. The chloroform fraction (50 mg/kg and 100 mg/kg) has a statistically significant anti-inflammatory activity. Maximum inhibition of mouse foot edema was observed with a chloroform fraction at 100 mg/kg at the end of the 5th hour compared with the control group.[29]

Anticancer

The anticancer effect of various doses of the Sapthaparna alkaloid fraction, *Alstonia scholaris* (ASERS), was studied *in vitro* in cultured human neoplastic cell lines (HeLa, HepG, HL60, KB, and MCF-7) and Ehrlich ascites carcinoma. The treatment of HeLa cells with 25 µg/mL ASERS increased in time, depending on the antineoplastic activity. The greatest activity was observed when cells were exposed to ASERS for 24 hours. However, cell exposure to ASERS for 4 hours resulted in 25% of cells being viable. Hence, this time interval was considered the optimal time for treatment and further research was carried out using this time. The treatment of various cells with ASERS resulted in a decrease depending on the proper cell concentration, and nadir reached at 200 µg/mL in all cell pathways studied. IC was found to be 5.53, 25, 11.16, 10 and 29.76 µg/mL for each HeLa, HePG, HL60, KB and MCF-7 cells. Likewise, giving ASERS, once a day for nine consecutive days in mice containing tumors, causes remission depending on the dose up to 240 mg/kg body weight, where the greatest antitumor effect is observed. Because 240 mg/kg ASERS shows toxic manifestations, subsequent lower doses of 210 mg/kg are considered the best effective dose, where 20 % of animals survive up to 120 days after cell inoculation after the tumor and no survivors in the saline-controlled control group. Administration of ASERS results in a dose-dependent increase in average survival time (MST) and average survival time (AST) to 240

mg/kg ASERS and decreases after that. The animals that survived were healthy and free of disease. The ASERS effect is better than cyclophosphamide, which is used as a positive control, where all animals die for up to 40 days, and MST and AST are 19.5 and 18.3 days, respectively. The effective dose of ASERS 210 mg is 3/10 of the LD dose, which increases MST and AST up to 54 and 49.5 days, respectively.[19]

The use of medicinal plants in modern medicine to prevent and treat cancer is an important aspect. Thus, it is essential to identify the antitumor triggering agents present in medicinal plants commonly used by human populations. We used in vivo and in vitro methods using chromosomal aberrations (CAs), sister chromatid exchange (SCE), and replication index (RI) as markers. Which were exposed by methyl methanesulfonate (MMS) and *Alstonia scholaris* alcohol extract in five increased concentrations 200, 250, 300, 350 and 400 mg/kg body weight for *in vivo* and 150, 200, 250 and 300 µg/mL of culture and three different durations 24, 48 and 72 hours in the presence and also the absence of S9 mixture. Alstonia extract reduced the total deviated cells from 10.0 % to 41.84 %, and the frequency of deviations in abnormal cells ranged from 220 to 124 against 290 causes of deviations due to MMS *in vivo*. Similarly, *in vitro*, it reduced CA (39.62 %, 32.83 %, and 38.48 %) and (45.31 %, 44.46 %, and 38.34 %) at 24, 48, and 72 hours of exposure respectively; in the absence and presence of a heart S9 fraction. It also reduced SCE from 7.70 to 4.20 per cell and increased RI from 1.45 to 1.64. Alstonia extracts significantly reduces the number of abnormal cells and frequency of irregularities per cell at each concentration and duration of exposure in vivo; and CAs and SCE in vitro and increasing RI.[20]

Alstonia scholaris R.Br (pulai) is one of the traditional forest plants to treat various types of diseases such as arthritis, diabetes, hypertension, and hyperlipidemia. On the other hand, research on this species as an anticancer is minimal. This study aims to determine the in vitro cytotoxic activity of three A. Scholaris skin fractions against breast cancer (MCF-7) and normal cells (Vero). Three fractions of A. Scholaris bark (fraction of n-hexane, chloroform, and ethanol) derived from 70 % of coarse ethanol bark extracted. MTT test (3- 4,5-dimethylthiazol-2- -2,5-diphenyl tetrazolium bromide) is applied to MCF-7 and Vero total cells. The results showed that the n-hexane fraction had the strongest cytotoxic effect on MCF-7 cells. Followed by the chloroform and ethanol fraction with an IC_{50} value of 109.01; 163.33; and 264.19 µg/mL respectively, but the ethanol fraction was the most toxic in Vero cell growth compared to the n-hexane and chloroform fractions with an IC_{50} value of 579.93;

459.47; and 396.24 µg/mL respectively. It is recommended that the ethanol fraction is the best fraction recommended as an anticancer agent because it is the lowest toxicity for normal cell growth, but is still toxic to cancer cells. It was concluded that the ethanol fraction was the best fraction for breast cancer cells.[34]

Antioxidant

Pulai (*Alstonia scholaris* R. Br), Apocynaceae family is one of the forest plants that function as a traditional medicine to treat fever, malaria, cough with phlegm, diarrhea, diabetes, cholesterol-lowering, intestinal worms, acute rheumatism, ulcers, and hypertension. One cause of heart disease, atherosclerosis, and cancer is oxidative stress. This stress can be cured or reduced by using antioxidants. Flavonoids are phenol compounds and are among the secondary metabolites in plants that function as antioxidants. This paper studies the total phenol content, total flavonoids, and antioxidant activity of bark extract. Quantitative determination of total phenol by the Folin-Ciocalteu method is expressed as gallic acid equivalent (GAE) per gram of extract. Total flavonoid levels by the $AlCl_3$ method is expressed as Quercetin equivalent (QE), and in vitro, antioxidant activity with DPPH (2, 2-diphenyl-1 -picrylhydrazyl) expressed in terms of IC_{50} (inhibition concentration). The results showed that the extraction of three replications in maceration with 96 % ethanol produced 4.1 9% filtrate. The total phenol content is 51.50 mg GAE/g extract, while the total flavonoid content is 0.35 mg QE/g extract. The IC50 value obtained from the antioxidant test results of stem bark extract was 211.54 µg/mL.[14]

Cough medicine

Alstonia scholaris (Apocynaceae) is documented as a useful herb for the treatment of chronic respiratory diseases in ethnopharmacy historically. Moreover, its crude leaf extract, which is used to release tracheitis and cold symptoms, is approved as a commercial formulation by the State Food and Drug Administration (SFDA). The investigation evaluated the anti-tussive and anti-asthma activities of ethanol extract, the main fraction, and alkaloids from *Alstonia scholaris* leaves to provide experimental evidence for traditional and modern clinical use. The most exciting part of us is revealing the active components for further development of new drugs. *Alstonia scholaris* leaves were extracted with ethanol and then separated into different fractions. Next, the alkaloids were isolated by the phytochemical method. The anti-tussive activity was evaluated using three different models, including ammonia or sulfur dioxide-induced cough, and citric acid-induced guinea pig cough. Anti-asthma activity was

investigated in guinea pig bronchoconstriction caused by histamine. The expectorant activity was evaluated by the volume of red phenol in the rat trachea. Alkaloids fraction significantly inhibits the frequency of mouse cough caused by ammonia, increases the latent period of mouse cough caused by sulfur dioxide, and increases the latent period of guinea pig cough and inhibits cough frequency. Also, alkaloid fractions increase delitescence from seizures, and drop guinea pigs in anti-asthma tests, and increase tracheal red phenol output in expectorant evaluation. Also, the primary alkaloid, picrinine, shows anti-tussive and anti-asthma activity in vivo. The alkaloid fraction is a component of the anti-tussive, anti-asthma, and expectorant activity of *Alstonia scholaris* leaves. It can also be a valuable starting material for the development of respiratory diseases. Picrinine, the main anti-tussive, and anti-asthma compound can be applied in product quality control of *Alstonia scholaris* leaves.[21]

Alstonia scholaris (L.) R. Br. (Apocynaceae) is a medicinal plant in China traditionally used to treat lung diseases, including bronchitis, whooping cough, asthma, and chronic obstructive pulmonary disease. To provide experimental data supporting the clinical adaptation of total indole alkaloids (TA) from *A. scholaris* leaves to treat emphysema. An emphysema model was induced by intratracheal instillation of pancreatic pigs followed by TA and four major alkaloid components (scholaricine, 19-epischolaricine, vallesamine, and picrinine) for 30 consecutive days. Cytokine levels, histopathological parameters and protein expression in lung tissue were examined. Administration of TA, picrinine, scholaricine, 19-epischolaricine, and vallesamine for 30 days effectively inhibits the accumulation and invasion of inflammatory cells in the lung tissue and alleviates lung tissue injury. Oxygen saturation is increased. Interleukin (IL) -1β, monocyte-chemo attracts peptide 1, IL-11, matrix metalloproteinase-12, transforms the growth factor-β level, and vascular endothelial growth factor growth is significantly reduced, possibly by suppressing too much activation height of alveolar macrophages and pulmonary fibrosis. Elastin levels are markedly increased, and fibronectin is reduced. Bcl-2 expression increased significantly, and factor-κB and β-catenin levels decreased (Figure 9). TA can potentially be a useful new drug for pulmonary emphysema and exerts its effects by inhibiting inflammation of the airway walls and resistance to airflow and increasing lung elasticity and protease / anti-protease balance.[30]

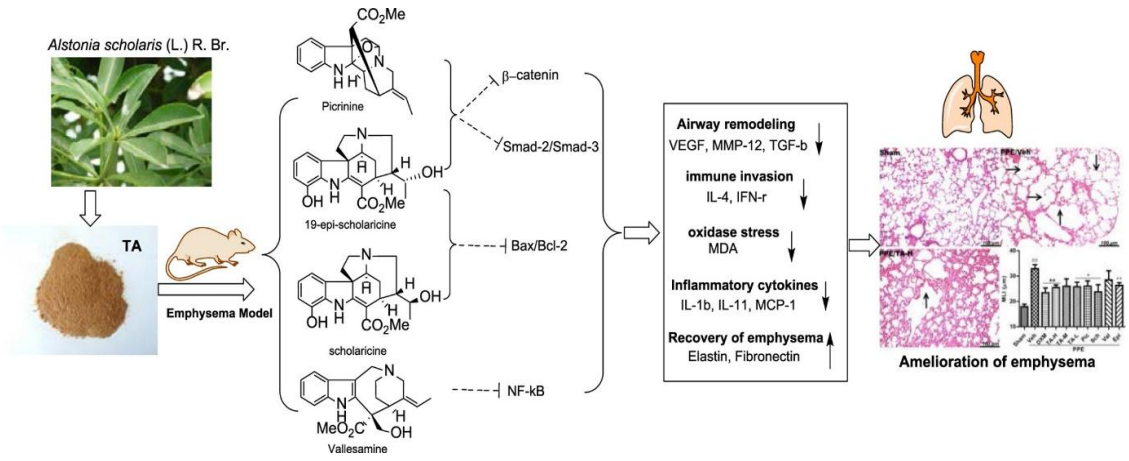

Figure 9. Testing emphysema of the total alkaloids of *A. scholaris* leaf extract.[30]

Other studies have shown that the ethanol extract of *Alstonia scholaris* (Apocynaceae) leaves induces marked bronchodilation activity in rats anesthetized with prostaglandins' possible involvement. However, in vitro guinea-pig tracheal preparations do not confirm this property, suggesting that bronchodilation is not due to direct relaxation of the tracheal smooth muscle. The vasodilatory activity of the extract does not depend on adrenergic or muscarinic receptors or prostaglandins, but mainly through the relaxation factor of endothelial derivatives, nitric oxide. The extract inhibits rabbit jejunum's spontaneous movement and the contractile effects of acetylcholine and histamine on rabbit ileum. The extract causes a decrease in contractions caused by barium chloride, potassium chloride, and calcium chloride in the guinea-pig ileum and pulmonary arteries, implying direct disruption of plant extracts by the entry of calcium ions into cells. However, the extract has no detectable effect on intracellular calcium mobilization. These results, coupled with the in vivo effect of ethanol extract, revealed that *Alstonia scholaris* leaves had broncho-vasodilatory activity mediated by prostaglandins, calcium antagonisms, and endothelial-derived relaxation factors.[22]

Immunostimulator

The immunostimulation effect of "Pule" extract (*Alstonia scholaris* (L.) R.Br., Apocynaceae) was studied in BALB/c mice. The extract is given orally once a day for seven consecutive days. The results showed that at the same dose (50, 100, and 200 mg/kg BW), the aqueous extract had a higher phagocytic index (1.39 - 1.79) than ethanol extract (0.81 - 0.93) in mice standard. Extract water at 50 mg/kg BW. It also significantly increased the phagocytic activity of immune-suppressed mice ($P < 0.01$) at 50 and 100 mg/kg BW. The extract prevents a decrease in the immune system caused by prednisone. Aqueous extract at 100 mg/kg BW significantly increased lytic activity of peritoneal exudate cells against *Escherichia coli* ($P <$

0.05). At doses of 50 and 100 mg/kg BW, water extract does not affect primary antibodies. Extract water at 50 mg/kg BW induces a transient cellular immune response, at 100 mg/kg BW inhibits the type of delayed hypersensitivity reaction.[23]

TOXICITY

Alstonia scholaris (L.) R. Br., A green tropical plant rich in indole alkaloids with significant physiological activity, is traditionally used to treat respiratory diseases in China. This study was carried out to establish the toxicity profile of *A. scholaris* leaf alkaloid extract (TA) in non-rat animals (Figure 10). After a single oral dose (4 g/kg BW), several transient symptoms, such as unstable gait, saliva, emesis, and redness of the peri-oral mucosa, were observed, but there was no treatment-related mortality. A subchronic toxicity study with various TA doses (20, 60, and 120 mg/kg BW) was carried out over a 13-week treatment period, followed by observations of recovery for four weeks. Except for emesis and saliva in most animals in the treatment group 120 mg/kg BW, no clinical changes were observed in animals given TA. Data from electrocardiography, bone marrow, urine, fecal, hematology, and clinical chemical analysis can be compared between animals treated with TA and control animals. There were no significant differences in control organ weights and evident histopathological characteristics between the groups treated with TA and the control group. Thus, the level of unobservable side effects (NOAEL) of TA is set as 120 mg/kg BW. Our results add further knowledge to the safety database for indole alkaloid extracts from *A. scholaris* with potential utility as new drug candidates.[27]

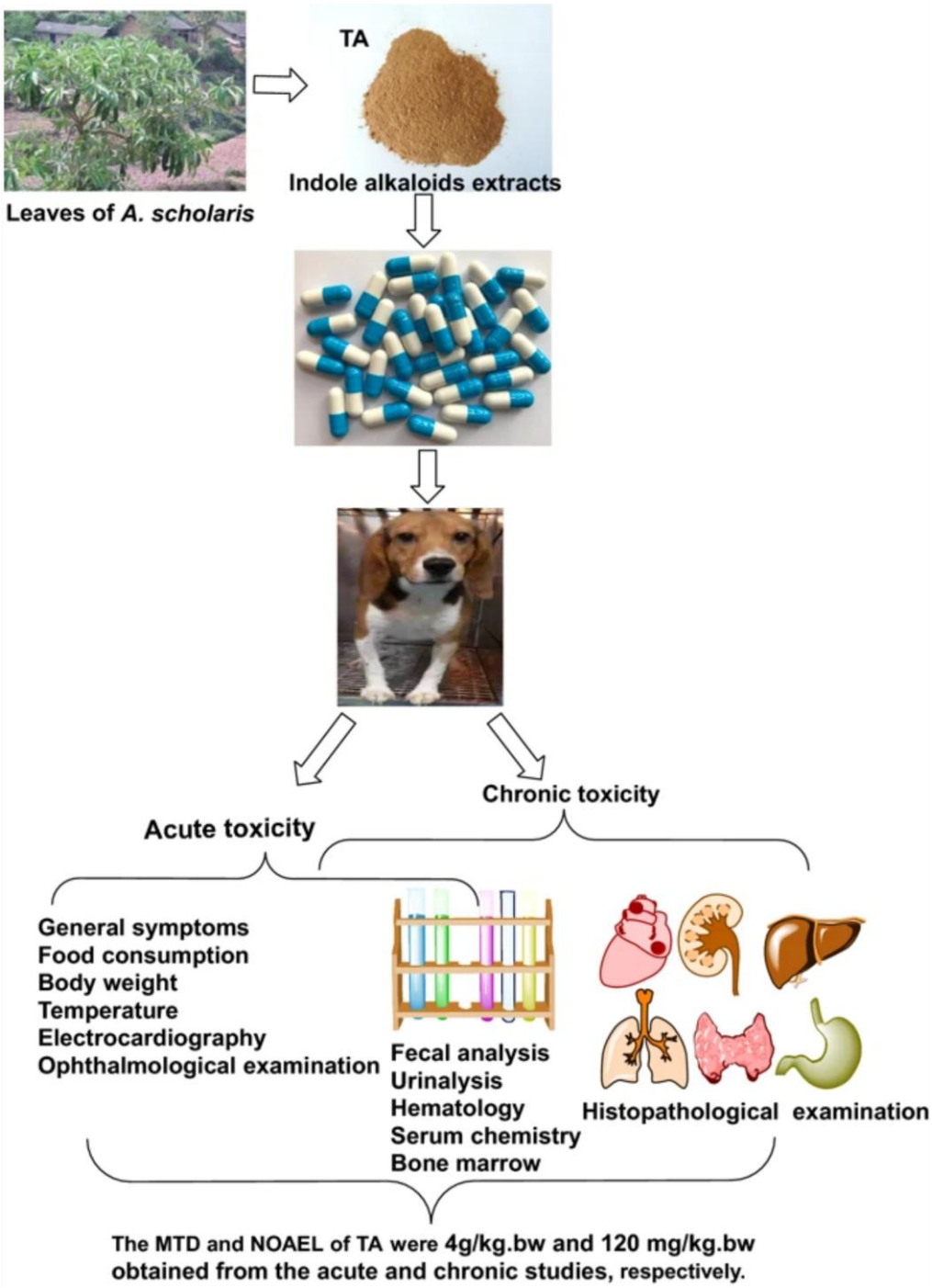

Figure 10. Toxicity testing of *A. scholaris* leaf alkaloid (TA) leaves in non-rat animals.[27]

CONCLUSION

The information gathered above regarding the use of pulai (*Alstonia scholaris*) in the world is adjusted to the available literature. This plant is used in traditional alternative medicine systems against various diseases such as asthma, malaria, fever, dysentery, diarrhea, epilepsy, skin diseases, snake bites, and others. In recent years, the use of ethnobotany and traditional natural compounds, especially those from plants, has received much attention because they

have been tested well for their efficacy and are generally believed to be safe for human use. It is the best classic approach in finding new molecules for the management of various diseases. All available literature regarding *Alstonia scholaris* illustrates that pulai is a popular drug among various ethnic groups and traditional practitioners for the treatment of diseases. Researchers are exploring the therapeutic potential of this plant.

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