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Phytochemical and Anticancer Investigation of Alstonia scholaris: a Review

Vikas R. Patil, Vikram R. Tadvi, Miss. Priyanka S. Ahire, Mr. Jayesh C. Chaudhari, Dr. Rajesh A. Ahirrao

P.G College of Pharmaceutical Science and Research, Chaupale, Nandurbar, 425411. Maharashtra, India

1, 2, Student of Pharmacy, P. G. College of Pharmaceutical Science and Research, Chaupale Nandurbar (Maharashtra) India.
3,4 Assistant Professor, P. G. College of Pharmaceutical Science and Research, Chaupale Nandurbar (Maharashtra) India. (Department of Pharmaceutics)
5 Principle of P. G. College of Pharmaceutical Science and Research Chaupale, Nandurbar (Maharashtra) India. (Department of Pharmacognosy)

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ABSTRACT
Alstonia scholaris, also known as the "devil's tree," has attracted a lot of scientific attention because of its diverse range of medicinal uses, especially in the treatment of cancer, and its rich phytochemical composition. Recent advancements in the pharmacological characteristics, phytochemical characterization, and therapeutic potential of A. scholaris are highlighted in this review, with a focus on its anticancer potential. Numerous bioactive substances, such as terpenoids, alkaloids, flavonoids, and phenolic compounds, have shown cytotoxic activity against various cancer cell lines. According to studies, these components may prevent the growth of new blood vessels (angiogenesis), inhibit tumor cell proliferation, and encourage programmed cell death (apoptosis). This paper compiles recent in vitro, in vivo, and limited clinical studies and discusses the future scope for therapeutic application.

I. INTRODUCTION

Cancer's incidence and mortality rates are continuously rising, making it a significant global health concern. According to the World Health Organization (WHO), cancer accounted for approximately 10 million deaths in 2020, or one out of every six deaths globally[1]. The urgent need for more creative, efficient, and secure treatment methods is highlighted by the rising cancer burden. Standard treatments like immunotherapy, radiation therapy, and chemotherapy have been essential in managing the disease, but they frequently have negative side effects, severe toxicity, and drug resistance. Interest in investigating natural products as complementary or alternative cancer treatments has increased as a result of these worries[2].

Bioactive compounds found in nature have long been essential for drug discovery. In actuality, natural products, especially those derived from plants, are the source of over 60% of anticancer agents that have been approved in recent decades[3]. Phytochemicals, which are secondary metabolites derived from plants, are known to have a wide range of biological activities, such as anti-inflammatory, antioxidant, immunomodulatory, and anticancer effects[4] . Because of its diverse pharmacological effects and rich phytochemical profile, Alstonia scholaris stands out among the many medicinal plants being investigated for their therapeutic potential.

The devil's tree, also called the blackboard tree or Alstonia scholaris (L.) R. Br., belongs to the Apocynaceae family and is widely distributed throughout tropical and subtropical regions of Asia, including China, Bangladesh, Indonesia, India, and the Philippines[5] . This evergreen tree is used extensively in traditional Chinese medicine, Ayurveda, and Unani medicine. The bark, leaves, latex, and roots of the plant have all been used historically to treat a variety of illnesses, such as fevers, skin conditions, digestive problems, and respiratory ailments[6] . Notably, extracts from A. scholaris have also been suggested to have therapeutic potential in treating chronic illnesses like cancer in certain traditional healing system

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Fig No. 1:Alstonia scholaris Plant

Numerous physiologically active components, including phenolic compounds, terpenoids, flavonoids, saponins, and indole alkaloids, have been discovered through phytochemical studies of Alstonia scholaris[8]. By inducing programmed cell death (apoptosis), inhibiting the growth of cancer cells, disrupting angiogenesis, and preventing metastases, these phytochemicals are thought to have anticancer activity[9] . Extracts from A. scholaris have demonstrated cytotoxic effects against a variety of cancer cell lines, including those from breast, liver, colon, and cervical cancers, in laboratory experiments[10]. Furthermore, studies using animal models have confirmed the plant's anticancer potential by showing smaller tumors and better survival rates[11].

Due in large part to the discovery of rare alkaloids like scholaricine, alstonine, villalstonine, and echitamine—compounds unique to this genus and known for their promising biological activities[12]—Alstonia scholaris has garnered increasing scientific attention in recent years. Interest in assessing the plant as a possible source of new anticancer agents has increased as a result of these findings. Early attempts to look into the safety, toxicity, and therapeutic potential of A. scholaris extracts in clinical settings have started, but the majority of studies have only gone as far as the preclinical stage. Comprehensive clinical trials are still rare, though.

In this review, the phytochemical composition and anticancer properties of Alstonia scholaris will be systematically compiled and evaluated, with an emphasis on in vitro and in vivo studies. It investigates the fundamental mechanisms of action, looks at toxicity data, and thinks about potential future research and clinical application avenues. Particular focus is placed on phenolic compounds and how they mediate anticancer effects. Additionally, advanced analytical techniques, especially High-Performance Liquid Chromatography (HPLC), are used to identify and characterize active constituents. This review aims to provide a strong foundation for the future development of anticancer agents derived from A. scholaris by compiling the most recent scientific data.

- **Botanical Background of Alstonia scholaris**

The medium- to large-sized evergreen Alstonia scholaris tree can grow up to 40 meters in height. It is a member of the Apocynaceae family, which is well-known for its latex-producing species and noteworthy therapeutic qualities[13]. Clusters of tiny, tubular, fragrant white flowers, whorled leaves arranged in circular patterns, and a straight, cylindrical trunk covered in greyish bark are the tree's defining features.


Fig No. 2:Alstonia scholaris fruit

Alstonia scholaris fruit is made up of thin follicles that spontaneously split open to release many seeds, each of which has tufts of silky, fine hairs that help the seeds spread by the wind[15].


Fig No. 3:Alstonia scholaris leaves

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Alstonia scholaris has thick, leathery leaves that can be oblong or oblanceolate in shape. Their characteristic midrib and lateral veins that curve and converge toward the leaf tip make them easy to identify. They are usually found in whorls of four to seven. The tree's bitter bark has long been used as a febrifuge in a variety of medical systems. A copious amount of white latex, which has antimicrobial and wound-healing qualities, is released when the plant is cut.

Native to Southeast Asia and the Indian subcontinent, Alstonia scholaris thrives in tropical environments. It is frequently grown in urban settings for ornamental purposes and as a shade tree, and it is frequently found growing in gardens, roadsides, and wooded areas. With sizable populations in areas like the Western Ghats, Assam, and the sub-Himalayan zones, the species is common in India's moist deciduous and semi-evergreen forests[17]

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- **Taxonomically, it is classified as:**

Kingdom: Plantae
Order: Gentianales
Family: ApocynaceaeGenus: Alstonia
Species: A. scholaris (L.) R. Br.
Alstonia scholaris is significant as a traditional medicinal plant and as a key topic in pharmacognostic and pharmacological research because of its unique morphological traits and rich phytochemical profile.

- **Traditional and Ethnomedicinal Uses:**

Traditional medical systems like Ayurveda, Siddha, and Unani have long used Alstonia scholaris. It is called "Saptaparna" in Ayurveda and has long been used as an astringent, bitter tonic, and antipyretic. The bark is particularly useful for treating long-term respiratory diseases like asthma, bronchitis, and tuberculosis[18]. Additionally, fever, diarrhea, dysentery, and malaria are treated with decoctions made from the bark.

The bark of Alstonia scholaris is used in traditional Chinese medicine to treat pneumonia, chronic bronchitis, and respiratory infections. The leaves are frequently boiled and eaten to clear up congestion in the chest and cough. Furthermore, the latex is applied topically to wounds, ulcers, and skin infections, and root extracts are occasionally used to treat parasitic worm infections and stomach pain[19]. A. scholaris has long been used by tribal communities in India and Southeast Asia to treat a range of conditions, such as inflammation, toothaches, skin rashes, and snake bites. Its use in wound healing, gastrointestinal issues, and as a general health tonic has also been documented by ethnopharmacological studies, especially in areas like Tamil Nadu, Assam, and Maharashtra[20].

Alstonia scholaris has a wide range of pharmacological potential, as evidenced by its numerous traditional uses. As interest in its potential anticancer properties grows, these ethnomedicinal insights provide important guidance for scientifically validating its therapeutic effects.

- **Phytochemical Constituents of Alstonia scholaris**

Numerous secondary metabolites have been discovered through phytochemical research on Alstonia scholaris, and these are believed to be responsible for the plant's broad range of pharmacological effects. Triterpenoids, alkaloids, flavonoids, phenolic compounds, and saponins are among the important components found. In order to isolate and characterize these bioactive compounds, advanced analytical techniques like Nuclear Magnetic Resonance (NMR) spectroscopy, Gas Chromatography-Mass Spectrometry (GC-MS), and High-Performance Liquid Chromatography (HPLC) have been essential[21].

- **Alkaloids**: Monoterpenoid indole alkaloids are particularly abundant in Alstonia scholaris. Scholaricine, villalstonine, echitamine, alstonine, and serpentine are important alkaloids that were separated from the plant; a number of these have demonstrated noteworthy antimicrobial, cytotoxic, and neuropharmacological qualities[22]. Of these, echitamine and scholaricine are notable for their potent antiproliferative effects on a range of human cancer cell lines.
- **Flavonoids:**Alstonia scholaris leaf extracts include flavonoids such as rutin, kaempferol, and quercetin. These substances' antioxidant properties and ability to control important signaling pathways implicated in the development of cancer are well known.[23]
- **Phenolic Acids:**Gallic acid, ferulic acid, chlorogenic acid, and syringic acid are among the phenolic acids that have been discovered to be present in different plant parts. These phenolics are potent scavengers of free radicals and have been shown to have protective effects against mutagenesis, DNA damage, and the start of carcinogenesis[24].

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- **Triterpenoids and saponins**: In cancer models, triterpenoids such as betulinic acid and oleanolic acid, which are found in the bark and latex of A. scholaris, have been demonstrated to induce apoptosis and inhibit angiogenesis. Furthermore, the extract's saponins support its cytotoxic and immunomodulatory effects.

Phytochemical types and concentrations in Alstonia scholaris can vary depending on a number of factors, including the plant's geographic origin, the part of the plant that is used, the extraction methods used, and seasonal fluctuations. The combined effects of these diverse compounds likely contribute to the wide-ranging therapeutic benefits reported in both traditional practices and scientific studies.

➢ Anticancer Properties and Mechanisms of Action

Alstonia scholaris's diverse phytochemicals, particularly its flavonoids, phenolic acids, and indole alkaloids, are largely responsible for its anticancer properties. These bioactive substances target several molecular pathways with known mechanisms of action to act at different phases of cancer development, from initiation to metastasis.

Inducing apoptosis is one of Alstonia scholaris's primary anticancer mechanisms. By boosting the expression of pro-apoptotic proteins like Bax and lowering levels of anti-apoptotic proteins like Bcl-2, alkaloids like scholaricine and echitamine encourage programmed cell death. Cancer cells undergo mitochondrial-mediated apoptosis as a result of this modulation, which also activates caspase-3 and caspase-9 [25]. Flavonoids and phenolic acids, such as gallic acid and quercetin, also play a role by increasing oxidative stress in tumor cells, which causes DNA fragmentation and apoptosis [26].

The induction of cell cycle arrest is another significant anticancer mechanism influenced by extracts from Alstonia scholaris. According to research, the plant's bioactive compounds can inhibit the growth of cancer cells at the G0/G1 or G2/M phases by modifying the expression of cyclins and cyclin-dependent kinases (CDKs) [27]. This cell cycle disruption efficiently suppresses the growth of cancer cells and promotes apoptosis.

Additionally, Alstonia scholaris has antiangiogenic qualities that are essential for preventing the development of new blood vessels that are required for tumor growth. It has been discovered that alkaloid-rich extracts inhibit vascular endothelial growth factor (VEGF) signaling pathways, which limits the blood flow to the tumor[28]. Furthermore, by lowering pro-inflammatory cytokines like TNF-α and IL-6, which are frequently increased in the tumor microenvironment and aid in the development of cancer, the extracts have anti-inflammatory properties [29].

By blocking matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are important enzymes in cancer cell invasion and metastasis, Alstonia scholaris extracts lastly exhibit encouraging anti-metastatic effects [30]. The plant's multi-targeted activity allows it to disrupt a number of vital cellular processes that contribute to the development of tumors.

➢ In Vitro Anticancer Studies

The cytotoxic effects of Alstonia scholaris on a variety of human cancer cell lines have been confirmed in large part through in vitro experiments. To evaluate their effects on cancer cell viability, growth inhibition, and apoptosis induction, researchers have primarily used methanol, ethanol, and aqueous extracts made from the bark, leaves, and roots.

With IC_{50} values ranging from 50 to 150 µg/mL, ethanolic extracts of the bark, for instance, demonstrated significant cytotoxicity against the cell lines MCF-7 (breast cancer), HeLa (cervical cancer), and HepG2 (liver cancer) [31]. Alkaloids like scholaricine and echitamine, which impair mitochondrial function and trigger apoptotic pathways, have been connected to this anticancer activity. Characteristic apoptotic characteristics, such as nuclear condensation, membrane blebbing, and cell shrinkage, were observed under a microscope [32].

Methanolic leaf extracts of Alstonia scholaris showed dose-dependent cytotoxic effects against HT-29 colon cancer cell lines and A549 lung cancer cell lines in a different study. According to MTT and LDH assays, the extracts dramatically reduced cell viability and increased the production of reactive oxygen species (ROS), which led to oxidative stress-induced cell death [33].

Furthermore, Alstonia scholaris extracts showed promise as an adjuvant therapeutic agent when combined with doxorubicin, increasing the sensitivity of resistant cancer cells [34]. These results were corroborated by flow cytometry analyses, which revealed that treated cancer cells had an

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increase in the sub-G1 cell population and cell cycle arrest. The cytotoxic potential of A. scholaris is generally well supported by the in vitro data, offering a strong foundation for additional research in animal models and clinical trials.

- **In Vivo Experimental Studies**

In order to confirm the anticancer effects and systemic safety shown in vitro, Alstonia scholaris in vivo studies have primarily used murine models. The potential of ethanolic and aqueous extracts to decrease tumor volume, enhance survival in mice with experimentally induced tumors, improve histopathological results, and modify hematological parameters has been investigated.

In comparison to untreated controls, a noteworthy in vivo study employing Swiss albino mice with Ehrlich Ascites Carcinoma (EAC) showed that oral administration of Alstonia scholaris bark extract at 200 mg/kg for 14 days significantly reduced the number of viable tumor cells, prolonged survival time, and decreased tumor volume [35]. Tumor tissue examined histopathologically revealed decreased mitotic activity and increased apoptosis. In a different study, mice with Dalton's lymphoma ascites (DLA) tumors that received leaf extract treatment showed better hematological parameters, including normalized hemoglobin and white blood cell counts, which may indicate a reduction in tumor burden and systemic toxicity [36].

Additionally, extracts from Alstonia scholaris have demonstrated protective effects on the kidneys and liver in animal models of cancer, suggesting that they play a dual role in organ preservation and anticancer efficacy. Elevated levels of enzymes like glutathione peroxidase (GPx) and superoxide dismutase (SOD) in treated subjects demonstrated the plant's antioxidant capacity [37]. All of these in vivo results support the progress of A. scholaris toward clinical evaluation by demonstrating its encouraging safety and therapeutic potential as an anticancer agent.

- **Clinical Trials and Human Studies**

There are currently few clinical studies involving Alstonia scholaris, despite promising preclinical research findings. There aren't any registered Phase I–III clinical trials evaluating its efficacy in cancer patients at the moment. However, small-scale pilot studies and ethnopharmacological surveys have documented its traditional use in cancer care in places like China, Indonesia, and Northeastern India [38]. In one Indonesian case report, for example, patients with breast cancer who took a decoction of bark from A. scholaris in addition to chemotherapy reported improvements in symptoms like decreased fatigue, increased appetite, and an overall improved quality of life, even though there was no discernible tumor shrinkage [39].

In cancer patients undergoing radiation therapy, a herbal formulation containing Alstonia scholaris and other ingredients showed mild cytoprotective effects, reducing oxidative stress markers and reducing skin irritation. The study's lack of strict controls, however, weakens the validity of these conclusions [40]. The lack of well-designed clinical trials highlights the urgent need for more studies to assess the pharmacokinetics, safety, bioavailability, and therapeutic potential of isolated compounds or standardized extracts of A. scholaris in human subjects.

- **Comparative Analysis with Other Anticancer Medicinal Plants**

Because of its unique alkaloid composition, Alstonia scholaris exhibits comparable or even greater efficacy in some experimental models when compared to other well-known anticancer plants like Withaniasomnifera, Tinospora cordifolia, and Curcuma longa. For example, curcumin from C. longa is known to have anti-inflammatory and antioxidant qualities, but its limited bioavailability is a drawback; this is less of an issue with extracts from A. scholaris [41]. A. scholaris has a greater variety of bioactive substances, such as flavonoids, phenolic acids, and indole alkaloids, than W. somnifera, which mainly uses withanolides to produce its effects. Its ability to target several cellular pathways at once is made possible by its chemical diversity, which increases its anticancer efficacy [42].

In preclinical research, Alstonia scholaris has also shown reduced toxicity and enhanced tolerability in comparison to some other alkaloid-rich plants, like Catharanthus roseus, suggesting that its extracts may be safer for long-term use [43]. These findings underline the necessity of more research and increased recognition of A. scholaris as a potentially effective medicinal plant with a variety of anticancer qualities.

- **Toxicological Profile and Safety Considerations**

In order to verify the safety of medicinal plants, toxicological evaluation is essential. When

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used at therapeutic levels, research on Alstonia scholaris typically shows a broad safety margin. Ethanolic extracts of the bark and leaves are safe at doses up to 2000 mg/kg, according to acute toxicity studies conducted in rodents, with no notable behavioral abnormalities or mortality reported [44]. Additionally, liver and kidney function markers like ALT, AST, creatinine, and BUN did not significantly change during sub-chronic toxicity evaluations conducted over 28 days at doses up to 500 mg/kg [45]. Additionally, histological examination of the liver and kidney tissues showed that the treated subjects had no signs of inflammation, fibrosis, or necrosis.

However, because latex extracts from Alstonia scholaris can irritate skin, care should be taken when using them. Higher dosages of bark extract have caused mild gastrointestinal discomfort in certain animal studies. Furthermore, the necessity of meticulous dose optimization and standardization is highlighted by the cytotoxic effects on healthy, non-cancerous cells that are seen at very high concentrations [46]. In conclusion, even though A. scholaris is usually regarded as safe at therapeutic dosages, thorough long-term toxicological and genotoxic analyses are necessary before it can be used with assurance in humans.

- **Future Prospects and Research Gaps**

The study of Alstonia scholaris has made significant strides, but there are still a number of significant gaps. Its acceptance in traditional cancer treatment is severely limited by the lack of clinical trials. Future studies ought to focus on:

- Plant extract standardization and the identification of important bioactive components
- Examining human subjects' pharmacokinetics and bioavailabilitythorough toxicogenomic and long-term safety evaluations
- Investigation of synergistic effects with well-known chemotherapy medications
- Creation of targeted and stable drug delivery systems

Additionally, Alstonia scholaris's genome sequencing and metabolomic analyses may help to clarify the biosynthetic pathways that produce its main anticancer alkaloids and make it easier to produce them synthetically [47]. In order to successfully convert traditional uses into scientifically validated and evidence-based therapies, interdisciplinary cooperation between botanists, chemists, pharmacologists, and oncologists will be necessary.

II. CONCLUSION

Because of its varied phytochemical makeup and demonstrated efficacy in both laboratory and animal studies, Alstonia scholaris stands out as a promising anticancer candidate. The plant's main bioactive components, alkaloids, flavonoids, and phenolic compounds, target several important mechanisms that contribute to the development of cancer, such as the induction of apoptosis, the inhibition of cell proliferation, thesuppression of angiogenesis, and the prevention of metastasis. This highlights the plant's potential as a multifacetedtherapeuticagent. The lack of well-designed clinical trials, however, continues to be a major obstacle to its clinical adoption despite its widespread traditional use and promising preclinical data. To fully realize its anticancer potential, extensive research assessing its safety, pharmacokinetics, and therapeutic efficacy in humans is necessary.

According to this review, Alstonia scholaris is a valuable resource that deserves more thorough scientific research and development. It has the potential to transform from a traditional medicinal plant into a reliable and efficient choice in contemporary cancer treatment paradigms with targeted research efforts and clinical validation.

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