PHARMACOGNOSTIC AND PHARMACOLOGICAL ACTIVITY OF ALSTONIA SCHOLARIS: A REVIEW

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Abstract-

The potential role of natural product have been identified for preventing or treating various diseases, our aim was to investigate The role of *Alstonia scholaris* leaves as anticancer. The phytochemical constituents of *Alstonia* sp. have been extensively investigated 2,3-secofernane triterpenoids, alstonic acids, were isolated from the leaves of *Alstonia scholaris.* first known examples of 2,3-secofernane triterpenoids. The plant *Alstonia scholaris* has a wide range of pharmacological activities. It is widely used in various traditional system of medicine as a medicine. It has been used since centuries as cooling agent, astringent, demulcent, appetizer; arthritis, tonic, aphrodisiac and in treatment of diarrhoea. Recent research carried out indicates its other uses such as antimicrobial, anti-fertility, anti inflammatory and antiemetic. The *in vitro* cytotoxic activity was performed by using **MTT** assay on Breast cell line **T47D** (organism- *Homo sapiens*, Human) and on breast cell line **MCF 7** (organism- *Homo sapiens*, Human). *Alstonia scholaris* concentration (µg/ml) was increased, the % growth inhibition also increased.

Keyword- MCF-7, Michigaen Cancer Foundation, MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetra sodium bromide)

Introduction

Cancer

Cancer is a group of disorder characterized by uncontrolled and uncommanded division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through *invasion* or by adhere into distant sites by *metastasis*. Metastasis is one of the cancerous stage in which oncogenes are transported through the bloodstream.

Epidemiology

The epidemiology of cancer is the study of the prevalence rate of the disease. The first case of cancer was identified by British surgeon Percivall Pott, who discovered in scrotum cancer in 1877.

Hepatocellular carcinoma (liver cancer) is rare in the West but is the main cancer in China and neighboring countries, most likely due to the endemic presence of HepatitisB and Aflatoxin in that population. Similarly, with tobacco smoking becoming more common in various Third World countries, lung cancer incidence has increased in a parallel fashion **(*BBC News online, 2000*)**.

Classification

Cancers are classified by the type of cell that resembles with tumor.

Carcinoma: malignant tumours derived from epithelial cells. The most common cancers are breast, prostate, lung and colon cancer.

1) *Lymphoma* ***and*** *Leukemia*: malignant tumours derived from blood and bone marrow cells
2) *Sarcoma:* malignant tumours derived from connective tissue, or mesenchymal cells
3) *Mesothelioma*: tumours derived from the mesothelial cells lining the peritoneum and the pleura.
4) *Glioma*: tumours derived from glia, the most common type of brain cell
5) *Germinoma*: tumours derived from germ cells, normally found in the testicle and ovary

Choriocarcinoma: malignant tumours derived from the placenta.

Etiology

Physical Factors

Physical irritants can also lead to cancer, such as continued abrasion of the linings of the intestinal tract by some type of food. The damage to the tissue leads to rapid mitotic replacement of the cells. The more rapid the mitosis the greater is the chances for mutations.

Hereditary Factor

In many families there is a strong hereditary tendency to cancer. This probably results from the fact that most cancers require not one mutation but two or more mutations. In those families that are particularly predisposed to cancer, it is presumed that one or more of the genes had already mutated in the inherited genome. Hereditary cancer syndromes are indicated by a strong family history e.g., familial retinoblastoma, familial adenomatous polyposis.

Cancer Vaccines

Treatment of cancer patient with Autologous tumour cell preparation is considered as the first use of Tumour Vaccine in human being. ***(Foon.K.A, 1999)***.

In October 2005, researchers found that an experimental vaccine for HPV types 16 and 18 was 100% successful for preventing infection with these types of HPV and, able to prevent the majority of cervical cancer cases. **(*Harper etal, 2004*)**. Process of tumorigenesis is associated with the alteration in gene sequences and expression level of various protein antigens ***(Fearson E, 1990.)***

History

Before the birth of Christ (probably date as far back as 2500 BC), the plants had been recognized as medicines for the human beings (and animals) in the history of progress of civilization. In Rikveda and in Ayurveda, (which is a part of Atharvaveda) the various parts of plant source and their extracts have been mentioned as crude drugs with the other type of sources e.g. animals and minerals. Previously, the people of India, Tibet and China etc, used to be habituated with plant medicines largely. A large section of people of India still and the people of other under developed countries depend almost on plant medicines in any sort of ailments. Traditional healers who are engaged with traditional medicines have given us lots of highly valuable information on medicines of natural sources which are chiefly of plant origin. So, the people on earth were/are dependent on plants. The mornings of us begin with plant materials and at night

we go to bed with the same. The plants were and are still maintaining a vital part of our daily lives. We start our days with Tea (containing an alkaloid, Caffeine), a central nervous system stimulant and go to the beds by taking a glass of water soaked with a spoon full of 'Isopgol' (containing a carbohydrate, Mucilage), an useful or helpful bulk laxative or using herbal cosmetics as health food for skin (Mukherjee, 2002).

It is revealed from Ayurveda that the basic principle of it is to follow the changing rhythm of nature as an integral part of the philosophy of life. It stresses the need to maintain the harmony of the individual with society and nature keeping greater emphasis on the preventive aspect of medicine.

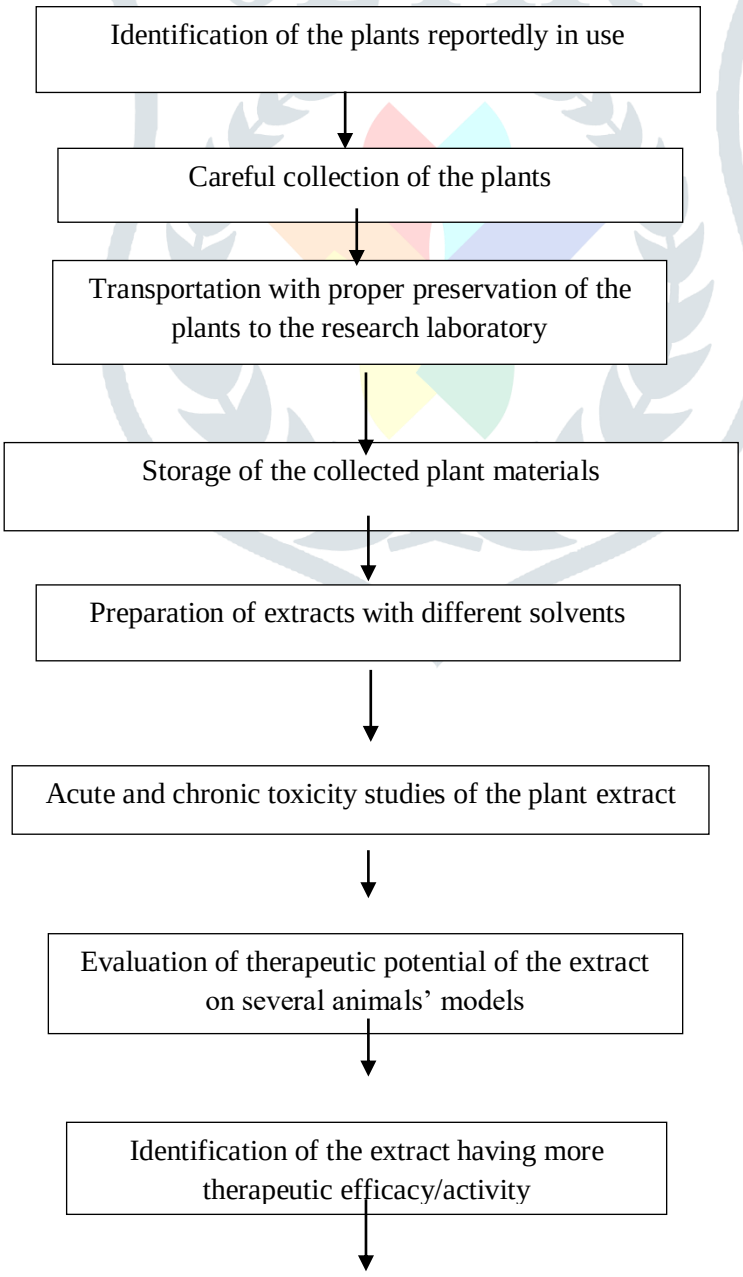
Historically, this knowledge was passed from generation to generation by memorization. The first written document of this ancient wisdom can be found in Charaka Samhita, and dates back to more than 700 BC. In Charaka Samhita, it is observed that superstition, blind faith and magic had been eliminated as causes of disease. It emphasized the use of rationale, concept, logic and the tools of scientific observation and investigation to arrive at the truth. Between 300 and 400 BC, Dhanvantari started a medical school for surgery to treat people who were injured during warfare. Surgical intervention at that time was only made when other methods of treatment failed. From this school came the brilliant surgeon "Sushruta" who wrote the best treatise on surgery called Sushruta Samhita. This book contains descriptions of techniques of surgery, rhinoplasty, surgical instruments and methods of dissection of dead bodies of human beings. Even in the western world, Sushruta is recognized as the father of plastic surgery.

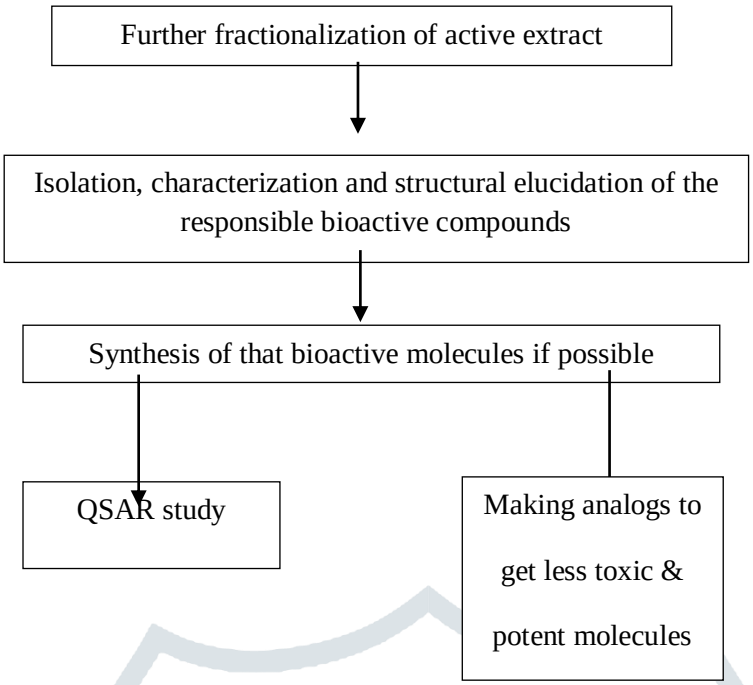
During this golden age of Ayurvedic medicine, a third major work, Astanga Samhita, was written by Vagbhata who worked in the medical school of Nalanda University. Vagbhata summarized Charaka and Sushruta and added his own experience and discoveries in the treatment of disease. In Astanga Samhita he described and organized eight different specialties: (i) Medicine; (ii) Pediatrics; (iii) Ear, Nose and Throat Specialty; (iv) Psychiatry (v) Surgery and Rhinoplasty; (vi) Toxicology; (vii) Rejuvenation and Longevity; and (viii) Vitalization. It is the general believes now a days that anything whether living or non-living, even the plants and human beings, had been created from or within the system of this universe. No one is made out of this universe. We may now to looking back to 'Big Bang' incident, with a huge blast our universe was formed. The earth or our globe was formed later on and then at a suitable time after that was environmentally accommodative for a single type of cell. With the time, after few crores of years two different types of cells, one for plant and the other for animal were emerged out possibly from algae. It means our ancestors were same from the view point of origin. Here we may come to the point that naturally we have the dependency to each other (Klein Richard M, 1987).

In modern days so many new therapeutically and highly effective medicines are in the market and those are from plant origin in spite of remarkable achievements of modern medicines in Allopathic system (Puri et al, 2001).

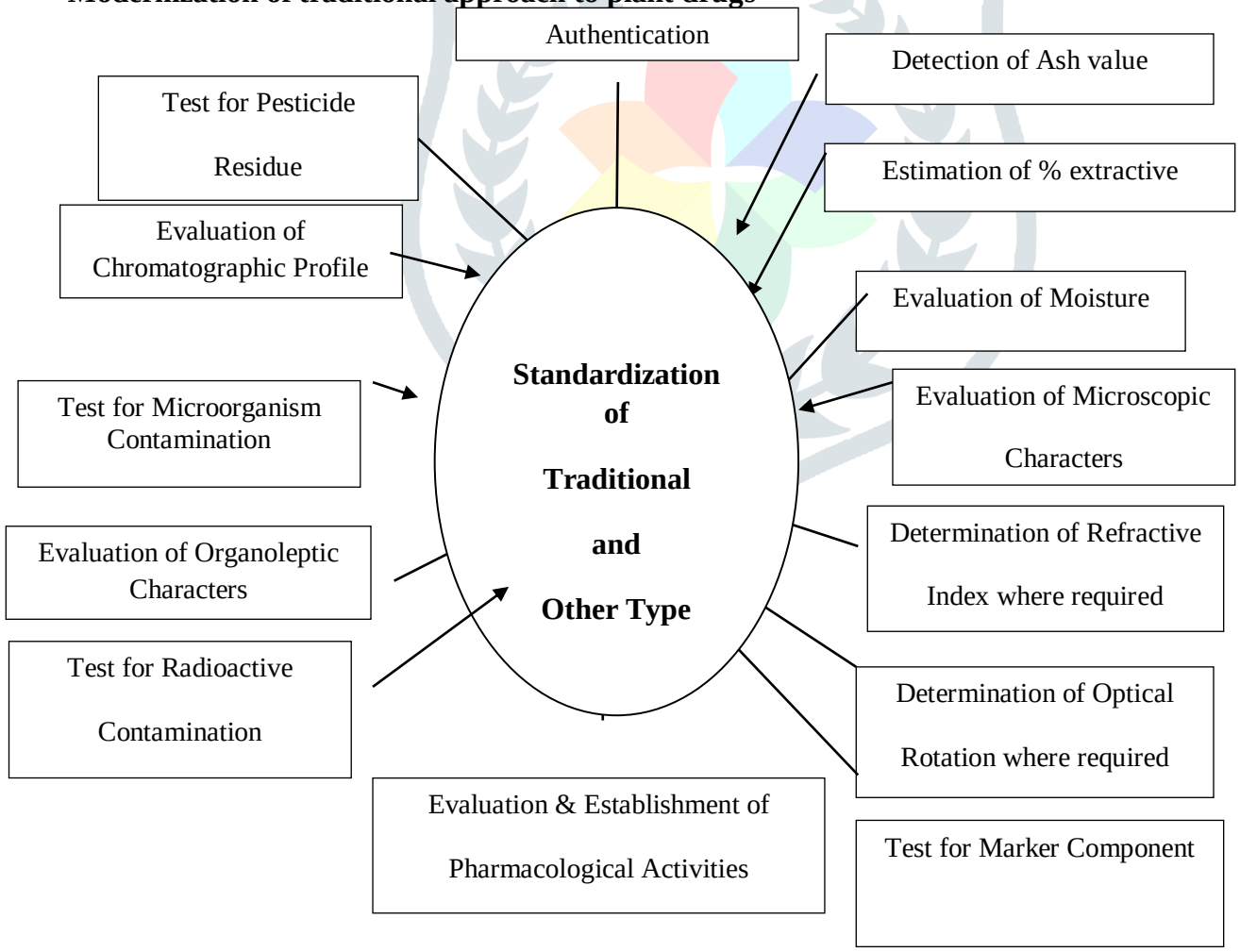
They are either the plants directly being used or active chemical constituents of plants after suitably isolated being used. A few names of such type of plants bearing some important constituents used as medicines in modern days may be mentioned here e.g. i) *Gingoloba* sp., ii) *Dioscorea* sp., iii) *Taxus* sp., iv) *Vinca* sp., v) *Senna* sp., vii) *Digitalis* sp., etc. Newer molecules for therapeutically active

medicines have been either isolated or synthesized using plants as raw materials. It is therefore now required to make use of medicinal plants with proper monitoring and make changes in the list of traditional medicines at primary health care centers to be based on current scientific evaluation. Fantastically, the plants are the living industries where from we get the readymade bioactive molecules having therapeutic values as well as prophylactic. WHO (World Health Organization) and UNICEF (United Nations Children's Fund) are also interested in plants and plant products for using in the diseases of children at primary health care levels like GIT (gastro intestinal tract) diseases, Respiratory diseases, UTI (urinary tract infection), etc. According to the estimation of WHO, 75-80% of the population of developing countries are almost exclusively using the principle components of traditional medicines (Narayana et al, 1998). The time has come now to study the safety and efficacy of traditional medicines especially the plant medicines for separating the good ones from the useless ones and for which purpose we require the modernization of traditional approach to plant drugs as shown in figure.





Modernization of traditional approach to plant drugs



Authentication and standardization of herbal drugs

Herbal plant

In order to alleviate and maintain the quality of life of human beings, plants play valuable role. There are many herbs, which are predominantly used to treat cardiovascular problems, liver disorders, central nervous system, digestive and metabolic disorders. It can be used as dietary supplements for management or treatment of diseases

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Ethno pharmacological studies on such herbs medicinally important plants continue to interest investigators. *A. scholaris*, have potential role in pharmacological activities ranging from anti-malarial to anticancer activities.

Many herbal remedies have been employed in various medical systems for the treatment and management of different diseases (Arulmozhi, 2007).

Plant Description

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* was originally named as Echites scholaris by Linnaeus in 1767. *A. scholaris* belongs to family Apocynaceae, grows throughout India, in deciduous and evergreen forests, also in plains. The plant is widely found in India in sub Himalayan 4 region from the Yamuna eastward ascending to 3000 feet above sea level, abundantly found in West Bengal and South India. 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 name scholaris suggests because it used as the wood of school's blackboards. The plant is a large evergreen tree up to 17-20 m in height with a straight often fluted and buttressed bole, about 110 cm in diameter. Bark is greyish 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 .The synonyms of the plant include *E. scholaris L.*, *E. pala Ham.*, *Tabernaemontana alternifolia Burm.* It is reported to contain various alkaloids, flavonoids and phenolic acids.

Throughout moist regions of India, especially in west coast forests, in the Himalaya it ascends up to 1000 m, also found in Bangladesh, Pakistan and the Philippines. Grows wild in the mountains and is cultivated as a shade tree (Kiritikar and Basu, 1999).

Taxonomical classification (www.wikipedia.com)

Kingdom : Planta

Order : Gentianales

Family : Apocynaceae

Genus : *Alstonia*

Species : *A. Scholaris*

Binomial name : *Alstonia scholaris*

Vernacular names (Kiritikar and Basu, 1999)

English names: Devil's tree, Dita bark.

Sanskrit names: Saptaparni, Saptaparna,

Other names: Asm: Chatiar, Ben: Chhatim, Hin: Chatian, Kan: Saptaparna **Ethanomedicinal information**

Bark: Stimulant, carminative, stomachic, bitter tonic, astringent, aphrodisiac, expectorant, febrifuge, alterative and anti periodic.

Bark in Ayurveda: Febrifuge, alterative, tonic and gastrointestinal sedative.

Infusion, Tincture: Galactogogue.

Fresh bark extract in milk: Leprosy, dyspepsia.

Amrit-ashtakapachana: 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, anti dysenteric and emmenogogue.

Ayush : Microfilaraemia.

Ethanolic extract of stem bark: Antileishmanial activity.

Milky Juice or latex of bark: Dental caries, pimple, pyorrhoea..

Tender leaves: Roasted, pulverized and made to a poultice which is used as a local stimulant also used in snake bite and scorpion bite.

Leaves: Anti ulcer, anti rheumatic, asthma.

Flower: Asthma, respiratory troubles

Root: Enlarged liver with pain

Traditional uses: The bark is bitter, astringent, acrid, thermogenic, digestive, laxative, anthelmintic, febrifuge, depurative, galactogogue, stomachic, cardiotonic and tonic. It is useful in malarial fever, abdominal disorders, diarrhoea, dysentery, dyspepsia, 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. The preparation infusion, 1-2 ozs., of tincture, 1-2 drachms diluted in water and of ditanin 5-10 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. 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 certain cases as a powerful galactogogue (Nadkarni, 1976).

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Plant of *A. scholaris*

Claims and reports

Goyal et al., (1995): reported the antimicrobial property of the plant constituents of *A. scholaris* (alkanes, alkanols and sterols).

Khan et al., (2003): evaluated the antibacterial activity of the petrol, dichloromethane, ethyl acetate, butanol fractions of crude methanolic extracts of the leaves, stem and root barks, while broader spectrum of antibacterial activity was reported in butanol fraction.

Patil et al., (1999): the anti-diarrhoeal effects of the aqueous and the alcoholic bark extracts of *A. scholaris* in mice.

Keawpradub et al., (1999): evaluated the anti-plasmodial activity of the methanolic extracts of various parts of *A. scholaris* which was tested against multidrug resistant K1 strain of *P. falciparum* cultured in 73 human erythrocytes. Pronounced anti-plasmodial activity was exhibited. They reported pronounced anti-

plasmodial activity mainly among the bis- indole alkaloids, particularly villalstonine and macrocarpamine with IC_{50} values of 0.27 and 0.36 μM, respectively. Ironically Gandhi and Vinayak (1990) have reported that the petroleum ether extract and methanol extract of the bark of *A. scholaris* were found to be devoid of anti-amalarial activity in mice infected with *P. berghei*

Lin et al. (1996): evaluated the hepatoprotective effect of *A. scholaris*. On liver injuries induced by carbon tetrachloride, H-Dgalactosamine, 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 H-Dgalactosamine in histopathological examination.

Keawpradub and Houghton, (1997): evaluated the methanol extracts of root barks of *A.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.

Lim et al., (1990): reported the antimutagenic effect of *A. scholaris* in micronucleus test in mice. Methyl methanesulfonate, 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 *A. scholaris* reduced the induction of micronucleated polychromatic erythrocytes by methyl methanesulfonate, mitomycin C and dimethylnitrosamine indicating that the plant has antimutagenic effect.

Jagetia and Baliga, (2003): reported the radio sensitizing effect of alkaloid fraction of *A.scholaris* (ASERS 5 μg/ml) was evaluated 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 prior administration of ASERS increased the effect of radiation which enhanced cell killing capacity when compared with the concurrent phosphate buffered saline (PBS) treated irradiation group. Their study suggested that ASERS administration enhanced the effect of radiation and disease free survival of the mice.

Jagetia et al., (2003): also reported the seasonal variation as well as cytotoxicity of different fractions of *A.scholaris* (ASE) against HeLa cells. They have also observed that treatment of HeLa cells with different doses of various fractions of the *A. 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.

Jagetia et al., (2005): reported the teratogenic effect of hydroalcoholic extract of *A.scholaris* (ASE) was studied in the pregnant Swiss albino mice by. 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 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. Lower doses had no developmental toxicity.

Iwo et al., (2002): reported the immune-stimulating effect of *A. scholaris* bark extracts was studied in BALB/c mouse. The aqueous extract at 100 mg/kg b.w. increased lytic activity of peritoneal exudate cells against *E. 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.

Channa et al., (2005): reported of bronchodilatory activity of the ethanol extract of *A.scholaris* leaves in anaesthetized rats. 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 *A. scholaris* leaves possess bronchodilation and vasodilatory activity mediated presumably by prostaglandins, calcium antagonism and endothelium derived relaxing factor.

The anti-fertility effect was reported by ***Gupta et al., (2002)*** The *A. scholaris* bark extract in male rats was evaluated by male wistar rats were given with oral (200 mg/kg) bark extract of *A. scholaris*, 60 days. The reduction in weights of testes, epididymes, seminal vesicle and ventral prostate was observed. The production of nineteen spermatids was reduced by 79.6%. 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.

Jagetia et al., (2004): 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 is greater than Cynodon dactylon while Morinda citrifoliais greater than Tylophora indica. The potency of Tectona grandis Aegle marmelos leaf is higher than Momordica charantia. Ocimum sanctum have higher potenvcy than Tinospora cordifolia. Boerhaavia diffusa activity greater than Eugenia jambolana (seed). The nitric oxide scavenging activity of Gingko biloba is greater than Picrorrhiza kurroa.* All the extracts evaluated Nitric oxide scavenging activity in a dose dependent manner. The *A. scholaris* bark showed its greatest NO scavenging effect of 81.86% at 250 µ/ml, as compared with *G. biloba*, where 54.9% scavenging was observed at a similar concentration.

Arulmozhi and Rasal, (2007): Malondialdehyde level was 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.

Arulmozhi et al., (2007): reported the effect of ethanolic extract of leaves of *A. scholaris* was evaluated in experimental models of pain and inflammation. The leaf extract at showed significant decrease in acetic

acid induced writhing in mice with a maximum of 65.76% at 400 mg/kg there was a significant inhibition in carrageenan induced paw edema with 200 and 400 mg/kg of the extract.

Arulmozhi et al., (2007): reported the ethanolic extract of leaves of *A. scholaris* was evaluated for anti ulcer activity by pyloric ligation method. They also reported the anthelmintic activity of the alcoholic extract of *A. scholaris* was investigated using *A. 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 *A. 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.

Arulmozhi, (2007): reported the effect of ethanolic extract of *A. scholaris* on various in vitro antioxidant parameters was evaluated. Ethanolic extract of *A. scholaris* had significant (DPPH.) free radical scavenging, metal ion chelating, hydrogen peroxide scavenging, superoxide anion radical scavenging and ferric thiocyanate reducing activities. Ethanolic extract of *A.scholaris* was found to prevent lipid peroxidation and radicalic chain reactions. The results observed were comparable to that of BHA, BHT, lascorbic acid and tocopherol.

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