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Azadirachta indica(neem)-Green Treasure

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Abstract: Neem is a popular medicinal plant in the world of Ayurveda which has been a part of traditional remedies with palm peel for about to years. This medical tree is a great example of how nature has kept the problem and treated both. Azadirachta indica is a remedy for thousands of problems like anti-allergenic, anti-dramatic, antifungal, anti-inflammatory, heart disease, larvicidal and other biological activities. All parts of this tree, particularly the leaves, bark, seed-oil and their purified products are widely used for treatment of cancer. Over 60 different types of bio-chemicals including terpenoids and steroids have been purified from this plant. This review aims at scanning scattered literature on "the anticancer biology of A. indica," related to toxicity problems and future perspectives.

Keywords: Neem, Azadirachta indica, Ayurvedic herb, anticancer drug

Introduction: The plant products or natural products play an important role in disease prevention and treatment of antioxidant activity inhibition of bacterial growth and improvement of genetic pathways. Due to their low side effects on the therapeutic role of plants in disease management and the affordable properties of neem extract and phytochemicals, many infectious metabolic diseases and cancer diseases are still being enthusiastically re-searched. Dried azadirachta indica leaves are kept in cupboards to ward off insects on clothes and to shore rice polyphenolic flavonoids extracted from fresh leaves of neem, quarantine and cy to sterol indicate bacterial and antifungal action. neem is also known as a "village pharmacy," particularly in India. This unique plant, has been closer to human culture and civilization since time immemorial. Cancer continues to be an enigmatic challenge for cancer biologists and medical practitioners. Several tantalizing claims for discovering a sure cure for cancer have been made by scientists from time to time; yet a dependable cure against most cancers remains a challenge even today. One of the primary reasons for this is the multiple pathways of survival adopted by cancer cells. Blocking a few pathways of their survival does not ensure their targeted elimination. That is why researchers are now trying to target them through multiple pathways with minimum possible side effects and discomfort to patients. In recent years, certain herbal products and ethnomedicines have drawn the attention of researchers and medical practitioners primarily because of convincing anticancer properties with negligible unpleasant side effects and discomfort to patients. During the last decade, the anticancer properties of neem have been investigated in detail from several scientific angles. The active ingredients obtained from the plant have been demonstrated unequivocally to induce apoptosis in several types of tumor cells and to organize and gear up the immune system to take on the cancer cells through cross priming. Regular use of neem and its preparations have been found to prevent onset of cancer through multiple mechanisms including production of substantial levels of antioxidants and carcinogen-detoxifying enzymes. Against a wide variety of human cancer cell lines and animal models for human cancers including colon, stomach, Ehrlich's carcinoma, lung, liver, skin, oral, prostate and breast Botanical Description of Neem Neem is a fast growing tropical evergreen tree related to a Mimosaceae family. It is found abundantly in tropical and semitropical regions like India, Bangladesh, Pakistan and Nepal. It will grow in areas where the rainfall is in the range of 450 to 1200 mm. It is a typical tropical to subtropical tree and has an annual mean temperature of 21 – 32 °C. Neem tree can grow in many different types of soil, but it thrives best on well drain deep and sandy soils. They are reported to live up to 200 years. Neem is a large growing tree with 20 - 23 m tall and trunk is straight and has a diameter around 4 - 5 feet. The leaves are compound, alternate, imparipinnate, with each comprising 5 – 15 leaflets. The petioles of Neem tree are short. The tree is often covered with delicate flowers in the early summer. The flowers are arranged in axillary, normally more or less drooping panicles which are up to 25 cm long. The fruits of Neem tree are green drupes which turn golden yellow on ripening in the months of June – August. Taxonomic position of Azadirachta indica is classified in Table 1: Taxonomic position of Azadirachta indica (Neem). Order Rutales Suborder Rutinae Family Meliaceae Subfamily Melioideae Tribe Melieae Genus Azadirachta Species indica Application Of Neem Table 2. Medicinal properties of neem (A. indica) tree preparations Anti-Carcinogenic and Anti-Mutagenic Effect of Neem That neem extracts possess potent ability to remove cancerous phenotype (tumor commonly termed as "nasoor"), has long been known to people in Asia, particularly in India. During the last two decades, researchers in India and abroad have gathered convincing data to suggest that the onset of cancerous phenotype due to certain mutagens and pro-carcinogens may be treated effectively by extracts obtained from various parts of the neem tree. The chemopreventive effects of dietary doses of aqueous neem leaf extract was studied on in vivo murine system against H-B- α -P (Benz- α -pyrene)-induced initiation of cancer measured in terms of H-B- α -P-DNA adduct. Their results indicated that neem leaf extract reduced the metabolic activation of H-B- α -P with consequent decrease in the level of H-B- α -P-DNA adduct formation. These molecular and biochemical modulations observed at the initiation phase of carcinogenesis highlight the chemopreventive significance of A. indica extracts. In another interesting study, Chaimuangraj et al. observed that dietary feeding of the neem leaf

extract (20, 100, 250 mg/Kg body weight) significantly inhibited the azoxymethane-induced aberrant crypt foci (ACF) and also significantly decreased the proliferating cell nuclear antigen (PCNA) labeling indices ($p < 0.0006$) in the colon epithelium in rats. The preventive action of neem flowers has been demonstrated by several research groups against the neoplastic developments due to chemicals including DMBA and BaP. These results indicate that dietary use of extracts from various parts of *A. indica* may play a promising role in future drug discovery and development programs as far as chemoprevention of cancer is concerned. Most of the ethnomedicinal and early studies on neem with respect to its anticancer properties suffered from lack of credible mechanistic principles. Serious attempts at unraveling the possible scientific interpretations of the chemopreventive/anticancer effects of neem extracts have been made in recent years. O₆-alkylguanines are potently mutagenic and *S. no* Therapeutic uses

Types of preparations 1 Immunostimulant activity Aqueous extracts of neem bark and leaf 2 Hypoglycaemic activity Aqueous extracts of neem leaves 3 Anticancer effect Aqueous extracts of neem leaf and bark 4 Antifertility effect Seed oil 5 Antimalarial activity Seed and leaf extracts 6 Antifungal activity Extracts of neem leaf, neem oil seed kernels 7 Antibacterial activity Aqueous leaf extract 8 Antiviral activity Aqueous leaf extract 9 Anticancer activity Aqueous leaf extract 10 Antioxidant activity Leaf and seed extract 11 Effect on central nervous system Leaf extract 4 Cancer Biology & Therapy Volume 12 Issue 6 Table 3. Non-terpenoid and non-steroid constituents of neem (*A. indica*) *S. no* Name of constituents Chemical formula Melting point (°C) Isolated from 1 Kaemferol C₁₅H₁₀O₆ 276 Blossoms 2 Quercetin C₁₅H₁₀O₇ 313 Blossoms and leaves 3 Myricetin C₁₅H₁₀O₈ 357 Blossoms 4 Sugiol C₂₀H₂₈O₂ 292 Trunk bark 5 Nimbiol C₁₈H₂₄O₂ 250 Trunk bark 6 Glucoside of Quercetin C₂₁H₂₀O₁₂ - Leaves 7 Glucoside of Kaemferol C₂₁H₂₀O₁₁ - Leaves 8 Melicitrin C₂₀H₁₈O₁₂ - Blossoms 9 Quercetin-3-galactoside (Hyperin) C₂₁H₂₀O₁₂ 237 Blossoms and leaves 10 Kaemferol-3-glucoside (Astragalol) C₂₁H₂₀O₁₁ 178 Blossoms 11 Quercitrin C₂₁H₂₀O₁₁ 250 Leaves 12 Rutin C₂₇H₃₀O₁₆ 214 Leaves 13 Isorhamnetin C₁₆H₁₂O₇ 305 Leaves 14 Rhamnoside of Quercetin C₂₁H₂₀O₁₁ 245 Leaves 15 5-Hydroxy-methyl furfural C₆H₆O₃ - Fruit Effect of Neem on Drug Metabolizing Enzymes In certain cases, neem preparations have also been observed to potentiate the antitumor activities of certain drugs besides affording protection against life threatening side effects of these chemotherapeutic agents. For example, pre-treatment of Swiss mice with NLP not only suppressed leucopenia and neutropenia but also potentiated the antitumor activities of cyclophosphamide concomitantly. In an interesting observation HPLC-generated neem leaf fractions have been shown as positive modulators of the phase-I and phase-II xenobiotic-metabolizing enzymes, lipid and protein oxidation and anti-oxidant defense enzymes leading to attenuation of the DMBA-induced HBP carcinoma in the Swiss mice. Table 4. Parts of neem (*A. indica*) tree with medicinal uses *S. no* Parts of neem tree Treatable ailments 1 Bark Analgesic, alternative and curative of fever 2 Twig Cough, asthma, piles, phantom tumor, intestinal worms, spermatorrhoea, obstinate urinary disorder, diabetes 3 Leaf Leprosy, eye problem, epistaxis, intestinal worms, anorexia, biliousness, skin ulcers, cancer 4 Flower suppression, elimination of intestinal worms, phlegm 5 Fruit Piles, intestinal worms, urinary disorder, epistaxis, phlegm, eye problem, diabetes, wounds, leprosy 6 Seed Leprosy, intestinal worms, cancer 7 Oil Leprosy, intestinal worms 8 Gum Scabies, wounds, ulcers, skin diseases

www.landesbioscience.com Cancer Biology & Therapy 5 Cisplatin (cis) and 5-fluorouracil (5-FU) are established chemotherapeutic agents against certain forms of cancer. But, they also cause terrible side effects including programmed cell death of circulating blood cells. In order to reduce these side effects granulocyte colony stimulating factor (GCSF) is often administered while treatment with cis and 5-FU. Recently pre-treatment with neem leaf preparation (NLP) has been found to protect circulating blood of cis and 5-FU treated Swiss mice significantly. NLP could, therefore, be a better substitute than GCSF which is expensive and is also known to promote angiogenesis. Skin tumor induction is often associated with upregulation of certain marker enzymes, such as alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase. Upon treatment with aqueous *A. indica* leaf extract (AAILE) there was significant decrease in the activity of these marker enzymes. The AAILE treatment reduced oxidative stress by decreasing lipid peroxidation levels and by enhancing the reduced glutathione contents. It is anticipated that oral administration of 5% (w/v) of *A. indica* extract suppressed the diethylnitrosamine and acetylaminofluorene induced pre-neoplastic nodules in the male Sprague-Dawley rats apparently by increasing the distribution of antioxidant elements and GST activity. Their results suggest that neem extract protects against onset of hepatocarcinoma with negligible side complications on normal cells. This is such a fine natural method of surgery that requires biochemical blades led by a host of caspase enzymes to wipe out the unwanted, redundant, wayward, incorrigible and irreparable cells of the body without shedding even a single drop of blood and without any material loss to the body as a whole. The medical practitioners have, therefore, accepted elimination of cancer cells through orchestration of apoptosis as a therapy of choice.

The Role of Neem in Bioimmunotherapy of Cancer The innate and the acquired immune systems keep vigil on the overall defense of the body. Gearing up the immune system against targeted attack on health risks has been contemplated as a dependable therapy known as bioimmunotherapy. Cancer biologists and medical practitioners have accepted bioimmunotherapy as one of the dependable therapeutic regimens against cancer. Several drugs of immunological origin are in great demand. For example, interferons (IFN) are well known therapeutic cytokines that are used as anticancer agents against many types of cancer cells in vitro and in vivo. It is used individually and in combination with other anticancer agents including ionizing radiations. Subversion of the body's immune and genetic system is often a prelude to initiation of cancer. Some recent inputs to cancer research demonstrate that neem exerts anticancer effects against various types of cancers efficiently by gearing up the body's immune response. Neem modulated active specific immunotherapy intends to boost the hosts' antitumor immune response by proper presentation of tumor-associated antigen (TAA) or its derivatives to B and T cells, where the role of antigen presenting cells (APC) is predominant. Closely in line with this view.

6 Cancer Biology & Therapy Volume 12 Issue 6 Toxicological Risk Factors Involved in the Use of Neem Extracts In spite of its versatile qualities neem deserves use with care. Indiscriminate use of its extracts, particularly when taken in overdoses, may cause unpleasant side effects. Some people are excessively allergic to neem products which may cause itching, swelling of mouth and throat, wheezing and sometimes breathing difficulties. Use of neem or its products may also be a reason for damage to liver and kidney that may result in jaundice and in low or no urine production, respectively. Although neem has some hematostimulatory effect as observed in mice, it may also destroy red blood corpuscles. Excessive use of neem may bring about neurotoxicity. One of the important concerns about its use is its ability to interfere with the normal reproductive systems fostering infertility. DNA methylation is a major epigenetic regulatory mechanism. A statistically insignificant reduction in methylated deoxycytidine has been observed in the infertile male group treated with neem than in the untreated ones. Neem has been in use since the dawn of civilization, yet no severe harmful effect has been reported. Since ancient times, therefore, neem tree is kept at bay from the regular dwelling places. Conclusion Neem (*Azadirachta indica*) has been an ancient source of herbal panacea against a variety of human health problems. Researchers have been trying to purify

the active ingredients from this plant and to work out their mechanistic, therapeutic and clinical aspects on the reliable systems. Over 60 various products from neem are available in the purified form. These products vis-à-vis the crude extracts of neem are being tested expediently on suitable in vitro and in vivo systems to establish their anti-cancer and immunomodulation effects. www.landesbioscience.com Cancer Biology & Therapy.

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