

A Review On The Therapeutic Role, Active Constituents in Disease Prevention And Tissue Culture Methods Of Neem (*Azadirachta indica*)

¹Suryakanta Ghosh, ²Efrit Karim, ³Subhasis Ghosh, ⁴Rajlakshmi Kundu, ⁵Anuska Das, ⁶Nibedita Rooj
¹Student, ²Treasurer, ³Student, ⁴Student, ⁵Student, ⁶Student

¹Department of Biotechnology, O.I.S.T, Purba Bardhaman, Vidyasagar University, W.B, India.

²Amal Foundation, Bangladesh.

³Department of Microbiology, B.B College, Asansol, Kazi Nazrul University, W.B, India.

⁴Department of Biotechnology, Sikhsha-Vabana, Visva-Bharati University, W.B, India.

^{5,6}Department of Microbiology, M.U.C Women's College, The University of Burdwan, W.B, India.

E.mail: ¹papun.biotech93@gmail.com, ²karimefrit@gmail.com, ³ghoshkatwa120@gmail.com,

⁴rajlakshi.kundu@gmail.com, ⁵das.anuska2002@gmail.com, ⁶nibeditarooj.2003@gmail.com

Abstract: *Alternative medicine and evidence-based phytomedicine, as well as their impact on the human body, are being combined in global health and medical practice. The therapeutic uses, antibacterial activity, and products of neem (Azadirachta indica) are highlighted in this paper, which also attempts to evaluate its micropropagation techniques. The therapeutic benefits of the Neem tree are found in all parts of the tree. Having the antibacterial, antifungal, antiallergic, antibiotic, antidermatic, anti-inflammatory, insecticidal, larvicidal, antimalarial, antiulcer activities, the nonwoody parts of neem including the leaf, bark, oil, flowers, fruits, and seed also show other biological effects. Antimicrobial action is confirmed by neem seed oil, which contains alkaloids such as tannin and hydrogen cyanide. Neem leaf juice and twigs help to clean the teeths, and the tonic is effective against Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Bacillus subtilis, Micrococcus luteus, Streptococcus faecalis, and Enterococcus faecalis. The methanol extract of A.indica is the most effective, chloroform is moderately effective, and hexane extract has little antibacterial activity. The stem and bark show strong antibacterial effect against Klebsiella and Streptococcus sp. Alkaloids, saponins, steroids, tannins, crude glycosides, and flavonoids are among the phytoconstituents that have a sterile effect against E. coli, Corynebacterium bovis and Staphylococcus aureus strains. Enterobacter aerogenes, Mycobacterium tuberculosis, Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa, and E. coli are all potent against the methanolic peel extract of neem. In contrast to dermatophytes, neem leaves, ethanol, and aqueous extracts showed anti-dermatophytic efficacy against two fungus strains, Aspergillus fumigatus and A. niger. Aqueous and alcohol extracts of wood scraps, leaves, and bark are highly potent antimalarial medicines, especially against chloroquine-resistant strains. Limonoids and polysaccharides (found in neem seed oil), leaves, and bark may reduce cancer and tumors. Neem oil has antipyretic properties, while bark extract is used to treat inflammatory stomatitis in youngsters. Neem leaf extracts and seed oil (NSO) are effective spermicides that prevent sperm mobility from being reduced. Nimbidin's antiulcer action helps to prevent acetylsalicylic acid, omethacin, serotonin-induced gastric lesions, and duodenal ulcers. Neem protects against chemically caused carcinogens and liver damages due to increase the antioxidant levels and also prevents diabetes and vitiligo. Neem oil contains limonoids, which block the mutagenic action of 7,12-dimethylbenz(a)anthracene while also having anti-cancer properties. Although 1-naphthalene acetic acid can induce maximal numerous shoots, modified MS medium (MS-RMN) supplemented for plant tissue culture with a combination of 6-Benzylaminopurine (BA) and Indole-3 butyric acid (IBA) is successful in shoot bud sprouting in both juvenile and adult trees (NAA). During micropropagation of neem, the highest frequency of roots is seen on a half-strength MS medium supplemented with IBA. Azadirachtin is a seed extract with considerable industrial demand due to its rapid applicability as an environmentally friendly, biodegradable biopesticide and a variety of other bioactivities.*

Key Words: *Different parts of neem plant, Activities of neem (antibacterial, antifungal, antiallergic, insecticidal, antioxidant), Phytohormones, Micropopagation and tissue culture, Phyto products, Biopesticide.*

1. INTRODUCTION :

The neem tree (*Azadirachta indica*) is a tropical evergreen tree native to the Indian subcontinent (deciduous in dry places) [1]. Because of its therapeutic characteristics, it has been utilized in Ayurvedic medicine for over 4000 years. In Sanskrit, neem is known as 'arista,' which means 'perfect, complete, and imperishable.' The majority of plant components, including fruits, seeds, leaves, bark, and roots, include antiseptic, antiviral, antipyretic, anti-inflammatory, antiulcer, and antifungal chemicals. 'Nimba' is derived from the Sanskrit term 'Nimbatiswasthyamadadati,' which means to bestow good health. Today, neem is traditionally utilized to provide "excellent health" to individuals who consume it [2,3,4]. The ancient documents 'Charak-Samhita' and 'Susruta-Samhita', which form the core of the Indian system of natural therapy, Ayurveda, highlight the benefits of neem. It belongs to the Meliaceae family and is known as 'Indian lilac' or 'Margosa.' 'Azad- Darakth- E- Hind,' which means 'Free tree of India,' is the Persian name for neem. Neem is regarded as a representative of India's genetic diversity. The neem tree is the world's most examined tree and is well-thought-out the most promising tree of the twenty-first era. It has a lot of potential in pest control, environmental protection, and medicine. Insecticides, pesticides, and agrochemicals are all naturally found in neem [5]. Neem is an enormous tree with a semi-straight to the conventional trunk, 3m in circumference, and spreading branches making a widepinnacle that grows to around 25m in height. The wood of the neem tree is renowned for its durability. Neem's non-wood products, such as flowers, fruits, seeds (oil, cake), leaves, bark, and gum, are also used in a variety of ways [6]. These compounds' antifungal, antibacterial, insecticidal, and other diverse biological actions are well known [7], and they find multipurpose usage in human daily life as a result. The tree's seeds, which provide 40% of the well-known 'Margosa oil,' are the tree's most important and valuable product. There are two species of neem: *A. indica* A. Juss, which is native to the Indian subcontinent, and *A. excels* Kack., which are only found in the Philippines and Indonesia [7,8]. In India, Bangladesh, Burma, Pakistan, Sri Lanka, Malaysia, Thailand, and Indonesia, the former grows as a wild tree. Neem trees are now found in about 72 countries around the globe, including Asia, Africa, Australia, North, Central, and South America [6,8,9,10,11,12]. Neem is a tree that belongs to the Mahogany family. Order: Rurales, Suborder: Rutinae, Family: Meliaceae, Subfamily: Melioideae, Tribe: Melieae, Genus: Azadirachta, Species: Indica, Order: Rurales, Suborder: Rutinae, Family: Meliaceae, Subfamily: Melioideae, Tribe: Melieae, Genus: Azadirachta, Species: There are anprojected 25 million trees growing in India, with 5.5 percent in Karnataka, which is in third place after Uttar Pradesh (55.7%) and Tamilnadu (17.8%), which are in first and second place, respectively. Andhra Pradesh, Assam, Bihar, Delhi, Gujarat, Haryana, Himachal Pradesh, Kerala, Madhya Pradesh, Maharashtra, Meghalaya, Orissa, Punjab, Rajasthan, West Bengal, and the Union Territory of Andaman and Nicobar Islands are amongst the other states in India where neem trees may be found [6,8,13,14]. India is the world's leading producer of neem seeds, with roughly 4,42,300 tons produced annually, yielding 88,400 tons of neem oil and 3,53,800 tons of neem cake [15].

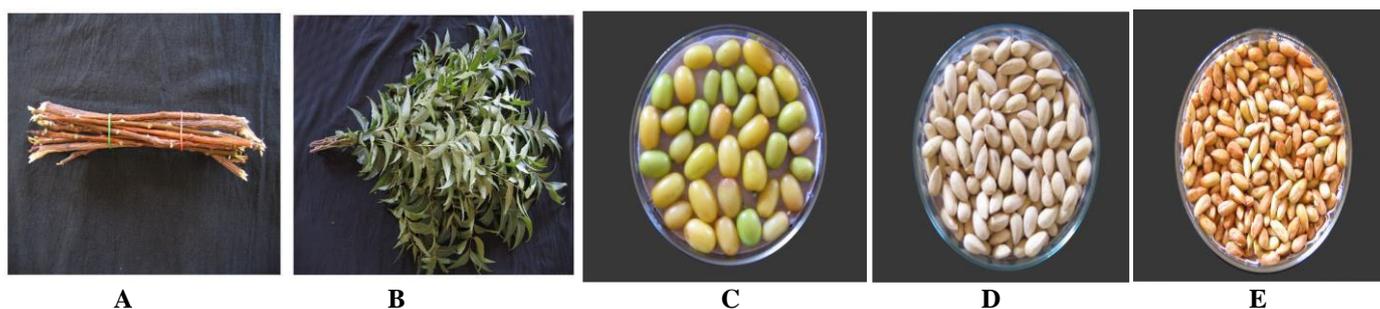


Figure 1. The Neem Products. (A) Twigs, (B) Leaves, (C) Fruits, (D) Seeds (with endocarp), (E) Seeds (without endocarp) [6].

After three-five years, a neem tree will start to bear fruit. It reaches full productiveness in around ten years. It can produce up to 50 kg of fruit in line with year after the 10-12 months. In keeping with legend, the plant can live for two centuries. The tree can adapt to the diffusion of climatic, geographic, and edaphic situations. It grows satisfactory on dry, stony shallow soils, as well as difficult calcareous or claypan soils at a shallow intensity. The neem tree most effective wishes touch water and lots of sunlight to thrive. The tree flourishes in environments with rainfall ranging from 450 to 1200 mm. It has, but, been successfully used even in places where rainfall is as little as a hundred and fifty to 250 mm. Neem can be located in altitudes of up to 1500 meters [7]. It can thrive in temperatures ranging from 0 to 490 levels Celsius. It can not deal with flooded locations or soils that aren't well-tired. The pH variety for neem tree increase is between 4 and 10. it is able to develop in nearly any type of soil, along with clayey, saline, and alkaline soils, but it prefers black cotton soils and deep, properly tired soil with lots of sub-soil water. The unique belonging of calcium mining in neem bushes allows them to neutralize acidic soils [8].

2. LITERATURE REVIEW:

Many physiologically active chemicals found in plants have the potential to be developed as therapeutic medicines. Herbal medications are already widely used in developing nations, but there has been a recent increase in the use of herbal treatments in industrialized countries [16]. Plants offer a different perspective on the hunt for new remedies [17]. The therapeutic benefits of the Neem tree are found in all parts of the tree. The non-woody parts of the Neem tree, such as the leaf, bark, oil, flowers, fruits, and seeds, have antiallergic, antifungal, antibacterial, anti-inflammatory, insecticidal, larvicidal, antimalarial, antiulcer, and other biological effects. In hyperglycemia, hypolipidemia, and hypotensive actions, a water-soluble extract of *Azadirachta Indica* is very important [18]. The presence of alkaloids with 48.09%, Tannin 0.362%, and Hydrogen cyanide 5.95 mg/100g is confirmed by early phytochemical screening of the extract of Neem seed oil. These molecules were said to be an indicator of antimicrobial agents' potential. Some of the biological components of neem, such as Azadirachtin, Meliantriol, Salannin, Nimbin, and Nimbodin, all of which have the same fundamental limonoid structure, may be responsible for the claimed effects of neem preparations [19].

1) Antimicrobial activity of neem

Neem has antimicrobial activity due to have a lot of physiologically active chemicals. The juice of neem leaves and twigs is used to clean teeth and as a tonic [20]. Neem extracts and its components are important in the suppression of a variety of microorganisms, including viruses, fungi, and bacteria. The antibacterial activity of *A. indica* extracts in methanol and hexane chloroform was tested against *E.coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Micrococcus luteus*, *Streptococcus faecalis*, and *Enterococcus faecalis*. The methanol extract was shown to be the most effective, chloroform to be somewhat efficient, and hexane extract to have little antibacterial action [21]. The following is a list of neem's antibacterial properties.

- **Antibacterial action of neem**

In remedy and pharmaceuticals, neem is normally applied. Neem's stem and bark show off antibacterial homes towards *Klebsiella* species, and *Streptococcus* sp. Methanolic extracts of Neem have been proven to have antibacterial motion in opposition to *Vibrio cholera*, while chloroform extracts has been proven to have antibacterial activity in opposition to *E.coli*, *B. subtilis*, *E. faecalis*, and *S. faecalis* [22]. Neem oil is effective towards Gram positive and Gram negative bacteria microorganisms, such as *Mycobacterium tuberculosis* and streptomycin-resistant forms when extracted. The crude extract of neem has been discovered to have antibacterial activity towards infections of the eyes and ears [23]. In opposition to *Candida albicans*, petroleum ether and methanol extract offer fine consequences [24]. The antibacterial pastime of neem and guava extracts in opposition to 21 lines of meals-borne pathogens changed into evaluation, and the findings advises that neem and guava extracts incorporate antibacterial additives that can be beneficial in resisting meals-borne pathogens and decomposer organisms [25]. Some other have a look at checked out the antibacterial houses of neem leaf, seed, bark, and fruit extracts on germs amassed from adults' mouths, and the consequences showed that leaf and bark extracts have an antibacterial hobby in opposition to all the bacteria studied [26]. Furthermore, only at higher concentrations of fruit and seed extracts show antibacterial interest. Oil derives from leaves, bark, and seeds have antibacterial efficacy in opposition to gram-positive and gram-negative microorganisms with streptomycin-resistant mechanisms, in addition to isolates of *M. tuberculosis* [27]. Alkaloids, saponins, steroids, tannins, crude glycosides, and flavonoids have been hired as phytoconstituents for sterile action in opposition to *E. coli*, *Corynebacterium bovis*, and *Staphylococcus aureus* traces [28]. The susceptibility of microorganisms exposes to neem extracts is compared to that of precise antibacterials. [29] Neem methanol extract suggests antibacterial movement in opposition to *B. subtilis* (28mm) [30]. Strepto neem leaf extracts have one of the quality antibacterial abilities, demonstrating the bioactive compound's efficiency and demonstrating the significance of neem flowers in main properly being preservation against *Bacillus pumilus*, *M. tuberculosis*, *S. aureus*, *P. vulgaris*, *E.coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, *E. faecalis*, *Streptococcus dysenteriae*, *Streptococcus salivarius*, *Streptococcus mutans*, and [31]. The agar properly diffusion method is used to observe the antibacterial activity of neem leaf extract in assessment to *S. aureus*, *Pseudomonas aeruginosa* (ATCC 27853), and *E. coli*. At doses of 200 mg/ml, 100 mg/ml, 50 mg/ml, 25 mg/ml, 12.5 mg/ml, 6.25 mg/ml, 3.125 mg/ml, and 156 mg/ml, respectively, ethanolic, aqueous, and methanolic extracts of the vegetal were employed. The antibacterial activity of the 3 extracts was determined to be quite robust, with the ethanolic extract having greater pastime than the methanolic and aqueous extracts. For the three extracts, the minimum inhibitory concentration (MIC) ranged from 1.56 mg/ml to six.125 mg/ml. The ethanolic and methanolic extracts displayed the most inhibition on those organisms while likened to standard antibiotics. Alkaloids, saponins, tannins, glycosides, steroids, terpenoids, and decreasing sugars were observed within the phytochemical analyses. Neem leaf extract is thus indicated for the remedy of human ailments as a result of those pathogens [32]. Antimicrobial interest becomes examined against *cyanobacterium*, *Fischerella* sp. remoted from neem bark. *E. aerogenes*, *M. tuberculosis*, *S. aureus*, *S. typhi*, *P.*

aeruginosa, and *E. coli* are all lively towards the methanolic peel extract of neem (*Azadirachta indica*). The antimicrobial activity was decided the usage of a barely changed Disk Diffusion Kirby Bauer susceptibility technique [33]. Neem becomes determined to be an antibacterial agent towards dangerous micro organisms (*Pseudomonas fluorescens*, *Aeromonas hydrophila*, *E. coli*, and *Mycobacteria* spp.) in fisheries [34].

- **Antifungal action of neem**

Compared to aqueous extracts, ethanolic extracts demonstrate more apparent action in some experiments [35]. Antifungal properties of *A. indica* methanolic and acetone extracts are examined against two fungal strains, *Aspergillus fumigatus* and *Aspergillus niger*. In comparison to acetone extracts, methanol extracts of plants shows superior antifungal activity. The neem leaf and seed extracts show antifungal activity against some dermatophytes. Seed extracts of neem when tested against several species of trichophyton and *Epidermatophyton floccosum*, the MIC of neem leaf extracts are lower than that of neem leaf extracts [36]. *Microsporum gypseum*, *Aspergillus terreus*, *Candida albicans*, *Aspergillus niger*, *Aspergillus fumigates*, and *Aspergillus flavus* are tested on the growth of pathogens using different neem extracts, including ethanolic, aqueous, and ethyl acetone extracts, using different concentrations, and the results show that these leaves extract stopped the growth of the tested path. The effect is amplified as the concentration is raised [35, 37, 38, 39, 40, 41].

2) Therapeutic effects of neem and its various components in health management

Alkaloids, Glycosides, Flavonoids, and Saponins are Phyto-constituents of neem that have antibacterial activity against a variety of diseases. 25 species of Pleopetera (beetles), 10 species of Diptera (flies), 25 species of Lepidoptera (moths), and 9 species of Orthoptera are all highly effective against numerous insects, mites, nematodes, and other plant pathogens (locusts). Some parts of the neem tree are used for physical problems such as heart disease, diabetes, a blood disorder, digestive and mental disorders, parasites, and maybe cancer, and leaf and fruit extracts have been tried on diverse pests with promising results. A study on Neem bark extract found that it aids in the reduction and healing of acid reflux and gastric ulcers [42].

- **Antimalarial activity**

When ball-shaped wood scrapes are saturated in 5% oil of neem (*A. indica*) diluted with acetone and placed in water storage overhead containers, *Anopheles stephensi* and *Aedes aegypti* propagation are organized in 45 days [43]. Nimbolide obtains from neem extracts, helps to inhibit of *Plasmodium falciparum* growth, shows antimalarial action [44]. Gedunin, finds in neem seed oil, has antimalarial properties [45]. It is shown that aqueous and alcohol extracts of leaves and bark are particularly potent antimalarial medicines, especially against chloroquine-resistant strains [46].

- **Antitumor and antiviral activity**

Neem seed oil contains limonoids and polysaccharides. Neem leaves and bark are good against cancer and tumors, as well as lymphocytic leukemia. Mitotic inhibition activity was discovered in leaf extracts. Virus inhibition assays have also revealed that neem leaf aqueous extracts have a substantial antiviral impact against Small Pox, Fowl Pox, Polio, and HSV (98100). Antiviral activity of neem aqueous leaf extracts and certain oils of neem fraction (Nim-76) against polioviruses and HIV [47].

- **Anti-inflammatory, antipyretic activities**

The chloroform extracts of neem's stem bark are effective against carrageenan, which causes paw edema in rats and ear irritation in mice. Inflammatory stomatitis in children is also treated with bark extracts. Neem oil has antipyretic properties, and leaf extracts from the plant are found to have antipyretic properties when injected into male rabbits [48].

- **Male antifertility activity**

Neem leaf extracts and seed oil (NSO) are effective spermicides that also impede spermatogenesis, hence decreasing sperm motility, quantity, and putting fertility on hold. Against rhesus monkeys and humans, neem oil extracts have spermicidal action. Vaginal biopsies demonstrate no adverse effects, whereas radioisotope analysis reveals non-antiovolatory and non-absorption in the vagina. All of these data backed up the "sensual" neem oil formulation, which is used as a potent contraceptive in India [49].

- **Antiulcer activity**

Nimbidin is known to have an antiulcer action, preventing ulcers caused by acetylsalicylic acid, omethacin, serotonin-induced gastric lesions, duodenal ulcers, or histamine [50]. Leaf extracts of neem have antiulcer properties, mucus depletion inhibition, and cell defragmentation as a probable mechanism [51].

- **Antioxidant compounds and anticancer action**

Neem increases antioxidant levels and protects against carcinogens and liver damage caused by chemicals. Neem has been used to manage diabetes due to its bitter taste and characteristics. It protects the liver from damage, and the liver helps to purify the blood. Vitiligo is an autoimmune illness in which skin patches lose their colour. Neem helps to prevent this. 4gm of neem leaves are taken three times a day, usually before a meal. The use of neem oil to the afflicted area aids in the reversal of discoloration [52]. Cancer is a complex disease that affects people all around the world. Changes in molecular pathways appear to play a role in cancer improvement and progression. The treatment is based on allopathy, which is effective on one hand but has certain negative consequences on a normal cell. According to previous research, different elements of plants restrict the formation of malignant cells via varying cellular proliferation, apoptosis, tumor suppression, and other molecular pathways. Flavanoids and other chemicals found in neem play a key function in cancer development inhibition. A vast number of epidemiological researches suggest that high flavonoid consumption is linked to lower cancer risk [53]. There are various components in neem oil. 7,12-dimethylbenz(a)anthracene carcinogenic action is inhibited by limonoid [54]. The cytotoxic impact of nimbolide funds in leaves and flowers on human choriocarcinoma (BeWo) cells are studied and inhibit the growth of BeWo cells with 2.01 IC₅₀ values and 1.19M for 7-24 hours, respectively [55,56]. The chemopreventive potential of the limonoids, azadirachtin, and nimbolide are investigated, and the results show that azadirachtin and nimbolide inhibited the development of DMBA-induced HBP carcinomas by influencing multiple mechanisms including prevention of procarcinogen activation and oxidative DNA damage, upregulation of antioxidant and carcinogen detoxification enzymes, and inhibition of tumor invasion and angiogenesis [57].

3) Micropropagation and tissue culture of Neem

Although 1-naphthalene acetic acid can induce maximal numerous shoots, modified MS medium (MS-RMN) supplemented for plant tissue culture with a combination of 2.0 mg/l, 6-Benzylaminopurine (BA) and 0.3 mg/l Indole-3 butyric acid (IBA) is successful in shoot bud sprouting in both juvenile and adult trees (NAA). During micropropagation of neem, the highest frequency of roots is seen on a half-strength MS medium supplemented with IBA [58].

4) Production of azadirachtin from differentiated *in vitro* cell lines of neem (*A. indica*)

Azadirachtin is a seed excerpt with considerable artificial demand due to its immediate connection as an environmentally respectable, biodegradable biopesticide as well as its multitudinous other bioactivities. Furthermore, azadirachtin production is higher in ordered *in vitro* callus cultures (redifferentiated) than in disorganized callus cultures (dedifferentiated). Redifferentiated immature zygotic embryo cultures are yielded the highest azadirachtin concentration of 2.33 mg g⁻¹ dry weight [59].

3. CONCLUSION:

There is a revived attention in traditional or "green drug," which is considered to be safer and further secure than precious synthetic medicinals, numerous of which have negative side goods. Now neem plays a crucial part as natural drug in so numerous developing nations. The tree's seeds, which give 40 of the well known 'Margosa oil,' are one of the tree's most important and precious products *A.indica*. *A. Juss* is native to the Indian key, and *A. excelsa* Kack finds in the Philippines and Indonesia. The remedial benefits of each section of the neem tree are different. Having the antibacterial, antifungal, antiallergic, antibiotic, antidermatic, anti-inflammatory, insecticidal, antimalarial, larvicidal, antiulcer conditioning, the nonwoody corridor of neem including the splint, dinghy, canvas, flowers, fruits, and seed also show other natural goods. The hydro extract of *A. indica* is relatively important in the treatment of hyperglycemia, hypolipidemia, and hypotensive. The presence of alkaloids with tannin and hydrogen cyanide in neem seed canvas shows the actuality of antimicrobial composites like tannin and hydrogen cyanide. Neem has a strong antimicrobial effect due to have so numerous biologically active composites. Nimbidin is known to have an antiulcer action, precluding ulcers caused by acetylsalicylic acid, indomethacin, serotonin- convinced gastric lesions, and duodenal ulcers. Having antioxidant properties, neem protects against chemically generated carcinogens and liver damages. Neem leaves helps to treat diabetes and vitiligo. The mutagenic goods of anticancer action may be suppressed by limonoids. During micropropagation (tissue culture system) of neem, modified MS medium (MS-RMN), 6-Benzylaminopurine (BA), Indole-3 butyric acid (IBA), and 1-naphthalene acetic acid (NAA) are effective in shoot cub sprouting and root induction in both juvenile and mature shops. Azadirachtin is a seed excerpt with considerable artificial demand due to

its immediate connection as an environmentally respectable, biodegradable biopesticide as well as its multitudinous other bioactivities.

4. FINANCIAL DISCLOSURE:

We declare that the authors have no conflict of interest.

5. REFERENCES:

1. Girish K., Bhat S., (2008): Neem- A Green Treasure: *Electronic Journal of Biology*, 4(3), 102-111.
2. Arumugam A., Agullo P., Boopalan T., Nandy S., Lopez R., Gutierrez C., Rajkumar L., (2014): Neem leaf extract inhibits mammary carcinogenesis by altering cell proliferation, apoptosis, and angiogenesis: *Cancer Biology and Therapy*, 15(1), 26–34.
3. Omobowale T O., Oyagbemi A A., Adejumobi O A., Orherhe E V., Amid A S., Adedapo A A., Yakubu M A., (2016): Preconditioning with *Azadirachta indica* ameliorates cardiorenal dysfunction through reduction in oxidative stress and extracellular signal regulated protein kinase signaling: *Journal of Ayurveda and Integrative Medicine*, 7(4), 209–217.
4. Patel S M., Venkata K C N., Bhattacharyya P., Sethi G., Bishayee A., (2016): Potential of neem (*Azadirachta indica* L.) for prevention and treatment of oncologic diseases: *Seminars in Cancer Biology*, 100–115.
5. Brahmachari G., (2004): Neem - an omnipotent plant: a retrospection: *ChemBiochem*, 5, 408-421.
6. M.K. Sateesh, (1998), Microbiological investigations on die-back disease of neem (*Azadirachta indica* A. Juss.), Ph.D thesis., University of Mysore, Mysore, India, (1-84).
7. Jattan S S., Shashikumar, Pujar G., (1995): Perspectives in intensive management of neem plantations: *Indian For*, 121, 981-988.
8. Hegde N G., (1995): Neem and small farmers constraints at grass root level: *Indian For*, 121, 1040- 1048.
9. Ahmed S., Bamofleh M., Munshi A., (1989): Cultivation of neem (*Azadirachta indica*) in Saudi Arabia: *Econ Bot*, 43, 35-38.
10. Koul O., Isman M B., Ketkar C M., (1990): Properties and uses of neem (*Azadirachta indica*): *Can J Bot*, 68, 1-11.
11. Radwanski S A., Wickens G E., (1981): Vegetative fallows and potential value of neem tree (*Azadirachta indica*) in the tropics: *Econ Bot*, 35, 398-414.
12. Sidhu D S., (1995): Neem in agro forestry as a source of plant derived chemicals for pest management: *Indian For*, 121, 1012-1021.
13. S K. Fathima, (2004), Investigations on the biology and management of *Phomopsis azadirachtae* on neem, Ph.D thesis., University of Mysore, Mysore, India, (1-68).
14. Bahuguna V K., (1997): Silviculture and management practices for cultivation of *Azadirachta indica* (Neem): *Indian For*, 123, 379-386.
15. Sindhuveerendra H C., (1995): Variation studies in provenances of *Azadirachta indica* (The neem tree): *Indian For*, 121, 1053-1056.
16. Moga M A., Bălan A., Anastasiu C V., Dimienescu O G., Neculoiu C D., Gavriș C., (2018): An Overview on the Anticancer Activity of *Azadirachta indica* (Neem) in Gynecological Cancers: *Int J Mol Sci*, 19(12), 3898.
17. Zingue S., Kamga S K., Fouba B I., (2019): Potential of Regular Consumption of Cameroonian Neem (*Azadirachta indica* L.) Oil for Prevention of the 7,12 Dimethylbenz(a)anthracene-Induced Breast Cancer in High-Fat/ Sucrose-Fed Wistar Rats: *Evid Based Complement Alternat Med*, 20 (3), 1460.
18. Aslam F., Rehman K U., Asghar M., Sarwar M., (2009): Antibacterial activity of various phytoconstituents of Neem: *Pak J Agri Sci*, 46(3), 209-213.
19. National Research Council. (2002): Neem-A tree for solving global problems: *National Academy Press, Washington, D. C.*, 31–107.
20. Banerjee S., Kim L M., Shariff M., Khatoon H., Yusoff S M., (2012): Antibacterial activity of neem (*Azadirachta indica*) leaves on *Vibrio* spp. Isolated from cultured shrimp: *Asian J Animal Veterinary Adv*, 3923, 1-7.
21. Divya K P., Shenoy S M., Khijmatgar S., Chowdhury A., Lynch E., Chowdhury C R., (2019): Antibacterial activity of new atraumatic restorative treatment materials incorporated with *Azadirachta indica* (Neem) against *Streptococcus mutans*: *J Oral Biol Craniofac Res*, 9(4), 321-325.
22. Shah F M., Razaq M., Ali A., Han P., Chen J., (2017): Comparative role of neem seed extract, moringa leaf extract and imidacloprid in the management of wheat aphids in relation to yield losses in Pakistan: *PLoS One*, 12(9), 0184639.

23. Mahmoud D A., Hassanein N M., Youssef K A., Zeid A., (2011): Antifungal activity of different neem leaf extracts and the nimonol against some important human pathogens: *Braz J Microbiol*, 42(3), 1007-1016.
24. Bhuiyan M M., Nishimura M., Matsumura S., Shimono T., (1997): Antibacterial effects of the crude *Azadirachta indica* Neem bark extract on *Streptococcus sobrinus*: *Pediatr Dent J*, 7(1), 61-64.
25. Bohnenstengel F I., Wray V., Witte L., Srivastava R P., Proksch P., (1998): Insecticidal meliacarpins (C-seco limonoids) from *Melia azedarach*: *Phytochemistry*, 50(6), 977-982.
26. Chauhan S., Jindal M., Singh P., Tewari S., (2015): Antimicrobial Potential of Aqueous, Methanolic and Ethanolic Extracts of *Azadirachta indica* against Bacterial Pathogens Isolated from Urinary Tract Infection Patients: *Int J Curr Microbiol App Sci*, 4(7), 211-214.
27. Cowan M M., (1999): Plant products as antimicrobial agents: *Clin Microbiol Rev*, 12(4), 564-582.
28. Debjit B., Jitender Y., Tripathi K K., Kumar K S., (2010): Herbal remedies of *Azadirachta indica* and its medicinal application: *J Chem Pharm Res*, 2(1), 62-72.
29. Dharmani P., Palit G., (2006): Exploring Indian medicinal plants for antiulcer activity: *Indian J Pharmacol*, 38(2), 95.
30. Dholi S K., Raparla R., Mankala S K., Nagappan K., (2011): In vivo Antidiabetic evaluation of Neem leaf extract in alloxan induced rats: *J Appl Pharm Sci*, 1(4), 100-105.
31. Dua V K., Nagpal B N., Sharma V P., (1995): Repellent action of neem cream against mosquitoes: *Indian J Malariol*, 32(2), 47-53.
32. Ugwu C C., (2019): Antimicrobial Activity of *Azadirachta indica* (Neem) Leaf Extract on Some Bacteria: *Int J Curr Microbiol App Sci*, 8(7), 431-437.
33. Asthana R K., Srivastava A., Singh A P., Singh S P., Nath G., Srivastava R., (2006): Identification of an antimicrobial entity from the cyanobacterium *Fischerella* sp. isolated from bark of *Azadirachta indica* (Neem) tree: *J Appl Phycol*, 18(1), 33-39.
34. Barua D R., Basavanna J M., Varghese R K., (2017): Efficacy of Neem Extract and Three Antimicrobial Agents Incorporated into Tissue Conditioner in Inhibiting the Growth of *C. albicans* and *S. mutans*: *J Clin Diagn Res*, 11(5), 97-101.
35. Jerobin J., Makwana P., Kumar R S., Sundaramoorthy R., Mukherjee A., Chandrasekaran N., (2015): Antibacterial activity of neem nanoemulsion and its toxicity assessment on human lymphocytes *in vitro*: *Int J Nanomedicine*, 10(1), 77-86.
36. Kelmanson J E., Jäger A K., Van S., Zulu J., (2000): Medicinal plants with antibacterial activity: *J Ethnopharmacol*, 69(3), 241-246.
37. Blum F C., Singh J., Merrel DS., (2005): *In vitro* activity of neem (*Azadirachta indica*) oil extract against *Helicobacter pylori*: *J Ethnopharmacol*, 232(25), 236-243.
38. Zihadi M A H., Rahman M., Talukder S., Hasan M M., Nahar S., Sikder M H., (2019): Antibacterial efficacy of ethanolic extract of *Camellia sinensis* and *Azadirachta indica* leaves on methicillin-resistant *Staphylococcus aureus* and shigatoxigenic *Escherichia coli*: *J Adv Vet Anim Res*, 6(2), 247-252.
39. Singaravelu S., Sankarapillai J., Sasidharn C A., Sinha P., (2019): Effect of *Azadirachta indica* Crude Bark Extracts Concentrations against Gram-Positive and Gram-Negative Bacterial Pathogens: *J Pharm Bioallied Sci*, 11(1), 33-37.
40. Bodiba D C., Prasad P., Srivastava A., Crampton B., Lall N S., (2018): Antibacterial Activity of *Azadirachta indica*, *Pongamia pinnata*, *Psidium guajava*, and *Mangifera indica* and their mechanism of action against *Streptococcus mutans*: *Pharmacogn Mag*, 14(53), 76-80.
41. Mistry K S., Sanghvi Z., Parmar G., Shah S., Pushpalatha K., (2015): Antibacterial efficacy of *Azadirachta indica*, *Mimusops elengi* and 2% CHX on multispecies dentinal biofilm: *J Conserv Dent*, 18(6), 461-466.
42. Jafari S., Saeidnia S., Ardekani M R S., Hadjiakhoondi A., Khanavi M., (2013): Micromorphological and preliminary phytochemical studies of *Azadirachta indica* and *Melia azedarach*: *Turk J Botany*, 37(4), 690-697.
43. Kumar P S., Debasis M., Goutam G., Panda C S., (2010): Biological action and medicinal properties of various constituent of *Azadirachta indica* (Meliaceae): an overview: *Ann Biol Res*, 1(3), 24-34.
44. Maragathavalli S., Brindha S., Kaviyarasi N S., Annadurai B., Gangwar S K., (2012): Antimicrobial activity in leaf extract of neem (*Azadirachta indica* Linn.): *Int J Sci Nat*, 3(1), 110-113.
45. Tiwari V., Darmani NA., Yue B Y., Shukla D., (2010): *In vitro* antiviral activity of neem (*Azadirachta indica* L.) bark extract against herpes simplex virus type-1 infection: *Phytother Res*, 24(8), 1132-1140.
46. Hossain M A., AlToubi W A., Weli A M., AlRiyami Q A., AlSabahi J N., (2013): Identification and characterization of chemical compounds in different crude extracts from leaves of Omani neem; *J Taibah Univ Sci*, 7(4), 181-188.

47. Irshad S., Butt M., Younus H., (2011): *In-vitro* antibacterial activity of two medicinal plants Neem (*Azadirachta indica*) and Peppermint: *Int Res J Pharma*, 1(1), 9-14.
48. Francine U., Jeannette U., Pierre R J., (2015): Assessment of antibacterial activity of neem plant (*Azadirachta indica*) on *Staphylococcus aureus* and *Escherichia coli*: *J Med Plants Stud*, 3(4), 85-91.
49. Purohit A., (1999): Antifertility Efficacy of Neem Bark (*Azadirachta indica* A. juss.) in Male Rats: *Anc Sci Life*, 19(1-2), 21-24.
50. Ofusori D A., Falana B A., Ofusori A E., Caxton M EA., (2010): Regenerative Potential of Aqueous Extract of Neem *Azadirachta indica* on the Stomach and Ileum Following Ethanol-induced Mucosa Lesion in Adult Wistar Rats: *Gastroenterology Res*, 3(2), 86-90.
51. Grover A., Bhandari B S., Rai N., (2011): Antimicrobial activity of medicinal plants- *Azadirachta indica* A. Juss, *Allium cepa* L. and *Aloe vera* L: *Int J Tech Re Pharm*, 3, 1059-65.
52. Oscar H C., Kainat E., Mahnoor W., Muzzamil S., Johnny A T J., Edwin E R., Cesar F Q., Ricardo A Y., Victor C C., (2019): *Azadirachta indica*: Antibacterial Activity of Neem Against Different Strains of Bacteria and their Active Constituents as Preventive in Various Diseases: *Pharmacogn J*, 11(6), 1597-1604.
53. Marchand L L., (2002): Cancer preventive effects of flavonoids-a review: *Biomedicine and Pharmacotherapy*, 56(6), 296-301.
54. Hao F., Kumar S., Yadav N., Chandra D., (2014): Neem components as potential agents for cancer prevention and treatment: *Biochim Biophys Acta*, 1846(1), 247-257.
55. Bhargava K P., Gupta M B., Gupta G P., Mitra C R., (1970): Anti-inflammatory activity of saponins and other natural products: *Indian J Med Res*, 58(6), 724.
56. Ara I., Siddiqui B S., Faizi S., Siddiqui S., (1989): Structurally novel diterpenoid constituents from the stem bark of *Azadirachta indica* (Meliaceae): *J Chem Soc Perkin*, 1(2), 343-345.
57. Priyadarsini R V., Manikandan P., Kumar G H., Nagini S., (2009): The neem limonoids azadirachtin and nimbolide inhibit hamster cheek pouch carcinogenesis by modulating xenobioticmetabolizing enzymes, DNA damage, antioxidants, invasion and angiogenesis: *Free Radical Research*, 43(5), 492- 504.
58. Srinidhi H.V., Gill R I S., Sidhu D S., (2008): Micropropagation of Adult and Juvenile Neem (*Azadirachta indica* A. Juss): *Journal of Crop Improvement*, 21(2), 42.
59. Singh M., Chaturvedi R., (2013): Sustainable production of azadirachtin from differentiated *in vitro* cell lines of neem (*Azadirachta indica*): *AoB PLANTS*, *Oxford University Press on behalf of the Annals of Botany Company*, 1-14.