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Exploring the supremacy of Azadirachta Indica (neem) as a Medicinal Agent

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Abstract

The historical use of herbs as medicine is confirmed in Islamic perception. Among the extensively used medicinal plants, neem is the essential one. Neem, a member of the family Meliaceae is being widely used in disease management now a day. It is well thought to be a safe and eco-friendly plant of this era. signalling parts of this plant, like leaves, stem roots, and flowers, hold a diversity of biologically active compounds. These compounds are being extracted. Among the chief compounds is azadirachtin. These compounds exhibit antimicrobial, antioxidant, anti-inflammatory, anti-fertility, hepatoprotective, and neuroprotective activities. Moreover, its constituents comprise a therapeutic inference in the induction of cell signaling pathways in cancer management. Recent studies have also exposed its neuroprotective affinity against a wide range of neurotoxins in brain tissues. This review summaries the major biochemical constituents of neem and their pharmacological miracles in the medical community.

Keywords: Antioxidant, anticancer, azadirachtin, querectin, signaling pathway, Methanolic extract, phenolic compound, antifungal

1 Introduction

Estimation of World Health Organization (WHO) is that 80 percent populace of developing countries' population depends solely on long established medications for their prime health concerns (V. S. Kumar & Navaratnam, 2013; Rupani & Chavez, 2018; Sharma et al., 2017). Now

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a day's words concentration is towards the development of medicine from natural products. The natural products possess an exceptional chemical structure, have drug like characteristics and can produce a variety of biological activities (Yuan et al., 2016). The exercise of medicine utilizing natural products happens since old ages for prevention and treatment of a variety of diseases. Natural products offer several advantages with regards to effectiveness and decision of target molecule hence they can be frequently utilized to deliver the vital requirement of medicines efficiently(Velu et al., 2018). With or without negligible side effects these natural products enclose active compounds having various cathartic activities against several diseases (Rout et al., 2009). Numerous sacred texts, like the Christ guidebook and the Holy Quran, also hold up the function of herbs in fitness and disease control. From an Islamic point of view, it is also confirmed that the role of herbs in the contagion curriculum and the Prophet Muhammad (Peace and Blessings to him) suggested a range of plants/fruits to treat the illnesses(Al-Bukhari & Sahi, 1976). That's why, in subcontinent additionally the eastern countries that are under the counter, the implement of traditional beside elliptic elixir is noticed where several healing customary standards like Ayurveda and Sowa-Rigpa, as these traditions set in stability as well as liveliness or a devout curative procedure. Remarkably, these customs get on exploitation of various remedies via a composite of condiments and plants such as Turmeric, Gooseberry, Holy basil, Gum resin and Neem (Rupani & Chavez, 2018). In general researchers consent that natural substances acquired from plants and other organisms are the creators of the most triumphant essence for new drugs. Scientists who discover drugs often propose these ideas as "leads," and chemicals with enviable features in laboratory tests are known as "lead compounds" (V. S. Kumar & Navaratnam, 2013).

Various herbal preparations or their components are extremely well-liked in many countries in the management of diseases. In view of this, i.e, Neem tree (Azadirachta indica) generally present in subcontinent and other Asian countries, has therapeutic significance in the treatment and conception relied upon the evidence, that A.indica can also be utilized to get rid of different ailments (Alzohairy, 2016).

Neem is a swiftly flourishing and enduringly fresh plant that has been used to treat a number of ailments for over 4000 years (Pankaj et al., 2011). Neem is very popular in Ayurveda (ancient art of Hindu prescription) in eastern populations, especially in India, urban as well as homeopathy, including in the Chinese Material Medicate. The neem tree is customary speculated as a 'rural medical store' to the expanded communities in India (Manogaran et al., 1998). Within final three decades complementary and elective solutions have ended up exceptionally prevalent and exceptionally neem is one of the restorative plant of financial significance within united states. Neem's role in arthritics, inflammations, fungal, microbial as well as tumor disorders is a core area to recent researches (Bandyopadhyay et al., 2004; Ebong et al., 2008; Girish & Shankara, 2008; Sultana et al., 2007).

2 Botanical, physiological and geographical report of Neem

A.indica is commonly cultivated in plenitude in equatorial and overgrown populaces such as sub-continent and neighboring states. This may be a swiftly aging plant of maximum 20–23 m height with a straight body with breadth of round about 4-5 ft. Its leaves are of compound and improvisate type, having 5–15 pamphlets each (Girish & Shankara, 2008). The seed comprises of a covering and bits which enclose the dynamic compound known as Azadirachtin along with its related chemical constituents (Onuki et al., 2008; Rupani & Chavez, 2018). Its outer hard covering contains organic constituents along with little quantity of Azadirachtin. The biologically active metabolite azadirachtin surrender diverges in the genotypes for natural intuitive (Allan et al., 1994).

Neem has two openly interrelated subtypes which are A.indica and Melia azedarac, the earlier mostly known as the Magrosa tree, whereas the other is called famously the Percian lilic(Benelli

et al., 2017; Gupta et al., 2017). A.indica is restricted to sub-continent and M.azedaraca is restrained to Philippines as well as Indonesian states (Trivedi et al., 2019).

3 Biochemical composition of A. Indica

A lot of biologically operative chemical constituents had been secluded by A.indica (Graz et al., 2018). There would be further researchers curious to inquire about auxiliary metabolites segregation along with categorization(Aerts & Mordue, 1997). Many researches reveal that the A.indica parts comprise of significant microelements like chlorophylls, calcium, thiamine, riboflavin, niacin, vitamin C, carotene, and corrosives, in shifted proportions(Ahsan et al., 2019; Graz et al., 2018; Nisbet, 2000). Additionally, it might be an antecedent of environmentally gracious commodities like neem oil biofuel (a renewable, nontoxic and ecologically safe) (Ali & El-Anany, 2017).

An extent of the vital phytocomponents isolated from neem are azadirachtin and gendenin (in seeds) (Alzohairy, 2016), querectin, β-sistosterol, polyphenolic flavonoids (in fresh leaves), (Govindachari et al., 1998) querectine-3, glactoside, rutin, iso-rhamnetin as well as vilasinin, nimbinin, nimbolines, kamoferol-3glucosides, meliantriol (in leaves) along with fatty components like margosinones etc (Simmonds et al., 1990). The supreme sum of the dynamic components in this plant can be unearthed from oil extracted out of its seeds, and a slighter amount is found within the bark and the leaves (Saleem et al., 2018). Neem oil holds tigenic acid (5-methyl-2 butanoic acid).The majority of these phytocomponents fit in the class of triterpinoids or limonoids that are somewhat water attracting in nature and with no difficulty soluble in organic solvent like alcohols, ethers etc(Ali & El-Anany, 2017). Moreover its gum or peel extractions hold an acerbic alkaloid called margosine (Nadkarni & Nadkarni, 1976). The Oil yielded from its seeds acts as stimulant and compelling for stiffness as well as skin infections additionally useful as a lotion in aching infections. In recent times nimbinin (a constituent of neem oil) had critical antiulcer action in an investigation, where it decreased the impact of gastric infections by decreasing stomach discharge (Pillai & Santhakumari, 1981). Neem tree components with their medicinal applications are listed in table 1.

Table 1: Neem tree components and their applications

Neem tree components	Medicinal and technical	Biochemical constituents	References
Fruits/seeds	Seeds out turn oil and cake, pile relieves, action against gastrointestinal grub, leprosy, urinary disorders, epitaxis, eye problems, wounds healing and diabetes.	Azadiradione 17β-hydroxy-azadiradione 17-epi azadiradione Nomolin Nimolocin	(Dwivedi et al., 2016; Nisbet et al., 1994)
Seed oil	Effectively used as antihelminthic, antiprotozoal, fungicidal, contraceptive, antipyretic, mosquitos and insect repellent. It is also useful in veterinary medicine and cosmetic like shampoos and hair oils, lubricants, soaps and tooth pastes.	Azadirone, salannin, meliantriol.	(Mandhwani et al., 2017; Reed & Majumdar, 1998)
Leaves	Effectively function as anticlotting agent, anti tuberculosis, antitumor, antiviral,	Rutin, Querectinisorhamnetinrhamnoside of querectin, nimbolide, b-	(Gupta et al., 2017; KANTH et

	insecticide, nematicide, insect and mosquito repellent.	sitoserol, glucose of qerectin.	al., 2016)
Neem cake	Recurrently utilized as soil protectant, soil neutralizer, soil moisturizer, animal feed, and soil fertilizer.		(Aerts & Mordue, 1997)
Twigs	Efficient tooth reliever, tooth cleaner, oral deodorant, asthma, cough, obstinate urinary disorders.		(Lin et al., 2008; Tuchinda et al., Tuchinda)
Flowers	Effective in bile suppression, phlegm and intestinal worms' removal. Technically used in nectarines as soaps and curries	Querectin3-galactoside(heparin) kaemeferol-3-gluocoside(astragalin) β-D-glucoside beta-sitosterol	(Benelli et al., 2017; Morales-Covarrubias et al., 2016)
Bark	In use as curative of fever, deodorant, antitumor, antiprotozoal.	nimbiol, nimbolide,6-deacetyl nimbinene, deacetylnimbin, nimbinin, sugiol, gallic acid.	(Allan et al., 1994; Mordue et al., 1995)
Roots	Skin infections just like ring worms, scabies, skin ulcers and wounds. Roots along with barks leaves and fruit are effectual in blood morbidity.		(Kim et al., 2011)
Gum	Wounds, skin diseases and scabies.		(Simmonds et al., 1990)

4 Pharmacological miracles of neem

Antimicrobial activity: The uninterrupted revelation of pathogenic bacteria V. vulnificus to antibiotics show the way to resistance against antimicrobial agents. That's why, now it's an instance to exchange the antimicrobial agents with the herbal medicinal flora like neem (42).

Antimicrobial efficacy of neem as antibacterial, antifungal and antiviral agent is summarized in table 2.

Table:2 The antimicrobial efficacy of neem:

Activities	Literature	References
Antibacterial	The antimicrobial properties of films were examined by using 5% w/w neem extracts (leaves) integration with seaweed polymer and neem biocomposite film emblazed by gamma radiations. In results the irradiated neem extract film revealed the improved functional properties against *S.aureus* and *B.subtilis* species as compared to control film. Hence neem biocomposite film can be used in sustainable packaging due to its storage steadiness.	(Rohani Shirvan et al., 2021)
	Neem emulsion's antibacterial activity against many pathogenic bacteria like Aeromonas salmonicida,	(Taylor & Webster, 2011)

	Klebsiellapneu-moniae, Vibrio sp., and Pseudomonas aeruginosa is widely studied. The smaller size of emulsions permits it to penetrate more into microbial plasma membrane. In several research studies Nano emulsion's effect was studied.	
	The results of MIC (150 µg/mL) had confirmed the antibacterial effect of neem against the *V. vulnificus* using well diffusion and disc method. The well-diffusion method exemplified that the NE (Neem) with concentration of 150 µg/mL revealed a zone of inhibition of 15.3±0.5 mm and in disc no zone was observed (10).	(Han et al., 2007)
	Neem oil expressed compact antibacterial efficacy contrary to all bacteria in its single use. Besides, neem blended with penicillin boosted the efficacy averse to *S. aureus, M. luteus, E. coli* and *P. aureginosa,* whereas its efficacy against *S. epidermis* and *B, megaterium* was declared reduced.	(Olive et al., n.d.)
	The unsympathetic action of extracts from leaf, bark, fruit and seeds of neem has been checked out in averse to bacteria obscured from mouth cavity. These extracts show maximum antibacterial efficacy at higher concentrations. Neem bark extract (NBE) blocks the HSV-1 entrance to cells at concentrations of 50-100mg/ml. The potential of neem against wound dressings has also been revealed.	(Ghonmode et al., 2013)(Hussain et al., 2017)
	In the present study, *A. indica* extract was proved most effective in term of mortality against *T. castaneum*	(Kanwal et al., 2021)
Antifungal	In a research, antifungal action of methanolic concentrates of neem leaves had been thought about opposing the *Alternaria solani* growth. The Leaf extract of *A.indica* showed more critical impact in impeding parasitic development than organic product extracts against *A. solani*.	(Jabeen et al., 2013)
	A new report has been assessed that adding up neem talc on acrylic gum dental replacement core materials unveiled the antifungal action through decreasing the attachment of *C. albicans* with denudates.	(Hamid et al., 2019)
	Anthracnose causing microbes exhibit great resistance to the existing fungicides.In a recent study *A.indica*'s taken out, Propyl disulfide (PD) was investigated in opposition to mango's anthracnose by applying different concentrations of PD against *fungi*	(Khan et al., 2021)

	Colletotrichum gloeosporioides and *Colletotrichum acutatum* in vapour and agar diffusion assays. Results have revealed that PD might be there the finest antimicrobial compound against a huge group of microbes.	
Antiviral	In a study blocking action of NBE was examined by pre incubating the extract with the virus except target cells are signifying an anti-HSV-1 quality of neem bark exudates.	(Tiwari et al., 2010)
	The neem leaves antiviral venture has been noticed because of the existence of flavonoids, glycosides along with them triterpenoids. The MIC (8000µg/ml) of the leaves extract were examined to show no virulence against Vero (African monkey) kidney cells.	(Ragasa & Hirpa, 2017)
	Neem leave's methanolic extracts have displayed virucidal action opposite to coxsackie virus B-4.	(Badam et al., 1999)

4.1 Antioxidant properties of neem

Potential effects of neem extracts have been demonstrated in several studies (Airaodion et al., 2019). Antioxidant properties of A. indica are credited to the occurrence of poly phenols in its leaf and seed extracts (Pokhrel et al., 2015). Therefore, total poly phenolic content is necessary to be retained for the overall antioxidant activity of different neem plant parts.

Gas chromatography Mass spectrometric evaluation of the plant's fractions has unearthed the presence of 62 metabolites. Most of the compounds in the list have been indicated as good source of antioxidant (Loganathan et al., 2021).The total poly phenolic components may be different with different geaographical places and abiotic factors. An incredible antioxidant activity is publicized by azadirachtin and nimbi(Ghimeray et al., 2009).

The antioxidant performance of seed extracts of neem has been described in vivo in period of its seed germination that is coincided with less amounts of lipooxygenase and lipid peroxidases activity (Yang et al., 2008). Though, the total poly phenol composition and redical scavenging functions of leaf extracts are correspondingly connected by way of antiradical and antimicrobial acivities. A new research has exposed the analogies between A. indica leaves and supplementary artificial on lipid oxidation in chilled unrefined beef (Ouerfelli et al., 2019). Methanolic extract of neem leaves are proficient to forage nitric oxide(6.3mg/ml), 1,1-diphenyl-2-picryl hydrazyl (DPPH) (6.65mg/ml), superoxide (9.21 mg/ml) and hydroxyl redicals(4.35 mg/ml) (Mali et al., 2019).

4.2 Anticancer activity

A research study has revealed, the separate and in composite functions of ethanolic neem leave's distillate and pH upon human breast cancer line cells MDA-MB 23 in several dosages(400, 600, 800 and 1600 µg/ml each in 1% DMSO) level with pH range 6.2-7.4. The exceptional outcomes had confirmed significance effect in composite trial of extracts (Ahmad et al., 2017).

Moreover the ethanol distillate of neem leaf resulted in destruction of prostate cancer cells (PC-3) through apoptosis (Kumar et al., 2006). One such study was conducted by (Pramanik et al., 2016)they experienced for the defencing analysis biochemical molecules present in neem i.e nimbolide, azadirachtin against buccel carcinogenesis in hamsters.

Along with the high quality suppression of NF-κβ pathway the reduction in expression profile of

proliferating cell nuclear antigen (PCNA), p21, cyclin D1, inhibitor of κβ, p53 were also observed (Manikandan et al., 2008).

Nimbolide had endorsed apoptosis through inflection of phosphinsitde-3-kinase (PI3K) / protein kinase B (Akt), (GSK-3β) signaling pathways in moth cancer(Sharma et al., 2017). Neem seed oil also stingers the apoptosis in MCF-7 and MDA MB-231 in breast cancer cells (Ahmad et al., 2019). Neem is utilized with cisplatin and other chemo protective in amalgam to enhance the performance of customary cancer therapies through declining chemoprotective measured quantity and lethalness of chemotherapy medicine (Sophia et al., 2018). Neem along with its particulates have a hand in averting the melanometa through the inflection of nanoscopic pathways of molecular pathways which are demonstrated in fig-1.

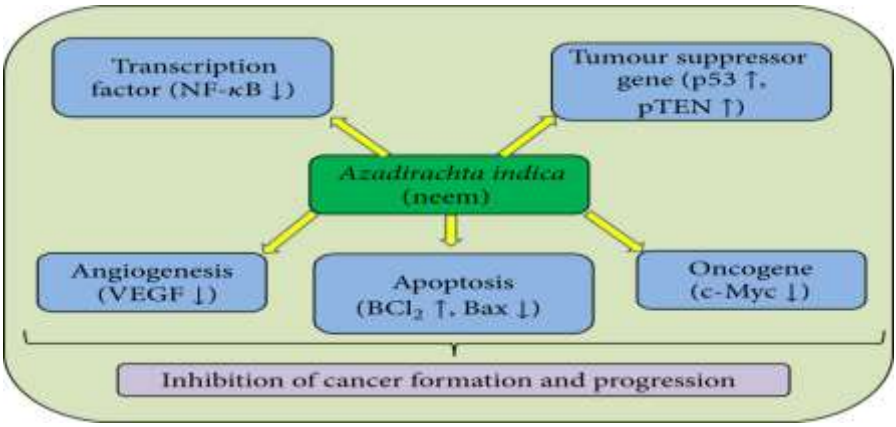

Fig 1: Anticancerous activities of neem through inflection of a range of cell signalling pathways (Alzohairy, 2016).

4.3 Anti inflammatory

Anti pyratic, analgesic(Kumar et al., 1946) and Anti-inflammatory behavior of oil extracted from seeds and immunomodulator effects of bark and leaves extracts had been studied in earlier investigations (Arora et al., 2011). One more study on albino rats via carrageenan-lured rear foot endema discovered the maximum (53.14%) inhibition of endema by increasing seed oil concentration of (0.25-2ml/kg) body weight (Naik et al., 2014). Moreover distillate of neem leaf relieves inflammation in foot edema in rats however its potential is not as much of Dexamethasone (Mosaddek & Rashid, 2008). In a recent study based on Liquid crystals presents vital hydration for accelerated healing of wounds induced by incision and deletion models and also arbitrate anti-inflammatory pathways as studied from carrageenan paw edema models(Banerjee et al., 2021).

4.4 Hepatoprotective activity of neem

The results of histology and ultra-structure in rats had revealed that azadirachtin-A controls the hepatotoxicity of (CCL4) and it was authenthicated that pretestings of azadirachtin-A had lessen hepatic cell death (Singh & Sastry, 1981).

Mixture of honey Juice and neem leaves have been used to nullify the poison in liver disorders(Gupta et al., 2017). This mixture is also helpful in antipruritic, thermogenic, thermogenic, tonic, stomachic and strokes controller (Ohtsuki et al., 2008). For Autoimmune hepatitis (AIH), a chronic liver disease, there is no effective treatment method discovered yet. But for the first time the anti-inflammatory function of nimboline was reported in AIH's mice as well as AML12 cells through HDAC3 gene expression and LPS stimulated hepatic cells. The above mentioned fallouts propose Nimbolide as a new cure to autoimmune hepatitis as well as HDAC3

might turn into a novel mark for autoimmune hepatitis.

4.5 Antifertility Activity

However, neem has not received much attention as a male contraceptive. Although antifertility effect of neem extracts of neem leaves by oral feeding in rats is reported in a few studies. One novel use of this conventional plant product to initiate a extensive duration blockage of fertility in males by a solitary intra-vas inoculation is reported in this recent study; the method could serve as an substitute to come within reach of vasectomy(Sinha et al., 1984).

4.6 Pesticidal activities of neem

Oil extracted from neem plant is among the low cost pesticides and had been utilized in field's defense. Neem oil preparations have Neem oil formulations have publicized effectiveness in opposition to insects species such as Sitophilus oryzae and Tribolium castaneum mature as well as larvae and pupae stages(Kanwal et al., 2021).

4.7 Antivenom response of neem

Ashi's et al examined an inhibitor phospholipase A2 which was obtained out the leaves together with the mod eof function of PLA2 inhibition by using AIPLAI in vitro conditions (Mukherjee et al., 2008). Neem in Veterinary medication: A study examined the ecotoxicological consequences of dosages of profitable chemical compound like fipronil, neem cake and neem distillates in the existence also in imitation of springtails (Falsomia candida), earthworms (Eisenia andrei), enchytraeidae (E. crypticus) in tropical unnatural soil. Veterinary medicines comprising of neem turnouts could be competently useful in soil in a rational manner due to their eco-friendly nature (Camarda et al., 2018).

4.8 Neuroprotective activities of neem

A recent research had carried out in order to explore the neuroprotective efficacies of A. indica in antagonistic towards noxiousness influenced by cisplatin (CP) and this research's outcomes revealed the unaffected brain tissues treated with of neem pre and post CP injections of CP (Zortea et al., 2018).

5 Conclusion

Natural products are being used as a nostrum to prevent and cure of a variety of diseases since long ago. For their primary health issues, 80 percent of the population in poor countries relies primarily on pharmaceuticals. Various religious writings, including the Bible and the Quran, support the use of plants for health and illness prevention. In India, Pakistan, Bangladesh, and Nepal, the neem tree (Azadirachta indica) is widely grown. Several researches are contending to disclose its antimicrobial, anti-inflammatory, hepatoprtective, antivenom as well as antifertility effectiveness in current studies. Neem is appropriately known as 'The Rural dispensary' and 'The Doctor tree' because of its unique properties. "One of the most gifted of all plants," according to the National Research Council (NRC) in Washington, D.C; "Ultimately the element is so as to help even a single human on earth. None of the plants can produce such a weird as well as diverse staples, nor does it have as many exploitable by-products".

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