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Medicinal and Ethnobotanical Utilities of Neem (Azadirachtaindica A. Juss.)

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Abstract: *Considered a mainstay of South Asian folk medicine over centuries and still of interest to scientists today, neem, Azadirachtaindica A. Juss., has a long tradition of being a central subject in folk medicine. This review is an assemblage of botanical, phytochemical and ethnobotanical data around the species, especially highlighting the traditional systems of Ayurveda, Siddha and Unani, where almost every component of the tree, including the bark and seed oil, has been given a medical use. Modern pharmacology screening has already started to support most of these applications: extracts and isolated limonoids in the form of azadirachtin, nimbin and nimbolide are antimicrobial, antioxidant, anti-inflammatory, anti-diabetic and anti-cancer in the laboratory and in animals. Applications outside the field of human medicine such as pest control in agriculture, veterinary practice and formulation of cosmetics are also taken into consideration in the review, and the fact that clinical validation in humans is limited, and that toxicity, especially in children who are exposed to neem oil, has been observed. Lacuna in standardization, dosage and long term safety information are the areas of priority in future research. It is hoped to provide a fair representation of what is actually known, what is realistic, and what remains that which requires stringent research before neem-derived compounds can make the transition to data-driven folk remedy and become a fully legitimate therapeutic agent.*

Keywords: Neem, Ayurveda, Azadirachtaindica, Pharmacology, Ethnobotany etc.

I. INTRODUCTION

Many centuries before bioactive compounds were a term of speech, societies all over the Indian subcontinent had already discovered that neem tree was a plant worth maintaining near the house through the centuries of trial and error. Even the elders in the village continue to prescribe the use of a neem twig to be chewed in the morning, leaves to be hung over a sickbed or to have a bath in water impregnated with some leaves. The Sanskrit books call the tree sarvaroganivarini or the curer of all diseases; this is a hyperbole, but it indicates how fully the plant was integrated into everyday health care. Azadirachtaindica is a Meliaceae species native to the Indian subcontinent, but which has now been introduced to most of the tropical African continent, most of Southeast Asia, and some of the Americas. Its ability to grow in poor soils and dry climates not only gave it a medicinal value, but a convenient shade and timber tree, which also likely solidified its cultural presence. (Puri, 1999 and Girish et al., 2008).

Modern neem fascination has since gone beyond an ethnobotanical interest. A multitude of decades of pharmaceutical and agrochemical research has been dedicated to isolating and characterizing the limonoids of the tree, and a sizeable amount of laboratory evidence now exists on the antimicrobial, antiparasitic, antioxidant and anticancer properties. To a large extent, though, this evidence is still preclinical and there is a difference between what the traditional healers have always argued and what has been verified using controlled human trials and trials that is worth exploring truthfully. This review gathers botanical, phytochemical, ethnobotanical and pharmacological data on neem, outlining the quality of evidence and its shortcomings. (Atawodi et al. 2009)

The botanical description and distribution.

Azadirachtaindica A. Juss. is an evergreen tree that is fast growing, with a height of 15 to 20 meters in most circumstances, but in some cases it can grow more than 20 meters. The trunk is frequently rather short and straight, and has grey-brown, moderately fissured bark. The leaves are pinnately compound, alternately placed with 8-19 serrated leaflets which are somewhat asymmetrical at the base which botanists use to tell the difference between neem and its

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close relative the chinaberry tree (Melia azedarach). The flowers are small, white or pale yellow, slightly fragrant, and growing out in axillary panicles; the flowering is usually in time with the commencement of the hot season in its native range where it is most extensive. The fruit is a smooth olive-shaped drupe which ripens and turns yellow and has a solitary seed that is encased by a bitter kernel where neem oil is produced. (Brahmachari, 2004)

Taxonomically, the species belongs to the family Meliaceae, to the order Sapindales, and to the genus Azadirachta, of which it is the only one named species, with one other named, Azadirachtaexcelsa, growing only in Southeast Asia. It is said to originate in the Indian subcontinent and neighboring areas of modern-day Myanmar, although there has been an argument amongst botanists over its focal point of origin. It has been able to expand far outside this original habitat because of its drought-tolerance, ineffective soil fertility, and tolerance to high temperatures, and now commonly propagates throughout sub-Saharan Africa, especially in Nigeria and Sudan, and in a small fraction of the Caribbean, Central America and Australasia, usually as an intentionally placed reforestation or shade crop. It is the adaptability of the tree, rather than any particular medicinal quality, that led to the interaction by so many cultures which had nothing in common with each other, and which eventually created their own uses of the plant. (Kumar et al., 2013).

Phytochemical Constituents of Neem.

The neem has a chemistry that is dominated by a group of tetranortriterpenoids often referred to as limonoids, and this body of compounds that are responsible for most of the bioactivity demonstrated by the plant. The best known of these, and the one most actively investigated, is azadirachtin, which was first isolated in the 1960s and is largely responsible to the insect-repellent and antifeedant effects of the tree, although subsequent studies have found other physiological effects of the plant. Similar limonoids are nimbin, nimbidin, nimbolide, gedunin, and salannin, which are found in varying amounts based on part of the plant, time of the year and geographical sources of the sample. (Chaudhary et al., 2017)

The most toxicity of azadirachtin and related limonoids occurs in seeds and seed oil, and hence, neem oil instead of extracts of leaves has traditionally been the preferred substance to be used in pest control preparations. The chemical composition of leaves, on the contrary, is slightly different, is richer in nimbin and quercetin, and a great number of polyphenols and flavonoids which provide antioxidant benefits. Bark contains tannins and a resinous gum with their own complement of bioactive constituents and flowers have low levels of essential oil. In addition to the limonoids, neem tissues are rich in a variety of secondary metabolites, including flavonoids like quercetin, kaempferol, phenolic acids, and other glycosides, but which probably do not work singly but, instead, work together to produce the effects of traditional use. This complexity is worth highlighting, as much of the pharma-logical studies to date have been done on isolated compounds or crude extracts individually, not necessarily replicative of what happens when the plant is used as a whole, as it is normally in folk practice. (Ogbuewu et al., 2011).

Ethnobotanical Importance

Neem has been used with as many simultaneous uses as few other plants have been put to use in South Asia. The rural families used to have a tree close to the house which was not just a decorative feature but also a practical pharmacy: the twigs as toothbrushes, leaves as medicine, oil as hair and wound cure, the bark and the fever. This has been the trend in local variant throughout much of the Indian subcontinent, and in some areas of Africa where the tree has been introduced in the twentieth century, the same practice has become established.

In most Indian villages neem leaves are still hung over doorways when there is an outbreak of chickenpox or measles - this is based on the belief that the leaves purify the air around the house and put off further transmission of the disease, although the biological explanation of this particular effect has not been strictly verified. One end of the neem twigs is chewed to a ragged brush, which still serves as a popular replacement of a toothbrush in rural regions, a practice that is both many years older than dental brush sales, and seems to be linked to a smaller number of oral complaints in those who have been using the neem twigs. The insect-repelling properties of the tree have long been known by farmers individually, who have kept grain under the leaves of neem or rubbed a standing crop with a crushed seed long before the chemistry of azadirachtin was known. Such cross-purpose use of neem, as a medicine, an agricultural crop, and even a ritual object, is typical of the ethnobotanical footprint of neem, and it makes it difficult to consider the plant as

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nothing more than a source of pharmaceutical leads, because neem has much more to it than medicine. (Sharma et al., 2011).

Traditional Medicinal Uses

Ayurvedic writings consider neem as tikta, or bitter, and explain it as a useful agent in balancing the pitta and kaphadoshas and recommend preparations of the leaf, bark and seed to treat skin diseases, fever and diseases caused by impurities in the blood. The same applies to siddha medicine, which is practised in large part in Tamil Nadu, where neem is used similarly, especially as a treatment of chronic skin disease, as well as a general detoxifying agent, which it is commonly mixed with in topical pastes. With a different theoretical basis based on the humoral balance, Unani physicians employ the use of neem preparations to cool what is perceived as excess heat in the body, and apply the use of neem to boils, ulcers, and some fevers. (Subapriya et al., 2005).

Within these systems and folk practices that are associated with them, there are a number of applications that are fairly consistent. Leaf paste or leaf-infused water is applied to eczema, acne, and ringworm, and other skin issues, and occasionally with neem oil where more stubborn. Intermittent fevers have been treated with a decoction of bark, and this was in practice earlier than the antimalarial drugs themselves became widely available, and may well have been indicative of certain real antipyretic or antiparasitic effect, even in cases in which a mechanism of action was not then recognized. Neem oil, though with a permanent odor, is used throughout traditional medicines in treating scabies, lice and other parasitic skin infections. In gastrointestinal disorders, barks or leaf decoctions have been used to treat intestinal worms, and generalized digestive ill will, and the flowers, thought gentler, are occasionally made into a tonic to lose appetite. Tipped in oral hygiene, which was noted above in an ethnobotanical setting, has a medicinal aspect as well, as it is said to treat the inflammation of the gums and bad breath. Traditional wound care practices involve crushed leaf or oil application over incisions and minor burns, and this method is also in line with the antimicrobial effects later determined in laboratory tests.

Pharmacology and Pharmacology.

Most of these traditional claims have been put to the test by laboratory research over the last several decades with at least some frequently positive results, but seldom conclusive at the clinical level. The leaf, bark and seed extracts have been found to be active against a variety of bacteria including Staphylococcus aureus and Escherichia coli and a variety of fungal species that cause skin infections and this offers some support to the long application of the plant in dermatological preparations (Biswas et al., 2002). It has also been found to have antiviral properties, with some extracts demonstrating in vitro anti-herpes simplex virus and anti-viral activity in other viral models, although the research in this field is not as advanced as the bacterial basis.

They have demonstrated antioxidant activity attributed to the flavonoid and polyphenol content of the leaves in a number of assay-based studies and this effect is often cited as a mechanistic rationale of the anti-inflammatory and hepatoprotective action of neem in animal models (Sithisarn et al., 2005). Extracts have decreased liver cell destruction indicators in rodents treated with hepatotoxic triggers, indicating a protective result, comparable to its conventional application as a generic detoxifying therapy, which has not been confirmed to be similarly effective at human hepatoprotection.

The studies on antidiabetic have yielded promising yet conflicting results. A number of animal trials have found decreased blood glucose levels following treatment with leaf extract, though the mechanisms of action have been suggested to include enhanced insulin sensitivity and decreased intestinal glucose absorption, though few clinical trials in humans have been done thus far, and the dosage has not been standardized (Alzohairy, 2016). Nimbolide and related limonoids have been extensively anticancer studied and have demonstrated antiproliferative effects against various cancer cell lines in culture, as well as a small degree of activity in animal tumor models, but are still preclinical (Paul et al., 2011).

In addition to its applications in human medicine, the neem insecticidal value, which is mostly due to azadirachtin, has seen it become a truly useful aspect of integrated pest management initiatives, providing an alternative to synthetic pesticides with a relatively positive environmental image (Schmutterer, 1990). Neem based preparations are used in the control of ectoparasites in livestock in veterinary practice and neem oil and extract are used in soaps, shampoos and

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skin preparations in the cosmetics industry based on its antimicrobial and antioxidant image, despite a lack of formal clinical substantiation.

II. SAFETY, TOXICITY AND LIMITATIONS.

Neem is not entirely harmless and this should be more than what it is commonly given in popular literature on the plant even though it is regarded as a harmless, purely natural remedy. Orally administered neem oil, especially in infants and young children has been linked to a syndrome of vomiting, drowsiness, metabolic acidosis, and in severe cases, encephalopathy, sometimes with fatal results. These cases are reported primarily in South and southeast Asia, and seem to be associated with the application of neem oil to infants in the treatment of numerous disorders, an application that was not generally promoted by traditional systems with infants and is now specifically discouraged by modern clinicians.

In addition to acute toxicity, there are concerns of long-term usage. Animal research indicates that large or chronic doses of neem extract can affect fertility, and this has made people cautious of its folk use as a birth control or an abortifacient, which, again, has not been shown to have the safety data required to be recommended. Persons with known liver or kidney dysfunction must be sensitive to internal neem preparations, since the substance is processed via these organs, but there is a dearth of systematic evidence on this group.

Another and more structural restriction is that of standardization. The extracted phytochemicals differ significantly in their mode of preparation, part of the plant, location of growth and time of year of harvesting, which all influence the concentration of phytochemicals and, therefore, the biological action. This inconsistency makes it hard to compare results between studies or to apply laboratory results to uniform dosing advice. A majority of pharmacological research up to now has been done in vitro or in animals; there are few well-designed human clinical trials and when they exist, the sample sizes are usually small. Such knowledge gaps do not nullify the body of evidence that has accumulated, but it implies that confident clinical recommendations, beyond topical and traditional low-dose use, are premature.

III. FUTURE SCOPE

There are a number of directions which appear to be pursued. The current research would be easier to compare with better standardization of neem extracts, such as reporting of part of the plant used, solvent used to extract the substance, and the geographic source of that extract. Improved background of future clinical endeavors would occur with better standardization of neem extracts. The use of isolated limonoids like nimbolide and gedunin, with their more selective and reproducible anticancer activity in the preclinical literature, are thought to be reasonable as further pharmacokinetic and toxicological characterization is undertaken before any consideration of a clinical trial. More intensive exploration of the antidiabetic and hepatoprotective properties of neem in controlled clinical trials is also possible, as most of the available evidence on neem is based on animal models which may not be directly applicable to humans. (National Research Council, 1992).

Ethnobotanical record is already incomplete in a number of areas, especially those areas of Africa where neem was later introduced and where the use of the plant has evolved somewhat outside the Indian tradition. Documenting such practices before they are lost to shifting land use and generational fluctuations in the transfer of knowledge would be important not only in preserving information of cultural interest, but also in terms of pharmacological potential. Instead of addressing ethnobotanical survey activity and modern phytochemical screening as two distinct domains, a combination of the two could be a more productive approach toward discovering what claims of the traditions are worth further investigation.

IV. CONCLUSION

Neem is in a peculiar place in the world of medicinal plants: both on the one hand, it is one of the most studied species in the ethnopharmacology field; and, on the other, its clinical evidence base is relatively thin in human terms. The folklore knowledge of Ayurveda, Siddha, Unani, and local folk medicine of the centuries-old use of Azadirachtaindica has been found to be a reasonably accurate indicator of where actual bioactivity can be found, especially in the domain of antimicrobial and antioxidant use. What is lacking is not laboratory verification, which is well supplyed, but of the sort of rigorous, well-energized human testing that would enable neem-derived compounds to pass beyond traditional

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medicine to a more regulated therapeutic involvement. Hitherto the plant is, perhaps, best thought of as an adjunct, which is well-supported by traditional practice, and a promising but incomplete topic on which pharmaceutical research is being pursued.

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