



Review Article

Neem - A Cynosure of Modern Medicine: A Review

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Abstract

Azadirachta indica, commonly known as Neem, has attracted worldwide prominence in recent years, owing to its wide range of medicinal properties. Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and thus has become a cynosure of modern medicine. Neem elaborates a vast array of biologically active compounds that are chemically diverse and structurally complex. More than 140 compounds have been isolated from different parts of neem. Each part of the neem tree has some medicinal property. All parts of the neem tree - leaves, flowers, seeds, fruits, roots and bark have been used traditionally for the treatment of inflammation, infections, fever, skin diseases and dental disorders. A wide array of biological activities have been demonstrated in neem such as anti-inflammatory, anti-arthritis, anti-pyretic, hypoglycaemic, anti-gastric, anti-ulcer, spermicidal, anti-fungal, anti-bacterial, diuretic, anti-malarial, anti-tumor, anti-viral, immunomodulatory, etc. In animals too, neem has a profound role to play, especially in wound healing and in treatment of reproductive disorders in bovine. The following review summarises the wide range of pharmacological activities of neem.

Key words: Antifertility, Endometritis, Immunomodulators, Neem, Nimbidin

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Introduction

Neem is perhaps the most useful traditional medicinal plant in India. It is well known in India and its neighbouring countries for more than 2000 years as one of the most versatile medicinal plant having a wide spectrum of biological activity (Biswas *et al.*, 2002). Each part of the neem tree has been shown to possess some medicinal property and is thus commercially exploitable. It is now considered as a valuable source of unique natural products for development of medicines against various diseases and also for the development of industrial products. De Jussieu in 1830 described the neem tree as *Azadirachta indica*.





Chemical Constituents of Neem

Investigation of the neem tree products started extensively in the middle of the twentieth century. More than 140 compounds have been isolated from different parts of neem (Koul *et al.*, 1990). These compounds have been divided into two major classes; isoprenoids and non-isoprenoids (Devakumar and Dev, 1996). The isoprenoids include diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivations, vilasinin type of compounds and C-secomeliacins such as nimbin, salanin and azadirachtin. The non-isoprenoids include proteins (amino acids) and carbohydrates (polysaccharides), sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin, tannins and aliphatic compounds, etc.

Medicinal Use of Various Parts of Neem

Various parts of the neem tree have been used as traditional ayurvedic medicine in India since time immemorial. As folk medicine, neem oil, the bark and leaf extracts are being therapeutically used to control leprosy, intestinal helminthiasis, respiratory disorders, constipation and also as a general health promoter (Kirtikar and Basu, 1975). Neem oil can be successfully used for controlling various skin infections (Chopra *et al.*, 1956). Moreover, bark, leaf, root, flower and fruit together can cure blood morbidity, biliary afflictions, itching, skin ulcers, burning sensations and pthysis (Mitra, 1963).

Nimbidin, a major crude bitter principle extracted from the oil of seed kernels, exerts several biological activities. Nimbidin and sodium nimbidate possess significant dose dependent anti-inflammatory activity against carrageenin induced acute paw edema in rats and formalin-induced arthritis (Bhargava *et al.*, 1970; Pillai and Senthakumari, 1981). In carrageenin induced edema, nimbidin at 40mg/kg dose level was found to possess significant anti-inflammatory effect. In formalin induced arthritis in albino rats, nimbidin showed a significant reduction of the edema of the ankle joint at 40 mg/kg and that of anti-arthritis activity at 80 mg/kg body weight. Oral administration of nimbidin causes significant hypoglycaemic effect in fasting rabbits (Pillai and Senthakumari, 1981). A decoction of tendu leaves, neem seed oil and nimbidin is hypoglycaemic when used in rabbits, reducing blood sugar by 24.77 to 26.38% within 5 hours.

Alcoholic extracts of neem leaves cures or improves all cases of eczema, ringworm infection and scabies within a short duration of application and has a distinct superiority over treatment with other chemotherapeutic agents (Singh *et al.*, 1979). Nimbidin, nimbiol and fats and glycerides of neem oil were inhibitory against ringworm fungus viz. *Trichophyton interdigitale* (0.1% conc.), fungistatic to *Canis immitis* and *Trichophyton mentagrophytes* (0.5% conc.). A 25% ointment of neem oil in petroleum jelly when applied topically on wound resulted in a faster rate of wound contraction, smaller and shorter scars and faster rate of healing (Rao *et al.*, 1986). Neem seed and leaf extracts are much effective against malarial parasites. Nimbolide, a terpenoid lactone, moderately inhibited *Plasmodium falciparum* *in vitro*. However,



nimbolide did not show any activity *in vivo* against *Plasmodium berghei*, when given orally or parenterally (Rochanakiv *et al.*, 1985). Methanolic leaf extract of leaves of *A. indica* when administered subcutaneously to mice infected with chloroquin-sensitive strain of *Plasmodium berghei* showed 41.2% suppression of parasitaemia (Obih and Mikiinde, 1985). A statistically significant suppression of *Plasmodium berghei* infection in mice has been obtained after four days of oral dosing with 500 mg/kg and 125 mg/kg of methanolic extract of leaves of *A. indica* (Abatan and Mikiinde, 1986). Badam *et al.* (1987) reported very good antimalarial efficacy against chloroquin sensitive and resistant strains of *Plasmodium falciparum* by components of ethanolic extracts of leaves and seeds of *A. indica*.

A methanolic leaf extract of neem exerts remarkable antipyretic activity in male rabbits. Okpanyi and Ezeukwu (Okpanyi and Ezeukwu, 1981) reported that leaf extract of *A. indica* when administered orally at the dose rate of 400 mg/kg to rabbits which were made hyperpyretic by injection of pyrogenic lipopolysaccharide reduces the existing fever by 15.7%. In contrast, indomethacin (4 mg/kg) and acetylsalicylic acid (200 mg/kg) reduces the pyrexia by 30.6 and 24% respectively, within 3 hours. It is necessary to recall that *A. indica* leaf extract is a mixture of several substances. A fractionation of the extract could yield an active antipyretic substance comparable in potency to indomethacin and acetylsalicylic acid. However, a herbal extract of neem contains non-specific immunostimulant, antimicrobial, antiviral and antifungal properties (Talwar *et al.*, 1997). It has also been reported that neem oil contains 1.1% nimbidin. Microbioassay indicated that one mg of nimbidin was equivalent to 800 units of penicillin and 0.5 mg of streptomycin sulphate (Singh and Sastry, 1981).

Bactericidal Properties of Neem Products

As early as 1917-18, the *in vivo* antibacterial activity of margosates obtained from neem oil was demonstrated in combating syphilis and other skin diseases (Chatterjee and Roy, 1917). An alcoholic extract of neem bark had a good antibiotic action against *Mycobacterium tuberculosis*, *Staphylococcus aureus* and *Vibrio cholera* (Chopra *et al.*, 1952). Oil from the neem leaves, seeds and bark possesses a wide spectrum of antibacterial action against both Gram positive and Gram negative microorganisms, *in vitro*. It inhibits *Vibrio cholera*, *Klebsiella pneumonia*, *Mycobacterium tuberculosis* and *Mycobacterium pyogenes* (Satyavati *et al.*, 1976). Murthy and Sirsi (1958) have been opined that Nimbidin has antibacterial properties against *Mycobacterium tuberculosis*. Moreover, a weak antibiotic activity of nimbic acid was also observed for *Bacillus subtilis*, *Corynebacterium diphtheria*, two strains of *Staphylococcus aureus* and *Staphylococcus epidermidis*.

Rao *et al.*, 1986, has obtained *In vitro* antibacterial effects of neem oil on two hundred clinical isolates of bacteria viz. *Pseudomonas aeruginosa* (55 strains), *Staphylococcus aureus* (83 strains), *Escherichia coli* (33 strains), *Proteus sp.* (24 strains) and *Klebsiella aerugenens* (5 strains). These bacterial isolates showed



92 per cent susceptibility, the minimum inhibitory concentration (MIC) varying between $1/4$ to $1/64$ dilutions. Inhibitory zones of 13-30 mm were obtained with 65.5% strains while 26.5% strains showed zones of 8-12 mm.

Neem and its Application in Reproduction

Neem (*Azadirachta indica*) has been used in traditional medicine in India for a variety of purposes. In regard to reproduction, it has components with spermicidal (Riar *et al.*, 1990; Garg *et al.*, 1998) and antimicrobial activities (Singh and Sastry, 1981). Neem also contains some ingredients that activate cell mediated immune reactions releasing cytokines detrimental to the progression of pregnancy (Upadhyay *et al.*, 1992). Recently, the oil fraction of neem seeds has been investigated for antifertility activity in rats, monkeys and human beings. It has demonstrated that single or multiple intravaginal application of neem oil during the pre and post implantation periods could prevent pregnancy in rats. However, no such study has been reported in the literature involving farm animals (Sinha *et al.*, 1984). Normal fertility was restored after 30 days of withdrawal of treatment. These aspects of neem led to a study in which oral administration of neem seed extracts in rodents and primates could completely abrogate pregnancy at an early post implantation stage. Complete restoration of fertility was observed in treated animals in the subsequent cycles. Neem leaf and seed extracts have been shown to act as immunomodulators that induce cellular immune reactions (Mukherjee *et al.*, 1999). In rats, injection of neem oil (100 μ l single dose) into uterine horns created an immunological response and prevented pregnancy for nearly five months (Upadhyay *et al.*, 1990). Talwar *et al.* (1997) has reported that purified neem extracts could successfully terminate pregnancies in rats, baboons and monkeys. The onset of pregnancy in all the test animals was confirmed by surgery and counting of implants on day 7 in rats and by CG (chorionic gonadotropin) and progesterone assay in primates. Treatment with purified neem seed extract was done for 6 days by administering orally 6 ml (in baboon) and 3 ml (in monkeys) of the preparation. Similarly, 50 μ l of neem seed extract was administered in rats for three days after implantation. Termination of pregnancy was defined by complete resorption on day 15 in rats and by bleeding and decline of CG and progesterone in baboons. Fertility was regained in both the species after one or two irregular cycles.

A potent polyherbal preparation called “Praneem” exerted a strong spermicidal action in vitro and its contraceptive efficacy was high in rabbits and monkeys (Talwar *et al.*, 1995). The antifertility activity of neem oil has been studied in male mice, rats, rabbits and guinea pigs by daily oral feeding of cold water extract of fresh green neem leaves (Sadre *et al.*, 1983). The treated male rats had 66.7% fertility reduction after 6 weeks, 80% after 9 weeks and 100% after 11 weeks. Its treatment did not affect spermatogenesis but sperm motility was reduced which was restored in 4-6 weeks. On the contrary, administration of 50%



ethanolic neem bark extract or petroleum ether extracted neem seed oil at a dose rate of 0.5g/kg body weight for 60 days caused cessation of spermatogenesis in male rats (Purohit and Dixit 1990).

In another study, Parveen *et al.* (1993) revealed that oral administration of dry powder of the leaves of *A. indica* at the dose rate of 20 mg, 40 mg and 60 mg/rat/day for 24 days results in loss of weight of seminal vesicles and ventral prostate reflecting an interference of treatment on the testosterone output. The significant decrease in the sperm count, sperm motility and relative percentage of normal sperm revealed deleterious effects of *A. indica*.

Use of Neem in the Therapy of Endometritis

Drastic decline in uterine bacterial load followed by 60% recovery of endometritis cows was observed with intrauterine infusion of crude neem oil at the dose rate of 50 ml over 3 days at 24 h interval (Bindrawan, 2001). Kumar *et al.* (2004) administered 50 ml (3000 mg TD) of aqueous extract of *Tinospora cordifolia* to the endometritis cows for 3 consecutive occasions at 24 hours interval. He obtained recovery rate and conception rate of 66.67 and 27.27%, respectively. The neem has the antibacterial and immunomodulatory properties. Thus, reported drastic decline in uterine bacterial load and subsequently inflammatory process (Owis *et al.*, 2005) and can be used as a therapy for endometritis in repeat breeding crossbred cows (Kumar *et al.*, 2013). Barman *et al.* (2009) fractionated crude neem oil by extracting with different polar and non-polar solvents and by column chromatography using silica gel. They found that the methanolic fraction of neem oil possessed very good antibacterial activity with a sensitivity pattern of 95%. In a separate study, Barman and Bangthai (2012) recorded that this methanolic fraction of neem oil possessed a significantly lower spermicidal activity with 31 and 34% motility and livability, respectively, compared to all the other fractions.

Conclusion

Different parts of neem tree have been used traditionally from ancient time to modern time, in Indian subcontinent. Though the use of neem in human being is well documented but research work in animals is limited. In this article, the use of neem in animals as therapeutic agent is trying to discover.

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