



## **Antifertility effects of *Azadirachta indica* (Neem) - A Review**

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### **Abstract**

*Most population studies conclude that today's skyrocketing growth in human population is creating a serious underlying threat to the well being of the world's natural and economic resources. Whether neem, can help to reduce runaway population growth is' uncertain. However, as noted earlier, exploratory research has indicated that certain neem, ingredients have contraceptive properties. Thus it is possible that, given research attention, products from this tree could come into widespread use for the reduction of unwanted pregnancies. This review gives a bird's eye view mainly on the contraceptive therapeutic potential of neem tree so as to promote the research on this magic tree.*

**Keywords:** *Azadirachta indica*, Contraceptive, Spermicidal, Implantation, Male fertility

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### **INTRODUCTION**

Neem, a native of Indian subcontinent is a highly esteemed tree for the people in the region. The plant is considered sacred and is used by the Hindus in several ceremonies, rituals and in worship of the New Year day [1]. It is associated with a rural festival "Ghatasthapana" to avert diseases [2-4]. The Juice of fresh green leaves of *Azadirachta indica* was believed to suppress "Kam vasna" (desire for sex) so saints and "sanyasees" in shrines and the pupils studying in "Gurukul" consumed it for the same purpose. From an initial caution and scepticism neem, has now been universally accepted as a miracle tree. During last three decades neem has attracted the brains of The scientific community and has attained a place of pride in national and international scenario. Neem has been found to contain a vast array of biologically active compounds, which are chemically diverse and have got an enormous therapeutic potential. Not only this many reviews have been already appeared from time to time on its constituents in general [5-7]. Its chemistry dates back to 1880-1890 when influenced by its folk-lore medicinal values the chemists took up the isolation of active principles and Siddiqui [8] was the first to report the isolation of three products namely nimbin, nimbidin and nimbinin from its oil. The National Research Council of USA has given an excellent account of this tree in their

publication 'Neem' A tree for solving global problems'. The society of pesticide science in India has also given an elaborative account regarding this tree in "Neem Research and Development". Two other comprehensive compilations on the multifaceted research involving diverse disciplines of science were done by Jacobson and Tiwari [9, 10]. This review has been done to provide an insight into pharmacological work done to substantiate traditional claims to establish its contraceptive potential in modern medicine demonstrated as anti-implantation effect, spermicidal effect, oral contraceptive, abortifacient, antispermatogenic effect and antifertility effect. Its contraceptive effect has been tried through oral, vaginal and subcutaneous routes of application. Either oil as such, or oil or leaf extracts have been used.

Neem is being projected as a cheap and effective antifertility agent. In 1959 the antifertility property of neem components in rats and human were published [11, 12]. In this study addition of aqueous solution of sodium nimbidinate salt to semen of rat and human being resulted in death of sperm in different percentage and in different time period. Similarly oil proved to be spermicidal against rhesus monkey and human spermatozoa in vitro [13], when used intra vaginally the oil prevented pregnancy in rats (20  $\mu$ l), rhesus monkeys and women (10ml). The oil did not reveal any side effects on repeated application as confirmed by histopathological studies on reproductive organs or other tissues where as oral dose of as low as 25 $\mu$ l oil demonstrated a complete anti-implantation effect in rat [14]. In vitro testing of spermicidal activity of neem oil posed a problem of mixing the oil with water phase i.e. semen. So cyclohexane, which had no effect on spermatozoa motility at 2% concentration, was used to dissolve most of the test neem products. After diluting the mixture with a solution of tween-80 (0.1 %), the spermatozoa movement could be observed under a microscope [15]. Both the pre-coital and post-coital antifertility effects of vaginal application of neem oil have been subsequently confirmed in rhesus monkeys [16]. According to a report from scientists of Defence Institute of Physiology and Allied Sciences (DIPAS), a neem extract (Nim-76) is believed to be refined to give birth control effect. This study showed that neem oil applied intravaginally before sexual intercourse prevented pregnancy without any adverse effect on vagina, cervix and uterus. Further radio isotopic studies indicated that neem oil is not absorbed from the vagina [14]. The active components of neem oil have been found to be absorbed through the vaginal mucosa into circulation and exerted antifertility effects in addition to direct spermicidal effect.

The spermicidal property in post-coital stages is rather undesirable because if used in pregnant women, it may lead to defects in embryonic development. Nim-76 a potent volatile fraction however inhibited spermatozoa motility in vitro in rat and human beings [17, 18]. It was found superior than raw neem oil in that it acts mainly by its spermicidal effect and no alterations in hormone values were observed. Several other studies have also shown that the mechanism of action of neem is not hormonal but probably direct spermicidal" [19, 20]. These findings were based on an analysis of the histoarchitecture of the uterus of treated rats and were subsequently confirmed by other workers [21]. Since the effect seems to be non-hormonal it would be expected to elicit fewer side effects than the steroidal contraceptives.

According to another report [22] neem oil in graded doses of 2, 4, 6 ml per kg. body weight did not inhibit ovulation activity in rabbits. According to other study neem oil constituents based formulation is 100% active to prevent pregnancy and does not produce any side effects [23]. Subcutaneous application of neem oil components like nimbidin or nimbidiol did not show any estrogenic activity [24,25]. In another report neem oil up to 0.3 ml/rat subcutaneously did not possess any estrogenic, anti-estrogenic, progestational or anti-progestational activity [26]. Subcutaneous administration of neem oil has been reported to inhibit pregnancy [27]. Study

indicates that the administration of neem oil may kill the blastocysts in the uterus of pregnant rats.

Another group of scientists have shown that feeding of neem extracts for shorter duration caused no significant changes in the ovarian or uterine histology however longer treatment did cause arrest of follicular growth and thickening and scattering of stromal and glandular cells [28].

Male rats when tested for fertility after feeding neem oil had been found to result in a significant loss of reproductive function [22]. There were no inhibitions of spermatogenesis in any of the groups demonstrating that probably the drug induced functional sterility without interfering with structural integrity of the testis or the process of spermatogenesis. Another report has given contrast results in which administration of neem bark extract (50% EtOH) or neem seed oil (petroleum ether extract at a dose of 0.5g/kg body weight for 2 months caused arrest of spermatogenesis [29]. An active principle in water extracts of crushed green leaves caused reversible antifertility action without inhibition of spermatogenesis. This active principle was thermo stable [30, 31]. This extract was also found active in mice, rats, rabbits and guinea pigs [32]. When 100 mg of dried leaf powder suspended in 1ml of distilled water per day, was given for a period of 24 days, it was suggestive of reversible antiandrogenic effect on the histological and biochemical parameters of testis of adult albino rats [33, 34].

Upadhyay *et al.* [35] observed a long-term contraceptive effect of single intra-vas administration of neem oil in male rats. The antifertility effect was observed for 8 months and was found to be an alternative approach to vasectomy. No inflammatory/obstructive changes in epididymis and vas deferens were observed. There was no change in blood testosterone levels. Purified neem seed extract called praneem was reported to cause termination of pregnancy by bleeding and a decrease in progesterone levels in rats, baboons and monkeys [36]. It was also reported to abrogate pregnancy in primates [37].

Indigenously available neem oil in its natural form as tested for its spermicidal activity (in vitro and in vivo). Undiluted neem oil was found to possess strong spermicidal action (within 30s.) against rhesus monkey and human spermatozoa in vitro, whereas 3 mg. of neem leaf extract, when treated with human spermatozoa, kills 100% of sperm within 20 s. The time taken by sperm to travel to the oviduct from the cervix in women is 5-68 min, when all conditions are favorable in the fertile period [38]. Therefore, neem leaf extract is more advantageous than the undiluted neem oil, which takes 30 s to kill the sperm.

Praneem polyherbal cream has been developed by garg *et al.* [39], which has synergistic spermicidal concentration for praneem (25%) reetha saponins (0.05%) and quinine hydrochloride (0.34%) and was found at this concentration to result in 100% immobilization of sperm within 20s [40]. Until now, neem seed extract or oil or oil components were studied as an effective contraceptive that is hydrophobic in nature. The neem leaf extract, which is hydrophilic in nature, mixes immediately with water as well as body fluids and kills sperm within 20 s, with its use, a more potent vaginal contraceptive may be developed.

A novel use of neem (*Azadirachta indica*) oil, a traditional plant product, for long-term and reversible blocking of fertility after a single intrauterine application is described by Upadhyay *et al.* [41]. Female Wistar rats of proven fertility were given a single dose (100  $\mu$ l) of neem oil by intrauterine route; control animal received the same volume of peanut oil. Whereas all control animals became pregnant and delivered normal litters, the rats treated with neem oil remained

infertile for variable periods ranging from 107 to 180 days even after repeated mating with males of proven fertility. The block in fertility was, however, reversible as half of the animal's regained fertility and delivered normal litters by five months after treatment, without any apparent teratogenic effects. Unilateral administration of neem oil in the uterus blocked pregnancy only on the side of application, whereas the contra lateral uterine horn treated with peanut oil had normally developing foetuses; no sign of implantation or foetal resorption was noted in the neem-oil-treated horn. The ovaries on both side had 4-6 corpora lutea, indicating no effect of treatment on ovarian function. The animal treated with neem oil showed a significant leukocytic infiltration in the uterine epithelium between days 3 and 5 post coitum i.e., during the preimplantation period. Intrauterine application of neem oil appears to induce a preimplantation block in fertility.

Neem oil in vitro proved to be a strong spermicidal agent. Rhesus monkey and human spermatozoa became totally immotile within 30 seconds of contact with the undiluted oil. In vivo studies in rats (20) rabbits (8), rhesus monkeys (14), and human volunteers (10) proved that neem oil has also been found to have anti-implantation/ abortifacient effect in rats and rabbits if applied intravaginally on day 2 to day 7 of expected pregnancy [42]. The minimum effective dose is 25 µl for rats. One month after the stoppage of neem oil application there was complete reversibility in fertility in these animals. It has no deleterious effect on the subsequent pregnancies and the offspring. Histopathological studies on rat's vagina, cervix and uterus showed no ill effects of neem oil in these tissues. In contrast, nonyl-phenoxy polyethoxy ethanol, a polyethoxy ethanol, a popular vaginal contraceptive cream, showed signs of severe irritant reaction in these tissues. Radioisotope studies indicated that neem oil was not absorbed from the vagina, it thus out its possible systemic effects. Results of the present study indicated that neem oil is an "ideal" female contraceptive, being easily available, cheap and non-toxic.

Another study was carried out to evaluate the effective concentration of aqueous extract of old and tender *Azadirachta indica* (neem) leaves to immobilize and kill 100% human spermatozoa within 20 s [43]. The results of the study revealed that the aqueous extract of old and tender neem leaves is a potent spermicidal, which is demonstrated through dose-dependent study on the effect of motility of spermatozoa and then confirmed by viability test. No morphological changes were found in the sperm head, mid-piece and tail when compared with untreated sperm. Therefore, 100% killing of sperm may be due to blockage of some biochemical pathway like energy utilization, which would require further investigation. The potency of lyophilized aqueous extract of old and tender leaves remains the same and the effectiveness does not change with storage time to 4 year.

According to Dhawan *et al.* [44] Ethanol/water (1:1) extract of the dried seed, administered orally to female rats at a dose of 100 mg/kg, did not demonstrate any antiimplantation effect. A similar type of study has shown inactivity of the seed oil administered by gastric incubation at a dose of 5.0ml/ animal [45]. Lal *et al.* [46, 47] has shown just contradictory results by demonstrating activity of essential oil administered orally to the rat a, the dose of 4.0 ml kg on days 1-3. In two different studies antispermatogenic effect of dried leaf extract was screened. Ethanol (80%) extract of the dried leaf, administered intragastrically to male rats at a dose of 100 mg/kg daily for 21 days was inactive for antispermatogenic activity however there was loss of libido in 100% males [48] whereas the dried leaf administered intra gastrically to male rats at a dose of 20-60 mg/animal daily for 24 days was active [49]. The seed oil has also been shown to effect the sperm/egg interaction at a concentration of 10-25% and thus inhibit fertilization and development of fertilized ova [50]. The dried seed administered intravaginally was active as spermicidal in baboon, monkey and rabbit [51].

## CONCLUSION

Keeping in view the importance of neem tree in national regional land international perspective there is an urgent need to locate collect and study its diversity and develop effect measures to store it for current and future use. At the same time it is also essential to undertake ethno botanical studies to link its various therapeutic uses with ethnic/ folklore remedies to evaluate how different tribes use neem in different areas of its occurrence. There is a dire need to document this folklore traditional knowledge, which is vanishing rapidly due to lack of awareness in these people, also effective measures are required to document available diversity and bring out systematic information for wider dissemination and utilization of world's genetic diversity in neem for exploring its therapeutic potential further.

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