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Antifertility Effect of Azadirachta Indica (Neem)

Dr. Abhay Kumar Meena[1]*, Dr.Renu[2], Dr. Vikram Singh Gurjar[3] And Dr. Bharat Lal Meena[4]
[1,2,3,4] Assistant Professor
[1]Department of Veterinary Gynaecology and Obstetrics,
[2]Department of Veterinary Pathology
[3]Department of Veterinary Medicine
[4]Department of Agronomy
[1,2,3]Post-Graduate Institute of Veterinary Education and Research, Jaipur, Rajasthan
[4] Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan
*Corresponding author: E-mail: abhaykumarmeena007@gmail.com
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Introduction

Phyto-contraceptives should be relatively cheap, widely accepted, effective, non-invasive in administration, non-hormonal in action and relatively long-acting. Several plants viz. Abrus precatorius Linn, Aegle marmelos Linn, A. lebbeck, Allium sativum, Aloe vera, Argemone mexicana, Asparagus officinalis, Azadirachta indica, Barleria prionitis, Calendula officinalis, Carica papaya, Cinnamomum zeylanicum Nees, Madhuka indica, Martynia annu, Leptadenia hastate, Mentha piperita labialae etc. have been reported to exert antifertility effects on male reproductive organs including testis, epididymis, and accessory sex glands and associated hormones (D' Cruz et al., 2010) and can be used as potential male antifertility agents. Neem (Azadirachta indica) is a tree species of the Meliaceae family, which is native to India and has been used for centuries for a wide range of purposes. A large number of bioactive compounds are present in seed, leaf, flower, bark, and roots of neem, which guarantee great versatility in their use (Ogbuewu et al., 2009). Oliveira (2009) warned of the possibility of neem causing sterility in some species of birds. Neem causes deleterious effects on the fertility of mammals (Auta and Hassan, 2016) and insects (Carvalho et al., 2015) and there is a possibility of the consumption of neem seeds to promote a negative effect on the reproduction of birds (Mohan et al., 1997).

Fig 1 : Neem (Azadirachta indica)

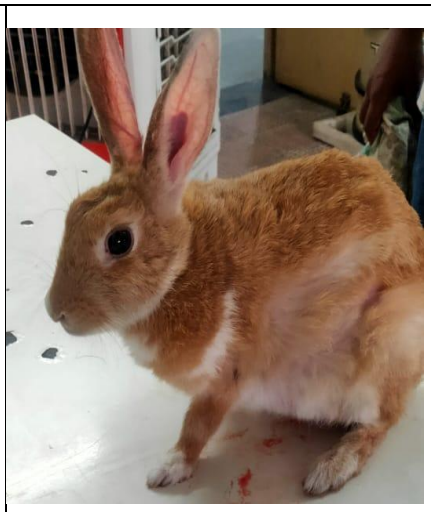

Fig 2 : Rabbit (Oryctolagus cuniculus)

Anti-fertility effects of neem

The neem leaf extract, which is hydrophilic, amalgams instantly with water as well as body fluids and kills sperm within 20s, with its use, a more potent vaginal Studies on antifertility effect of Azadirachta indica in male rabbits contraceptive may be developed. Khan and Awasthi (2003) stated that Azadirachtin in neem leaves causes toxicity in murine germ cells at the cellular level. It causes the variations in the sperm chromosomal number, structure and effect on synaptic disorders during an early stage of cellular division metaphase I. Decline in overall sperm count and incline in sperms with the abnormal head was observed. Auta and Hassan (2016) studied reproductive toxicity of aqueous wood ash extract of Azadirachta indica (neem) in male albino mice after oral administration at the dose rate of 0, 5, 50 and 100 mg/kg body weight for 7 days and reported that reproductive toxicity was dose-dependent as no significant effect was observed on testes weight and FSH, LH and testosterone levels ($p>0.05$). Sperm motility decreased, while live-dead sperm ratio and abnormal sperms increased ($p<0.05$).

Effect of neem leaf extract on follicle stimulating hormone (FSH)

Follicle stimulating hormone (FSH) is a group of glycoprotein hormones, and FSH receptors (FSH-R) are the connected receptors of G proteins; it is also called seven transmembrane receptors or hepta helical receptors (O'Shaughnessy, 2014). Sertoli cells have receptors for the FSH hormone which regulate spermatogenesis. FSH receptor mutations are associated with a decrease in the number of spermatozoa. FSH hormones, both singly and synergistically with testosterone, can prevent apoptosis of testicular germ cells (Aigbiremolen and Odigie, 2018). FSH hormone plays an important role in all spermatogonia cycles and acts to optimize the production of spermatogonia germ cells (Akpantah et al., 2011). The FSH

hormone binding to receptors in Sertoli cells activates all the factors needed for survival and differentiation of germ cells .The FSH function is the most important part of the complex hypothalamus pituitary-gonadal axis, and its feedback control mechanism regulates testicular function. The FSH hormone plays an important role in determining the number of Sertoli cells and maintaining spermatogenesis. In addition to the proliferation and differentiation of Sertoli cells, FSH also regulates interactions between cells and genes needed for metabolism and transport of regulatory substances and nutrients from Sertoli cells to germ cells. In rat with FSH deficiency, the number of spermatozoa was significantly reduced. In humans, FSH-R receptor inactivation causes azoospermia and inhibits spermatogenesis (Jiang et al., 2012). The results showed that the neem leaves extract affected FSH concentrations. The administration of neem leaf extract in male rats with a dose of 50, 100 and 150 mg/kg body weight every day for 15 days showed decrease in FSH concentration (Sofikitis et al., 2008). Don and Stelzer (2002) also reported decreased concentration of FSH in male rats following feeding of neem leaves at dose rate of 200 mg/kg body weight for 28 days. Decreasing FSH concentration will disrupt the process of spermatogenesis, which will affect spermatozoa production (Oduwole et al., 2018).

Effect of neem leaf extract on spermatogenesis

Neem leaves have an antifertility effect (Kumar et al., 2016). Neem leaf extract can affect spermatogenesis through the antifertility activity. This occurs because of several histological changes, disorders of spermatogenesis, and changes in reproductive hormone levels after the administration of neem leaf extract (Daniyal and Akram, 2015). Mishra and Singh, (2005) reported that administration of neem leaf extract in male rats orally @ of 50 and 100 mg/kg body weight did not cause changes in the histology of the epididymis, but changes occurred at doses of 200 mg/kg body weight. Neem leaf extract caused damage to the seminiferous tubules, chromatin condensation disorders, germinal cell degeneration, which caused disruption to spermatogenesis and thus reduced motility, morphology, and the number of spermatozoa of male rats. However, 42 days of cessation of treatment, the male reproductive organs returned to normal. Other studies have shown that administration of neem leaf extract in male rats at a dose of 100 mg orally caused intracellular abnormalities and vacuolization within Sertoli cells, reduced cytoplasmic inclusion in Leydig cells and disruption in the final stages of spermatids. Ultrastructural changes due to the administration of neem leaf extract can affect spermatogenesis (Kasturi et al., 2002). Extract of neem leaves at dose rate of 500 mg/kg body weight causes atrophy of the seminiferous tubules with widened space between cells, Leydig cells degenerate, the number of Leydig cells and their core diameter decreases significantly. The antiandrogenic and anti-spermatogenic properties

of neem leaves caused a reduced fertilization ability of spermatozoa (Aladakatti and Ahamed, 2005). Neem leaf extract in male rats at a dose rate of 100 mg/kg body weight for ten weeks caused impaired spermiogenesis, deformity, and sperm motility (Parshad et al., 1998). Ethanolic extract of neem leaves orally in male rats at dose rates of 0.5 mg, 1.0 mg, and 2.0 mg/kg of body weight for six weeks caused chromosome damage in the meiosis stage and disruption of gene regulation responsible for spermatozoa formation. In addition, there was a decrease in the number of spermatozoa and an increase in spermatozoa abnormalities (Awasthy, 2001). Administration of neem leaves at the dose rates of 5 mg, 10 mg, and 50 mg/kg body weight showed no toxicity in male mice reproduction (Srivastava and Raizada, 2007). Neem leaf extract can inhibit spermatogenesis, which in turn reduces the motility and concentration of spermatozoa. After 4-6 weeks of cessation of the administration, the changes become normal again (Ogbuewu et al., 2011). In rabbits fed neem leaf-based food caused a decrease in semen volume and the number of spermatozoa and an increase in morphological abnormalities of spermatozoa. In addition, it was reported that there was no decrease in libido in rabbits fed neem-based foods (Ogbuewu et al., 2009). Neem leaf extract also had a strong spermatotoxic effect. The extract of neem leaves caused 100% immobilization and mortality of human spermatozoa at dose rate of 3 mg/kg weight within 20 seconds (Khan and Awasthy, 2003; Khillare and Shrivastav, 2003). Khan et al. (2013) recorded that neem leaf extract causes changes in Leydig cell structure and seminiferous tubules of the testes, reducing sperm motility and sperm density.

Conclusion

Oral administration of the ethanolic leaf extract of *Azadirachta indica* produced a clear antifertility effect in male rabbits. This outcome was supported by notable alterations in testicular morphometry, distinct histopathological changes, and a significant reduction in serum testosterone levels. Furthermore, the extract disrupted the normal testicular architecture and adversely affected the spermatogenesis process, reinforcing its potential role as a natural antifertility agent.

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