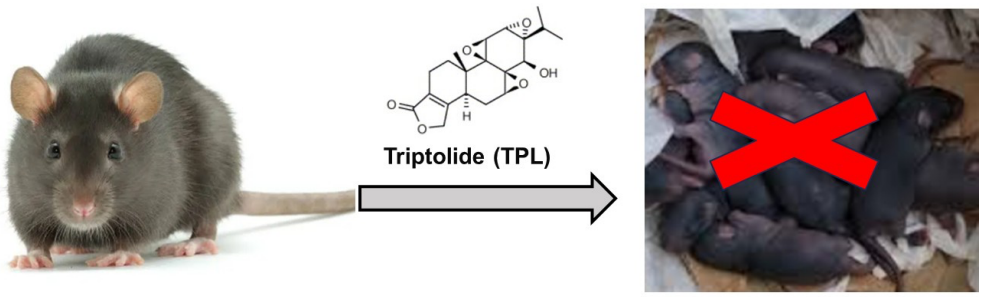
REVIEW PAPER

A Comprehensive Strategy for Rodent Control with Antifertility Attributes using Triptolide

Parul Dhar[1*], Preeti Kalia[2], Shyna Bhalla[3], Kritika Saini[4], Anita Sharma[5], Aditi Bisht[6]

[1*]University School of Life Sciences, Rayat Bahra University, Mohali, Punjab-140103, India.
[2]Department of Zoology, Goswami Ganesh Dutta Sanatan Dharma College, Chandigarh-160032, India.
[3]University School of Life Sciences, Rayat Bahra University, Mohali, Punjab-140103, India.
[4]University School of Life Sciences, Rayat Bahra University, Mohali, Punjab-140103, India.
[5]University School of Life Sciences, Rayat Bahra University, Mohali, Punjab-140103, India.
[6]Department of Biosciences (UIBT), Chandigarh University, Mohali, Punjab-140413, India.

Graphical abstract



Antifertility Effect of Triptolide (TPL)

ABSTRACT

Rodents, as pests, cause tremendous negative impacts on the global economy, food resources, and human health. The conventional trapping methods are appropriate only for small scale which specifically can address rat problems at the domestic settings, however they don't show propitious results in agricultural fields and commercial scale. Rodenticides play an important role in rodent pest management against *Rattus* sp., *Mus* sp., *Bandicota* sp., and other field rats but alone they are not that much effective. To stop rodent nuisance effectively, a better-opted approach has been the development of integrated control programs that includes mechanical, chemical, and biological strategies. Chemical control like use of rodenticides when integrated with antifertility drugs is anticipated to enhance the effective control over rodents, and one of such antifertility plant-based substance is triptolide which has highly promising results. Triptolide is a compound derived from *T. wilfordii,* a perennial Chinese twining vine and has shown substantial promise in tackling the rodent infestation. The present review highlights the scope of antifertility properties of triptolide, supported from earlier investigations in managing rodent problems. The integration of reproductive control techniques using triptolide along with rodenticide offers very promising and long-lasting approach for the management of rodents as pests.

Keywords: Rodents, Pests, Rodenticides, Antifertility agent, Triptolide.

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INTRODUCTION

In agriculture, vertebrate pests are a major cause of production loss both during pre-harvest and post-harvest times. One of the most pervasive and persistent vertebrate pests responsible for causing damage to agriculture crops are rodents. Globally around 10 % of different rodent species are primarily responsible for agriculture damage [1]. They pose social issues owing to their near proximity to human habitations, environmental issues due to the rodenticides required to control them, economic issues for the reason of extent of harm they do to agricultural systems, and health issues pertaining to the zoonosis they spread [2,3]. Moreover, with their eating and chewing patterns, rodents are also responsible for the contamination, deterioration, spoilage, and vulnerability to bacterial and fungal growths before and after the harvest stages, which consequently results in direct and indirect damage to the commodities.

In addition, rodents also feed on the eggs or offspring of birds and thus compete with the local wildlife species for their food and habitat. This has resulted in to be a major

*Author for Correspondence: parul.19123@rayatbahrauniversity.edu.in

management and recovery issue for at risk species, especially in island environments. Estimates of overall losses to crops, the weeds account for 45%, illnesses for 20%, insects for 35%, and rodents, birds, and other pests account for 5%. The worldwide agricultural crop losses total about 30% during each year according to research [1]. The Indian agricultural sector experiences losses of 25% during preharvest grain collection period alongside 25%-30% during postharvest storage period [4].

Rodents pose two-fold dangers because they both destroy crops quantitatively and cause physical damage using their urine and excreta. Food grains receive damage when rodents spread mycotoxigenic fungus and leave their waste on stored foods. consumables and spread of diseases to livestock and humans [5]. Township slum residents experience rodent attacks on elderly people and unwatched infants thus risking their safety throughout the night. The incidents can become hazardous threats to those affected individuals [6]. People normally use ineffective rodent control approaches and depend primarily on rodenticides which negatively affect both target and non-target organisms in the same area. The control methods cause limited destruction of rodents while generating minimal environmental protection and minimal success against target organisms. Rodenticides function as the primary management technique for controlling rident damage despite predictions that they will persist as the fundamental control method. It is vital to combine rodenticides with different possible control strategies including the use of plant-derived antifertility agents. The rodent being a prolific breeder, and many exhibit cyclical population growth that depends on the availability of food, use of rodenticide as a sole measure to handle rodents is insufficient and it is also harmful to non-target species [7]. We need to explore better management options by combining chemical control with fertility control measures and utilizing any such material that has a negligible impact on non-target species. The present review highlights the scope of antifertility properties of triptolide, supported from earlier investigations in managing rodent problems.

2. Tactics for Regulating Rodents

A wide variety of lethal and non-lethal techniques can be used to curb rodent pest populations. Lethal pest management methods often involve physical killing and trapping, chemical methods like the use of rodenticides and biological methods including predators and parasites which provide an immediate solution. Environmental management, the use of deterrents, barriers, rodent proofing, etc. are considered non-lethal measures [8,9]. Yet, each of these lethal and non-lethal techniques has inherent drawbacks that limits their widespread usage for management. The employment of environmental and mechanical approaches on a wider scale is labour-intensive, expensive, and difficult. Because a predator's impact on its prey is only transitory and biological control measures are only temporary therefore, rodents have easy access in developing nations like India because storage facilities especially in villages are typically very rudimentary and commercial storages are not of global standards. Such storage facilities could frequently benefit from relatively minor alterations or upgrades that would significantly reduce damage, but these changes and improvements are rarely made and kept up [6].

Although ecologically based rodent pest management (EBRPM) was created in Vietnam and other South-East Asian countries in the late 1990s to control rodents in rice-based farming systems, rodenticides are still the most widely used and effective method of rodent control in agricultural, rural, and urban settings [9]. A number of issues, including bait shyness, resistance development [10], non-target toxicity concerns [11], the inhumanity of their action, and low efficacy when high-quality food is available, can result from the overuse of rodenticides, particularly anticoagulants. Rodent control techniques used by farmers are often reactive and mostly rely on chemical and physical techniques [12, 13]. Poisons may be helpful in the initial stages to control the high-density population, helping to lessen the damage they immediately do. As a result, the effectiveness of rodent control programs should be assessed based on the achievement of pertinent goals (such as preventing crop damage or rodent infestations in warehouses or feed mills) rather than just counting the number of rats killed or the quantity of poison bait consumed. As a result, no single management approach will be effective in every situation. In order to reduce rat pest species, fertility control has been considered as an appropriate and effective method in addition to the use of rodenticide as a blend for long term strategy.

3. Fertility control

To control rodent population, different strategies have been undertaken from time to time, however, no single strategy has been proven to work universally in every circumstance. Among the already existing management programmes, fertility control has been considered as an appropriate, environmentally conducive and effective method over the poisoning of rodents [14, 15]. This approach being non-lethal, more penetrating, has the ability to offer long-lasting control, as well as to address a few shortcomings of traditional pest managing methods. It encompasses a range of compounds, including spermicidal, anti-spermatogenic, anti-implantational, antifertility and resorptive ones, which are used to control breeding activity in rodent population [14]. In addition, a variety of synthetic compounds having rodents' spermatogenesis arrest or induction of functional sterility properties has also been reported [16]. Researchers also explored the potential ability of various chemosterilants- synthetic estrogens, progestins and steroids, as reproductive inhibitors, but the observations were not found to be species-specific or permanent. It has resulted in side effects on people in frequent numbers. Additionally, it was a challenge to employ these steroids continuously in bait-delivered formulations since quite a few of them were unpleasant at the concentrations

needed for achieving desired results [17]. At present the research is also focussing upon the role of antifertility effect of certain hormones on the reproductive potential in both male and female rodents [18].

The dangers of prolonged usage of synthetic chemicals and pesticides together with the exorbitant cost of these compounds, have prompted a demand for increasing study on ecologically benign phytochemicals to develop innovative and improved fertility managing agents. The products obtained from plants have the potential of controlling pests' population, because of their cost-effectiveness, selectivity, easily biodegradable makeup and low mammalian toxicity [19]. A variety of plant chemicals (secondary metabolites) were investigated over the past two to three decades for their potential to prevent pregnancy in several rodent species which includes gossypol as one of the products obtained [20,21]. Plant molecules known as secondary metabolites help protect plants from diseases, herbivores, and rival plants. Mammalian herbivores are discouraged by these chemical defences because they negatively affect their physiology. A species' propensity to tolerate a specific chemical depends on its dose, method of action, metabolism, and nutritional status. There are approx. 105 plants with antifertility action in males, according to a 25-year literature review (1980–2005) [22]. They have also described the status of more active plants and *T. wilfordii* is one of them.

3.1 Tripterygium wilfordii

Tripterygium wilfordii (TWHF), commonly known as Seven-step Vine or Thunder God Vine, is a perennial twining vine that is native to China and found in abundance. The plant belongs to the Celastraceae family and TWHF has been utilised as a medicine by the Chinese dated back to more than 2000 years in the form of crude formulations and extracts. This plant has demonstrated its medicinal value and is widely used in herbal treatment for a variety of ailments, including rheumatoid arthritis. Nearly, a fifth of the world's population resides in China, a developing country that has undertaken major attempts to control population increase. The main activities being highlighted, involves the research into the effectiveness of using Chinese herbal treatments in fertility management. It has long been known that TWHF root extracts can reversibly make male rats, mice, and humans sterile [23]. The sperm quantity and motility decreased significantly after *T. wilfordii* extract-induced infertility, although LH and testosterone levels in the serum remained unaffected. The mechanism by means of which this plant influences reproductive ability, possible toxicity and expected negative effects are major areas of current research. A number of case studies together with clinical observations support the concept of TWHF negatively affecting the female reproductive system, including irregular menstruation and amenorrhea [24].

In 1986, a report on the effects of *T. wilfordii* extract on reversible infertility in both male rats and men gained worldwide interest. The active constituents being tripterygium have anti-inflammatory, immunosuppressive, and antifertility properties. Based on research, further six males antifertility diterpene epoxides have been found and includes triptolide, triptolidenol, tripdiolide, tripchlorolide, 16-hydroxytriplide, and a substance T7/19 (unidentified) [25] (Fig. 1). Along with the previously stated substances, research on *T. wilfordii* leaf extracts resulted in the identification of two other novel diterpenoids by chromatography, called tripdioltonide and 13, 14-epoxide 9, 11, and 12-trihydroxytriptolide. Triptolide 12, 13-chlorohydrin, a byproduct of triptolide's obtained from reversible reaction with HCl, was also discovered to be a potent antifertility compound [26].

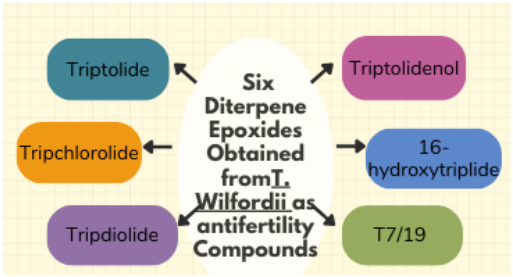

Fig. 1: Diterpene Epoxides of *T. wilfordii*

The World Health Organisation (WHO) pioneered research effort discovered a new molecule called tripchlorolide (T4), which has no negative effects on the preventive dose and has indicated no impact on libido, hormonal level or immune system functioning [27]. It was found that more than 80% of the epididymal spermatozoa were decapitated, and also the spermatozoa had fractured midpieces and disrupted connecting pieces among other structural flaws. No physiological/ gross testicular changes were seen in any of the treated animals, despite considerable epididymal spermatozoa loss. According to Lu [28], T4 therapy results into inhibited spermatogenesis as well as nuclear proteins turnover in late stretched out spermatids in the rat testes. Lu [29] found that T4 therapy led to sperm head tail separation, coiling of midpieces, and displaced axial fibres when compared to rats treated with gossypol (0.01 mg/kgbw/day for 7 weeks). It was shown that T4 suppressed MDH, LDH, and LDH-X in the mitochondria. T4 marginally but not considerably changed the enzyme activity in the kidney and liver. Qian *et al.* [30] reported that sperm counts, sperm motility, and the proportion of faulty sperm were significantly lower in men receiving extracts of *T. hypoglaucum* for the treatment of arthritis in comparison to controls. According to the motility grade of 0.8 in treated rats, the sperms migrated non-progressively and were unable to fertilise. Men receiving 15g of *T. hypoglaucum* root decoction daily as a treatment for arthritis had sperm counts that were on average <1% of normal. Due to their unpredictable travels, 26% of the remaining sperm were unable to reach an egg. However, T. *hypoglaucum* extracts had no effect on luteinizing hormone, follicle-

stimulating hormone, or testosterone levels in men receiving treatment for rheumatoid arthritis.

Wang and co-workers [27] found that tripchlorolide had no influence on process of testicular spermatogenesis. Male rats' fertility was unaffected by tripchlorolide administration at concentration of 50 µg/kg bw/day for 3 weeks, however the rats were infertile after 5 weeks of the said dose administration. Spermatozoa isolated from cauda epididymides showed significant reduction in density and motility. Epididymal weights, L-carnitine concentrations, and the amount of α-glycosidase in the epididymal fluidwere found to be reduced. The epididymal spermatozoa underwent morphological modifications, primarily the separation of the head and tail or the curvature of the acrosome.

The immunosuppressive impact of tripchloride, an antifertility compound poses a notable drawback for its usage. However, if the dosage required for immunosuppression is considerably higher than that for its antifertility effects, the compound might still be deemed a safe contraceptive, as per a key study on toxicity assessment. At ED95 dosage levels, they primarily damaged microtubules, microfilaments, and membranes while exfoliating metamorphosing spermatids, testicular, and epididymal spermatozoa, delaying spermiation, and separating sperm by their heads and tails [23].

Studies were also carried out to note the reversible antifertility effects brought on by *T. wilfordii* extracts. After discontinuing the therapy with *T. hypoglaucum* extracts for 6–12 months, the semen parameters of eight men were comparable to those of the control group [30]. Studies have shown that triptolide-containing *T. hypoglaucum* root extracts (ETHR) fed orally to Mongolian gerbils in a lab setting at a concentration of 160 mg/kg bw for 30 days had antifertility effects. They discovered a significant rise in the proportion of misshaped sperms and notable fall in sperm motility, density, and testicular and epididymis weights. There was a remarkable decrease in the number of litters born in comparison to the control group. In addition, the average proportion of pups per male decreased from numeral 34 to 0.87. Reversibility tests showed a consistent improvement in testis and epididymis weights, sperm indices, and fertility after stopping the dosing of triptolide for 30 days [31].

***3.2 T. wilfordii*multi-glycosides**

Multi-glycosides (GTW), the active components isolated from *T. wilfordii*, significantly affect rat and mouse reproductive regulation [32] and clinical studies have shown they effectively reduce proteinuria in chronic kidney disease in China. Research on GTW, indicates that reversible contraception can be achieved at doses three to four times lower than those often recommended for healthcare conditions. Low doses of GTW in rats resulted in lower sperm counts, impaired swimming, and malformed sperm, but no changes in body weight, mating behaviour, or hormone levels were seen [28]. However, male rats treated with GTW showed sterility, marked by a sharp drop in the density and viability of epididymal sperm, while body growth remained unaffected and the rats displayed normal mating behavior. This treatment was administered via gastric gavage six days per week at a dose of 10 mg/kg/day. Additionally, normal serum testosterone levels were observed together with no effect on libido and potency.

In tests using agricultural rats and mice with GTW at doses of 30 and 50 mg/kg/day, Miao *et al*. [33] observed a 32.6% drop in the birth rate. Although the histology of the seminiferous tubules and the amount of testosterone in the semen remained same, all the male rats treated with GTW (10 mg/kg/day) became infertile within 8 weeks [24]. However, it was observed that the majority of the sperm heads along the tubular lumen's surface changed from their typical sickle shape to a spherical one, indicating a potential mutagenic effect.

Bai *et al.* [34] reported dimethylzeylasteral and celastrol, two isolated monomers of GTW, affect the sperm acrosome response and the Ca^{2+} channels in mice spermatogenic cells. The results showed that dimethylzeylasteral blocked Ca^{2+} current in the sperm cells in a concentration-dependent, partially reversible way. The Ca^{2+} current in the cells was permanently and time-dependently reduced by celastrol. Additionally, both of these chemicals exhibit substantial suppression of the sperm acrosome reaction induced by progesterone, suggesting their significance in antifertility actions. Shi *et al*. [24] have noted that *T. wilfordii* plant extracts partially debilitate sperm by obstructing calcium ion channels.

According to research it was demonstrated that GTW has been found to act primarily on spermatogenic cells and its antifertility effect may be caused by a suppression of sperm transformation and maturation due to its target on the cells in the testis [24]. According to some clinical observation, men who had GTW treatment had decreased number of spermatozoa overall together with reduction in sperm life. In the epididymis of GTW-treated rats, improperly segregated spermatozoa were also seen. Embryonic ectoderm development (EED) is capable of binding to methylated lysine residues on a histone protein on a target gene during spermatogenesis and thus EED is a possible target for GTW binding as a result. Results showed that via influencing spermatogenesis, GTW can have an impact on male fertility. Both in-vivo and in-vitro experiments also showed that this disruption in sperm production begins at an early stage, specifically in spermatogonial stem cells. According to in-vitro analysis, the EED receptor is competitively inhibited between GTW and methylated H3K9. These findings imply that GTW may serve as a promising herbal male contraceptive due to the fact that GTW-induced infertility is temporary and recoverable [35]. Triptolide has been linked to reports of infertility in male rats [36], but research on its effects on female reproduction in

animals has not been as thorough. Amenorrhea and irregular menstruation have been seen in case studies and clinical trials, which point to adverse effects of TWHF on the female reproductive function [24].

3.3 Triptolide

One of *T. wilfordii's* most effective, potentially beneficial compound and with several pharmacological actions is triptolide (Fig. 2). Triptolide has been earlier used to treat rheumatological and dermatological conditions, later on reported to cause infertility in male rats is a diterpene triepoxide derived from the Chinese medicinal plant *T. wilfordii Hook* f, [37, 38]. Experimental studies and clinical observations have shown that triptolide can result in significant reproductive damage, including decreased sperm activity and quantity, decreased expression of ovarian tissue marker enzymes, and physiological malfunction of the ovaries and epididymis [39].

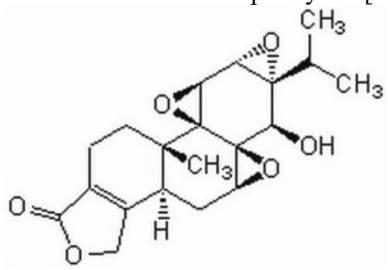

Fig. 2: Structure of Triptolide

3.3.1 Triptolide's impact on the weights of reproductive and critical organs

Huynh *et al.* [40] studied that the male rats which were given high dose of triptolide for an extended length of time (100 mg/Kg bw/day for 82 days), their testicular weights were reduced to 26% that was lower than those for the vehicle control group. Nevertheless, the rats exposed with concentration (0.025, 0.05, and 0.1%) of triptolide through bait for (7 and 14 days), and evaluated after 30 and 60 days following treatment termination, there was no significant changes of triptolide therapy in the weights of the reproductive organs [31]. There is reduction in thymus and testis weights in both continuous and delayed triptolide treatment tests, according to research by Faul et al. [41] on the effects of triptolide on reproductive and other vital organs. However, there was no discernible difference in the weights of the kidney, spleen, and liver between the treated and control groups. According to earlier research, oral medication given daily for a short period of time caused a significant decrease in testicular and epididymal weights compared with the controls [31, 42]. Liu *et al.* [43] reported the female rats given 200 and 400 µg/kg bw/day of triptolide had a decrease in the relative weights of their uterus and ovaries even after 28 days.

3.3.2 Effects of antifertility in male rats

Triptolide is responsible for causing infertility in male rats. When male rats were treated with multiglycosides of *T. wilfordii* (GTW) at a dose of 10 mg/kg/day for eight weeks via gastric gavage, they developed infertility along with a sharp decline in the density and viability of epididymal spermatozoa [44]. Preliminary toxicological experiments have shown that triptolide is safe at quantities that cause infertility, but at greater dosages (approximately 5 -12 times higher than its antifertility dose), it may exert immunosuppressive effects [23, 45]. Triptolide at a dose of 100 µg/kg bw/day for 70 days given to male rats were fully rendered infertile.

It mostly affects cauda epididymal sperm and has no or minimal effect on the testes, although it had no or very little effect on spermatogenesis process. However, the group of rats given a high dosage of triptolide showed a minor (15%) reduction in the tubule volume and a decreased number of round spermatids when compared to the control values. There were more spherical spermatids in the low dose group than in the high dose group, where five of the six men were viable. This suggested that the mild spermiogenic interference caused by triptolide was unrelated to its antifertility impact [46]. Rats treated with triptolide and rendered infertile had a 68% drop in cauda epididymal sperm production. Since no motile sperm were observed in the group treated with triptolide, sperm motility was substantially compromised. Triptolide did not affect the circulating levels of LH, FSH, testosterone, or intratesticular testosterone concenterations.

Severe structural flaws have been observed in majority of the cauda epididymal sperms. The most notable alterations were the dissociation of the head and tail, the premature decondensation of sperm nuclei's chromatin, the lack of the entire middle and main components' plasma membrane, the disarray of the covering of mitochondria, and the accumulation of numerous flagella. Rats treated with triptolide had a 0% pregnancy rate while control rats had a 100% pregnancy rate [40]. The triptolide-treated groups (200 mg/kg bw for 24 and 48 hours, 6 days, 2, 4, and 8 weeks) did not vary from the control group in terms of food intake or body weight [47]. But, according to Liu *et al*. [43], male rats that fed on 200 and 400 µg/kg/day of triptolide for a period of 28 days showed signs of anorexia, diarrhea, leanness, and a decrease of food intake and weight increase. Despite the fact that these findings could not definitively explain the mechanism of action of this substance, they do reveal new information on the subcellular processes connected to triptolide's antifertility effects. For instance, motile sperms are unlikely to have a plasma membrane that is intact. Furthermore, cauda epididymal sperm nuclei's chromatin decondensation is a sign of sperm dysfunction and may be a factor in the reported sterility [48]. In rats given triptolide, Miao *et al.* [33] documented that there was damage to the testicular tissue along with a decrease in the quantity and activity of spermatogenic cells, showing that the medication had an impact on the development and proliferation of spermatogenic cells. It interferes with spermatogenesis [49]. Male rats were rendered completely infertile, had nil sperm motility, and had 68% less cauda epididymal sperm content following oral administration of 0.1 mg/kg concentration of

triptolide for 70 days [46]. Triptolide was observed to have impact on cauda epididymal sperm ultrastructure while negligible effect was shown on the fine structural cytology of the testes [36]. Oral delivery of 20–30 mg of TWHF extract for eight weeks in Chinese men showed a sharp decline in the quantity and motility of their epididymal sperm [23].

Singla *et al*. [14] showed the antifertility capabilities of different triptolide dosages coupled in bait for its action against *R. ratttus* for the first time in India. Significant antifertility effects were observed on sperm parameters and testicular histomorphology were seen after a 14-day treatment with 0.1% triptolide in a no-choice technique. In a lab environment, Deng *et al.* [31] showed that oral dosages of *Tripterygium hypoglaucum* extracts containing triptolide had antifertility effects on Mongolian gerbils. The weight of the testis and epididymis, as well as the density and motility of the sperm, were all markedly reduced. The average population of pups per male dropped from 3.4 to a number of 0.87, when they were compared to the untreated control group. This decline was considered to be a noticeable drop in the population of litters generated.

3.3.3 Effects of antifertility in female rats

According to clinical and case studies by Shi *et al*. [24], TWHF has detrimental impacts on the reproductive system of female such as ovarian atrophy. amenorrhea, irregular menstruation, suppression of weight increase, food intake, and leanness. As TWHF has its effect on reproductive system of female, it was successfully utilised to cure endometriosis and uterus myoma [50, 51, 52]. A reproductive toxicant can affect the ovaries, directly or indirectly, the hypothalamus and/or pituitary glands [53]. Treatment with 200 as well as 400 g/kg dose of triptolide decreased the comparative weights of the uterus and ovaries. The estrous cyclicity is also disrupted by a drop in progesterone (P) and estradiol (E2) levels in the blood. As a result of positive and negative feedback mechanism on the female hypothalamus and pituitary glands, E2 and P control the pituitary gland's secretion of LH and FSH as well as follicular development. Consequently, unsuccessful reproduction will ultimately arise from any imbalance in ovarian steroidogenesis. Triptolide has been shown to negatively affect female rats' reproductive characteristics, according to Xu and Zhao [54]. In female rats given a larger dose (120 µg/kgbw/day), the average estrous cycle was noticeably longer. According to Liu *et al.* [43], treatment with 200 and 400 µg/kg concentration of triptolide raised FSH as well as LH and dramatically decreased E2 and P quantities in the serum. The relative weights of the uterus, along with ovary, were considerably lower at these dosage levels. In treated animals, there was an increase in atretic follicles and a decrease in developing follicles, according to a qualitative histological examination of the ovaries. Estrous cycles were also noticeably extended.

3.3.4 Triptolide's impact on the enzyme and hormone levels in male rats

According to Xu *et al*. [42], triptolide intoxication caused hepatotoxicity at various dosages. According to Liu *et al*. [43], rats treated with triptolide exhibited hepatotoxicity and elevated ALT and AST levels. ALP is a significant marker of germ cell growth and is broadly distributed in the testis. Rats given a dosage of 1000 µg/kg triptolide showed an increase in serum ALP activity. According to El-Kashoury *et al.* [55], one marker enzyme that is believed to be a helpful indication of spermatogenesis is ACP. A variety of mechanisms requiring the mobilization of phosphate ions or the process of dephosphorylation, in the form of catabolism, anabolism, and transfer processes, involve phosphates. To further synthesise the chemical energy needed to deal with stress, the phosphatases transfer the phosphate group from nucleotides [56]. The degree of cellular damage is typically correlated with changes in enzyme activity [57, 58]. Because, there was no discernible difference in the plasma levels of tested hormones (LH, FSH, and testosterone) as well as quantity of intratesticular testosterone between the control and triptolide-treated rat groups, triptolide had no effect on the endocrine function of male rat testis [36, 46].

3.3.5 Triptolide's impact on the enzyme and hormone levels in female rats

The serum levels of E2 and P were lowered at a dose level of 200 and 400 µg/kg triptolide. In contrast to this corresponding vehicle control, the lower doses had no effect on the FSH, LH, or E2 levels in treated rats [43]. Preovulatory follicles mature and ovulate during the estrous cycle as a result of the balanced and combined impacts of ovarian and extraovarian hormones. Any imbalance in these hormones results in irregularities in the ovaries operation and also affects how long the estrous cycle lasts. E2 encourages the development of follicles and granulosa cell proliferation. It has been suggested that progesterone is essential for mediating LH-induced ovulation and potentially luteinization. According to Xue *et al.* [59], inactivation of liver P450s diminishes the liver capacity to metabolise triptolide, leading to an increase in the drug's bioavailability as well as toxicity in vivo. In addition, 1000 and 300 µg/kg/bw/day oral administration of the triptolide for 2 weeks showed that the female counterparts were more susceptible for triptolide-induced hepatotoxicity than male rats [60]. Moreover, latest trails have shown that ContraPest, a liquid bait which is having two active components viz 4-vinylcyclohexene diepoxide (VCD) and triptolide has marked effect on ability of female and male rodents' fertility [49, 61].

Conclusion:

Due to rodents' high reproductive rate and growing resistance to rodenticides, fertility control combined with rodenticide is a safer and more efficient method of population management. Triptolide, therefore, has emerged as a prospective option after demonstrating

promising contraceptive abilities in various rodent species. Rodents are an unchecked threat that may be eliminated with the proper use of triptolide and other management measures. It should be a combined effort of all control methods and community involvement in the management of rodents rather than just the single result of any control approach or IPM.

Conflict of interest: No conflict of interest

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