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Review Article

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The antifertility effects of oshar and abamectin on experimental animals

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Abstract

Research on the reproductive toxicity of *Calotropis procera* (*C. procera)* (Oshar) and abamectin on test animals indicates that the two drugs exhibit high levels of antifertility, with abamectin having endocrine and gonadal effects. *C. procera* extracts are bioactive and can induce organ-specific toxicity, hormonal imbalances, and dose-dependent adverse effects; hence, the need to develop standardized extracts. Antiandrogenic properties of latex and root extracts have demonstrated significant inhibitory effects on androgen activity, potentially interfering with androgen receptor signaling and reducing testosterone-mediated physiological functions, including complete induction of implantation in female rats when subjected to a specific dosage of Oshar extract. Exposure to abamectin can disrupt reproductive hormones by elevating follicle-stimulating hormone, luteinizing hormone, and prolactin and altering testosterone homeostasis and inducing oxidative and nitrosative stress, ultimately resulting in poor fertility. Additional evidence shows that the developmental toxicity and gametogenesis malady may occur with abamectin even at lower doses relative to maternal toxicity; the no-observed-adverse-effect level (NOAEL) in mammals has been determined as low as 0.1 mg/kg/day. The two agents exhibit quite dissimilar forms of reproductive toxicity jointly, implying standardized doses, research of their mechanism of action, and more extensive reproductive testing.

Keywords: Abamectin; Antifertility; Oshar extract; Pest control

1. Introduction

The ecological impact of rodent species in most terrestrial habitats is undisputed; nonetheless, they are also one of the worst agricultural and public-health pests [1, 2]. They are quite difficult to control due to their rapid reproductive rate, constant feeding, and the possibility to adapt to both natural and human-altered environments [3, 4]. The conventional programs have been relying primarily on lethal equipment, which in most cases does not give long-lasting effects, as rodents are able to regenerate in a shorter period [5]. As noted by Singleton et al., reducing rodents by killing them usually gives only short-term relief, since the surviving animals reproduce fast enough to restore the population [6]. Even though rodenticides and mechanical traps remain popular, their disadvantages are more visible over the last few years. Most of such poisons subject rodents to severe and long-term pain, particularly glue traps and anticoagulants, which are known to inflict distress over a long duration before death. In addition to the animal-welfare concern, non-target organisms often suffer damages caused by these toxicants, and they often cause environmental pollution, especially via second-degree poisoning of predators and domesticated animals [7, 8].

These issues have pushed people towards non-lethal measures, particularly fertility control, which has proved to be a much

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better and sustainable solution. In contrast to poisons, fertility-control agents inhibit reproduction, not by killing, but by a more stable effect of suppression with time [9]. Such techniques may be employed in regions where toxic chemicals cannot be employed, such as in storage facilities of food and ecologically sensitive environments. Antifertility compounds can act in a number of different ways; they can disrupt the formation of sperm in males [10, 11], they can discontinue the ovulation, fertilization, implantation or early embryo development in females [12]. Since they do not pose the issues of welfare and environmental risks that are related to lethal rodenticides, fertility-control compounds have been promoted by researchers and actors.

In the larger quest to identify useful fertility-controlling agents, there have been increased efforts at focusing on botanical preparations as well as synthetic chemicals that demonstrate reproductive toxicity on laboratory animals [12, 13]. Oshar is a widely used plant in traditional medicine that is composed of many biologically active components that can affect reproductive physiology [14]. On the same note, Abamectin, a popular macrocyclic lactone pesticide, is characterized by its neurotoxic and endocrine-disrupting effects, and a number of studies have also implicated it in the potential to damage fertility in laboratory animals [15]. Researching the antifertility properties of Oshar and Abamectin is thus significant both in the evaluation of their role in rodent population management as well as the assessment of the risks of reproductive health that are caused by exposure to environmental factors. The current review aims at comparatively analyzing the agents and explaining their mechanisms of action, toxicology, and future use in the integrated and sustainable rodent management strategies.

2. *Calotropis procera* (Oshar)

2.1. Botanical description and phytochemistry

Calotropis procera, commonly known as Oshar, Sodom apple, or Giant milkweed, is a perennial shrub belonging to the family Apocynaceae. It is widely distributed across southwestern Asia and Africa but is now widespread in tropical and subtropical regions, including India, Pakistan, Egypt, Malaysia, and northeastern Brazil. The plant thrives in arid and semi-arid regions, overgrazed lands, roadways, sandy and high-aluminum soils, and even saline coastal dunes [16, 17]. Oshar commonly grows to a height of 2-6 meters and is typified by thick, erect stems as well as broad, opposite leaves having a leathery texture (Figure 1). When damaged the plant produces a copious milky latex, which is a characteristic of the Apocynaceae family. The flowers are big and waxy, and they are organized in terminal or axillary clusters and are of either white, lilac, or purple. It bears a big and inflated follicle with a lot of seeds having silky hairs that help to disperse the wind [17, 18].

C. procera is a plant that contains numerous biologically active secondary metabolites that have become the basis of the pharmacological and toxicological effects of this plant. It contains in its latex and its leaves cardiac glycosides like calotropin, calotoxin, uscharin, and similar cardenolides and are the most conspicuous compounds in *C. procera* that exhibit prominent pharmacological activities [16, 19]. Flavonoids occur considerably in different parts of the plant, such as the quercetin, rutin, and kaempferol derivatives; other flavonoids have been found to be kaempferol, luteolin, quercetin, and rosmarinic acid [20, 21]. Phenols are also present in abundance in *C. procera*, with polyphenol concentrations of 3.3-4.9% in leaves and stems, respectively. Additional phenolic acids have been determined to be caffeic acid, p-coumaric acid, and ferulic acid [16, 20]. Other compounds found in the plant are the alkaloids, terpenoids (such as 2-amyrin, alpha-amyrin, and lupeol), and triterpenoid sapogenins, most of which have cytotoxic or hormone-modulating activity [19, 22]. Its latex also contains proteolytic enzymes like calotropin and procerin. Other ingredients, such as saponins, tannin, resin, and sterols such as β-sitosterol [23].

2.2. LD_{50} of *C. procera* extract in rodents for reproductive toxicity studies

The first thing that occurs to the mind when talking about the reproductive toxicity of *C. procera* is its LD_{50}, which, by the way, would provide us with a reference point to figure out how much of the extract can be administered to the animals before making it unsafe. This is not a simple procedural nicety to be determined in rodent models, but it predetermines all dose-response studies that come thereafter, and in particular those studies that focus on subtle reproductive effects, not on overt systemic toxicity.

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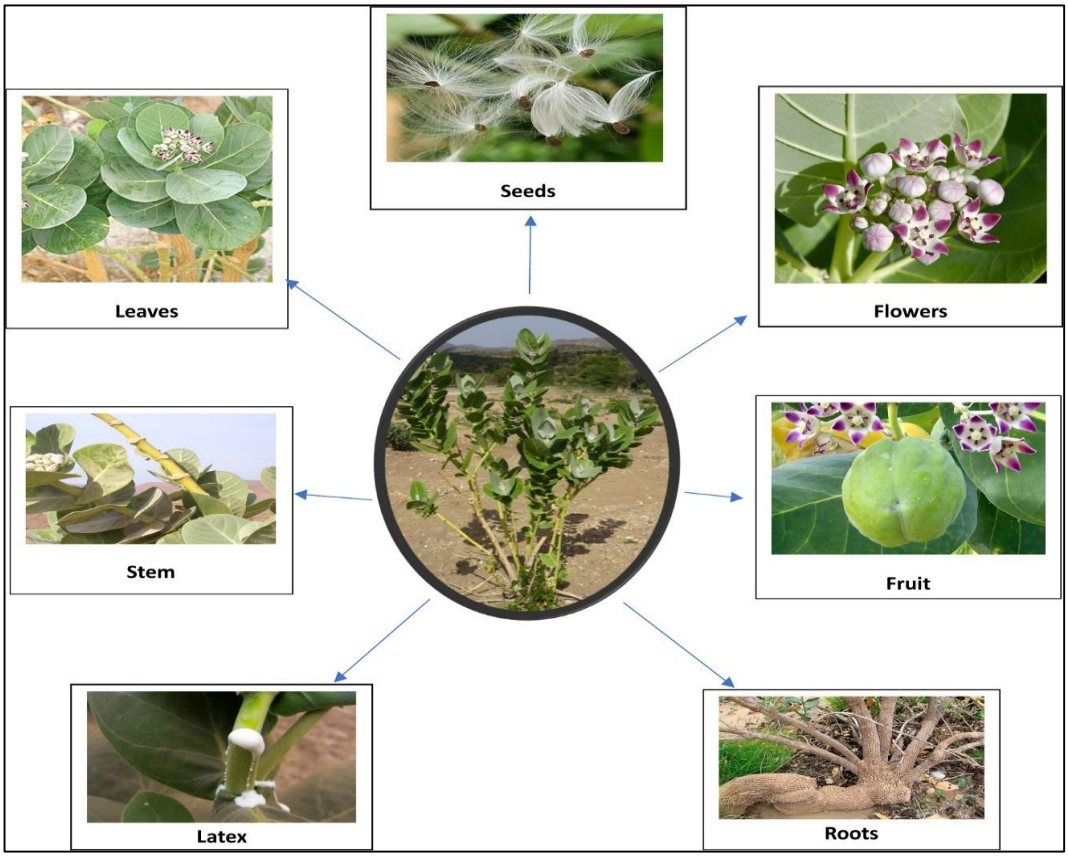


Figure 1. Various plant parts of *C. procera* (Oshar) [17, 18].

There are reports of the LD_{50} of aqueous leaf extracts in rabbits of approximately 2435 mg/kg already suggesting a relatively powerful toxic profile should the same tendencies be seen in rodents [24]. In the case of reproductive studies, though, extracts of various parts of the plants exhibit their own range of toxicity. An example is the study of ethanolic flower extracts, which have recommended an LD_{50} over 2000 mg/kg, and dried latex preparations, which have been even less toxic with values over 3000 mg/kg, and no death has been reported at 2000 mg/kg in acute oral experiments [25, 26]. These figures aid in putting the reproductive studies into perspective since researchers normally do not want to use anything that is close to lethal; they choose doses that reflect a fraction of the LD_{50}. Another popular method, which is commonly applied in rodent reproduction studies on a wide variety of plant extracts, is to operate at a fraction of the LD_{50}, say 25%. A single published study (in another species, but methodologically applicable to this case) administered 500 mg/kg following the determination of a 2000 mg/kg cutoff in rats [27]. This particular protocol has not been directly applied to *C. procera*, but the reasoning is the same.

The difficult thing that makes the picture is what makes LD_{50} determination so significant is the extraction variability that is added by the methods. Various solvents do not retain the same set of phytochemicals, such as alkaloids, flavonoids, and saponins, and such a variation will certainly alter the pharmacological and toxicological profiles [28, 29]. Aqueous extracts cannot replace ethanolic ones, and latex components react differently yet again. Such variability can affect not only hormonal disruption but also oxidative stress responses, which are also pertinent to the way in which the plant interferes with reproduction.

Therefore, in practice setting, the LD_{50} of each extract type is not so much a matter of determining a level of danger but rather a matter of making the doses to be used in the reproductive toxicity studies meaningful, interpretable, and safe enough to be handled in a controlled experiment. In the absence of this anchor point, it is almost impossible to make

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inferences as to whether the effects of observed fertility are due to particular biological interactions or are due merely to generalized toxicity. Concisely, LD_{50} research will give the baseline upon which scientifically responsible reproductive research of *C. procera* can proceed.

2.3. Antifertility effects of Oshar (*C. procera*) on experimental animals

C. procera has been explored widely due to its having antifertility properties and several experimental studies have proven that the property has great effects on both male and female reproduction. The plant is rich in phytochemicals, especially cardenolides, proteolytic enzymes, alkaloids, and triterpenoids, which have the potential to interfere with reproductive physiology in several pathways (Table 1) [14]. The existing evidence indicates the antifertility effect of *C. procera* to be primarily caused by its anti-implantation effect as well as its prominent uterotropic effect [30]. The ethanolic root extract is one of the tested preparations that has demonstrated the highest effect on numerous occasions [31]. Surprisingly, such actions do not appear to be based on anti-estrogenic processes, and other molecular targets are probably involved [32]. Although the general pattern is obvious, the exact compounds of such effects have not been yet completely determined. Subsidiary research, especially that which isolates constituents and follows the downstream molecular interactions, will be necessary to understand the exact mechanisms at work.

2.4. Antifertility effects of Oshar (*C. procera*) in male experimental animals

It has been reported that the antifertility action of *C. Procera* on males occurs in several mechanisms (Figure 2), which has been supported by several experimental studies and reviews. Its ethanolic and latex extracts of the leaf inhibit testosterone, FSH, and LH by a significant extent, resulting in dysplastic spermatogenesis and dysfunctional testicular activity [14, 33]. Further works support high antiandrogenic effects, which reduce testicular and epididymal weights, motility, count, and morphology of sperm in immature male rats [33].

Even though there is no antiestrogenic activity of ethanolic root extracts, suggesting that the antifertility effect has nothing to do with estrogen receptor antagonism, the effect of the plant is also very evident at the testicular level [37], where latex and leaf extracts cause degeneration of the seminiferous epithelium, necrosis, inflammatory infiltration, and the existence of abnormal multinucleated germ cells and empty interstitial spaces that are devastating to spermatogenesis [38, 39]. Further on, flower extracts show strong antispermatogenic and spermicidal effects, resulting in functional infertility in the treated male mice and generating massive germinal tubules and epididymal sperm loss without libido impact [40]. Together, these results indicate that *C. procera* suppresses male fertility by a combination of endocrine suppression, direct testicular cytotoxicity and interference with sperm production and quality, which is facilitated by oxidative stress and inflammatory reactions that further worsen reproductive dysfunction [16].

Table 1. Major phytochemical classes in *C. procera* and their relevance.

Phytochemical Class	Plant Part(s)	Biological Activity	Potential to Antifertility	References
Cardenolides	Latex, whole plant	Cardiotonic, cytotoxic	Implicated in antifertility	[16 ,20, 27, 34–36]
Steroids	Whole plant	Hormonal, cytotoxic	Known antifertility agents	
Flavonoids	Leaves, flowers	Antioxidant, cytotoxic	Known antifertility agents	
Alkaloids	Whole plant	Cytotoxic, hormonal	Known antifertility agents	
Tannins	Whole plant	Antioxidant, cytotoxic	Known antifertility agents	
Saponins	Whole plant	Cytotoxic, hormonal	Known antifertility agents	
Terpenoids	Whole plant	Antioxidant, cytotoxic	Implicated in antifertility	

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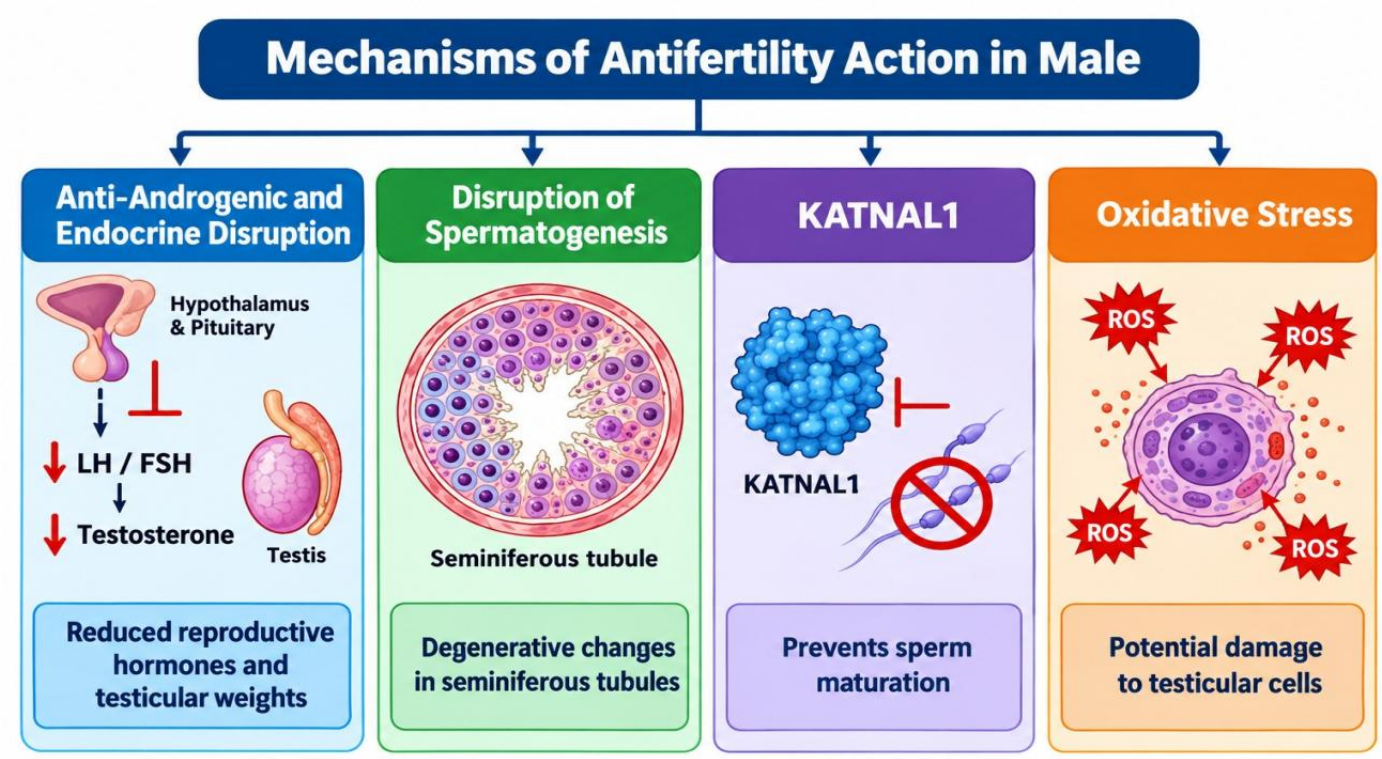


Figure 2. Mechanisms of action affecting the antifertility of Oshar (*C. procera*) in male experimental animals.

2.5. Antifertility effects of Oshar (*C. procera*) in female experimental animals

Continuing on the increased interest in the reproductive effects of *C. procera*, some studies have experimentally investigated the effects of its root extracts on the main reproductive functions of the female animal models. Combining these results, one can conclude that the plant has the ability to modulate the estrous cycle and early pregnancy phases, but the underlying mechanisms behind these effects are a little bit subtle [16, 41]. As an example, the ethanolic and aqueous root extracts have been identified to alter the normal estrous cycle of rats; 60% and 80%of treated rats, respectively, have been reported to exhibit a definite break in cycling [42]. The lengthened dioestrous phase was the most similar finding, and this condition inherently inhibits ovulation. This is a close similarity to the effect obtained by a commercial oestro-progestinic agent, which influenced 100% of rats treated. However, the extracts themselves, despite this resemblance, were not active as estrogens in immature, bilaterally ovariectomized rats, which is a good reminder that their action is not dependent on mere estrogen mimicry. The antifertility picture of *C. procera* is further manifested when considering the initial gestation stages. The ethanolic root extract at a dose of 250 mg/kg (which is about a quarter of LD_{50}) generated an overall 100% anti-implantation outcome in albino rats [32]. In reality, implantation of fertilized ova was not possible even in animals in which normal mating between the sexes had taken place. This observation is supported by other studies of *C. procera* origin in which the anti-implantation activity is always observed [43]. Interestingly, the same dose that had prevented implantation also produced a measurable uterotropic effect, suggesting a more widespread impact on uterine architecture or cytotoxicity, which may have contributed to the plant's overall antifertility effect.

Antifertility agents in female mammals can be directed to various points of the reproductive axis, such as the hypothalamus, anterior pituitary, ovary, oviduct, and uterus. It is not a secret that certain estrogen-like compounds of plant origin can inhibit the gonadotropin secretion (FSH and LH), and thus, ovulation and estrous cycles can be inhibited [44]. Although *C. Procera* extracts did not show classical estrogenic effects in particular test models, their behavior to extend dioestrus, block ovulation, and inhibit implantation

suggests that they might still have an effect on the hypothalamic, pituitary, and ovarian axis or alter uterine receptivity via other biochemical mechanisms [43]. Consequently, it is possible to conclude that the existing evidence suggests a complex antifertility effect, which is consistent with more general physiological trends seen in endocrine and uterine disruptors [45].

3. Abamectin

Abamectin is a naturally occurring compound that is formed as a result of the fermentation of the actinomycete Streptomyces avermitilis that inhabits the soil. It is a member of the Avermectin family of macrocyclic lactones, which is notorious for its strong antiparasitic and insecticidal effect [46, 47]. Avermectin B1a and B1b are usually combined as commercial formulations, with B1a constituting at least 80% of the active ingredient [48]. These molecules are structurally 16-membered macrocyclic rings of lactones commonly connected to typical sugar moieties (Figure 3) [49]. Despite the fact that Abamectin is closely related to ivermectin, the two compounds have slight differences at the C22-23 position: Abamectin has an unsaturated double bond, but ivermectin has a reduced single bond [50]. This minor structural deviation helps to lead to physicochemical behavioural, and biological activity differences. Abamectin is very lipophilic, and it is in the form of off-white to yellow crystals. It is readily dissolvable in several organic solvents, such as chloroform, methylene chloride, acetone, alcohols, toluene, cyclohexane, dimethylformamide, dimethyl sulfoxide, and tetrahydrofuran [51].

3.1. Use and toxicity

Due to its strong insecticidal, acaricidal, and nematicidal effects, Abamectin has gained popularity as an agent of agricultural and veterinary use [46, 47, 49]. It is frequently used as an anthelmintic for livestock, companion animals, and, in certain situations, humans, as well as for crop protection and aquaculture. The mode of action of the compound is well-defined. Abamectin in invertebrates has a high affinity to glutamate-gated chloride channels (GluCl) and, to a lesser degree, γ-aminobutyric acid (GABA) receptors [51]. Attachment to these sites increases the influx of chloride ions, resulting in pronounced hyperpolarization of nerve and muscle cells. With further loss of neuromuscular transmission, involved organisms become progressively paralyzed with diminished feeding behavior and, most frequently, die [52]. In mammals, the blood brain barrier restricts the accessibility of Abamectin to central GABA receptors, and this is one of the reasons why it has a relatively good safety profile when administered within the recommended exposure range [53]. Even though Abamectin is very selective to its target invertebrate, it might cause significant damage to a wide range of non-target species [48]. It has been reported to cause severe toxicity in fish, aquatic arthropods, honeybees, earthworms, soil microbiota, birds, and a number of free-living mammals [49]. Significant exposure can cause multi-organ effects in mammals [54]. The oral LD_{50} of rats is reported to be about 11 mg/kg, and when exposed dermally, LD_{50} was found to be more than 330 mg/kg, meaning that there is limited absorption via the skin [55]. Its classification as a relatively low-toxicity chemical under typical exposure conditions is supported by rodent experiments showing that up to 20 mg/kg can cause neurological symptoms, including tremors, but these doses did not result in death within the 24-hour period. Higher oral doses have been associated with high systemic toxicity and poor reproductive effects in the experimental studies [56]. The seriousness of acute high-dose exposure of up to 100 mg/kg is highlighted by documented cases of human poisoning, some of which are fatal [53, 55].

3.2. Toxicological profile

3.2.1. Neurotoxicity

The neurotoxic effects of Abamectin are mainly caused by its interaction with the neurotransmitter system of GABA, whereby it increases the permeability of the chloride channels in neuronal and muscle cells [51, 55]. This hypertonic inflow of chloride ions inhibits neural excitability, which eventually slows neuromuscular transmission, resulting in paralysis [57]. The compound typically has limited access to the mammalian central nervous system, though this is overcome in cases of high systemic doses. In this scenario, Abamectin can have GABA mimetic effects in the brain, which will result in a range of neurological symptoms, such as hyperexcitability, loss of coordination, tremors, hypotension, ataxia, progressive unconsciousness, respiratory depression, and, in severe situations, death [58]. Evidence of this is obtained through experimental evidence that Abamectin can disrupt the

integrity of blood-brain barriers and also accumulate in neural tissues, as seen in carp and other sensitive aquatic species [59]. Efflux transporter ATP-dependent P-glycoprotein (P-gp) is a normal barrier that prevents the penetration of Abamectin into the brain. But in cases where P-gp is blocked or is overloaded at high concentrations, its protective ability is lost, and neurotoxic effects are much more likely to occur, and their severity is much greater [60]. Neurotoxic impacts produced by Abamectin are reported in Table 2.

3.2.2. Organ-specific toxicity

Exposure to Abamectin has been linked to diverse structural and functional disruptions in tissues of mammals. It causes significant changes in the morphology of hepatocytes in the liver, such as cytoplasmic degeneration, abnormal deposits of glycogen, and increased biochemical evidence of hepatic injury [66, 67]. These effects are also related to the enzyme and signaling molecule upregulation of CYP 2E1 and p38 MAPK that amplifies oxidative stress and favors apoptotic mechanisms [68]. In line with these processes, DNA double-strand breaks and apoptosis have been reported in the hepatic cells after treatment [56]. Renal toxicity is also noticeable as the effect of Abamectin exposure. Experimental research indicates that there are huge rises in serum creatinine and blood urea nitrogen levels as well as mitochondrial impairment of kidney tissues [66]. The alterations are generally associated with oxidative stress reactions and the prompting of inflammatory signal pathways, which cause severe histopathological damage. Heart damage has also been reported and includes myocardial necrosis, blood lesions, inflammatory infiltrations, and dysfunction of the heart [69]. These conditions usually go along with high cardiac biomarkers, including CK-MB, BNP, and troponin-I, and the expression of apoptosis-associated genes.

The gastrointestinal tract is also vulnerable, and clinical changes in the affected animals include diarrhea and vomiting, and histological evidence includes hyperplasia of the epithelial cells and inflammatory cell infiltration [70]. It is important to note that sex-related differences have also been documented: female rats seem more susceptible to neurobehavioral disruptions and hepatic changes, displaying more oxidative stress load and more severe mitochondrial dysfunction than their male counterparts [60].

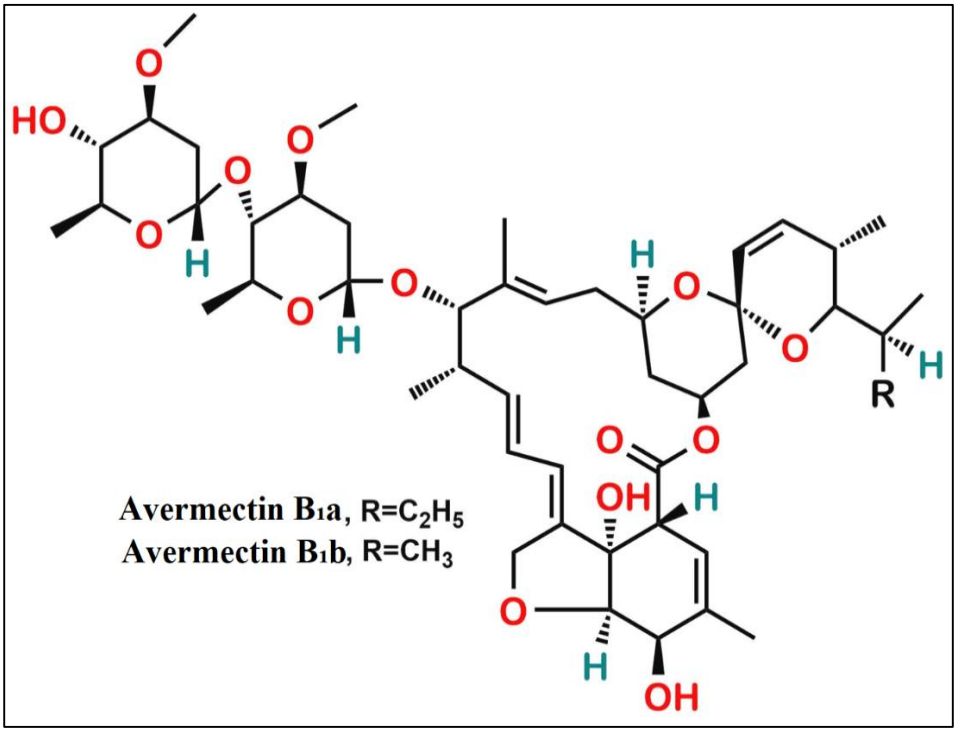


Figure 3. General structural outline of Abamectin.

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Table 2. Neurotoxic effects of Abamectin in experimental animals.

Species observed	Dose range	Outcome	Reference
Mice	3.8 mg/ kg/ day	Memory deficit and depressive behavior.	[61]
Rats	1 to 20 mg/kg	Causes elevation in both AST and NO	[62]
Rats	1 mg/kg	Elevated ROS; decreased antioxidant enzymes; mitochondrial dysfunction	[60]
Chickens	High doses	Showed severe diarrhea in chickens	[63]
Mammals		Blood–brain barrier sensitivity	[64]
Mice	0.5 μM/kg	Neurite & cytoskeletal disruption	[65]

3.2.3. Endocrine-disrupting potential

According to the current regulatory assessments, the major authorities, such as the European Union and the Danish Centre on Endocrine Disruptors, do not consider Abamectin as an endocrine-disrupting compound [71]. While some studies on pesticide groups mention insecticides and potential endocrine disruption, Abamectin is not consistently identified as a major endocrine disruptor in these broader reviews. Its toxicology is rather characterized by the well-known effects of neurotoxicity, hepatotoxicity, oxidative stress, and tissue-specific cytotoxicity, none of which have been conclusively associated with classical endocrine processes [67]. In spite of this regulatory position, changes in reproductive performance were recorded in a number of experimental research studies subsequent to exposure to Abamectin, especially during the most sensitive phases of development, such as gametogenesis and early embryonic development [13].

There is no decisive data to indicate that such effects are caused by direct contact with endocrine receptors or disruption of steroidogenic pathways, but available data does point to reproductive hormone disturbances and gametogenic developmental problems [72]. The findings indicate that Abamectin does not interact with estrogen or androgen receptors and lacks evidence of affecting hormone synthesis consistent with established endocrine-disrupting mechanisms. The lack of clear mechanistic information has been identified as a weakness of the existing literature, and more specific studies are required to establish whether the identified reproductive toxicity is endocrine-mediated disruption or driven by alternative pathways, including oxidative stress, mitochondrial damage, or systemic toxicity.

3.2.4. Abamectin causes reproductive toxicity in experimental animals

There is strong experimental evidence that confirms that Abamectin can induce reproductive toxicity in various species [70, 73–77]. In rodents, it specifically affects the male fertility and testicular function at moderate to high doses. Further evidence of reproductive effects on aquatic species and invertebrates of the soil also exists. The effects are dependent on dose and occasionally sensitive with regard to sex disparity [13, 60]. Regulatory conclusions can, however, differ depending on the interpretation of statistical significance and dose-response relationship. Conversely, not all regulatory reviews (e.g., the European Food Safety Authority) found any significant reproductive toxicity based on the lack of statistical significance and dose-response in some studies [13].

3.2.5. Effects on male fertility

Abamectin has been widely researched for its consequences on male reproductive health. In rodents and other mammals, some of the studies have established that exposure to Abamectin causes severe reproductive toxicity [73, 78, 79]. This is a toxicity that impairs fertility, sperm quality, hormones, and testicular structure and functionality. Exposing the male rats to Abamectin led to a significant reduction in fertility in these rats, as demonstrated by the reduced pregnancy rates and viable fetuses in female rats mated with the treated male. The resorptions, also, increased significantly, which means that there was more periimplantation mortality, probably the result of poor sperm

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quality [13, 72]. Reduced sperm count and motility following exposure to Abamectin was reported in many studies. These effects were dose-dependent and dose- and time-dependent, with dose-dependent reductions in sperm motility and sperm number as well as augmented damages in seminiferous tubules [15, 78]. Abamectin interrupted sperm capacitation and the acrosome reaction, which is important in fertilization. It also influenced significant signaling pathways, such as protein kinase A (PKA) and tyrosine phosphorylation and diminished intracellular ATP levels, which further damaged sperm activity [73].

The serum testosterone concentration of male rats was lower, and follicle-stimulating hormone (FSH) levels altered in response to Abamectin exposure, which shows that the androgen biosynthesis pathway is disrupted and may result in alterations in hypothalamic-pituitary-gonadal axis stimulation [15]. A histological analysis revealed that there were several abnormalities, including a deposition of connective tissue between seminiferous tubules, a reduction in the number of seminiferous tubules, premature release of spermatid, and overall testicular damage [80]. Exposure to Abamectin augmented oxidative stress indicators (including 4-HNE-modified proteins), stimulated poly(ADP-ribose) polymerase (PARP), and led to mitochondrial stress, resulting in testicular tissue experienceing apoptosis [79].

Though both the male and female rats are affected, there are some studies, which show that males have greater susceptibility to reproductive toxicity, particularly in terms of testicular injury and sperm parameters [81]. Toxic effects on male reproductive functioning were observed at doses as low as 0.04 mg/kg/day but were more pronounced at the higher dosage (1.0 to 4.0 mg/kg/day) [15]. The developmental toxicity is observed to occur at 1.0 mg/kg/day, and the no-observed-adverse-effect dose (NOAEL) of reproductive toxicity was established at 0.1 mg/kg/day [13].

Bai [74] and Yin et al. [78] also found that farmworkers who were exposed to Abamectin exhibited lower sperm quality and motility, and plasma concentrations were comparable to those that were effective on animals. Additionally, Kong et al. [79] discovered that the human occupational and environmental exposures have been associated with reduced sperm concentration and quality, and safety practices are important to those who handle abamectin. Some previous studies of Abamectin affecting male reproductive toxicity are shown in Table 3.

3.2.6. Effects on female fertility

It has been demonstrated through numerous research studies that female mammals and other animal models can be affected by chronic exposure to Abamectin and have their fertility impaired [77, 82]. The evidence used in these studies demonstrates direct and indirect impacts on the reproductive parameters, ovarian structure, and the development of offspring among females. These effects are dose-dependent and also species-dependent in magnitude and nature [83]. Nevertheless, the statistics always show a higher sensitivity in females, especially in connection with oxidative stress and damage to reproductive organs [60]. Prolonged exposure to Abamectin can cause an endocrine disturbance that interferes with the estrous cycle among female mammals.

Table 3. Main impacts of abamectin on male reproductive health.

Effect	Evidence in rodents	Reference	Evidence in humans	Reference	Mechanism(s) involved
Reduced fertility	Yes	[13]	Yes	[74, 78]	Sperm quality, hormone changes
Decreased sperm count/motility	Yes	[73]	Yes		Oxidative stress, apoptosis
Testicular damage	Yes	[80]	Not directly		Histopathology, apoptosis
Hormonal disruption	Yes	[15]	Not directly		Endocrine disruption
DNA replication stress	Yes	[78]	Not directly		MCM6-CDT1 inhibition

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There was no negative effect of chronic oral exposure of female rats at 0.1, 1.0, and 2.0 mg/kg/day of Abamectin on 10 weeks of mating, conception, or fertility [13]. There were no differences in the average values of mating, conception, fertility, and pregnancy indexes of treated females and those of the control group. Whereas the conception and fertility indexes were reduced by 20 and 15% at 1.0 and 2.0 mg/kg/day, respectively, the reductions were not found to be significant and were explained by the decreased male fecundity instead of direct effects on the female. Although the majority of rodent studies show no significant direct impact of Abamectin on female fertility with lower doses, high doses and chronic exposure compared with the dose of Oshar plant extract may affect the estrous cycle and ovarian architecture and cause offspring mortality, especially when exposed to the drug via the mother. Tlili et al. [82] found that the percentage of death of offspring was highest when the Abamectin was exposed to the mother, which is in agreement with past studies which reported the accumulation of the Abamectin in the female milk has detrimental effects on the survival of the offspring. Abdelhafez et al. [60] stated that Abamectin 4 mg/kg/day (6 weeks) had an effect of impairing the estrous cycle, which is indicative of endocrine-disruptive effects in female albino rats. This was linked to the augmented reactive oxygen species (ROS), oxidative stress, dysfunction of mitochondria, and histopathological changes in reproductive and other tissues. Nonetheless, the subchronic exposure of rabbits caused disorder of the ovarian tissues such as follicular atresia, hemorrhagic follicles and ovarian degeneration [82]. The cell proliferation and apoptotic markers (Ki67, P53, Bcl-2) altered expression was also noted in ovarian tissue, which indicates that Abamectin might have an impact on ovarian structure and function by modulating proliferation and apoptotic pathways in cells [13]. In addition, it was observed that ovarian tissue disorganization such as follicular atresia and degeneration was observed by Tlili et al. [82], which implies potential subchronic effects on the ovarian structure. Some previous studies of Abamectin affecting female reproductive toxicity are shown in Table 4.

4. Missing gaps and future perspectives

Even though some significant progress has been achieved in the study of the effect of *C. procera* and Abamectin on the reproductive biology, there are still some important gaps that should be considered more closely. The existing literature is based on isolated studies or studies that are focused on a specific area, and consequently, it is hard to create a complete or coherent picture of their reproductive impact on both sexes. In the case of Oshar, specifically, female reproductive outcomes, including the more detailed patterns of estrous regulation, implantation, and uterine responsiveness, are still reported significantly less comprehensively than male outcomes [16]. The same can be said about Abamectin, although the reproductive information is still incomplete and frequently replaced by research focusing on the neurotoxicity or the overall systemic impact. This introduces an apparent imbalance of the available evidence and brings up the question of the extent to which the available findings reflect the actual extent of reproductive risk [60].

Table 4. Main findings of Abamectin on female reproductive health.

Parameter	Outcome with Abamectin exposure	Dose	Reference
Mating, conception, fertility	No significant detrimental effect	0.1–2.0 mg/kg/day, 10 weeks	[13]
Estrous cycle	Impairment at high dose	4 mg/kg/day, 6 weeks	[60]
Ovarian/uterine weights	No significant change	Subchronic, rabbits	[82]
Ovarian structure	Disorganization, atresia, degeneration	Subchronic, rabbits	
Offspring mortality	Increased with maternal exposure	Subchronic, rabbits	
Oxidative stress, apoptosis	Increased, females more sensitive	1 mg/kg/day, 6 weeks	[60]
NOAEL for reproductive toxicity	0.1 mg/kg/day	Rats	[13]

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The second area that needs to be examined closer is associated with the variability of methods. Different plant parts extracted using various solvents might vary radically with regard to their phytochemical composition, and thus cross studies are challenging and can be deceiving. Extensive biological analyses have also identified *C. procera* as a promising pharmacological agent but have also cautioned that toxic outcomes can easily be observed with overdosing and has to be supplemented with well-formulated dosing systems in reproductive studies. In the absence of standardized extraction procedures and chemically characterized reproductive effects, it is not easy to conclude whether the reproductive effects observed are biologically targeted or are due to nonspecific toxicity [31].

Any other significant gap is that of the long term reversibility of the reproductive impact of both agents. Available research does not tend to continue to follow exposed animals past the time of treatment and therefore the question remains open of whether disturbances in estrous cycling, implantation success or gametogenesis continue to persist once exposure is discontinued. This is especially interesting when reports indicate that Abamectin can cause developmental toxicity in the non-maternal toxicity dose, which includes the early embryonic development and changes in reproductive outcome of both sexes. The solution to this problem will involve long term and multigenerational research, which takes into consideration the recovery times, intricate endocrine profiling, and reproductive performance indicators [13, 82].

Lastly, as emerging research keeps uncovering the various pharmacological activities of *C. procera*, such as antioxidant and protective actions under some conditions, it will be necessary to balance such results against its proven reproductive dangers. Similarly, since Abamectin has extensive environmental distribution and has established impacts on gonadal tissues in vertebrates, further research is required to establish the impacts of chronic and low dose exposures on reproductive health in ecological and agricultural environments. These gaps will be critical to the development of a balanced, evidence-based picture of the reproductive risks and possible controlled uses of each of the two compounds.

5. Conclusion

In summary, the overall results of the recent toxicological and reproductive research point to the fact that both *C. procera* and Abamectin are biologically active substances with explicit fertility control and reproductive health implications. *C. procera* extracts have significant antifertility potential due to dose-dependent toxicity, endocrine interference, and organ selectivity that have been identified as demonstrating the need to prepare extracts and be careful with dose selection in experimental models. Similarly, Abamectin has a complex reproductive toxicology, having been reported to cause endocrine disruption, oxidative stress, and histopathological damage of both mammalian and aquatic organisms, supporting the notion of its wider ecological and physiological effects. With both agents still finding extensive application in environmental, agricultural, and medicinal environments, comprehensive, mechanistic, and long-term evaluations are needed now more than ever. Conclusively, it will necessitate methodological rigor, cross-species validation, and integrative toxicology models that will be able to differentiate between therapeutic and biological risk.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Data will be available upon request.

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