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A Systematic Review of Traditional Medicinal Plant-Based Contraceptives in Female and Male Rodents

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Abstract

RODENT population control is of significant importance, and there is a need for a systematic literature evaluation on traditional medicine-based contraceptives as a humane alternative to rodenticides. This study aims to conduct a comprehensive literature review on the utilization of traditional medicine as contraceptives for rodents. We applied the PRISMA 2020 method to select and review relevant literature published from 1990 to 2023 using three databases (Scopus, ScienceDirect, and PubMed databases). A total of 668 searches were conducted, resulting in the final identification and review of 34 publications. These publications were categorized based on four dimensions: (1) Effects of traditional medicine on the reproductive system of female rodents; (2) Mechanisms used in traditional medicine to reduce fertility in male rodents; (3) Strengths and limitations of traditional medicine as a contraceptive for rodents; (4) Challenges to the use of traditional medicine as a contraceptive for rodents. The findings from 34 studies indicate that traditional medicinal compounds can disrupt hormone levels and uterine and ovarian function and interfere with the implantation process in female rodents. Also, have shown the potential to affect male fertility by influencing sperm motility, morphology, and reproductive system ultrastructure. Various traditional medicine compounds like (*Tripterygium wilfordii*, *Carica papaya*, *Ruta graveolens*, *Wedelia trilobata, Celastrus paniculutus and Gloriosa superba*) and have shown promising antifertility activities for both female and male rodents with side effect can reversible, highlighting their potential as contraceptive agents. More research is needed to rigorously address the efficacy of different plant extracts in terms of inhibiting the fertility of either male and/or female rodents. Currently there is limited scientific evidence on mechanisms of action, durations of effect, humaneness, potential toxicities and non-target impacts. These studies must be undertaken before considering broadscale application.

Keywords: Antifertility, Contraceptive, Reproductive system, Rodents, Traditional medicine.

Introduction

Rodents are a widespread pest and concern in industrialized nations, as they can cause significant damage to the economy and society [1, 2]. Also, due to their nesting and chewing activities, these rodents have been responsible for widespread crop failures and the spread of zoonotic diseases [3]. Especially in food shortages worldwide, it is essential to consider the role of invading vertebrate pests in limiting

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pastoral and agricultural productivity across the globe [4]. So, more agricultural planting leads to lengthening the breeding cycles of rodent pests [5]. The high reproduction rate of rodents is the primary cause of the problems. Despite rodenticides' highly influential role in controlling rodent populations, they tend to accumulate in rodents' bodies, leading to contamination of predators and unacceptable effects on non-target animals [6]. Also, the use of rodenticides may be questionable because of the impact on "clean and green" agricultural output and potential impacts on human health. Therefore, there is a new method targeting the biological source of overabundance called contraceptives. Contraceptives are an alternative way to reduce the number of rodents born. There are several ways to reduce fertility, including limiting the number of pups or frequency of litter or some work by inducing abortions [7], which many people consider to be less than ideal or impractical to use. Not all fertility control methods work in the same way. Many hormones, chemicals, and plant agents can reduce rodents' fertility, some already being developed [8]. Plants possess a rich historical background in the field of medicine. Several medicinal plants have been used against several serious ailments. The study of Mustafa et al. [9] supports the potent effects of curcumin as option for promoting wound healing and preventing complications. Moreover, there are some plants like *Physalis angulata* fruit may be useful in rescuing the destructive tendency of chemical drugs like paracetamol that is commonly abused as an analgesic [10]. As some of medical plant in relation to its phytochemical constituents, and pharmacological effects can used as anti-ulcer like Liquorice root extract [11], phytochemicals as antioxidant and antibacterial [12]. Although have proven to **Crocin** has a therapeutic effect that can enhance disturbed endocrine function resulting from exposure to cadmium [13]. While, Mohammadpour et al. [14] found that administering a high dose of Crocin had adverse effects on the male reproductive system of mice. Identifying plant-based substances that are safe and capable of disrupting the natural reproductive process is essential. For Example, in (2022) “Viamedix Veterinary Division” established a study on the efficacy of Conntraceptol® Forte as an effective and humane solution for rat control. This research has demonstrated that the formulation of this product includes several botanical extracts such as stone seed root, silphium herbal, blue cohosh, and rue herb. The formula of Conntraceptol® Forte is deemed entirely safe, composed of natural ingredients, and devoid of hazardous substances [15]. Using botanical extracts with anti-fertility properties has been observed to lead to a significant decrease of up to 97% in the rat population [15]. However, the potential harm of birth control is much less severe than that of rodenticides because lethal pesticides affect non-target populations by killing or causing physical damage to pests. In this context, there is a need for research on traditional medicine-based contraceptives as an alternative to rodenticides for controlling rodent populations. In this review, the objective is to explore whether traditional medicine contraceptives exhibit anti-fertility and reversible anti-fertility effects against rodents. So, we seek to address the gap in the literature regarding the use of traditional medicine-based contraceptives and their potential as a humane and environmentally friendly approach to rodent population control.

Material and Methods

Data collection

Identifying the study's question(s)

The primary aim of this systematic review is to identify and examine studies about the impact of traditional medicine on the reproductive systems of male and female rodents. The following research questions were asked during the review to gain a more thorough understanding of this subject.

1. What is the target effect of traditional medicine on the reproductive system of female rodents?
2. Which mechanisms are involved to reduce fertility in male rodents by using traditional medicine?
3. What are the strengths and limitations of using traditional medicine as a contraceptive for rodents?
4. What is the most popular method for evaluating the effect of traditional medicine as a contraceptive for rodents?

Search strategy and information sources

The systematic review and meta-analysis protocols included the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The Scopus, ScienceDirect, and PubMed databases were used to search for publications. The keywords that were used include ("Birth control" OR "Contraceptive" OR "Antifertility" AND "Traditional medicine"), ("Birth control" OR "Contraceptive" OR "Antifertility") AND ("Traditional medicine" AND "Rats") and ("Birth control" OR "Contraceptive" OR "Antifertility") AND ("Traditional medicine" AND "Rodents").

Study selection and extraction process

All the articles from the search engine were exported as CSV in Microsoft® Excel, and the duplicates were removed. All the potentially related articles were imported to the Mendeley® Reference Manager software to organize the reports and further the screening process. A consistent data collection format was created to obtain the required information from the reports. The information collected included the study's title, the first author's last name and title, year of publication, source, abstract, index keywords,

and document type. Samples of rodents that participated in the research were selected, such as *Sprague Dawley* rats, *Wistar albino* rats, house rats, *albino* mice and *Swiss albino* mice. Then, the identified articles' titles, keywords, and abstracts were reviewed. We gathered the documents and assessed their suitability for inclusion. Duplicate reports, research on other animal species, and materials that were not sufficiently pertinent were excluded. The original study was reviewed to clarify if there were any data discrepancies.

Data Analysis & Synthesis

Literature review

Initially, 668 potential articles were retrieved from Scopus, ScienceDirect, and PubMed. However, after carefully reviewing the titles and abstracts, 538 articles were irrelevant to this study and removed from consideration. The remaining 129 articles were considered for full-text reading. Five articles were excluded from the analysis because the studies needed a sufficient summary. In addition, one article was written in Chinese. Finally, 123 papers met the inclusion requirements. After being filtered, it was noted that 89 papers had been duplicated in Scopus, ScienceDirect, and PubMed, so only 34 articles finally met the inclusion requirements. The PRISMA diagram below depicts the steps for selecting the relevant studies can be seen in Fig 1.

Study characteristics

The research design was included in 34 studies undertaken worldwide, spanning across Eurasia, Africa, and South America, investigating the effects of traditional medicine on the reproductive system of rodents, with a particular focus on eleven countries. Thirteen articles were from India, followed by Nigeria with six articles, Iran with four articles, Ethiopia with three articles, Indonesia with two articles, the Ivory Coast, Cameroon, China, Mexico, Brazil and Trinidad & Tobago with one article each. The 34 reviewed papers, published between 1990 and 2022, are summarized (Table 1), which includes the plant name along with its family name, the publishing country, and information regarding its use and/or effects of these plant as contraceptive. In addition, Fig 2 illustrates the yearly distribution of the 34 chosen papers. According to the graph, articles focused on data mining applications in traditional medicine remained relatively consistent during the initial 12 years, with five articles identified during this period. However, the subsequent chart indicates a noticeable upward trend in the number of articles, culminating in a peak of four articles in 2012.

Methods of determining how conventional medicines affect the reproductive system of rodents

In Table 2, researchers employed various animal models to study the effects of medical plants on the reproductive system of rodents. These models include Male and Female *Wistar albino* rats, Male and Female *Sprague Dawley* rats, Female *albino* mice, Male house rats (*Rattus rattus*), Male mice, White mice (*Mus musculus*), and *Swiss albino* mice Male and female. The sample types analysed in these studies include the uterus, ovaries, uterine horns, vagina, vagina plug, vaginal smears, testes, sperm, epididymis, prostate gland, cauda epididymal ducts, seminal vesicle, mated animals, counting pups, liver, kidneys, adrenals, pituitary glands, blood, body weight, bait. By utilizing these animal models, sample types and methods, researchers can gain insights into the effects of conventional medicines on the reproductive system of rodents, including changes in hormone levels, organ weights, histological alterations, and fertility parameters. These studies contribute to understanding the potential effects of traditional plants on reproductive system as contraceptives and aid in assessing their safety and efficacy.

Parts of medicinal plants that affect the reproductive system

The herbal plants are classified in Table 3 according to the parts of these plants that were used as contraceptives and the type of extracts. A total of 106 medicinal plant species were reviewed in this paper. In 1994 Desta's comprehensive analysis was conducted on 210 extracts/fractions derived from 70 indigenous Ethiopian herbs to evaluate their uterotonic and anti-implantation properties. The study conducted by Malpani [32] used roots of *Gloriosa superba* as an aqueous extract. While, Malpani and Mahurkar [44] assessed the same plants but different forms (aqueous extract, ether, chloroform, and ethyl-alcohol) and all extracts assayed the antifertility efficacy of in female rats. Dhanapal et al. [35] conducted a study on the effects of the leaf and root of *Urena lobata* in a dry form, specifically in male rats. However, Handayani et al. [48] conducted laboratory research focusing on the effects of the leaf aqueous extract of *Urena lobata*, this time specifically in female rats. Also, *Tripterygium wilfordii* were used by Xu and Zhao [30], and Singla and Challana [40] in the same type of extract but with different sexes and species of rats, one being female *Sprague Dawley* rats and the others being male house rats (*Rattus rattus*). Finally, two parts of *Carica papaya* stem bark extract in male *Sprague Dawley* rats [21] (Kusemiju et al., 2002), and the other was root extract in male *Wistar* rats [46]. Unlike all, *A. laxiflora, P. erinaceus, C. nitida extracts* [22] and *Rosmarinus officinalis* [37] were used in ethanol-aqueous form. Fig 3 shows a diverse range of medicinal plant parts used as contraceptives. Roots are the most commonly used, possibly due to their bioactive compounds [51]. Leaves are also highly valued for their contraceptive properties. Researchers employed seeds and stem bark less,

while they used fruit and the whole plant in a few cases. Less commonly used parts include resin, rhizomes, milky exudate, fruit pulp, stem, and tender branches.

Statistical data analysis

The data extracted from the selected articles were entered and organized into a Microsoft® Excel spreadsheet. The results were compiled and described using figures and tables.

Results

This section demonstrates the results from articles on the effects of traditional medicines as contraceptives on the reproductive system of rodents. Firstly, a comprehensive overview of the selection process outcome is provided, followed by the individual reporting of results for each study topic.

Overview of the selected studies

Through a comprehensive search across three digital databases, we successfully identified 34 papers for data extraction and presented answers that addressed the research questions posed in this systematic review. Researchers are increasingly interested in creating novel herbal contraceptives derived from natural products. Studies have been conducted on these plants, which are components of traditional herbal remedies and are believed to have contraceptive qualities since the plants examined in this research are historically recognised for having antifertility qualities. So, they can choose contraceptive medicines for rodents and become acceptable because they are derived from natural products.

Presenting the findings of the review

Target effects of traditional medicine on the reproductive system of female rodents

Various studies have focused on the contraceptive effects of traditional medicine compounds, which can affect ovarian and uterine function to prevent implantation, disrupt hormone levels and achieve birth control [52]. For instance, Handayani et al. [48] investigated the effect of *Urena lobata* (pulutan) leaf extract on the follicles in ovaries mice, revealing an increase of atresia follicles and decrease monolaminar primary, multilaminar primary, secondary, and de Graaf follicles at 7.5% concentration. While Nwafor et al. [19] investigated the contraceptive activity of the methanolic extract of *Asparagus pubescent* root, it inhibited fetal implantation by exhibits antiestrogenic activity. Xu and Zhao [30] investigated the effects of triptolide at low dose with 60 mg/kg and high dose with 120 mg/kg for 35 days on ovarian follicular apoptosis and development, revealing inhibition of the oestrous cycle and induction of apoptosis in secondary follicles, resulting in the inhibition of sexual function in female rats. Extracts from *Afrormosia laxiflora*, *Pterocarpus erinaceus* and *Cola nitida* were also tested for their potential contraceptive effects by Benie et al. [22]. These extracts exhibited weak antioestrogen-like activity, leading to a blockade of ovulation and disruption of the oestrous cycle in female rats by decreased the secretion of the gonadotropin release (both LH and FSH). Gebrie et al. [24] suggested that phytosterols and polyphenols present in the powdered root and methanolic extract of *Rumex steudelii* might be responsible for significant reduction ($p < 0.01$) in litters was seen with the extract. It had a dose-dependent antifertility impact and a temporary contraceptive effect. Furthermore, the extract considerably extended the oestrus cycle ($p < 0.05$) and dioestrus phase ($p < 0.01$) in rats. Both the ovaries and uterus had considerably reduced wet weights ($p < 0.01$, $p < 0.05$). On the other hand, certain medicinal plants have been found to exhibit abortifacient activities in addition to inhibiting implantation sites. Similarly, Dhanabal et al. [20] tested the alcoholic leaves extracts from various Rubus species, including *Rubus ellipticus, R. niveus, R. racemosus*, and *R. rugosus var. thawaitesii*. They observed decreased implantation sites and increased resorption sites, due to anti estrogenic and androgenic activities. Also, the hot aqueous extract of *Guaiacum officinale* Linn was evaluated by Offiah and Ezenwaka [23] for its antifertility effects. In pregnant mice, the *Guaiacum officinale* Linn extract lowered litter size in the first trimester (day 5) and caused abortion in the second and third trimesters. Another study by Ravichandran et al. [27] explored the 200 and 400 mg/kg, p.o. doses of the stem bark extract of *Ailanthus excelsa Roxb* showed substantial anti-implantation (72%) and abortifacient (56%). Additionally, the extract significantly ($P < 0.05$) increases uterine weight of rats. The extract demonstrated strong anti-implantation and abortifacient activities. Malpani [32] conducted a study on the aqueous extract of *Gloriosa superba* and found significant oxytocic activity and early abortifacient activities because the extract contained alkaloids such as colchicine. Finally, Shibeshi et al. [26] conducted a bioassay using an extract of *Achyranthes aspera* on rat uteri, significant ($p<0.05$) abortifacient action and elevated pituitary and uterine wet weights.

Mechanisms of traditional medicine to reduce fertility in male rodents

Traditional medicine has a long history of exploring various methods to reduce fertility in male rodents. One approach involves using plant-based compounds with potential contraceptive properties. For instance, researchers studied the contraceptive effects of the aqueous crude extract of *Carica papaya* bark on male rodents. The study conducted by Kusemiju et al. [21] found the 100 mg/kg of *Carica papaya* extract generated histological changes from seminiferous tubular deformation to its complete

destruction. In addition, extract-treated rats had disorganised and hypocellular testicular interstitial. Moreover, the extract significantly decreased sperm count and motility ($p < 0.05$). Additionally, Nwaehujor et al., [46] examined the impact of fractions derived from the methanol root extract of *Carica papaya* on the fertility of male *Wistar* rats. The researchers evaluated parameters such as sperm count percentage of defective sperm cells and conducted biochemical and hormonal analyses. The findings demonstrated that 2000 mg/kg, *C. papaya* root extract caused CNS-related symptoms and diuresis but no deaths. The fractions considerably ($P < 0.01$) reduced sperm counts and increased faulty sperm cell percentage. Significant ($P < 0.05$) elevations in levels of aspartate aminotransferase (AST) and blood urea nitrogen (BUN) were observed. Histopathological examinations revealed mild kidney and cardiac hyperaemia. While, Dhanapal et al. [34, 35] explored the effects of ethanolic extracts of *Feronia limonia* fruit pulp (250 and 500 mg/kg), *Enicostemma axillare* leaves (375 and 750 mg/kg), and *Urena lobata* roots (300 and 600 mg/kg) on male Wistar albino rats. Extracts did decrease epididymal sperm count, motility, viability, and aberrant sperm. Especially, at higher dose of all the extracts reduced epididymal and testicular protein by 24.58% and 29.86%, respectively, and glucose-6-phosphate dehydrogenase and Δ^5 -3^{β} -hydroxy steroid dehydrogenase levels by 42.82% and 38.08% However, testicular cholesterol and ascorbic acid increased significantly. In the study of Halvaei et al., [36], a significant reduction in sperm motility was seen in ca200se groups compared to controls after one hour of *Ruta graveolens* extract administration (36% vs. 68.15%, $p < 0.01$). At same time, spermatozoa in each group showed no significant changes in viability, shape, or DNA structure. Compared to controls, treatment groups had no significant testosterone changes. Cordero-Martínez et al. [41] evaluated the acute toxicity and functional effects of aqueous of *Echeveria gibbiflora* on mouse sperm through an in vitro study. The study revealed that *Echeveria gibbiflora* exhibited low toxicity. At concentrations of 0.25 and 0.5 mg/mL, even at the maximum concentration of 1.0 mg/mL, it inhibited total and progressive motility of mouse sperm, along with a decrease in motility kinematic parameters. Additionally, it reduced capacitation and the acrosome reaction, which coincided with a reduction in calcium influx. In an in vivo study involving rats, Cordero-Martínez et al. [41] administered *Echeveria gibbiflora* extract intraperitoneally at doses of 100 and 200 mg/kg daily. The study examined the effect of the extract on sperm motility. Furthermore, an in vitro fertilization (IVF) assay was performed using mice treated with the extract to determine their ability to fertilize an oocyte. The results showed that sperm from the treated mice exhibited an IVF rate of 13.3%, whereas the control group had a rate of 52.3%.

The strengths and limitations of using traditional medicine as a contraceptive for rodents

Using traditional medicine as a contraceptive for rodents, particularly as a means of rodent population control, can have both strengths and limitations. Here are some of them:

Strengths

Environmental friendliness

The consumption of oestrogens has been associated with potential adverse effects on animal health, including impacts on metabolism, physiology, and endocrine function, due to their estrogenic properties [53,54]. In contrast to conventional medicine, a recent study by Karthika et al. [49] has determined that utilizing an aqueous extract derived from *W. trilobata* exhibits potential as an herbal contraceptive medication. This extract can augment oestrogen levels due to phytoestrogen compounds, notably beta-sitosterol. Importantly, the administration of this extract does not appear to adversely impact the functioning of other organs, including the liver and kidney. Additionally, traditional medical treatments could cause adverse effects, but these effects can be reversed or recovered over time. In other words, although there may be initial negative consequences, the body or the individual's health can gradually recover from them with time. For instance, Bidwai et al. [17] conducted a study on the extract derived from the seeds of *Celastrus paniculutus*, examining its impact on spermatogenesis and exploring its potential as a male fertility regulator. The researchers aimed to determine whether the extract would adversely affect essential organs. The liver of rats treated with extracts was investigated based on this concept. Necrotic foci were observed in the liver 15 days after administering the extract. However, during the 45-day recovery period in treatment groups, a complete restoration of the histophysiology of liver parenchyma was observed. Intermediate stages of regeneration were observed in group rats, which had a 30-day recovery period. The findings of this study indicate that the administration of *Celastrus paniculutus* seed extract can elicit adverse effects on hepatic function. However, it is noteworthy that these alterations are reversible within 45 days following discontinuation of the treatment. This suggests that specific traditional medical therapies may demonstrate reversible harmful effects.

Accessibility

The investigation conducted by Desta [18] yielded a total of 210 extracts/fractions obtained from 70 plants native to Ethiopia that have been historically utilized. Notably, the botanical specimens exhibiting uterotonic and anti-implantation properties are among the plant species traditionally employed with

high frequency for fertility regulation. This attribute renders traditional medical treatments that make them highly beneficial in areas where modern contraceptive methods or resources are limited. These treatments can serve as an advantageous alternative due to their accessibility and potential effectiveness.

Cultural acceptance

Compared to the utilization of anticoagulant rodenticides, the implementation of fertility control through traditional medicine holds the potential for a higher degree of humaneness in controlling rodents. Additionally, it encompasses many pharmacological activities, increasing its likelihood of receiving more significant approval [55]. As proof, *Tripterygium wilfordii* has been extensively employed in managing inflammatory diseases, autoimmune disorders, organ transplantation, and neoplastic conditions [56]. Furthermore, Singla and Challana [40] discovered that administering bait containing 0.2% *Tripterygium wilfordii* over five days resulted in a notable decrease in sperm motility and viability in the cauda epididymal fluid of male *Rattus rattus* compared to untreated rats.

Cost-effectiveness

Traditional medicine methods for rodent contraception often rely on natural substances and locally available resources, which can be cost-effective compared to other rodent control methods [57]. Pepper is well recognized as a prominent spice on a global scale among many traditional herbs. It is commonly referred to as the 'King of Spices. This substance's unique and pronounced taste can be attributed to an alkaloid known as piperine [58]. The cost of pepper is accessible to all individuals, thereby rendering it a common ingredient in traditional Chinese and Indian medicinal practices. Moreover, piperine has demonstrated a range of biological actions, including anti-infective, antibacterial, insecticidal, anti-inflammatory, anti-ulcer, and antidepressant properties [59, 60]. According to the findings of Chinta et al. [43], it was shown that piperine had a disruptive effect on the functional integrity of the testis in male *albino* rats. Alterations in germ cell markers, antioxidant status, and testicular hormones manifested this disruption. The findings of this biochemical investigation, the effectiveness of piperine treatment, was substantiated through the evaluation of superoxide dismutase (SOD), catalase (CAT) and Glutathione S-transferases (GST) enzyme activity levels, along with the histological analysis indicating reduced spermatogenesis.

Limitations

Limited scientific evidence

Traditional medicine approaches for rodent contraception often lack rigorous scientific studies and standardized protocols to validate their effectiveness and safety. Attah et al. [47] reported work investigated the *in vitro* and *in vivo* utero-active and contraceptive potentials of cold and hot aqueous extracts of *M. oleifera* leaves (MOL) commonly used in Nigerian traditional medicine. Attah et al. [47] summarised that ingesting *M. oleifera* leaves just before conception, at conception, and during pregnancy may be inimical to foetal development. So, research is ongoing to determine specific uterotonic metabolites, which may be of chemotaxonomic relevance, and the mechanism of action of the extracts in their interference with female fertility in rodents.

Limited action

Some traditional medicine contraceptives for rodents may have an effect but at a long duration and administration at high doses. For example, an extract from *Rosmarinus officinalis* (Rosemary) induces infertility in male rats. In a Heidari-Vala et al. [37] conducted experiments on *Wistar* strain rats where the rats were given *Rosmarinus officinalis* orally for 60 days. Initially, there was no noticeable change in testosterone levels in the rats' serum when comparing low and high doses of *Rosmarinus officinalis* with the control group. However, in the middle of the experiment, there was a significant decrease in testosterone levels at high doses compared to the control group. Therefore, *Rosmarinus officinalis* may have some effects on the hormones and cells in the testes. However, the effects at high doses within a long time after treatment can affect the spermatogenesis process in rats.

Chronic toxicity effect

An effective anti-fertility agent should possess a sufficiently long half-life in the body following intake to induce the intended effect while avoiding any accumulation within the organism. Diosgenin, a phytosteroid saponin, is utilized as dietary supplements, contraceptives, and hormone replacement therapy for various disorders and diseases. The study by Khushboo et al. [50] examined the chronic toxicity of Dioscorea. They investigated its potential as an endocrine disruptor and reproductive toxicant in Swiss albino mice using a 90-day repeated dose study. Prolonged exposure to diosgenin resulted in the production of oxidative stress, reduction in antioxidant enzymes, disruption of reproductive hormone balance, hindered steroid production, increased germ cell apoptosis, impaired gametogenesis, decreased sperm quality, disturbed oestrous cycle, and negatively impacted reproductive performance in the offspring. While, previous research conducted by Lima et al. [61] indicated that diosgenin has antinociceptive and anti-inflammatory effects in rodent models. Additionally, there were no indications of acute or sub chronic toxicity. The

findings indicate that shorter time exposure to Dioscorea will be acceptable

Lack of palatability

A bait base must be highly attractive, similar to rodenticidal products, to ensure effective bait uptake over a significant period. At variance, some of the medicine plants reduce bait acceptability. It has been observed that high doses of *Azadirachta indica* extracts reduced the palatability of the bait [25]. Despite this, *Azadirachta indica* extracts have various effects on the fertility of both males and females of rats. They disrupt spermatogenesis and the estrous cycle, inhibit follicle development and implantation, and induce abortion. It should be noted that the ovaries are indirectly affected by *Azadirachta indica* extracts, which influence the synthesis and release of hormones that regulate ovarian follicle development [25].

The challenges of using traditional medicine as a contraceptive for rodents

Mechanisms and implications

Exploring the mechanisms and implications of traditional medicine on rodents is a scientific endeavour riddled with challenges and complexities. Moreover, they uncover the implications of these mechanisms of traditional medicine as contraceptives for rodents, as they often have far-reaching consequences on rodents. According to Asongalem et al. [28], the study was to determine the effect of *A. montanus* aqueous extract on the oestrous cycle pre- and post-implantation in *Wistar* rats and its mechanism of action. At high doses, the extract caused appreciable preimplantation losses, while none of the doses caused post-implantation losses. The extract also caused delayed foetal growth. The result from the extract causing delayed foetal growth suggests a potential adverse effect on the development and growth of the foetus.

Further investigations and studies are necessary to understand the mechanisms underlying delayed foetal growth and assess the long-term implications on offspring health. On the other hand, Kooti et al. [39] mentioned that consuming celery in males decreases the number of offspring and increases the sex ratio of males because it does not affect parturition in female rats. However, they did not explain the implications of these results. While the study conducted by Das et al. [38] provides valuable insights into the abortifacient and anti-implantation activities of the methanolic extract of *Drynaria quercifolia* rhizome, several challenges arise when considering the safety and potential side effects associated with its use.

Registration of traditional medicine compounds as anti-fertility

When registering fertility control products, it is essential to provide comprehensive information regarding their mode of action and classification. The specific registration requirements can vary between countries, and multiple regulatory agencies may be involved. Typically, the registration process involves meeting efficacy and environmental safety standards for rodent anti-fertility agents. In the European Union (EU), the identification of hazards related to endocrine-disrupting properties is mandated by regulations for biocidal products and plant protection products [62,63] (EU Commission, 2017, 2018). Several plants contain estrogenic phytoconstituents that have the potential to inhibit implantation, making them potential candidates for fertility control products. For instance, in a study by Malpani and Mahurkar [44], the anti-fertility activity of various *Gloriosa superba* Linn root extracts was investigated in female Wistar albino rats. The results demonstrated a significant reduction in the number of implants and pups born in all groups compared to the control group. All the extracts exhibited statistically significant abortifacient activity when compared to the control group. As mentioned earlier, the registration of fertility control agents with high abortifacient activity [44] would be a complex process due to the potential risk of causing abortions in non-target animal species [6].

Scientific negligence

Incorporating traditional medicinal plants into formal healthcare requires a scientific approach to validate their efficacy. *Tristania sumatrana* is a traditional medicinal plant commonly used as a contraceptive in West Sumatra. Syamsurizal [45] researched the effects of *Tristania sumatrana* to bridge the gap between traditional medicine and medical practice extract on female mice. The study found that treatment with *Tristania sumatrana* extract significantly decreased ovarian weight and the number of Graafian follicles, corpus luteum, and live foetuses in female mice. These findings suggest that *Tristania sumatrana* extract treatment can reduce fertility in female mice. However, further exploration and investigation are required to understand better the experimental outcomes and their implications for *Tristania sumatrana*

Discussion

Plant-based treatments have gained widespread popularity and attention as potential contraceptive options. Their effectiveness, combined with the ease of preparation, has made them attractive alternatives for rodent control. Also, using traditional medicine poses significantly lower risks compared to rodenticides. While deadly pesticides can cause fatal or severe physical harm to unintended animal populations or impact the ecosystem [64], fertility control agents are far less dangerous. If a non-target wild animal were to consume plant-based treatments

in doses meant for rodents, the most likely outcome would be temporarily reduced fertility. This is in stark contrast to the potentially lethal effects of rodenticides, which can cause severe internal injuries or death. The comparative safety of contraceptive approaches makes them a more environmentally friendly option for rodent population management. In this systematic review, 106 medicinal plants allocated in 67 families were classified and determined an effect of the use of plant-based medicine on reproductive organs as a contraceptive. The contraceptive and abortifacient effects of various traditional medicine compounds have been the subject of several studies, with the aim of discovering new methods of birth control and understanding the mechanisms behind these effects. Xu and Zhao investigated the effects of triptolide at low and high doses on ovarian follicular apoptosis and development in female rats, finding that it inhibited the oestrous cycle and induced apoptosis in secondary follicles, leading to the inhibition of sexual function. Additionally, Guo et al. [65] found that triptolide affected the oestrus cycle in female rats, and in male rats, the testicles and sperm were damaged. Other studies have investigated the use of triptolide appropriately, particularly as an anti-tumour agent, with high efficacy and low toxicity. They found a safe and non-toxic dose range for specific target organs [66], which could be considered the best choice for use as a contraceptive. On the other hand, certain medicinal plants have been found to have abortifacient activities, such as the alcoholic leaf extracts of various Rubus species, which were found to decrease implantation sites and increase resorption sites due to antiestrogenic and androgenic activities. Therefore, the use of abortifacient plants carries significant risks to the health of female rats, leading to complications such as bleeding or damage to reproductive organs. Also, the use of abortifacient plants raises ethical concerns [67]. Traditional medicine has been used to explore various methods to reduce fertility in male rodents, including the use of plant-based compounds with potential contraceptive properties. Two studies by Kusemiju et al. [21] and Nwaehujor et al. [46] have investigated the potential contraceptive effects of Carica papaya extract in male rodents. The extracts caused histological changes in the testicular tissue and significantly decreased sperm count and motility. However, Nwaehujor et al. [46] found that high doses of the extract were found to cause CNS-related symptoms and elevations in aspartate aminotransferase and blood urea nitrogen levels. It is important to consider the potential side effects and safety of Carica papaya before it can be recommended for use. Halvaei et al. [36] investigated the effects of Ruta graveolens extract on sperm motility in male rodents. The study found that a significant reduction in sperm motility was seen in case groups compared to controls after one hour of extract administration. However, the study found no significant changes in sperm viability, shape, or DNA structure. The use of traditional medicine for rodent contraception has several strengths and flaws. Environmental friendliness is an advantage of traditional medicine methods, as they do not rely on harmful chemicals or contribute to pollution. Research has shown that certain traditional medicines, such as an aqueous extract derived from Wedelia trilobata, can augment estrogen levels due to phytoestrogen compounds and did not show any impact on the functioning of other organs, including the liver and kidney [49]. While Williams et al. [68] confirmed through a range of comprehensive literature surveys to examine the sociological, environmental, and economic effects of hormonally active contraceptives, it is important to note that traditional medicines can also have adverse effects. However, these effects can be reversible over time. For instance, the extract derived from the seeds of Celastrus paniculatus has been found to elicit adverse effects; however, these alterations are reversible within 45 days following discontinuation of the treatment. The International Agency for Research on Cancer (IARC) Monographs program provided more detailed information about hormonal agents used in combined oral contraceptives and in the treatment of menopausal symptoms, which can be carcinogenic to the uterine cervix and liver [70]. One flaw of some traditional medicine contraceptives for rodents may have effects that are noticeable only after a long duration and administration at high doses. For example, the extract from Rosmarinus officinalis (Rosemary) was shown to induce infertility in male rats over 60 days [37]. Another study found that chronic exposure to traditional contraceptive agents is a significant concern. For example, Khushboo et al. [50] found that prolonged exposure to Dioscorea in Swiss albino mice led to oxidative stress, disruption of reproductive hormones, impaired gametogenesis, and decreased sperm quality. Some traditional medicine plants, such as Azadirachta indica, which have effects on rodent fertility, may reduce the palatability of bait. Despite their contraceptive effects, high doses of Azadirachta indica extracts can impact bait acceptability [25]. Particularly, Massei et al. [69] developed a framework to guide researchers in assessing the effectiveness of a potential contraceptive agent for a particular species, and one of these frameworks is the simulation of contraceptive delivery using bait markers. While traditional medicine approaches for rodent contraception offer potential benefits, they also pose significant challenges related to scientific validation, duration of action, chronic toxicity, and palatability issues. The use of traditional medicine as a contraceptive for rodents is a complex issue that poses several challenges and raises important questions about its mechanisms and implications. While traditional medicine compounds have shown

promise as fertility control agents like Tristania sumatrana [45], their safety and efficacy remain a concern. This lack of understanding makes it difficult to register these compounds as anti-fertility agents, as the European Union (EU) requires rigorous testing and evaluation of their efficacy and environmental safety [62, 63]. Furthermore, the use of traditional medicine as a contraceptive raise concerns about potential side effects and risks to non-target species [55]. For instance, the abortifacient activity of some plant extracts could lead to unintended consequences, such as abortions in non-target animal species. Therefore, field trials at a management scale are needed regarding their suitability for delivering effective doses to target species and minimizing uptake by non-targets. Overall, the systematic review paper highlights the need for further research and development in this area. There is a need for more studies that investigate the mechanisms underlying the effects of traditional medicine on rodents' reproductive systems, as well as their safety and efficacy as fertility control agents. Additionally, more research is needed into the development of novel, targeted, and safe fertility control methods that can be used in conjunction with traditional medicine compounds.

Conclusion

Some of the numerous traditional medicine compounds have demonstrated contraceptive effects for female rodents by disrupting hormone levels and uterine and ovarian function and interfering with the implantation process. Studies on various plant extracts such as *Asparagus pubescens, Afrormosia laxiflora, Pterocarpus erinaceus, Cola nitida,* and *Rumex steudelii* have shown significant anti-implantation and anti-fertility activities. The other hand, *Rubus ellipticus, R. niveus, R. racemosus, R. rugosus var. thawaitesii, Guaiacum officinale, Ailanthus excelsa Roxb, Gloriosa superba,* and *Achyranthes aspera* indicate their anti-implantation and early abortifacient activities. These findings highlight the potential of traditional medicine compounds as contraceptive agents, although further research is required to understand their mechanisms and ensure their safety and efficacy fully. Also, there are studies on traditional medicine have demonstrated the potential of plant-based compounds, such as *Carica papaya, Feronia limonia, Enicostemma axillare, Urena lobata, Ruta graveolens,* and *Echeveria gibbiflora* to affect male fertility in rodents. These compounds have shown effects on sperm motility, morphology, steroidogenesis function, and reproductive system ultrastructure, suggesting their potential as contraceptives for male rodents. The use of traditional medicine as a contraceptive for rodents has the potential to offer environmentally friendly and cost-effective solutions for rodent population control. However, the limited scientific evidence, potential for long durations and high doses of administration, potential toxicity effects, and challenges with palatability highlight the need for further research and careful evaluation before widespread implementation of traditional medicine-based contraceptives for rodents. Finally, exploring the mechanisms and implications of traditional medicine as a contraceptive for rodents is complex, and studies indicate potential adverse effects on foetal development and growth. Further investigations are needed to understand these mechanisms and assess long-term implications. So, the registration of traditional medicine compounds as anti-fertility agents require comprehensive information on their mode of action, efficacy, and environmental safety, considering the presence of estrogenic phytoconstituents that inhibit implantation. Additionally, the empirical experience of using traditional medicinal plants highlights the need for a scientific approach to integrating them into formal health services for rodent control, as seen with *Tristania sumatrana*, which has shown a significant decrease in fertility in female mice and requires further exploration.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Figures

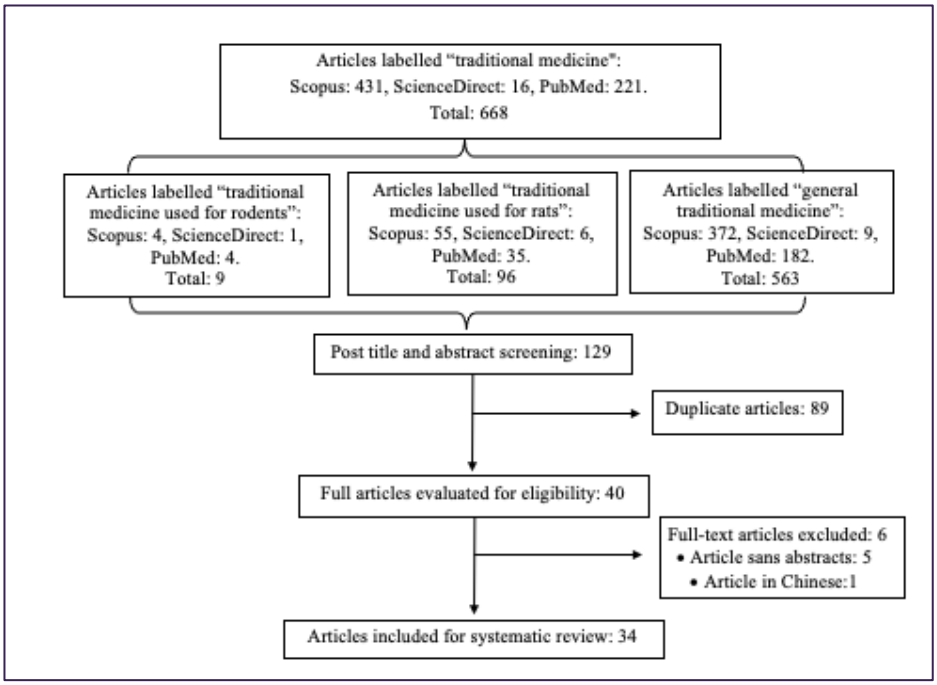

Fig. 1. Flow chart of article selection for systematic review on traditional medicines as contraceptives in rodents. (Page et al.[16]

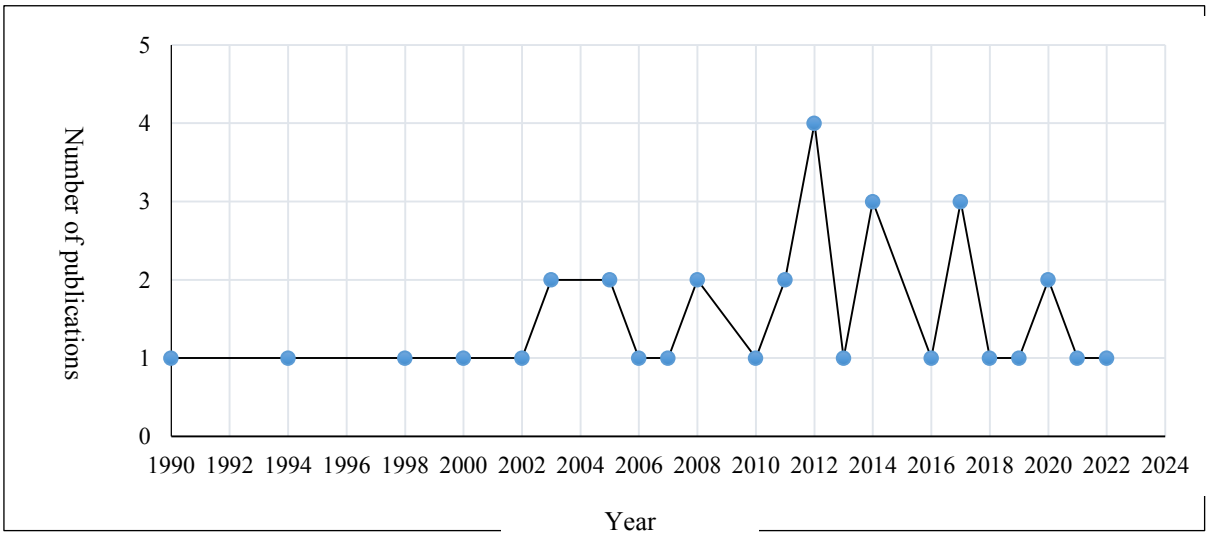

Fig. 2. Distribution of the 34 selected studies on plant-based contraceptive according to year.

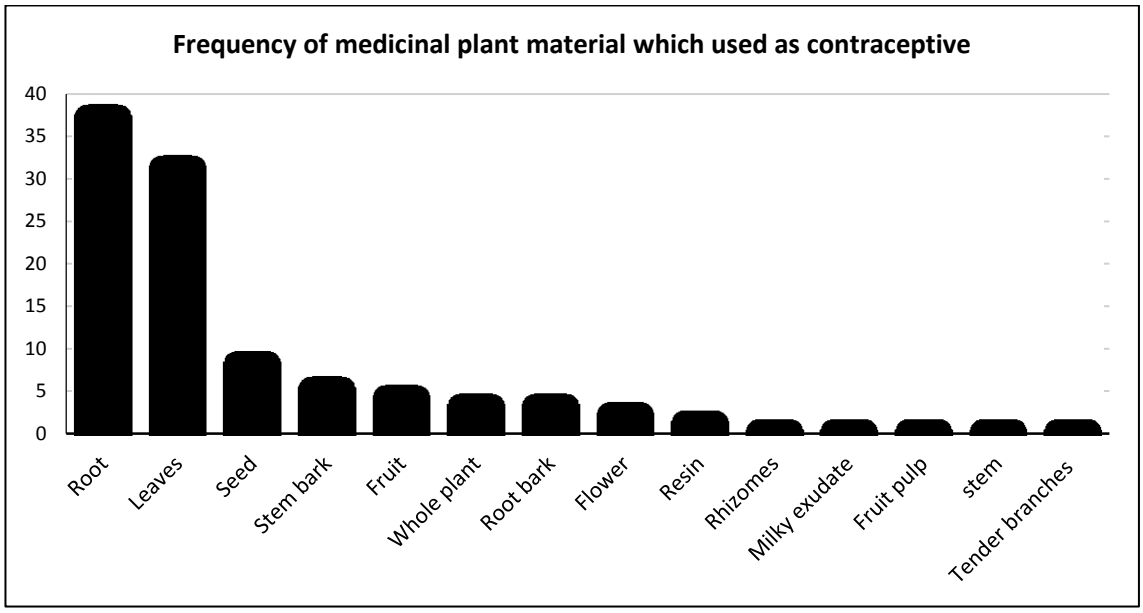

Fig. 3. Parts of plants used as contraceptives in traditional medicine

TABLE 1. **A comprehensive overview of medicinal Species and these therapeutic Impacts on Rodents.**

Agent *name* (Family name)	Publishing Country	Use and/ or Effects	Reference
Celastrus paniculutus (Celastraceae)	India	Used as anti-spermatogenic	[17]
210 extracts/fractions from 70 plants traditionally used in Ethiopia	Ethiopia	Preventive and control fertility	[18]
Asparagus pubescens (Asparagaceae)	Nigeria	Possesses hormonal properties that are used in contraceptive activity	[19]
Rubus racemosus, Rubus ellipticus, Rubus rugosus var. thawaitesii and *Rubus niveus* (Rosaceae)	India	*Rubus ellipticus* is used in anti-implantation. *R. racemosus, R. rugosus var thawates* and *R. niveus* have been used widely by tribals for abortifacient action	[20]
Carica papaya (Caricaceae)	Nigeria	Excellent candidate in reducing spermatogenesis activity	[21]
Cola nitida (Malvaceae). *Afrormosia laxiflora* and *Pterocarpus erinaceus* (Fabaceae)	Côte d'Ivoire	Contains lithospermic acid, an anti-gonadotropic chemical	[22]
Guaiacum officinale Linn (Zygophyllaceae)	Trinidad & Tobago	Antifertility agent, especially for early pregnancy and foetus rejection	[23]
Rumex steudelii Hochst (Polygonaceae)	Ethiopia	Used as an abortifacient. Also shown as anti-implantation	[24]
Azadirachta indica and *Melia azedarach* (Meliaceae)	India	Anti-sperm and anti-fertility	[25]
Achyranthes aspera (Amaranthaceae)	Ethiopia	Placental retention, postpartum haemorrhaging, and fertility control	[26]
Ailanthus excelsa Roxb (Simaroubaceae)	India	Early abortifacient and anti-implantation effect	[27]
Acanthus montanus (Acanthaceae)	Cameroon	Cures pain and inflammation and threatened abortion	[28]

Agent ***name*** **(Family name)**	**Publishing Country**	**Use and/ or Effects**	**Reference**
Spondias mombin (Anacardiaceae)	Nigeria	Facilitates birth and helps small ruminants discharge the placenta	[29]
Tripterygium wilfordii (Celastraceae)	China	Effect growing follicles in females and spermatogenesis	[30]
Carpolobia lutea (Polygalaceae)	Nigeria	Hasten labour and treat male sexual diseases	[31]
Gloriosa superba (Colchicaceae)	India	Abortifacient and oxytocic activity	[32]
Heracleum persicum (Apiaceae)	Iran	Harmful effects on sperm chromatin condensation	[33]
Feronia limonia (Rutaceae)	India	Contribute to sperm maturation, motility, and semen development	[34]
Enicostemma axillare (Gentianaceae) and *Urena lobata* (Malvaceae)	India	Inhibition of steroidogenesis and spermatogenesis	[35]
Ruta graveolens (Rutaceae)	Iran	Used for its purported anti-conceptive activity	[36]
Rosmarinus officinalis (Lamiaceae)	Iran	Reproductive failure and abortion	[37]
Drynaria quercifolia (Polypodiaceae)	India	Effects on hormone release and prevention of implantation	[38]
Apium graveolens (Apiaceae)	Iran	Stimulates the libido and causes miscarriage	[39]
Tripterygium wilfordii (Celastraceae)	India	Reversible infertility	[40]
Echeveria gibbiflora (Crassulaceae)	Mexico	Used as vaginal rinse post-coital	[41]
Hibiscus rosa-sinensis (Malvaceae)	Brazil	Antifertility by estrogenic activity	[42]
Piperine (Piperaceae)	India	Female reproductive disorders such as dysmenorrhea amenorrhea, and menopause	[43]
Gloriosa superba (Colchicaceae)	India	Early abortifacient activity	[44]
Tristania sumatrana (Myrtaceae)	Indonesia	Anti-fertility activity in female as it tampers with the reproductive process	[45]
Carica papaya (Caricaceae)	Nigeria	Reduction in spermatogenesis activity	[46]
Moringa oleifera (Moringaceae)	Nigeria	Increases the supply of breast milk	[47]
Urena lobata (Malvaceae)	Indonesia	Decrease the numbers of follicles in ovary	[48]
Wedelia trilobata (Asteraceae)	India	Used to prevent menstrual and general pain	[49]
Dioscorea (Dioscoreaceae)	India	Inhibited sperm count, motility, and testosterone levels	[50]

TABLE 2. Rodent Fertility Control: Species, Genders, Sample Categories, Analytical Techniques, and Results.

Animal Model	Sample Type	Method	Duration of treatment	Key findings	Reference
Male *Wistar* rats	Liver and testes	Histological staining, histochemical and biochemical estimations	30 days	*C. paniculutus* causing vacuolization, germ cell depletion and spermatogenesis arrest in the testis, and focal necrosis in the liver; these effects were reversible within 45 days post-treatment	[17]
Female *Sprague Dawley rats*	Uterine horns and vaginal smears	*In-vitro* for uterotonic activity and bioassay for anti-implantation activity	Uterotonic activit one days and anti-implantation activity 16 days	70 plants had uterotonic and anti-implantation activity	[18]
Female rats and mice	Pups, uterus and vagina	Determine Acute toxicity, and antifertility activity	Toxicity study one day, antifertility activity 4 days	Puppies exhibited treat by *A. pubescens* alterations in weight and length, along with a reduction in uterine weight, but there were no instances of early vaginal openings	[19]
Female *Wistar albino* rats	Pregnant of female rats	Implantation sites	Seven days	*R. ellipticus*, *R. racemosus, R. rugosus var thawates* and *R. niveus* decreased implantation sites and increased resorption sites	[20]
Male *Sprague Dawley* rats	Reproductiv e organs, kidneys and adrenals	Body and organs weight, changes in tests and semen histology	28 days	Although body weight, reproductive organ, kidney, and adrenal weights were unchanged after exposure to *C. papaya*, but testis histology and semen analysis changed dramatically	[21]
Female *Wistar* rats	Vaginal smears, pituitary glands, uterus, and uterine horns	Oestrous cycle, (LH), (FSH) and reproductive organ weight	Oestrous cycle one day, gonadotropin s 14 days while on uterine horn 7 days, and effect on progesterone receptor 3 days	*C. nitida*, *A. laxiflora* and *P. erinaceus* act to oestrous cycle blockade at the dioestrus II stage and decreased gonadotropin release (LH and FSH)	[22]
Female *albino* mice and rats	Pregnant mice and rats	Observed vaginal bleeding, fatal discharge and death	One day	*G. officinale* caused second and third-trimester abortions	[23]
Female *albino* rats, male and female *albino* mice	Uterus, vaginal smears and blood	antifertility activity and toxicity	Antifertilit y activity 7 days, oestrous cycle 21 days and LD50 one day	*Rumex steudelii Hochst* reduced number of litters and safe	[24]
Female *albino* rats	Ovaries	Histological staining	18 days	Average follicle numbers, normal single-layered and follicular development stages I-VII follicles decreased significantly by *A. indica* and *M. azedarach* extracts	[25]

Continues

Animal Model	Sample Type	Method	Duration of treatment	Key findings	Reference
Female *Wistar* rats	Foetuses, uterus, pituitary and blood	Count foetuses, weight organs, hormone assay and lipid profile	Abortifacient activity 24 days, estrogenicity 7 days, pituitary weight 15 days, hormones and lipid profile 14 days	*A.aspera* act to abortifacient and increase in the wet weights of the pituitary and uterus. It did not impact the levels of ovarian hormones or lipids, except for a reduction in HDL level	[26]
Female and male *albino* rats	Uterus	Number of implantation and litters, resorption rate, uterine weight and vaginal cornification	Seven days	*A. excelsa* cause significant anti-implantation (72%), abortifacient (56%), antiestrogenic solid effects and increases uterine weight	[27]
Female *Wistar albino* rats	Vaginal smears, ovaries and uterus	Estrogenic and pregestational properties, histological, observation of implanted and non-implanted embryos	15 days	Exposure to *A. montanus* prolonged metestrus and dioestrus stages but did not affect estrogenic or pregestational properties. No extract dose caused post-implantation losses; however, it caused considerable preimplantation losses. Inhibited foetal growth	[28]
Female *Wistar* rat	Vagina plug	Acute toxicity test, ability to induce abortions and prevent conception	Toxicity test one day, followed by 4 days each for abortifacient and oestrogenic activity	A non-toxic plant. After the third trimester, the *Spondias mombin* was anti-conceptive but not abortifacient	[29]
Female *Sprague Dawley* rat	Ovaries and vaginal smear	Variables include oestrous cycle, follicle count and apoptosis rate	35 days	Control and low-dose of *T. wilfordii* exhibited shorter oestrous cycles than the high-dose group. The primordial and antral follicles did not change, although both treatment groups had larger secondary follicles than controls and increased secondary follicular apoptosis	[30]
Albino rats and mice	Counting pups, vagina, uterus, and visceral organs	Acute toxicity, hormones activity and various weights	Four days	Significant pup length and weight changes compared to control. Over 30 days, puppies showed no abnormalities. Low dosages of the *C. lutea* were estrogenic, while high doses were anti-estrogenic	[31]
Female *Wistar* rats	Uterine horns, uterus, and carotid artery	Assess pregnancy traits, monitor blood pressure, electrocardiogram, and nervous system features for lethality	Toxicity study one day, antifertility activity 7 days, estrogenic activity 28	Early abortion was found in antifertility study. But *G. superba* did not affect cardiac parameters, blood pressure, uterus and decidual weight, extract yield was safe	[32]

Continues

Animal Model	Sample Type	Method	Duration of treatment	Key findings	Reference
			days, progestogenic activity 13 days, *In-vivo* and *In-vitro* assay one day		
Female *Wistar* rats	Blood and ovaries	Histological analysis and Hormone assay	21 days	*H. persicum* act to increased number of primordial and primary follicles, whereas preantral and antral decreased. While number of atretic follicles, and the FSH level was not change	[33]
Male *albino* rats	Blood, tested, cauda epididymal ducts, seminal vesicle, and sperm	Haematological profiles, sperm parameters and biochemical estimation	55 days	*F. limonia* decreased sperm count, motility and viability. High doses reduced epididymal and testicular protein, G-6-PDH, and 5-3β-HSD while boosting cholesterol and ascorbic acid. After 55 days of drug cessation, haematological indicators did not change	[34]
Male *Wistar albino* rats	Blood, sperm, seminal vesicles, cauda epididymal ducts, and testes	Haematological profiles, sperm parameters and biochemical estimation	55 days	Body weight did not decrease with either *E. axillare* and *U. lobata* , but testis, epididymis, and seminal vesicles did. Significantly lowering sperm and epididymal and testicular protein. A larger dose of extracts led to increased testicular cholesterol and ascorbic acid and lower activity of G-6-PDH and Δ5-3β-HSD	[35]
Male *Wistar* rats	Sperm and blood	Sperm count, motility, viability, morphology, florescent microscope for DNA integrity and testosterone hormone	Six hours	One hour after dosing of *R. graveolens*, sperm motility decreased significantly. While motility reached the control group after 6 hours. Spermatozoa showed no significant changes in viability, shape, or DNA structure. No testosterone level changes	[36]
Male *Wistar* rats	Blood, testes, and sperm	Testosterone profile and sperm studies	60 days	Testosterone level was decreased significantly in both doses of *Rosmarinus officinalis***.** The extract did not change the motility, count, viability of sperm and testes weight	[37]
Female *Wistar albino* rats	Uterine horns and blood	Uterine contractile activity, hormone assay	Ex-vivo assay one day, abortifacient activity 9 days , anti-implantation activity 7	Uterotonic action of methanol and aqueous of *D. quercifolia* but were non-toxic. The methanolic extract is more effective at aborting, preventing implantation, and hormone release	[38]

Continues

Animal Model	Sample Type	Method	Duration of treatment	Key findings	Reference
			days		
Male *Wistar* rats	Mated animals	Rats mated and several offspring recorded	35 days	There is notable reduction in the number of offspring in both dosage of *A. graveolens*	[39]
Male house rat (*Rattus rattus*)	Bait, male reproductive organs and sperm	Bait acceptance, record reproductive organ weight and sperm activity	Five days	Rats consumed little *T. wilfordii* bait. Reduced sperm motility, viability considerably and pregnancy rates by 100%	[40]
Male mouse	Mouse sperm	Sperm viability and capacitation, sperm acrosome reaction, motility and acute toxicity evaluation.	Seven days	*E. gibbiflora* act to decreased Ca2+ influx, capacitation and acrosome response. Inhibition of sperm total and progressive motility and IVF rates. Extract was as a low toxic	[41]
Female *Wistar* rats	Serum, liver	Biochemical profile	From 0-7th day of pregnancy (implantation period), from 8-14 days (embryonic period) and from 15-20 days (foetal period)	The *H. rosa-sinensis* did not result in any toxicity, but it did have detrimental impacts on both cardiac and reproductive systems	[42]
Male *Wistar albino* rats	Blood, testes, testicular, and gonadosomatic	Hormones, organ weights, enzymatic and nonenzymatic detection, antioxidants and histopathological studies.	60 days	Piperine dramatically reduced reproductive organ weights and hormonal imbalance in both groups. Also, it lowered germ cell markers and Leydig cellular steroidogenic enzymes in both groups after 60 days. After withdrawal, all affected values returned to normal	[43]
Female *Wistar albino* rats and *Swiss albino* mice	Uterine	Mated, then laparotomies and counting of implants present in uterine horns.	Seven days	In all *G. superba* groups, antifertility action reduced implants and pups. The extracts all showed considerable abortifacient efficacy	[44]
White mice (*Mus musculus*)	Ovaries and foetuses	Ovaries weight, histology and number of live foetuses	First treatment group 10 days and second treatment group 20 days	*T. sumatrana* administration drastically reduces ovarian weight, follicles Graaf number, corpus luteum, and live foetuses	[45]
Male *Wistar* rats	Blood, sperm, and testes	Biochemical analysis, sperm concentration motility, morphology and histopathology	Oral toxicity one day and experimental procedures 28 days	*C. papaya* caused CNS symptoms and diuresis but no deaths in acute toxicity testing, drastically reduced sperm counts, and increased faulty sperm. Blood urea nitrogen	[46]

Continues

Animal Model	Sample Type	Method	Duration of treatment	Key findings	Reference
				and aspartate aminotransferase increased significantly. Histopathology showed modest renal and heart hyperaemia	
Female *Wistar* rats	Uterine horns and mated animals	Uterine muscle isometric contractile force and discovery of sperm cells throughout the day via vaginal smear	*In vitro* experiment each horn was placed in a petri dish for 90 minutes , and *In vivo* experiment 14 days	*In vitro*, cold and hot aqueous of *M.oleifera* increased uterine contractility. Cold aqueous extract contracted more than hot. *In vivo*, cold aqueous extracts before and after mating inhibited conception 100% and 80%, while hot extracts 96.6% and 58%	[47]
Female mice *Balb-C* strain	Ovary	Calculation of the number of all types of follicles.	15 days	At 7,5% concentration of *U. lobata* extract, multilaminar primary and de Graaf follicles decreased, and atresia follicles increased, while 10% concentration reduced mono laminar primary and secondary follicles	[48]
Female *albino* rats	Serum, liver, uterus and ovary	Biochemical Assays, haematological and hormonal reports	Seven days	*W. trilobata* extract were contraceptive and excellent antioxidant and antimicrobial properties	[49]
Female and male *Swiss albino* mice	Serum, sperm, cauda epididymis, testis, seminal vesicle, adrenal and ovary	Biochemical, reproductive hormones profiling and molecular bioassays	90 days	Chronic exposure to *Dioscorea* in mice disrupted endocrine and reproductive functioning and caused transgenerational reproductive harmful consequences	[50]

Note.
LH = luteinizing hormone
FSH = follicle-stimulating hormone
HDL = high-density lipoprotein
Δ^5-3β-HSD = testicular protein, glucose-6-phosphate dehydrogenase
Δ^5-3β-HSD = Δ5-3β-hydroxy steroid dehydrogenase
IVF = in vitro fertilization
CNS = Central nervous system

TABLE 3. Botanical contraceptives used in traditional medicine: An overview by species names, and part of plant applications.

Agent *name* (Family name)	Part	Extract Type	Reference
Celastrus paniculutus (Celastraceae)	Seed	Oily	[17]
210 extracts/fractions from 70 plants traditionally used in Ethiopia	Stem bark: 3, Fruit: 2, Leaf: 19, Milk: 1, Root: 31, Root bark: 2, Resin: 2, Seed: 6 Whole plant: 4	Aqueous, ethanol, and alcoholic for each fraction	[18]
Asparagus pubescens (Asparagaceae)	Root	Methanolic	[19]
Rubus racemosus, Rubus ellipticus, Rubus rugosus var. thawaitesii and *Rubus niveus* (Rosaceae)	Leaf	Ethanolic	[20]
Carica papaya (Caricaceae)	Stem bark	Aqueous	[21]

Agent *name* (Family name)	Part	Extract Type	Reference
Cola nitida (Malvaceae), *Afrormosia laxiflora* and *Pterocarpus erinaceus* (Fabaceae)	Stem bark	Aqueous-Ethanolic	[22]
Guaiacum officinale Linn (Zygophyllaceae)	Leaves, flowers, fruits, and tender branches	Aqueous	[23]
Rumex steudelii Hochst (Polygonaceae)	Root	Methanolic	[24]
Azadirachta indica and *Melia azedarach* (Meliaceae)	Seed	Oil	[25]
Achyranthes aspera (Amaranthaceae)	Leaf	Methanolic	[26]
Ailanthus excelsa Roxb (Simaroubaceae)	Stem bark	Hydroalcoholic	[27]
Acanthus montanus (Acanthaceae)	Leaf	Aqueous	[28]
Spondias mombin (Anacardiaceae)	Leaf	Ethanolic	[29]
Tripterygium wilfordii (Celastraceae)	Root bark	Dry	[30]
Carpolobia lutea (Polygalaceae)	Root	Methanolic	[31]
Gloriosa superba (Colchicaceae)	Root	Aqueous	[32]
Heracleum persicum (Apiaceae)	Fruit	Hydroalcoholic	[33]
Feronia limonia (Rutaceae)	Fruit pulp	Dry	[34]
Enicostemma axillare (Gentianaceae) and *Urena lobata* (Malvaceae)	Leaf and root	Dry	[35]
Ruta graveolens (Rutaceae)	Leaf	Aqueous	[36]
Rosmarinus officinalis (Lamiaceae)	Leaf, flower, and stem	Aqueous-Ethanolic	[37]
Drynaria quercifolia (Polypodiaceae)	Rhizome	Dry	[38]
Apium graveolens (Apiaceae)	Leaf	Hydroalcoholic	[39]
Tripterygium wilfordii (Celastraceae)	Root bark	Dry	[40]
Echeveria gibbiflora (Crassulaceae)	Leaf	Aqueous	[41]
Hibiscus rosa-sinensis (Malvaceae)	Flowers	Aqueous	[42]
Piperine (Piperaceae)	Fruit	Dry	[43]
Gloriosa superba (Colchicaceae)	Roots	Ether, chloroform, and ethyl-alcohol	[44]
Tristania sumatrana (Myrtaceae)	Stem bark	Ethanol	[45]
Carica papaya (Caricaceae)	Root	Methanol	[46]
Moringa oleifera (Moringaceae)	Leaf	Aqueous	[47]
Urena lobata (Malvaceae)	Leaf	Aqueous	[48]
Wedelia trilobata (Asteraceae)	Leaf	Aqueous and ethanolic	[49]
Dioscorea (Dioscoreaceae)	Roots	Saline	[50]

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مراجعة منهجية لوسائل منع الحمل الطبية التقليدية المستندة إلى النباتات في القوارض

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[٦] قسم الكيمياء الصيدلية، كلية الصيدلة، جامعة أحمد دحلان، جى .كاباس 9، سيماكي، أمبولهارجو، يوجياكرتا 55166، إندونيسيا.

الملخص

إن التحكم في أعداد القوارض أمر بالغ الأهمية، مما يستلزم إجراء مراجعة منهجية لوسائل منع الحمل المستندة إلى الطب التقليدي كبديل إنساني لمبيدات القوارض. تجري هذه الدراسة مراجعة شاملة للأدبيات حول دور الطب التقليدي كموانع الحمل للقوارض، باستخدام طريق PRISMA 2020 .لقد قمنا بفحص الأدبيات من عام 1990 إلى عام 2023 عبر Scopusو ScienceDirect و PubMed، مما أدى إلى 34 منشورًا من 668 عملية بحث. تم تصنيف هذه المنشورات بناءً على أربعة أبعاد: التأثيرات على الأنظمة التناسلية الأنثوية، وآليات تقليل الخصوبة لدى الذكور، والقوة والقيود، والتحديات التي تواجه الطب التقليدي كموانع للحمل لدى القوارض. تكشف الدراسات الـ 34 أن المركبات الطبية التقليدية يمكن أن تؤثر على مستويات الهرمونات، ووظيفة الرحم والمبيض، والزرع في القوارض الإناث. كما أنها تؤثر على خصوبة الذكور من خلال التأثير على حركة الحيوانات المنوية، وشكلها، والبنية الدقيقة للجهاز التناسلي. تُظهر المركبات مثل (*Tripterygium wilfordii* و *Carica papaya* و *Ruta graveolens* و *Wedelia trilobata* و *Celastrus paniculutus* و *Gloriosa superba*) أنشطة مضادة للخصوبة واعدة مع آثار جانبية عكسية، مما يشير إلى إمكاناتها كعوامل منع الحمل. يعد إجراء المزيد من البحوث أمرًا ضروريًا لتقييم فعالية المستخلصات النباتية في تثبيط خصوبة القوارض. حاليًا، هناك أدلة علمية نادرة حول آليات العمل ومدة التأثير والإنسانية والسموم المحتملة والتأثيرات غير المستهدفة، مما يستلزم إجراء دراسات شاملة إضافية قبل التطبيق على نطاق واسع.

الكلمات الدالة: مضادات الخصوبة، وسائل منع الحمل، الجهاز التناسلي، القوارض، الطب التقليدي.