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REVIEW ARTICLE
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Mode of Action of Medicinal Plants to Enhance Fecundity and Treat Infertility in Female Animal Models: Rats, Mice and Rabbits

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ABSTRACT

For millennia, medicinal herbs have been utilized to enhance health and address many ailments, including infertility and reduced fertility in female animals. This review seeks to examine current research on the effect of medicinal herbs in enhancing fecundity and addressing infertility in female animal models, including rats, mice, and rabbits. Narrative reviews were conducted on 45 scientific articles published between 2014 and 2024. The findings indicated that extracts from 41 plant species belonging to 29 families significantly influenced reproductive hormone control, folliculogenesis, restoration of the estrous cycle, and enhancement of fertility indices. The species comprise *Myrianthus arboreus, Rumex vesicarius, Jatropha tanjorensis, Schumanniophyton magnificum, Allium cepa, Allium ampeloprasum, Glycine max* L., *Curcuma longa* L., *Nigella sativa, Salvia officinalis, Foeniculum vulgare, Moringa oleifera,* and *Viscum album*. The primary bioactive substances identified include polyphenols, flavonoids, isoflavones and phytoestrogens, which contribute to the regulation of hormonal equilibrium (estrogen, progesterone, LH, and FSH), mitigation of oxidative stress, and enhancement of ovarian morphology, oocyte quality, and the estrous cycle. Certain plant medicines, including *Punica granatum, Withania somnifera, Tribulus terrestris, Phyllanthus muellerianus, Glycyrrhiza glabra*, and *Cinnamomum verum*, are efficacious in managing polycystic ovarian syndrome, reinstating reproductive function, and enhancing fertility. This study highlights the necessity of advancing medicinal plant extracts as a safe, cost-effective, and eco-friendly therapeutic alternative to improve female reproductive health and promote the sustainability of animal populations.

Keywords: Animal models; Female fertility; Infertility; Phytoestrogens; Medicinal plants

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INTRODUCTION

The utilization of medicinal plants for the treatment of ailments in people and animals has persisted for generations due to the presence of phytochemical substances with therapeutic qualities (Dhama et al., 2018). In numerous underdeveloped nations, herbal medications are preferred due to their safety, physiological effects, and lower costs compared to synthetic pharmaceuticals (Jaradat & Zaid, 2019). The demand for herbal medicines and plant extracts is rising across multiple sectors, such as functional foods, pharmaceuticals, and cosmetics, thereby propelling the investigation of bioactive compounds for the treatment of various diseases, including reproductive

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disorders (Aminudin et al., 2021; Belhaj & Zidane, 2023). Infertility is a significant issue in female animal reproduction, resulting in decreased fecundity, population reduction, and eventual extinction (Dunbar & Shultz, 2021). The impacted reproductive system encompasses the ovaries and reproductive tracts, including the ovary and uterus, along with hormonal regulation influencing the estrus cycle. Infertility is defined as the failure to achieve conception despite engaging in copulation across multiple estrus cycles. This phenomenon is becoming more prevalent among livestock, including cattle, goats, and poultry, as well as endangered species like Sumatran tigers and Javan rhinos, necessitating mitigation strategies to ensure the viability of their populations (Malhi et al., 2022; Mekonen, 2020).

Numerous variables, including hormonal imbalances, infections, metabolic problems, hypothyroidism, anatomical anomalies, stress, excessive physical exertion, and inadequate management practices influence infertility in livestock (Assersohn et al., 2021). Insufficient nutritional consumption also leads to hormonal abnormalities that impact reproductive capacity (Silvestris et al., 2019). Female infertility frequently results from dysfunctions at multiple phases of reproduction, including ovulation, conception, implantation, and embryonic development. Variations in estrogen and progesterone hormone levels have been documented to influence the estrus cycle, hence affecting ovulation (Tan et al., 2022). This syndrome can diminish libido and sperm quality in males, exacerbating overall reproductive issues (Vander Borght & Wyns, 2018). Despite numerous infertility treatment endeavors, success rates frequently remain low due to the intricacies of the patient's situation, leading to financial losses and heightened maintenance expenses. The administration of synthetic medications for infertility is sometimes costly and may result in problems, such as behavioral alterations and emotional issues in animals. A comprehensive strategy is required that encompasses enhanced maintenance management, superior nutrition quality, and the creation of more cost-effective and eco-friendly reproductive therapies to promote the sustainability of livestock and wildlife populations (Muhie, 2022).

Over the past ten years, there has been a growing interest in using medicinal herbs as agents for improving fertility. Numerous in vitro and in vivo investigations have examined the capacity of medicinal plants to enhance the reproductive system and augment the fertility of female animals (Moshfegh et al., 2015; Sirotkin et al., 2018). The efficacy of medicinal plants in enhancing fertility correlates with the presence of phytoconstituents in their extracts, including polyphenols, flavonoids, curcumin, terpenoids, and carotenoids, which exhibit activities analogous to estrogen, progesterone and genistein (Ofem et al., 2014; Contero et al., 2015; Mvondo et al., 2017). Certain active compounds are involved in the regulation of reproductive hormones (Uchiyama et al., 2014), exhibit estrogenic effects (Jie et al., 2015), enhance sperm quality (Adelakun et al., 2018), facilitate folliculogenesis (Jahromi et al., 2021), and optimize steroidogenesis (Alrezaki et al., 2021).

Moreover, herbal extracts demonstrate efficacy in addressing infertility situations, including polycystic ovarian syndrome (PCOS), in model organisms. *Cinnamomum verum* leaf extract administered at a dosage of 1 mg/kg over 20 days enhanced the ovarian architecture in mice with PCOS (Dou et al., 2018). The amalgamation of crude extracts from *Withania somnifera* and *Tribulus terrestris* Linn (198mg/kg) effectively reinstated the estrus cycle and elevated sex hormones in Wistar rats with PCOS, whereas the aqueous extract of *Myrianthus arboreus* leaves (110–220mg/kg) enhanced fertility and pregnancy metrics by up to 100% in albino rats with PCOS (Mvondo et al., 2020). *Viscum album* and other mistletoe species have been documented to elevate sex hormone levels and enhance biochemical and clinical parameters associated with PCOS, hence positively influencing fertility in animal models (Ofem et al., 2014; Oseni et al., 2019). This review seeks to investigate the efficacy of medicinal plant extracts as fecundity enhancers and their mechanisms in modulating reproductive hormone regulation, estrous cycles, puberty onset, ovarian follicle development, estrogenic effects and various fecundity metrics in female animal models, encompassing follicle count, corpus luteum presence, implantation rates, pregnancy indices, offspring numbers, survival rates and fecundity indices.

MATERIALS & METHODS

A thorough search was performed to gather the most pertinent literature on the subject published over the past decade (2014-2024) from the scientific databases Google Scholar, PubMed, and ScienceDirect. The search terms included "medicinal plant," "herbs," "extract herbs," "phytochemical," or "phytoestrogens" in conjunction with "female fertility," "fecundity," "infertility," "sex hormone," "folliculogenesis," "oocyte," "ovary," "GnRH," "LH," "FSH," "PCOS," and "animal models." This evaluation primarily encompasses original publications, research articles, and clinical trials involving experimental animals, excluding conference papers, theses, and dissertations. The study's limitations pertain to female animal models, encompassing immature, adult, pregnant, and infertile specimens affected by PCOS. This review encompassed detailed characteristics, including the scientific name of the plant, species/genus, plant component, extraction method, bioactive content, and animal model, route of administration, dose, duration, outcome, efficacy, and pharmacological mechanism of action, as illustrated in Table 1.

RESULTS

The research identified over 300 studies on medicinal plants and their association with fertility in test animals, published between 2014 and 2024. From them, 45 pertinent papers were chosen for comprehensive analysis (Table 1). Publication mapping indicates a high in 2020, with six articles, followed by five pieces each in 2015, 2016, 2021, and 2022. The lowest counts were recorded in 2019 and 2024, with two articles each. Forty-one medicinal plant species from twenty-nine families were found, with the most extensively investigated families being Amaryllidaceae, Fabaceae, and Zingiberaceae, followed by Euphorbiaceae and Lamiaceae (Fig. 1). The mistletoe plant of the Santalae family garners interest due to the

Table 1: In vivo investigations utilizing animal models to assess the efficacy of plant extracts in enhancing fecundity and addressing infertility.

No	Plant Species	Family	Part used	Preparation/ extract	Animal models	Route	Dose, Duration	Outcome/Efficacy	Reference
1	*Phoenix dactylifera*	Arecaceae	Pollen	Date palm pollen	Balb/C mice	Oral	100, 200mg/kg, 10 days	Increases serum levels of LH, FSH, estrogen, and progesterone. Increases ovary index, number of primary, secondary, and graafian follicles, and corpus luteum. Increases mating percentage, mass index, and crown-rump embryos, ovarian diameters, and the number of basic sex cells of offspring.	(Moshfegh et al., 2015)
2	*Curcuma longa* L	Zingiberaceae	Rhizoma	Tumeric powder	New Zealand White rabbits	Oral	5 and 20g/kg feed diets, 235 days	Increases the number and diameter of primary, secondary, and tertiary follicles. The conception rate increased, resulting in more live births (21%) and weanings (25%).	(Sirotkin et al., 2018)
3	*Ilex guayusa, Medicago sativa*	Aquifoliaceae, Fabaceae	Leaves, Plant	Ethanol 96% extract	*Rattus norvegicus*	Oral	9, 18, and 36mg/kg, 15 days	Increases uterine and ovarian weight and serum estrogen in immature female rats. Uterine and ovarian weight, as well as serum estrogen, increased in immature female rats.	(Contero et al., 2015)
4	*Milicia excelsa*	Moraceae	Roots	Aqueous extract	Immature Wistar rats	Oral	14mg/kg, 7 and 15 days	Increased serum concentration of gonadotropin (FSH) and ovarian hormone (estradiol) in both treatment periods (7 and 15 days), resulting in increased uterine wet weight, uterine and vaginal epithelial height. Accelerate sexual maturity from 90 to 52 days without affecting animal body weight.	(Mvondo et al., 2017)
5	*Viscum album*	Santalaceae	Leaves	Methanol extract	Wistar rats	Oral	150, 300, and 450mg/kg, 4 weeks	Increased FSH, LH, and testosterone, and decreased serum prolactin, but at high doses, increased prolactin	(Ofem et al., 2014)
6	*Lepidium meyenii*	Brassicaceae	Radix	Petroleum-ether extract	Sprague Dawley rats	Oral	30g/kg feed diets, 7 weeks	Increase in serum levels of LH and FSH.	(Uchiyama et al., 2014)
7	*Panax ginseng*	Araliaceae	Radix	Aqueous extract	Immature mice	Oral	12, 18, and 24g/kg, 7 days	Increased uterine weight and thickness of the endometrium and vaginal epithelial cell layer; Significantly induced upregulation of ERα and ERβ expression in reproductive tissues, where ERα upregulation was more substantial than ERβ; Extract also increased circulating estrogen levels	(Jie et al., 2015)
8	*Cucurbita pepo*	Cucurbitaceae	Seeds	Hydro-alcoholic extract (80%)	Wistar rats	IP	200mg/kg, 21 days	Increased serum levels of estrogen, progesterone, LH, FSH, and the number of follicles de Graaf.	(Jahromi et al., 2021)
9	*Salvia officinalis*	Lamiaceae	Plant	Hexane and dichloromethane extract	Virgin Wistar rats	Oral	60mg/kg, 14 days	Increased serum estrogen levels, primordial follicles, and decreased the number of abnormal follicles. Improve ovarian function by stimulating folliculogenesis and steroidogenesis.	(Alrezaki et al., 2021)
10	*Cinnamomum verum*	Lauraceae	Stem bark	Extract powder	Pre-pubertal C57BL/6 mice with PCOS	Oral	1mg/kg, 20 days	Restores normal estrus cycle, insulin resistance, and enhanced ovarian morphology in developing follicles and corpus luteum. Restores serum testosterone, LH, and FSH levels close to control values. Attenuates higher IGF-1 expression and lower IGFBP-1 expression in the ovary.	(Dou et al., 2018)
11	*Myrianthus arboreous*	Cecropiaceae	Leaves	Aqueous extract	Wistar rats with PCOS	Oral	20, 110, and 220mg/kg, 30 days	Improved ovarian structure: increased number of tertiary follicles, Graafian, and corpus luteum, while cystic and atretic follicles decreased. Increased serum estradiol, decreased ovarian oxidative stress, normalized estrus cycle, enhanced uterine epithelial cells, and increased fertility index (from 0% to 75%) and pregnancy rate (from 0% to 100%).	(Mvondo et al., 2020)
12	*Viscum album*	Santalaceae	Leaves	Aqueous extract	Rats PCOS	Oral	50, 100, and 200mg/kg, 30 days	Reduces serum levels of FSH and testosterone, and increases serum LH levels. Improve ovarian structure and reduce the number of cystic and atretic follicles.	(Oseni et al., 2019)
13	*Schumannio-phyton magnificum*	Rubiaceae	Stem bark	Decoction	Immature Wistar rats	Oral	400 and 800mg/kg, 30 days	Induction of sexual maturation was earlier by 5-6 days than in the control. Increased body and ovary weight, uterine weight and protein level, gonadotropin hormone synthesis (FSH and LH), and ovarian follicle development stages. Increased pregnancy index (80-100%), number of implantation sites, and live births.	(Bend et al., 2018)

14	*Jatropha tanjorensis*	Euphorbiaceae	Leaves	Aqueous extract	Virgin Wistar rats	Oral	500mg/kg, 28 days	Increased FSH and estrogen hormone levels in nulliparous rats; increased birth weight and offspring length. Improved reproductive performance, including fertility, gestation, and fecundity index.	(Ukoh et al., 2022)
15	*Salvia officinalis*	Lamiaceae	Plant	Aqueous extract	Virgin Wistar rats	Oral	60 and 100mg/kg, 14 days	Increased level of serum FSH and LH; more Graafian follicles; Enhanced body and ovary weight, and implantation sites in pregnant rats.	(Abdrabou et al., 2022)
16	*Momordica charantia*	Cucurbitaceae	Leaf	Ethanol extract	Virgin Sprague-Dawley	Oral	100mg/kg, 14 days	Increases fertility by 20% and the number of implantation sites and live fetuses. Significantly increases the weight and length of offspring.	(Subair et al., 2022)
17	*Ficus deltoidea*	Moraceae	Leaves	Methanol 95% extract	Sprague-Dawley rats with PCOS	Oral	250, 500, and 1000mg/kg 15 days	Decreased insulin resistance, obesity index, total cholesterol, triglycerides, LDL, MDA, testosterone, LH, and FSH, and increased HDL, estrogen, and superoxide dismutase (SOD) levels in PCOS rats approaching typical values. Increased the number of Corpus luteum and endometrial thicknesses.	(Haslan et al., 2021)
18	*Foeniculum vulgare*	Apiaceae	Seeds	Ethanol extract	Virgin albino rats	IP	100 and 200mg/kg, 5 days	Significantly increases serum levels of estrogen, progesterone, and prolactin.	(Sadeghpour et al., 2015)
19	*Senecio biafrae*	Asteraceae	Leaves	Aqueous extract	Immature Wistar rats	Oral	8, 32, 64, and 128mg/kg, 20 days	Increase uterine and ovarian serum protein and estrogen, and decrease ovarian cholesterol levels. Increase ovarian weight, number of primary, secondary, and antral follicles, and corpus luteum, and induce puberty in immature rats.	(Lienou et al., 2015)
20	*Punica granatum*	Lythraceae	Fruits	Juice extract	White rats with PCOS	Oral	400mg/kg, 30 days	Increases levels of serum estrogen and decreases testosterone and androstenedione.	(Hossein et al., 2015)
21	*Albizia amara*	Fabaceae	Leaves	Methanol 70% extract	Mice	Oral	200mg/kg, 4 weeks	Induces downregulation of CYP19 and LH genes and upregulation of GST genes.	(Kassem et al., 2016)
22	*Alchornea cordifolia*	Euphorbiaceae	Leaves	Aqueous and Ethyl Acetate extract	Wistar rats	Oral	800mg/kg, 21 days	Increased FSH, LH, and progesterone serum levels and improved oogenesis-related infertility.	(Ebenyi et al., 2016)
23	*Withania somnifera, Tribulus terrestris*	Solanaceae, Zygophyllaceae	Fruits and roots	Hydro-alcoholic extract	Wistar rats with PCOS	Oral	198mg/kg, 28 days	Normalizes the estrus cycle, increases FSH and estradiol, and decreases LH, total cholesterol, testosterone, and ovarian and uterine weight, returning to nearly normal levels.	(Saiyed et al., 2016)
24	*Mentha spicata*	Lamiaceae	Plant	Essential oils	Mature Wistar rats	Oral	150 and 300mg/kg, 20 days.	Reduces body weight, testosterone levels, ovarian cysts, and atretic follicles, and increases Graafian follicles.	(Ataabadi et al., 2017)
25	*Nigella sativa*	Ranunculaceae	Seeds	Hydro-alcoholic extract	Pregnant Wistar rats	Oral	100 and 400mg/kg, 20 days	More number of Graafian follicles and corpus luteum. Significantly increased maternal body weight, offspring birth weight, and serum estradiol and prolactin levels.	(Pakdel et al., 2017)
26	*Myrianthus arboreous*	Urticaceae	Leaves	Aqueous and methanolic 95% extract	Immature Wistar rats (21 days)	Oral	20, 110, and 200mg/kg, 30 days	Induces vaginal opening and early uterine growth. Increases the concentration of gonadotropin hormones (FSH and LH), progesterone, estradiol, number of ovarian follicles, maturation of Graafian follicles, fertility index, and pregnancy rate.	(Awounfack et al., 2018)
27	*Zingiber officinale*	Zingiberaceae	Rhizoma	Ginger powder	Adult Wistar rats	Oral	100mg/head, 5 and 10 days	Increases the number of antral follicles and VEGF of ovarian and endometrial stroma.	(Yılmaz et al., 2018)
28	*Moringa oleifera*	Moringaceae	Leaves	Extract powder	NIH Swiss mice	Oral	4% of the diet feed	Increases litter size, birth weight, and litter survival. Decreased serum MDA in male and female mice, sperm abnormality levels, and Bax expression.	(Zeng et al., 2019)
29	*Phyllanthus muellerianus*	Phyllanthaceae	Leaves	Aqueous and methanol extract	NMRI mice with PCOS	Oral	30, 60, and 120mg/kg, 14 days	Restoring the estrous cycle and ovarian structure to normal, increasing serum estrogen levels, and reducing the number of cystic follicles, LH, and testosterone levels.	(Ndeingang et al., 2019)
30	*Allium sativum, Curcuma mangga, Acorus calamus*	Amaryllidaceae, Zingiberaceae, Acoraceae	Leaves	Aqueous extract	Adult Wistar rats	Oral	50-75mg/kg, 15 days	Increases serum concentrations of estrogen and progesterone hormones, endometrium and myometrium thickness, and endometrial glands.	(Muchtaromah et al., 2020)
31	*Foeniculum vulgare*	Apiaceae	Seeds	Hydro-alcoholic extract	Mice	Oral	500 and 1000mg/kg/day, Day 1 pregnancy - 56 days	Increased body weight and offspring ovaries with an average number of primordial, primary, pre-antral, and pre-ovulatory follicles and corpus luteum. Lower number of atretic follicles. Higher serum Total Antioxidant Capacity (TAC) levels.	(Pourjafari et al., 2020)
32	*Syzygium cumini*	Myrtaceae	Stem bark	Ethanolic extract	Adult virgin Wistar rats	Oral	500mg/kg, twice a day for 14 days	Improved microscopic structure of the ovaries showing normal histoarchitecture and an increased number of primary follicles and corpus luteum.	(Prasad & Venugopal, 2020)

33	*Plukenetia conophora*	Euphorbiaceae	Leaves	Ethanol and ellagic acid extract	Infertile albino rats	Oral	100mg/kg, 30 days	Increased levels of HDL, triglycerides, testosterone, and steroidogenesis.	(Oladimeji et al., 2020)
34	*Glycyrrhiza glabra*	Fabaceae	Roots	Hydro-alcoholic extract	NMRI mice with PCOS	Oral	100-150mg/kg, 3 weeks	Increased number of healthy follicles (primary follicles, preantral, Graafian) and corpus luteum, with a decrease in atretic follicles and cysts. Increased fertilization index and blastocyst stage embryo development.	(Shamsi et al., 2020)
35	*Nigella Sativa*	Ranunculaceae	Seeds	Hydro-alcoholic extract	Wistar rats with PCOS	Oral	50, 100, and 200mg/kg, 30 days	Reduces serum levels of luteinizing hormone, testosterone, glucose, and malondialdehyde, while increasing insulin sensitivity; also improves insulin resistance. Additionally, it increases estrogen and progesterone levels, as well as those of antioxidant enzymes, and enhances ovarian tissue structure.	(Khani et al., 2021)
36	*Eucommia ulmoides*	Eucommiaceae	Leaves	Aqueous extract	Sprague-Dawley rats with PCOS	Oral	50, 110, and 220mg/kg, 21 days	Improves histopathological findings in the ovary and pancreas of rats with PCOS, inhibits ovarian hyperplasia, regulates glucose and lipid metabolism disorders, and enhances sex hormone secretion by regulating the expression of proteins related to the PI3K/AKT signaling pathway in the ovary and Kiss1/IGF-1/LEPR/AR in the HPO axis.	(Peng et al., 2021)
37	*Fagonia arabica*	Zygophyllaceae		Ethanolic extract	Virgin Wistar rats	Oral	50mg/kg, 23 days	Increased the number of offspring (10.00±2.00) and fertility index (87.52%) compared to the control (8.67±2.08 and 62.51%).	(Wazir et al., 2022)
38	*Rumex vesicarius*	Polygonaceae	Seeds	Aqueous extract	Mice	Oral	50mg/kg, 5 days, 1 week before mating	Increases the development of ovarian follicles and corpus luteum, fertility rate, and embryo development.	(Alhimaidi et al., 2021)
39	*Glycine max L.*	Fabaceae	Seeds	Powder	Immature NMRI Mice	Oral	15-35% feed diets, 3 months.	Affects the morphometric characteristics of the ovaries: increased pre-antral and antral follicle volume, the ratio of cortex volume to total ovarian volume, the ratio of corpus luteum volume to total ovarian volume, the ratio of total follicle volume to total ovarian volume, and also the volume of oocytes in follicles. Increased serum estrogen and progesterone levels.	(Sakifard et al., 2022)
40	*Allium sativum*	Amaryllidaceae	Bulbus	R10 fraction	NMRI mice with PCOS	IP	20mg/kg, 1-2 weeks	Increase the number of primary follicle development, primordial follicles, and corpus luteum, and reduce the number of cyst follicles. Increase IL-4 modulation and decrease IL-17 and IFN-γ levels. Reduce serum estradiol, progesterone, and testosterone levels in mice with PCOS.	(Falahatian et al., 2022)
41	*Calendula officinalis*	Asteraceae	Flowers	Hydro-alcoholic extract	Albino Rats PCOS	Oral	200, 500, and 1000mg/kg, 14 days	Reduces ovarian MDA levels and the number of atretic and cystic follicles. Restores the number of multilaminar, antral, and de Graaf follicles, and corpus luteum. Increases ovulation, LH, FSH, and progesterone levels, while reducing testosterone and estradiol, as well as insulin resistance.	(Gharanjik et al., 2022)
42	*Parquetina nigrescens*	Apocynaceae	Leaves	Ethanol 98% extract	Wistar rats with PCOS	Oral	50 dan 100mg/kg, 14 days	Restores the estrus cycle. FSH, HDL, and progesterone concentrations increase, while LH and total cholesterol decrease.	(Femi-Olabisi et al., 2023)
43	*Curcuma Longa* L	Zingiberaceae	Rhizoma	Curcumin	Wistar rats with PCOS	Oral	200mg/kg, 14 days	Decreases serum levels of LH, FSH, testosterone, and HOMA-IR index and increases serum levels of progesterone, estradiol, and ghrelin.	(Mosa et al., 2023)
44	*Allium cepa*	Amaryllidaceae	Bulbus	Ethanolic extract	White rats	Oral	150mg/kg daily, up to the end of the lactation period.	Increases litter size, hemoglobin levels, serum FSH and LH levels, and glutathione peroxidase activity. Reduces total lipids, LDL, and cholesterol. Improving ovaries, follicle development stages, and increasing fecundity.	(Suri et al., 2024)
45	*Allium ampeloprasum*	Amaryllidaceae	Leaves	Aqueous extract	Wistar rats with PCOS	Oral	192, 384, and 768mg/kg, 15 days	Reduces body weight, abdominal fat weight, total cholesterol, LDL, serum LH and testosterone levels, atherogenic index, and increases HDL in PCOS rats. Reduces ovarian oxidative stress, induces uterine epithelial cell hypertrophy, restores the estrus cycle, increases the number of de Graafian follicles and corpus luteum, reduces the number of cystic and atretic follicles, and increases fertility.	(Tedongmo & Mvondo, 2024)

therapeutic properties of all its components. The leaves are the most frequently employed component, followed by seeds, rhizomes, stem bark, root bulbs, roots, flowers, fruits, and pollen (Fig. 2). The majority of investigations employed crude extracts (35 publications), utilizing extraction procedures that involved water, methanol, ethanol, and hydroalcohol. Seven papers utilized powder extracts, whereas one article each employed fractionated compounds, essential oils, and juice extracts.

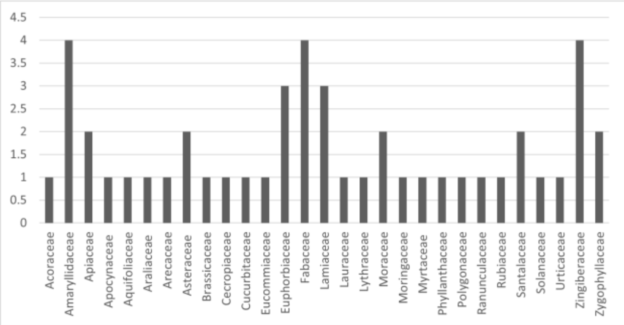

Fig. 1: Frequency of families of medicinal plants reviewed.

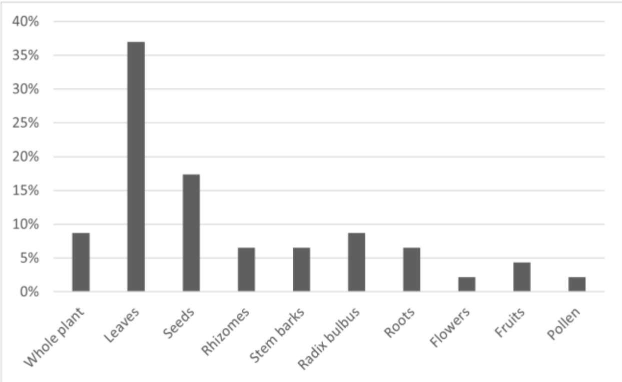

Fig. 2: Parts of the medicinal plant were employed for female fertility research.

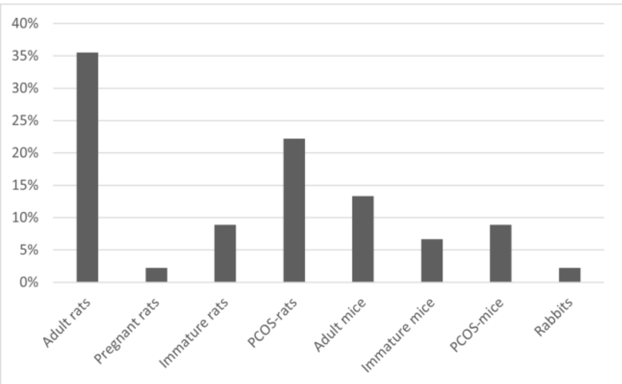

Fig. 3: The type and condition of female experimental animals.

The animal models employed comprised 11 research studies using mice, 33 studies involving mice, and 1 study involving rabbits. The examined female animals comprised healthy individuals with diverse reproductive statuses, including immature females, virgin adults, pregnant females, and those rendered infertile due to polycystic ovary syndrome (PCOS) (Fig. 3). Twenty-eight papers investigated the impact of plant extracts as fertility boosters. In contrast, seventeen articles addressed their function as agents for infertility therapy. The majority of research administered the extract orally (42 studies), whilst three studies utilized the intraperitoneal method. The dosage and timing of extract administration significantly differ due to the lack of a standardized protocol. Several publications mention the LD_{50} technique and the conversion of herbal ingestion doses in humans; nevertheless, most papers fail to elucidate the rationale behind the dosing.

DISCUSSION

Medicinal Plants Enhance Female Fecundity

Historically, plant extracts have served as alternative medicine for the prevention and treatment of numerous diseases, including female's reproductive issues (Belhaj & Zidane, 2023). Traditionally, natural remedies are employed to alleviate breast pain and dysmenorrhea, control menstrual cycles, enhance fertility, and address female infertility (Dhama et al., 2018). Plant extracts exert pharmacological effects on the female reproductive system, impacting multiple target organs, including the hypothalamus, anterior pituitary gland, ovaries, fallopian tubes, uterus, and vagina (Maggi et al., 2016). Various plant substances exhibit estrogenic, anti-estrogenic, and antinociceptive properties that enhance fertility (Tjeerdsma et al., 2023). Isoflavone chemicals included in soybean extract and licorice exhibit considerable estrogenic activity (Shamsi et al., 2020; Sakifard et al., 2022). Genistein isoflavones in soybeans, functioning as phytoestrogens, possess a structure analogous to estradiol and engage with estrogen receptors to elevate endogenous estrogen levels and influence reproductive hormone function (Mochamad et al., 2019; Tjeerdsma et al., 2023).

Numerous plant extracts have demonstrated enhancement of reproductive performance according to in vivo investigations (Subair et al., 2022). Phenolic chemicals are present in crude water extracts from Senecio biafrae leaves (Lienou et al., 2015), ethanol extracts of *Allium cepa* (Suri et al., 2024), and water extracts of *Allium ampeloprasum* (Tedongmo & Mvondo, 2024). Total flavonoids have been identified in methanol extracts of *Albizia amara* (Kassem et al., 2016) and in water extracts of *Eucommia ulmoides* (Peng et al., 2021). Additional research has detected the presence of alkaloids, tannins, phenolics, flavonoids, glycosides, saponins, anthraquinones, and steroids in the crude extracts of *Withania somnifera, Tribulus terrestris* Linn (Saiyed et al., 2016), *Plukenetia conophora* (Oladimeji et al., 2020), *Viscum album* (Oseni et al., 2019), *Fagonia arabica* (Wazir et al., 2022) and *Parquetina nigrescens* (Femi-Olabisi et al., 2023).

A primary method by which plant extracts enhance fertility is their antioxidant activity, which neutralizes free radicals and mitigates oxidative stress. Oxidative stress is recognized for its detrimental effects on cellular structures in the ovaries, testes, and embryos (Vander Borght & Wyns, 2018). In female animals, oxidative stress disrupts ovulation, follicle maturation, oocyte integrity, and the production of steroid hormones. Furthermore, excessive generation of reactive oxygen species (ROS) can harm the endometrium, impede embryo implantation, and elevate the likelihood of miscarriage (Wang et al., 2021). Various polyphenolic substances, including quercetin, curcumin, resveratrol, epigallocatechin gallate, and genistein, may mitigate the detrimental effects of oxidative stress on reproductive organs via antioxidant and anti-inflammatory pathways. The active chemicals in plant extracts enhance reproductive hormone control, facilitate folliculogenesis, and restore the estrous cycle (Mosa et al., 2023).

Specific research indicates that plant extracts may enhance reproductive parameters in test subjects. The extract of *Salvia officinalis* elevates the levels of FSH and LH hormones, ovarian mass, the quantity of de Graaf follicles, and the rate of embryo implantation in mice (Abdrabou et al., 2022). *Medicago sativa* and *Ilex guayusa* expedite sexual maturation in mice by enhancing uterine and ovarian development as well as elevating blood estrogen levels (Contero et al., 2015). Rats administered *Myrianthus arboreus* extract (110-220mg/kg, 30 days) exhibited enhanced ovulation, a pregnancy rate of 100%, and an increase in fertility index from 0 to 75% (Awounfack et al., 2018). Other studies say *Momordica charantia* increases female fertility by 20%, and also the number of implantation sites and live fetuses (Subair et al., 2022). Comparable efficacy was observed in mice administered a 50mg/kg dose of *Rumex vesicarius* seed water extract, commencing one week before mating and continuing until five days post-mating (Alhimaidi et al., 2021) and in rats treated orally with a 500mg/kg dose of *Jatropha tanjorensis* leaf water extract for 28 days (Ukoh et al., 2022). The stem bark of *Schumanniophyton magnificum*, administered at a dosage of 400-800mg/kg for 30 days, demonstrated an enhancement in the fertility rate, embryo implantation count, and a pregnancy index ranging from 80-100%, including litter size (Bend et al., 2018). The fertility effect was demonstrated by *Fagonia arabica* leaf extract at a dosage of 50mg/kg/day in Wistar rats (Wazir et al., 2022) and by *Allium cepa* at a dosage of 150mg/kg/day (Suri et al., 2024). Additionally, the incorporation of turmeric powder into the diet of albino rabbits over 235 days increased the number of offspring born and weaned (Sirotkin et al., 2018). Administration of *Glycyrrhiza glabra* extract at 100-150mg/kg for 21 days resulted in healing in PCOS mice, restoring ovarian function and reproductive performance (Shamsi et al., 2020). Additionally, *Allium ampeloprasum* extract demonstrated efficacy in infertile Wistar rats (Tedongmo & Mvondo, 2024).

Medicinal plants have demonstrated considerable potential in enhancing the fertility and fecundity of female animals, including mice and rabbits. Research indicates that the administration of plant extracts, including *Fagonia arabica, Date pollen, turmeric, Myrianthus arboreous, Rumex vesicarius, Jatropha tanjorensis, Schumanniophyton magnificum, Allium cepa, Allium ampeloprasu*m, and *Glycyrrhiza glabra*, can enhance fertility indices, pregnancy rates, embryonic development, and the number of offspring produced. The efficacy typically relies on the dosage and time of extract administration. Conversely, certain plants exhibit notable antifertility properties in pharmaceutical and reproductive health research, including neem (*Azadirachta indica*), papaya (*Carica papaya*), and *Aloe vera* (Aloe vera), which are recognized for their ability to inhibit ovulation, diminish sperm motility, or disrupt embryo implantation. Consequently, additional research is required to ascertain the safety and efficacy of its application as a natural alternative to reproductive treatments and contraception.

Impact of Medicinal Plants on the Upregulation of Reproductive Hormones

The typical reproductive system in female animals is governed by hormones from the pituitary gland, adrenal cortex, and gonads (Campbell & Jialal, 2019). During puberty, light signals are transmitted to the hypothalamus, prompting the secretion of gonadotropin-releasing hormone (GnRH) and prolactin hormones (PRH and PIH), which activate the anterior pituitary gland to release FSH, LH, prolactin, and inhibin (Dhamsaniya et al., 2016; Maggi et al., 2016). FSH is involved in oocyte creation within the follicle, whereas LH facilitates ovum maturation, ovulation, and steroidogenesis, including estradiol and progesterone, which exert negative feedback on GnRH production (Sreerangaraja Urs et al., 2020). Flavonoid chemicals, including quercetin and curcumin, regulate reproductive hormones through distinct processes that influence enzymes, hormone receptors, and oxidative stress modulation (Peng et al., 2021). Isoflavones, as flavonoid derivatives, function as phytoestrogens by binding to estrogen receptors and modulating the expression of genes involved in the estrus and ovulation cycles (Sakifard et al., 2022). Furthermore, quercetin inhibits the aromatase enzyme, which is involved in the conversion of testosterone to estrogen, thereby aiding in the maintenance of hormonal equilibrium (Mochamad et al., 2023). This process is particularly crucial in situations like polycystic ovarian syndrome (PCOS), characterized by diminished progesterone and estrogen levels alongside a notable elevation in testosterone levels (Hossein et al., 2015).

Estrogen and progesterone are the primary hormones involved in female reproductive development, fertility, the estrous cycle, and maintaining pregnancy. Additional hormones, including prolactin, DHEA, and inhibin, can influence fertility (Campbell & Jialal, 2019). Certain research indicates that extracts from medicinal plants may elevate reproductive hormone levels. *Lepidium meyenii* extract, provided to Sprague-Dawley rats for 7 weeks, markedly elevated FSH and LH levels (Uchiyama et al., 2014). The hydro-alcoholic extract of *Cucurbita pepo* and the ethanol extract of *Foeniculum vulgare* elevated serum levels of FSH, LH, estrogen, progesterone, and prolactin in Wistar rats (Sadeghpour et al., 2015; Jahromi et al., 2021). Concurrently, the treatment of *Senecio biafrae* leaf extracts and *Milicia excelsa* root extracts expedite sexual development and elevate blood estrogen levels. Comparable results were observed in infertile Wistar rats administered *Alchornea cordifolia* leaf extract, resulting in elevated levels of FSH, LH, and progesterone and enhanced oogenesis-related infertility (Ebenyi et al., 2016). The heightened modulation of sex hormones is believed to be associated with phenolic chemicals in *Senecio biafrae* extract and genistein-like activity in *Milicia excelsa* (Lienou et al., 2015; Mvondo et al., 2017).

Plant extracts have demonstrated efficacy in treating animal models of PCOS. *Myrianthus arboreus* water extract corrected LH, testosterone, total cholesterol, and LDL levels, while also decreasing body weight and abdominal fat in letrozole-induced PCOS mice (Mvondo et al., 2020).

Comparable effects were observed in *Allium ampeloprasum* extract, which elevates estradiol levels and diminishes ovarian oxidative stress (Tedongmo & Mvondo, 2024). The administration of *Eucommia ulmoides* extract resulted in enhancements in ovarian and pancreatic morphology, modulation of glucose and lipid metabolism, and elevated secretion of sex hormones via the PI3K/AKT and Kiss1/IGF-1/LEPR/AR signaling pathways within the Hypothalamic-Pituitary-Ovarian axis (Peng et al., 2021). Punica granatum juice markedly elevates levels of estrogen, testosterone and androstenedione (Hossein et al., 2015). Extracts of cinnamon and *Nigella sativa* have demonstrated the ability to reduce insulin resistance and regulate LH and testosterone levels (Dou et al., 2018; Khani et al., 2021). Curcumin derived from *Curcuma longa* reduced levels of LH, FSH, testosterone, and HOMA-IR index while elevating progesterone, estradiol, and ghrelin levels in PCOS rats (Mosa et al., 2023).

Certain phytochemical substances may elevate sex hormone levels by a process analogous to that of metformin, a medication frequently employed in the treatment of PCOS. The leaf extract of *Viscum album* can elevate levels of FSH, LH, and testosterone while reducing prolactin levels (Ofem et al., 2014). The genistein isoflavones present in the mistletoe Dendrophthoe pentandra may exhibit estrogenic effects (Lazuardi et al., 2024). Simultaneously, *Plukenetia conophora* leaf extract enhances the production of steroid hormones, including estrogen, progesterone, and testosterone (Oladimeji et al., 2020). Administration of *Nigella sativa* extract resulted in elevated levels of prolactin and estradiol, while also exerting an antidepressant effect by inhibiting dopamine activity (Khani et al., 2021). Genistein and curcumin influence the modulation of estrogen and progesterone receptors as well as the regulation of steroidogenic enzymes, thereby assisting in the equilibrium of LH and FSH levels through the enhancement of hypothalamic-pituitary axis functionality (Mvondo et al., 2017). This medicinal plant, possessing anti-inflammatory and antioxidant properties, protects the ovaries and endometrium from oxidative stress and chronic inflammation, which frequently disrupts reproductive function (Zeng et al., 2019; Khani et al., 2021). This extract mitigates insulin resistance and excessive androgen production in PCOS, consequently reinstating the normal hormonal cycle (Haslan et al., 2021; Gharanjik et al., 2022).

Impact of Medicinal Plants on Folliculogenesis and Oogenesis

Folliculogenesis is the process of ovarian follicle development from the primordial phase to the pre-ovulatory phase, which affects female's fertility and is influenced by the hormones FSH and LH (Pangas et al., 2015; Campbell & Jialal, 2019). Disruptions in this pathway, such as anovulation or follicular atresia, can lead to infertility (Oladimeji et al., 2020). Recent research shows that therapeutic plants can increase the number and maturation of healthy follicles in pathological conditions such as polycystic ovary syndrome (PCOS), which is induced in animal models with letrozole, DHEA, or estradiol valerate (Dou et al., 2018; Haslan et al., 2021; Peng et al., 2021). Oxidative stress, which plays a role in fertility issues, causes oocyte damage through ROS and lipid peroxidation, as well as disrupting granulosa cell communication (Pourjafari et al., 2020; Oladimeji et al., 2020). Phytochemicals in medicinal plants can stimulate antioxidant enzymes such as SOD and GPx to neutralize ROS, protect oocytes, and repair DNA damage during meiosis (Haslan et al., 2021; Suri et al., 2024). Thus, antioxidant phytochemicals can improve oocyte quality and fertilization success (Bend et al., 2018; Shamsi et al., 2020; Ukoh et al., 2022).

Certain medicinal herbs have demonstrated the potential to enhance follicle development and optimize ovarian structure. The extract of *Phoenix dactylifera* augmented the quantity of primary and secondary follicles in rats following 10 days of administration (Moshfegh et al., 2015). The extract of *Nigella sativa* enhances the number of Graafian follicles and corpus luteum, hence augmenting fertility (Pakdel et al., 2017). Hydroalcoholic extracts of *Foeniculum vulgare* seeds, provided during gestation and lactation, enhance ovarian weight and the quantity of primordial, primary, antral, and pre-ovulatory follicles in progeny (Pourjafari et al., 2020). The bioactive component diosgenin in this plant exhibits estrogenic activity that can promote folliculogenesis. Polyphenolic chemicals in *Senecio biafrae* were correlated with a higher quantity of primary, secondary, and antral follicles in mice (Lienou et al., 2015). Furthermore, the administration of 100mg/head/day of *Zingiber officinale* powder augmented the quantity of antral follicles, elevated VEGF levels, and enhanced the architecture of the ovarian and endometrial stroma (Yılmaz et al., 2018).

Additional research indicates that plant extracts, including *Syzygium cumini, Curcuma longa, Salvia officinalis, Cucurbita pepo,* and *Myrianthus arboreus*, exhibit pro-fertility effects by augmenting the quantity of healthy follicles and diminishing the prevalence of abnormal follicles in animal models (Awounfack et al., 2018; Prasad & Venugopal, 2020). Essential oil from *Mentha spicata* and extracts from other plants, including *Allium sativum, Calendula officinalis*, and *Viscum album*, have demonstrated efficacy in enhancing ovarian health in PCOS model mice by reducing cystic follicles and promoting the development of follicles and corpus luteum (Ataabadi et al., 2017; Falahatian et al., 2022) Phytochemical substances from medicinal plants have been demonstrated to facilitate folliculogenesis by mitigating oxidative stress, enhancing ovarian structure, boosting oocyte quality, and modulating reproductive hormones (Gharanjik et al., 2022). These findings indicate the potential application of medicinal plants in the treatment of reproductive problems, including PCOS, to enhance ovulation and increase the likelihood of successful conception (Oseni et al., 2019).

Medicinal Plants Influence the Estrous Cycle

The estrus cycle is a sequence of ovarian activity enabling females to alternate between receptivity and rejection, facilitating copulation and pregnancy (Dou et al., 2018). The cycle comprises a luteal phase, which includes metestrus and diestrus, and a follicular phase, which encompasses proestrus and estrus (Ndeingang et al., 2019). The duration of the estrus cycle varies among species and is influenced by multiple factors, including environmental conditions, temperature, illumination, and nutritional intake. Numerous compounds from medicinal plants have been shown to accelerate puberty in female animal models. The extract of Senecio biafrae can expedite puberty in prepubescent mice (Lienou et al., 2015). Wistar rats administered a decoction of Schumanniophyton magnificum bark for 30 days attained sexual maturity 5-6 days earlier (Bend et al., 2018). The water extract and methanol of Myrianthus arboreus expedite puberty, evidenced by an earlier vaginal opening, which serves as a preliminary sign of the commencement of the estrus cycle (Awounfack et al., 2018).

In an infertile animal model exhibiting polycystic ovarian syndrome (PCOS), the estrous cycle becomes irregular due to an extended diestrus phase (Femi-Olabisi et al., 2023). This condition is linked to the interruption of folliculogenesis and alterations in sex hormone levels. Numerous extracts from medicinal plants are recognized for their efficacy in regulating sex hormone levels and the folliculogenesis process in PCOS rats. The extract safeguards the histomorphometric architecture of the ovary from oxidative stress-induced damage, evidenced by reduced MDA levels and elevated SOD and total antioxidant capacity (Khani et al., 2021; Mvondo et al., 2020). The anti-inflammatory and antioxidant properties of this medicinal plant contribute to the protection of the ovaries and endometrium from damage caused by chronic inflammation and oxidative stress, which frequently disrupt reproductive function (Pourjafari et al., 2020; Haslan et al., 2021). Moreover, the bioactive constituents in botanical extracts can regulate LH and FSH concentrations by enhancing the functionality of the hypothalamic-pituitary axis (Jahromi et al., 2021). In cases of PCOS, plant extracts assist in diminishing insulin resistance and curtailing excessive androgen production, hence facilitating the restoration of regular hormonal cycles (Hossein et al., 2015; Gharanjik et al., 2022). The amalgamation of flavonoid components, including quercetin, curcumin, and isoflavones in these plant extracts, presents a potential treatment for reproductive problems such as infertility, endometriosis, and estrous cycle abnormalities.

Estrogenic Effect of Diverse Medicinal Plants

Females Estrogen in females plays a crucial role in the development of reproductive organs, regulates the menstrual cycle, and supports the function of the reproductive system (Jie et al., 2015). Moreover, estrogen influences other bodily systems, including the urinary, musculoskeletal, cardiovascular, and central nervous systems. This hormone is synthesized by the ovaries, with a minor contribution from the placenta in pregnant females (Contero et al., 2015). Estrogen comprises three primary types: estrone, which is predominant in menopausal females; estradiol, which regulates the menstrual cycle and prepares the uterine lining for pregnancy and estriol, which is significant throughout pregnancy and the preparation for delivery (Maggi et al., 2016). Low-dose estrogen therapy is advised for the management of premenopausal osteoporosis, menopausal symptoms, vaginal atrophy, hypogonadism, primary ovarian insufficiency, and prostate problems (Belhaj & Zidane, 2023).

Elevated estrogen levels in young girls result in the emergence of secondary sexual characteristics, including pubic hair growth, breast development and the maturation of the vagina and uterus, along with heightened libido (Awounfack et al., 2018). Research with young Wistar rats demonstrated an elevation in uterine and ovarian mass following the injection of ethanol extracts from *Medicago sativa* and *Ilex guayusa* (Contero et al., 2015). The estrogenic action is characterized by the thickening of the vaginal epithelial layer following the administration of *Panax ginseng* extract (Jie et al., 2015) and Milicia excelsa water extract (Mvondo et al., 2017). The amalgamation of *Allium sativum* extract, *Mango Curcuma*, and *Acorus calamus* enhances uterine weight, endometrial thickness, myometrium, and endometrial glands (Muchtaromah et al., 2020). An augmentation in wall thickness and vascularization of the endometrial stroma was noted following the administration of *Zingiber officinale* powder extract (Yılmaz et al., 2018) and *Ficus deltoidea* leaf extract in PCOS rats over 15 days (Haslan et al., 2021), thereby establishing favorable conditions for embryo implantation. Furthermore, *Schumanniophyton magnificum* extract was documented to enhance the number of embryo implantations, leading to birth (Bend et al., 2018; Subair et al., 2022).

Females with reproductive abnormalities caused by PCOS exhibit elevated ovarian weight and irregularities in the estrous cycle. Numerous medicinal plant extracts rich in potent phytochemicals have demonstrated the capacity to normalize the uterus, ovaries, and estrous cycle in PCOS animal models, including hydroalcoholic extracts of *Tribulus terrestris* and *Withania somnifera* (Saiyed et al., 2016), as well as leaf extracts of Phyllanthus muellerianus (Ndeingang et al., 2019). The estrogenic properties of medicinal plants are associated with weight regulation in animal models, a reduction in the body mass index of PCOS mice, and the mobilization and metabolism of lipids, resulting in decreased total cholesterol, LDL, and increased HDL (Femi-Olabisi et al., 2023; Suri et al., 2024; Tedongmo & Mvondo, 2024).

Conclusion

This study demonstrates that medicinal plants provide a viable remedy for reproductive issues, particularly in female animals. Bioactive substances in plant extracts, including flavonoids, polyphenols, isoflavones, and phytoestrogens, have demonstrated efficacy in regulating reproductive hormone equilibrium, inducing folliculogenesis, and reinstating the disrupted estrus cycle. Numerous *in vivo* investigations have demonstrated that medicinal herbs enhance ovarian structure, prepare the uterus for implantation, improve fertility and fecundity indices, and restore normal reproductive function, particularly in animal models of polycystic ovary syndrome. This medicinal plant has the potential to enhance cattle productivity and contribute to the conservation of endangered species. Nonetheless, the challenge encountered is the absence of criteria for establishing the dosage and duration of treatment. Consequently, additional research is required to determine the efficacy, safety, and mechanism of action of this medicinal plant. The creation of more targeted herbal formulations and the application of contemporary extraction methods can enhance its advantages as a sustainable and eco-friendly reproductive medicine.

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