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Review Article

Review on Effect of Medicinal Plants on Female Reproductive System

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ABSTRACT

Women, who account for 51% of Africa's population, face health issues including infertility. Most discussions, however, are centered on male reproductive health issues, such as erectile dysfunction, while ignoring reproductive issues that affect women of reproductive age. Plant extracts in the form of concoctions or infusions are utilized to treat a variety of diseases in this traditional medical system. Many of these plants are used to improve female reproductive health. The purpose of this review was to highlight the various mechanisms of action of known medicinal plants on the female reproductive system. The research outcomes reviewed were obtained after conducting a thorough search on scientific databases such as Science Direct, Google, PubMed, and Medline. The understanding of the effect of botanicals conventionally used on female reproductive system was extracted.Various mechanisms of action on the female reproductive system were observed for these traditional medicinal herbs and their phytochemicals, varying from folliculogenesis, upregulation of sex hormones, restoration of anomalous estrous cycle, reduction of postoperative adhesion development, and estrogenic effect, while some medicinal plants exerted antifertility effect through various mechanisms. Considering the diversification of herbal preparations use by women for various reasons, there is still much work to be done in terms of pharmacological and phytochemical characterization of traditional medicines.

***Keywords*:** Medicinal Plants; Phytoconstituents; Female reproduction; Pharmacology.

Introduction

Complications in reproductive health increase indisposition and death among reproductive women worldwide.[1,2] There have been several studies on the impact of menstrual morbidity on women's health. Menstrual complications cause low self-esteem because they affect women's education and health in low-income countries. Affected women are frequently subjected to isolation or neglect from family members.[3-5] Most discussions, however, are centered on male reproductive health issues, such as erectile dysfunction, while ignoring reproductive issues that affect women of reproductive age. The assessment and management of reproductive health conditions in women is frequently overlooked, limiting clinical research on this topic.[6,7]

Women, who account for 51% of Africa's population, continue to be the backbones of the continent's economic development.[8-10] Unfortunately, many women face health issues, including infertility. This is evident in women who are unable to conceive after l2 months of continuous sexual intercourse without the use of contraceptives. Women who have an abnormal menstrual cycle are more likely to experience infertility.[11-14] Infertility affects about 15% of reproductive-age couples worldwide.[15-18] In Sub-Saharan Africa, secondary infertility affects more than 30% of premenopausal women. Changes in hormonal levels may affect menstrual function, which in turn affects ovulation.[19-22]

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Access to safe and active medicinal plant is an effective measure for improving women's reproductive health. Treatment options in western countries, where menstrual complications and infertility are frequently presented as medical conditions, include hormonal therapy (which includes the use of contraceptives) or nonsteroidal anti-inflammatory medications. Some of these medical interventions, in addition to being out of reach for many rural women, have serious side effects. In low-income countries where medical treatments are sometimes unavailable or prohibitively expensive, particularly in rural areas, the affected women did not seek medical attention until their condition became severe. Women in these tropical countries, which are endowed with abundance of flora, prefer traditional medicines for their health issues, whether as a cure for menstrual disorders or as a means of family planning.[23-27] There is, however, little information on the effects of these medicinal plants on female reproduction. The purpose of this review was to highlight the various mechanisms of action of known medicinal plants on the female reproductive system.

These research outcomes reviewed were obtained after conducting a thorough search on scientific databases such as PubMed, Google, Medline, and Science Direct. Journals were searched for using the key words such as 'medicinal plant and female reproductive system', 'medicinal plant, folliculogenesis', 'medicinal plant, sex hormone', 'medicinal plant, adhession', 'medicinal plant, estrogenic effect', 'medicinal plant, estrous cycle' and 'medicinal plant, infertility'. This review excluded publications that linked antioxidant activity to female reproduction, while other information obtained was used in this review.

Medicinal plants' effect on female reproduction

Historically, medicinal plants have been utilized as herbal remedies and have been crucial in the treatment and prevention of disease.[28-30] This conventional medicinal approach uses plant extracts as mixtures

or infusions to treat a range of illnesses. The health of female reproduction is enhanced by the use of many of these plants. Throughout history, women have made various attempts to control or increase their fertility with differing degrees of public acceptance. Since then, plant-based medicines have been utilized for their effects on reproductive function, particularly to cure breast pain, reduce dysmenorrhea, control menstrual cyclicity, and prevent fertility (Figures 1 and 3). Health issues related to reproduction and post-reproduction have also been treated with various medicinal plant parts.[31-35] In Table 1, the impact of various therapeutic plants on female fertility is shown.

The hypothalamus, anterior pituitary, ovary, oviduct, uterus, and vagina are the locations where fertility and/or antifertility drugs are active in females (Figure 1). The reproductive system is affected by the estrogenic, anti-estrogenic, as well as antinociceptive properties of these plants. Particularly high levels of estrogenicity have been detected in phytoconstituents with estrogen-like characteristics. It is appropriate to refer to phytochemicals possessing estrogenic activity as phytoestrogens since they mimic some of the effects of estrogen through pathways mediated by estrogen receptors (Figure 2). Moreover, the amount of endogenous estrogen influences how they work.[36-44]

Folliculogenesis

The process of ovarian follicle development known as folliculogenesis begins with a reserve of dormant primordial follicles created early in life and ends with either ovulation or follicular death via atresia.[45] Folliculogenesis is essential for ovarian function because it promotes ovulation and the generation of estradiol and progesterone, two essential sex steroid hormones. Therefore, it is crucial in reproduction to understand the processes and substances that govern and control folliculogenesis.[46-47]Some medicinal plants' effect on folliculogenesis have been investigated. When the pharmacological effect of *Justicia insularis* aqueous extract on pregnancy was examined, it was shown that albino rat pre-and post-implantation losses were significantly increased. Thus, *J. insularis* aqueous extract instigates ovarian folliculogenesis.[48] Similar to how eicosapentaenoic and docosahexaenoic acids in fish oil work, flaxseed (*Linum usitatissimum*) oil and its component (α-linolenic acid) increased the proportion of oocytes that matured into blastocysts, enhancing folliculogenesis in dairy cows.[49]Both *Citrus hystrix* and the hydroethanol extract from *Foeniculum vulgare*, which was given to pregnant and lactating mice to increase offspring folliculogenesis, enhanced folliculogenesis in female albino rats.[50,51]

In polycystic ovary syndrome-afflicted rats, spearmint (*Mentha spicata*) extract decreased body weight and testosterone levels, raised corpus luteum, decreased ovarian cysts, and atretic follicles. It was discovered that spearmint can help with polycystic ovarian syndrome-related issues like high testosterone levels as well as ovarian cysts.[52] Cystic follicles decreased in letrozole-induced PCOS albino rats after administration of *Phyllanthus muellerianus*.[53] Similarly, *Calendula officinalis* hydroalcoholic extract revived folliculogenesis and increased ovulation in albino rats with PCOS and nonovulation.[54]

By causing an increase in ovarian weight, the ethanol extract of *Syzygium cumini* stem bark promotes fertility of wistar rats.[55] Aqueous extract of *Senecio biafrae* leaves and stems promoted puberty onset as well as ovarian folliculogenesis in premature female rats.[56]*Foeniculum vulgare* induced folliculogenesis as well as augmented the number of growing ovarian follicles in mice. It was proposed that diosgenin, an estrogenic component of *F. vulgare*, might be responsible for this effect.[57]*Schumanniophyton magnificum* had a significant beneficial effect on the onset of puberty, gonadotropin synthesis, and ovarian folliculogenesis in wistar rats.[58] The antioxidant quercetin, found in most fruits and vegetables, improved folliculogenesis in mice and rabbits.[59-62] The restoration of folliculogenesis to normal after treatment with *Tetracera potatoria* leaf methanol extract in PCOS albino rats may be explained by the physiological role played by apigenin in the *T. potatoria* extract, which supports the steroidal integrity and allows fertility to be recovered.[63]

Upregulation of sex hormones

During human reproduction, the endocrine system plays essential roles.[64] Estradiol and progesterone, which are produced by the ovaries and are hormones involved in female development, fertility, menstruation, and pregnancy maintenance, are important female hormones.[65]

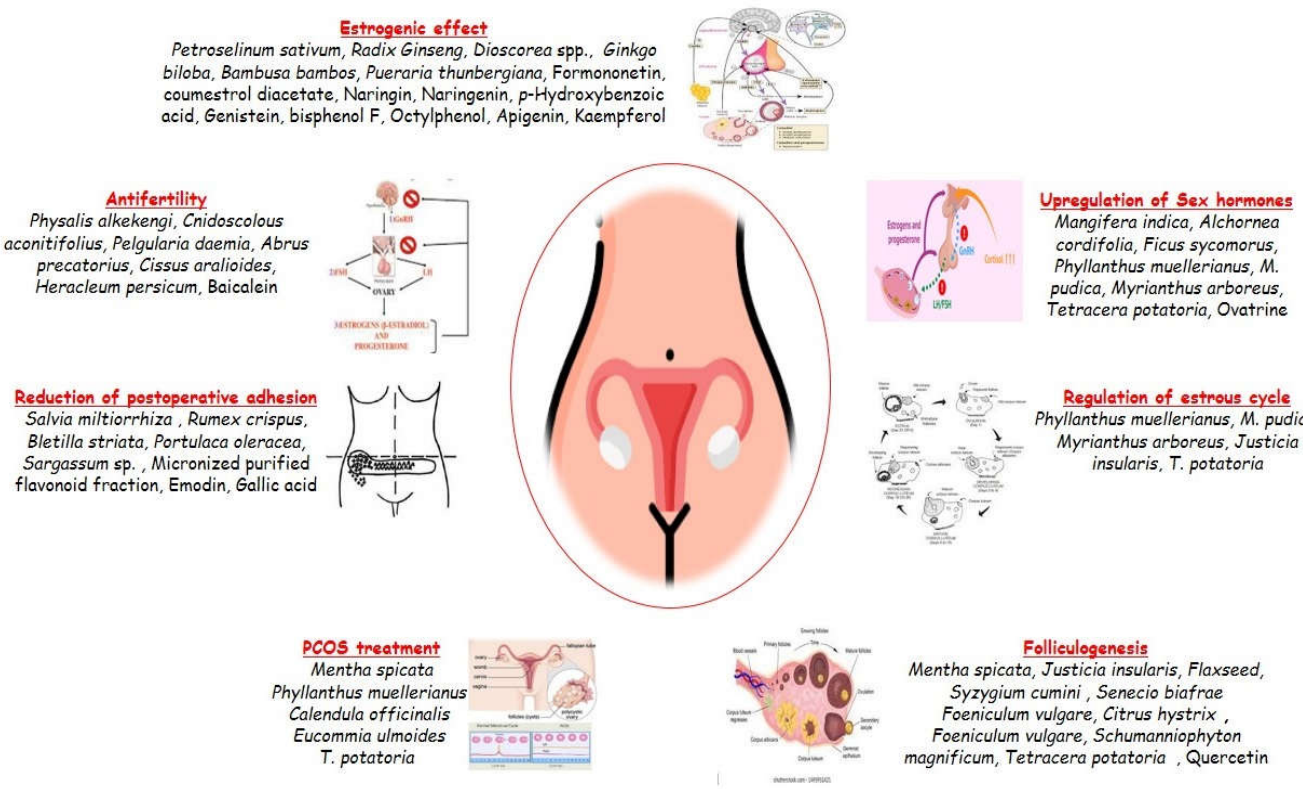


Figure 1: Mechanisms of action of botanicals reviewed on female reproduction

Table 1: Mechanisms of reviewed medicinal plants on female reproductive system

S/N	Plants	Family	Mechanisms of action
1	*Justicia insularis* T. Anders	Acanthaceae	Folliculogenesis[48]
2	*Mangifera indica* L.	Anacardiaceae	Upregulation of sex hormones[70]
3	*Foeniculum vulgare* Mill.	Apiaceae	Folliculogenesis[51]
4	*Heracleum persicum* Desf. ex Fisch.	Apiaceae	Antifertility effect[121]
5	*Petroselinum sativum* (Miller) Fuss.	*Apiaceae*	Estrogenic effect[102]
6	*Pelgularia daemia* (Forsk.) Chiov.	Apocynaceae	Antifertility effect[119]
7	*Panax ginseng* C.A. Mey	Araliaceae	Estrogenic effect[103]
8	*Calendula officinalis* L.	Asteraceae	Folliculogenesis[54]
9	*Senecio biafrae* Oliv. & Hiern	Compositae	Folliculogenesis[56]
10	*Tetracera potatoria* Afzel ex G.Don	Dilleniaceae	Folliculogenesis[63]; Upregulation of sex hormones[63]
11	*Dioscorea* spp.	Dioscoreaceae	Estrogenic effect[104]
12	*Eucommia ulmoides* Oliv.	*Eucommiaceae*	Upregulation of sex hormones[72]
13	*Alchornea cordifolia* (Schumach. & Thonn.) Müll.	Euphorbiaceae	Upregulation of sex hormones[71]
14	*Cnidoscolous aconitifolius* (Mill.) I.M.Johnst.	Euphorbiaceae	Antifertility effect[118]
15	*Phyllanthus muellerianus* (O Ktze) Exell	Euphorbiaceae	Folliculogenesis53; Upregulation of sex hormones53
16	*Plukenetia conophora* Müll.Arg.	Euphorbiaceae	Upregulation of sex hormones[76]
17	*Abrus precatorius* L.	Fabaceae	Antifertility effect[116]
18	*Mimosa pudica* L.	Fabaceae	Upregulation of sex hormones[73]
19	*Puerariamirifica* Airy Shaw & Suvat.	Fabaceae	Upregulation of sex hormones[75]
20	*Pueraria thunbergiana* (Siebold & Zucc.) Benth.	Fabaceae	Estrogenic effect[114]
21	*Ginkgo biloba* L.	Ginkgoaceae	Estrogenic effect[105,106]
22	*Mentha spicata* L.	Lamiaceae	Folliculogenesis[52]
23	*Salvia miltiorrhiza Bunge*	Lamiaceae	Reduction of postoperative adhesion development[88]

24	*Linum usitatissimum* L.	Linaceae	Folliculogenesis[49]
25	*Syzygium cumini* (S. cumini) (L.) Skeels	Myrtaceae	Folliculogenesis[55]
26	*Bletilla striata(Thunb.) Rchb.f.*	Orchidaceae	Reduction of postoperative adhesion development[91]
27	*Bambusa bambos (L.) Voss*	Poaceae	Estrogenic effect[107]
28	*Rumex crispus* L.	Polygonaceae	Reduction of postoperative adhesion development[90]
29	*Drynaria fortunei* (Kunze ex Mett.) J. Sm.	Polypodiceae	Estrogenic effect[110,111]
30	*Portulaca oleracea* L.	Portulacaceae	Reduction of postoperative adhesion development[92]
31	*Schumanniophyton magnificum* (K.Schum.) Harms	Rubiaceae	Folliculogenesis[58]
32	*Citrus hystrix* DC.	Rutaceae	Folliculogenesis[50]
33	*Sargassum* sp.	Sargassaceae	Reduction of postoperative adhesion development[93]
34	*Physalis alkekengi* L.	Solanaceae	Antifertility effect[117]
35	*Myrianthus arboreus* P.Beauv	Urticaceae	Upregulation of sex hormones[74]
36	*Cissus aralioides* (Welw. ex Baker) Planch.	Vitaceae	Antifertility effect[120]

The pituitary gland gonadotropins, FSH and LH control the generation of these sex hormones. DHEA, prolactin, and DHEA-S are other hormones that affect fertility.[66]*Ficus sycomorus* stem bark and other plant components have purportedly been used traditionally in some parts of Africa to treat sterility and infertility in both people and animals.[67,68] Nevertheless, this plant had no effect on female sexual behaviour in albino rats, implying that there is no scientific basis for the extract's use as an aphrodisiac in females.[69]In contrast, *Mangifera indica* leaves methanol extract improved serum estradiol concentrations while decreasing progesterone levels in Chinchilla rabbits.[70] In albino rats, aqueous as well as ethyl acetate extracts of *Alchornea cordifolia* induced a significant increase in testosterone, FSH, LH, and progesterone levels.[71]

Furthermore, *Phyllanthus muellerianus* decreased LH level while increasing estradiol concentration in letrozole-induced PCOS albino rats.[53] Methanol extract of *T. potatoria* leaf cured the hormonal imbalance caused by PCOS in albino rats.[63] In an albino rat model of PCOS-IR, *Eucommia ulmoides* increases the release of sex hormones.[72]*Mimosa pudica* root extract affected gonadotropin release as well as estradiol secretion in albino mice, according to the examination of the key hormones responsible for controlling the estrous cycle (prolactin, FSH, estradiol, LH, and progesterone).[73]*Myrianthus arboreus* induced early puberty, increased progesterone and gonadotropins, and induced ovarian follicle maturation in albino rats, affirming its conventional use for treating female infertility.[74] The daily administration of *Pueraria mirifica* to menopausal cynomolgus monkeys lowered gonadotrophin as well as luteinizing hormone (LH) levels while increasing follicle stimulating hormone (FSH).[75]*Plukenetia conophora* leaves aqueous ethanolic extract as well as ellagic acid treatment resulted in a significant increase in testosterone levels in female albino rats.[76] In female wistar rats, *Myrianthus arboreus* enhanced serum estradiol levels.[77] Upon receiving "Ovatrine" (an herbal formulation) twice daily for 30 days, the level of follicle stimulating hormone in the serum also increased in albino rats.[78]

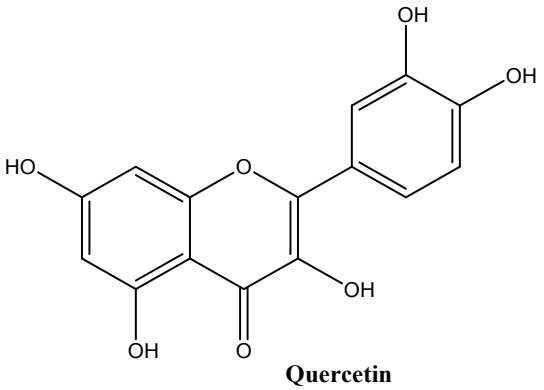
Restoration of irregular estrous cycle

The estrous cycle is the cyclical pattern of ovarian activity that allows females to transit from a state of receptivity for reproduction to one of non-receptivity, eventually enabling the creation of pregnancy after mating.[79,80] The length of the estrous cycle is reportedly influenced by the environment, heat, photoperiod, and diet.[81-82]In wistar rats, *Myrianthus arboreus* causes the estrous cycle to resume, uterine epithelial cell hypertrophy, and an increase in fertility index as well as gestation rate .[77] After 14 days of treatment, *Phyllanthus muellerianus* restored estrous cyclicity in letrozole-induced PCOS albino rats with a remarkable effect.[53] The estrous cycle in albino mice was lengthened by *Mimosa pudica* root extract when given orally at a dose of 300 mg/kg body weight/day. The duration of the diestrous phase also increased significantly.[73]In wistar rat, aqueous extract of *Justicia insularis* corrected the abnormal estrous cycle and restored fertility.[83]*Tetracera potatoria* leaf methanol extract administration improved irregular menstrual cycles in PCOS albino rats.[63] Prenatal baicalein exposure, on the other hand, was found to lengthen the estrous cycle by prolonging the metestrus and diestrus phases, resulting in a significant decrease in female fertility outcome.[84]

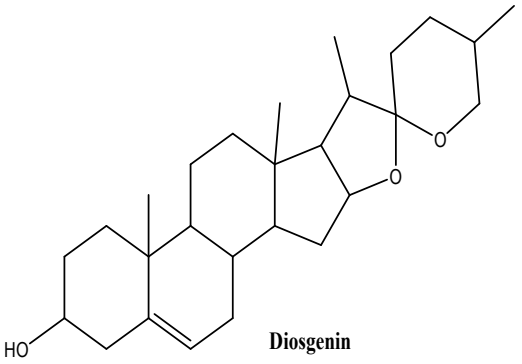
Reduction of postoperative adhesion development

Postoperative adhesion, which can cause infertility, pain, and intestinal blockage, are a normal side effect of surgical tissue trauma and recovery. There is inadequate evidence to support the claims that the use of surgical barriers improves fertility, reduces discomfort, or reduces the risk of intestinal blockage following surgery, although many of them are effective in reducing postoperative adhesions.[85-87] Peritoneal adhesions were significantly decreased by a hydroalcoholic extract of *Salvia miltiorrhiza* leaf that has antioxidant and anti-inflammatory properties. Thus, it is advised to employ *S. miltiorrhiza* as an anti-peritoneal post-operative adhesive agent.[88] Treatment with micronized purified flavonoid fraction (MPFF) intraperitoneally and orally reduced adhesion scores on both macroscopic as well as microscopic measures in albino rats.[89]In albino rats, inflammation cells, inflammatory cytokines, and adhesion scores were all decreased by *Rumex crispus* root hydromethanol extract.[90] In a rat abrasion model, *Bletilla striata* prevented the formation of abdominal adhesions and reduced the expression of a key substance that increased postoperative peritoneal adhesions.[91]

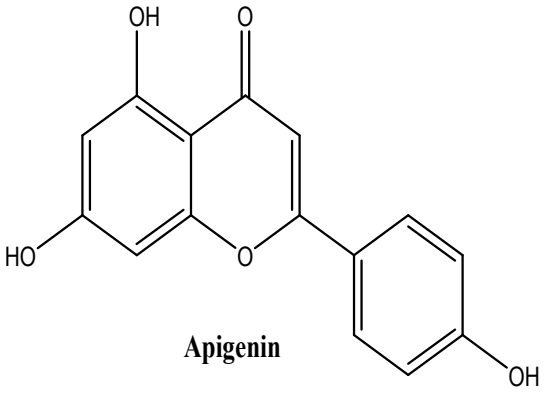
Through reduction of oxidative factors, fibrosis, inflammatory cytokines, angiogenesis biomarkers, and oxidative stress, oral treatment of *Portulaca oleracea* hydroethanolic extract improve postoperative peritoneal adhesion. *Portulaca oleracea* can therefore be considered a potential herbal remedy for the treatment of postoperative peritoneal adhesions. However, additional clinical studies are required to confirm the effectiveness of this plant.[92] Post-operative abdominal adhesions in albino rats were dramatically decreased by the use of *Sargassum* sp. aqueous extract.[93] Emodin significantly reduced the formation of intra-abdominal adhesions in a rat model.[94] Gallic acid also prevents inflammatory and fibrogenic responses, which prevents the formation of postoperative intra-abdominal adhesions in rats. For intra-abdominal adhesions, gallic acid is a promising treatment.[95] Gallic acid could be used as a treatment for adhesion band development since it decreased adhesion band formation in rats both macroscopically and microscopically.[96]



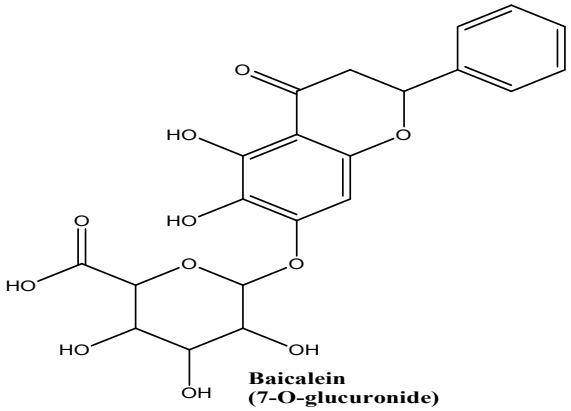
Quercetin



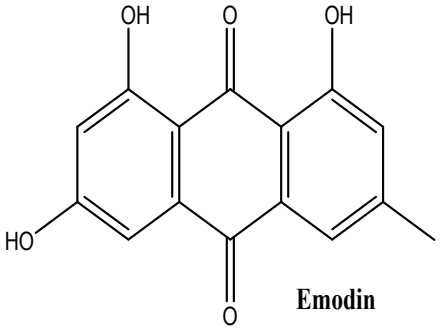
Diosgenin



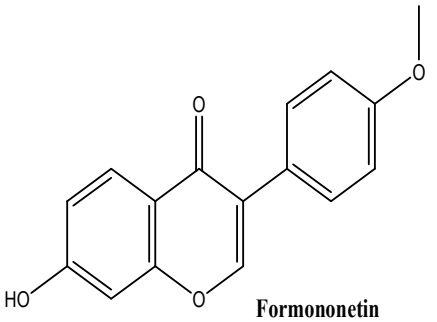
Apigenin



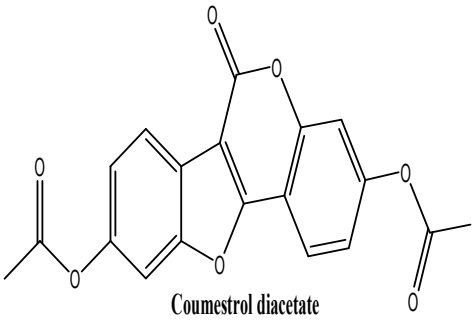
Baicalein
(7-O-glucuronide)



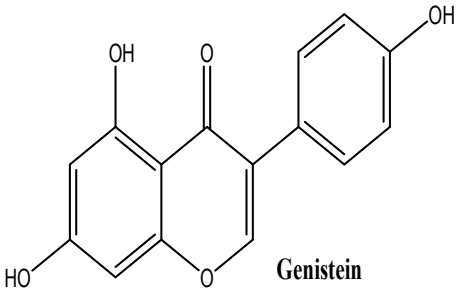
Emodin



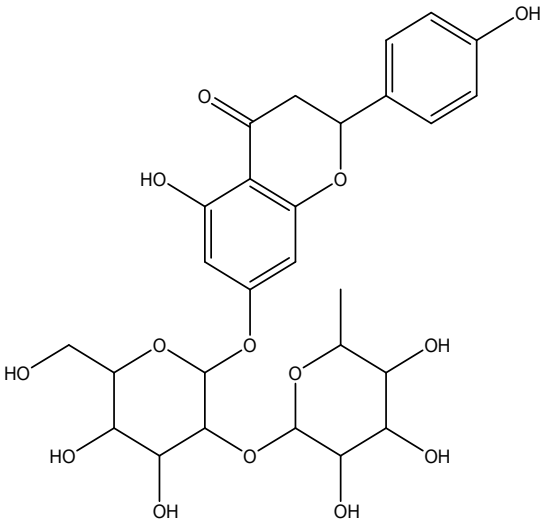
Formononetin



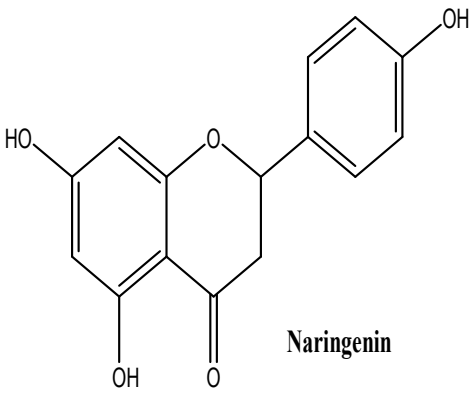
Coumestrol diacetate



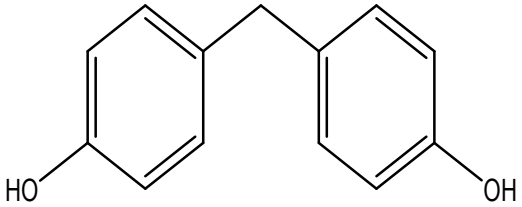
Genistein



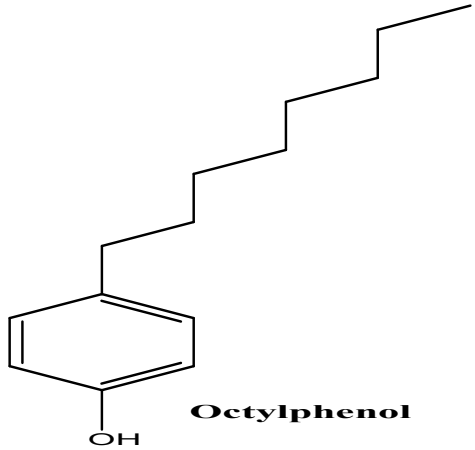
Naringin



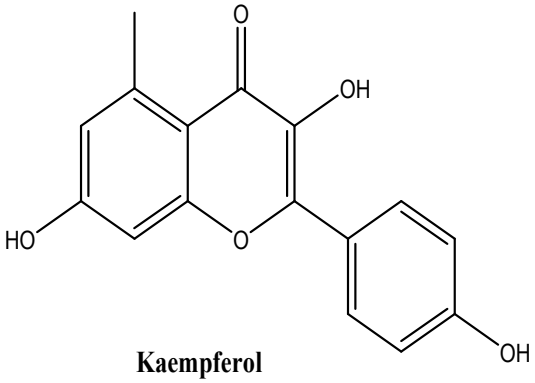
Naringenin



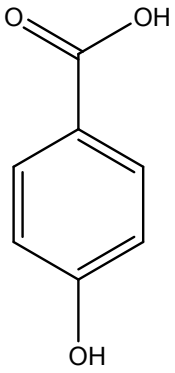
Bisphenol F
(4,4'-dihydroxydiphenylmethane)



Octylphenol



Kaempferol



p-hydroxybenzoic acid

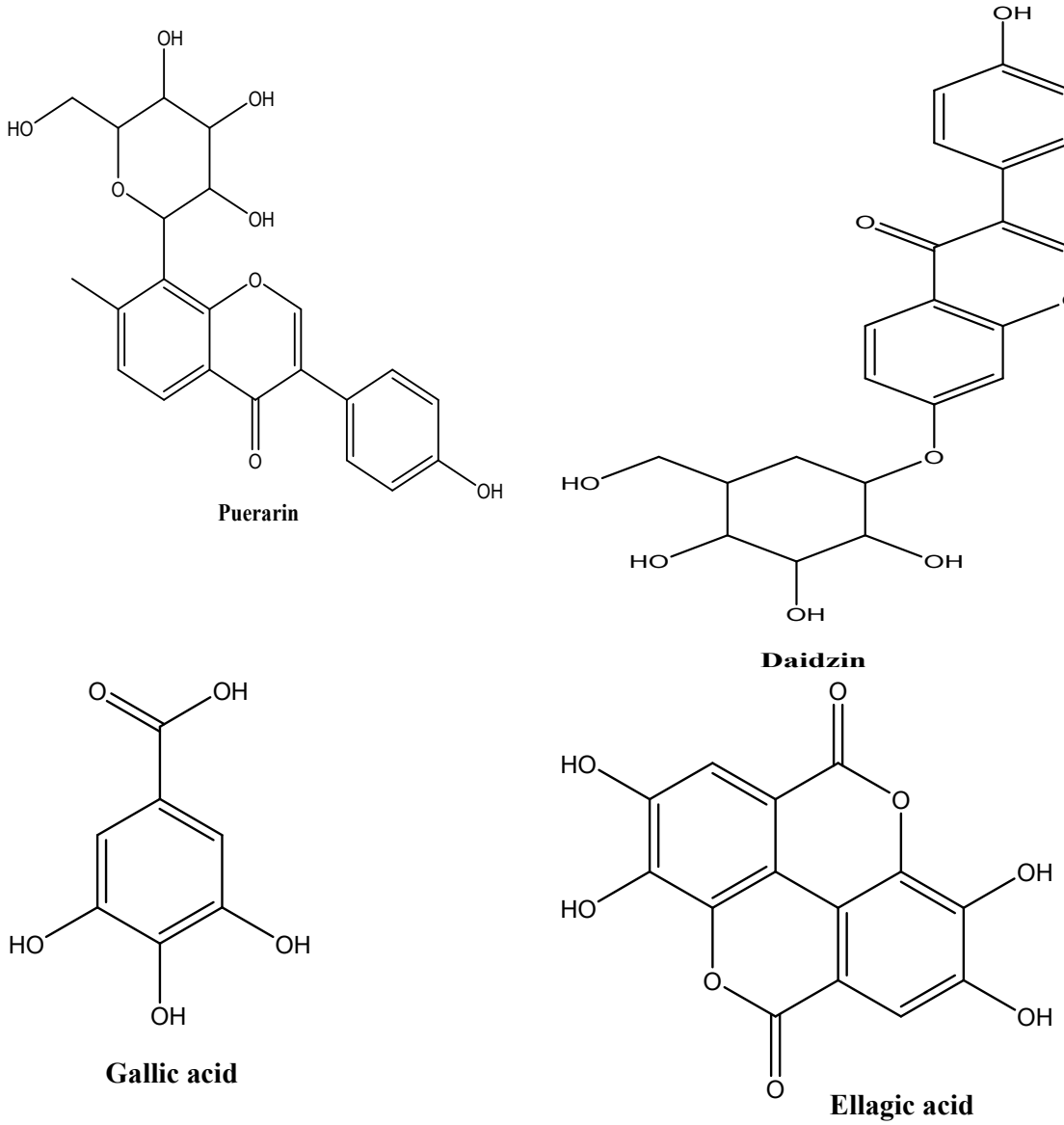


Figure 2: Reported phytoconstituents effecting female reproduction

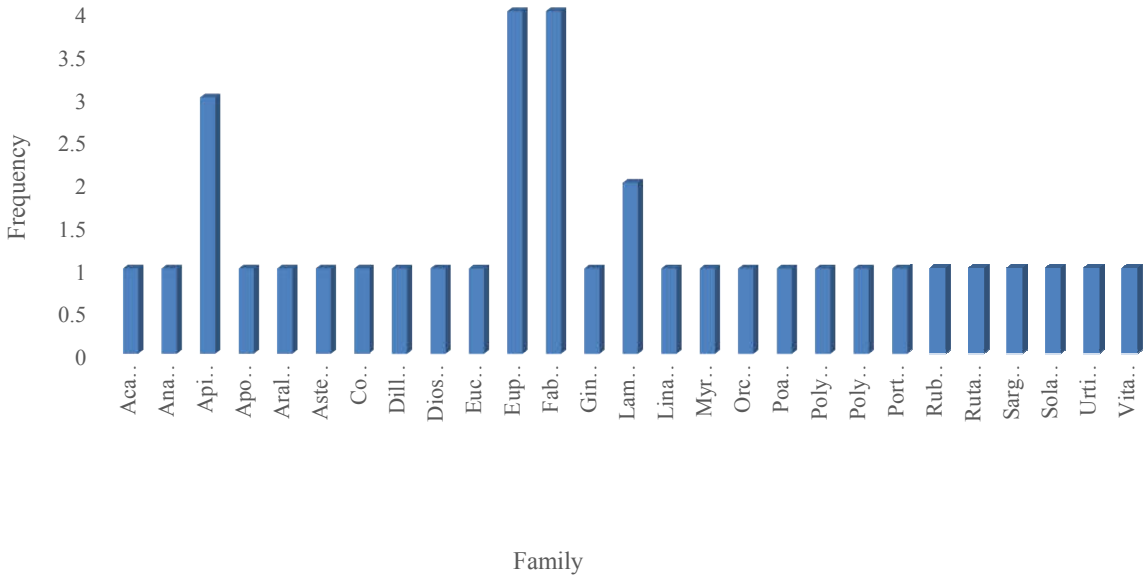


Figure 3: Frequency of family of medicinal plants reviewed on their effect on female reproduction

Estrogenic effect

The development of a woman's sexual and reproductive organs is significantly influenced by a class of hormones known as estrogens. Moreover, secondary sexual characteristics like pubic as well as underarm hair start to develop when estrogens level rise. The cardiovascular, musculoskeletal, and nervous systems are just a few of the organ systems that estrogen affects.[97,98] Although a woman's fat cells and adrenal glands also produce a little amount of estrogen hormones, her ovaries produce the majority of it.[99] In addition to its function in controlling the menstrual cycle, estrogen also affects the reproductive system, urinary system, heart and blood vessels, bones, breasts, skin, hair, mucous membranes, pelvic muscles, and the brain.[100-101] In female albino rats, *Petroselinum sativum* extract had a significant estrogenic effect.[102]*Panax ginseng* had an estrogenic effect on immature mice reproductive tissues by stimulating estrogen biosynthesis in circulation and upregulating ERα and ER_{β}.[103] Although the precise mechanism is unknown, consuming yam (*Dioscorea* spp.) in place of two-thirds of staple foods for 30 days increases sex hormone, lipid, as well as antioxidant status.[104]Ginkgo biloba and genistein demonstrated potential estrogenic activities in ERα and ER_{β}, as well as induction of the estrogen-responsive gene pS2 in MCF-7 cells, suggesting that they could be used as an effective hormone replacement therapy.[105-106] Bambusa bambos had the same effect on MCF-7 cell proliferation rates as standard 17β-estradiol. As a result, this plant extract may provide a safe alternative to estrogen replacement therapy.[107]

Formononetin demonstrated observable antioxidant and estrogenic effects in ovariectomized mice, and the estrogenic activity was not dose-related.[108] In the uterus of the ovariectomized rat, coumestrol diacetate and genistein, two non-steroid substances, were found to accelerate the incorporation of labelled precursors into protein, phospholipid, and ribonucleic acid as well as to increase acid soluble uridine triphosphate.[109] The compounds naringin and naringenin, discovered from "Rhizoma drynariae", a herbal product from *Drynaria fortunei*, showed a dual-directional role of estrogenic and anti-estrogenic actions.[110-111] Genistein, bisphenol F, octylphenol, apigenin, and kaempferol were found to be estrogenic in young albino rats during uterotrophic and vaginal cornification investigations on young and ovariectomized rats.[112] A phenolic compound, *p*-hydroxybenzoic acid, produced a dose-dependent estrogenic action in adult and immature ovariectomized mice.[113] Interestingly, *Pueraria thunbergiana* has been shown to exhibit strong estrogenic action when exposed to intestinal bacteria that can hydrolyze puerarin and/or daidzin.[114] Also connected to an increased risk of type 2 diabetes, hypertension, and dyslipidemia is an irregular amount of endogenous estrogens or exposure to environmental estrogens.[115]

Antifertility effect

Abrus precatorius extract demonstrated anti-implantation effect as well as the propensity to impair gross foetal morphometry in Sprague-Dawley rats, despite the successful mating of female rats with high-fertility male rats on the twelfth day of treatment. Uterine dissection on postcoital revealed no implantation or resorption sites in any of the treated animals.[116] Administration of *Physalis alkekengi* extract during the first five days of pregnancy in albino rats significantly decreased the number of implantation sites as well as the number and weight of newborns.[117]When *Cnidoscolous aconitifolius* leaf extract was administered, serum levels of prolactin increased while levels of estradiol, progesterone, follicle-stimulating hormone, and luteinizing hormone decreased. The extract appears to have a detrimental effect on follicle growth and ovulation based on its effects on female rat reproductive hormones. As a result, the extract might prevent female rats from becoming pregnant.[118] By altering the estrous cycle, *Pelgularia daemia* extract and its steroidal constituents have been demonstrated to have antifertility activity in mice.[119]In Sprague-Dawley rats, the methanol extract of *Abrus precatorius* seed inhibited ovulation while disrupting the estrous cycle in normally cyclic rats.[116] The hydroalcoholic extract of *Heracleum persicum* suppressed

folliculogenesis and resulted in infertility in females, whereas the aqueous leaf extract of *Cissus aralioides* lowered circulating estrogen levels in female Wistar rats.[121]

Conclusion

Rich in diverse flora, the tropical forest remains to provide ingredients for the development of new medicinal products.Various mechanisms of action on the female reproductive system were observed with these traditional medicinal herbs and their phytochemicals, varying from folliculogenesis to estrogenic effect, while some medicinal plants exerted antifertility effect. Considering the diversification of herbal preparations use by women for various reasons, there is still much work to be done in terms of pharmacological and phytochemical characterization of traditional medicines.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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