ANNALS OF MULTIDISCIPLINARY RESEARCH, INNOVATION AND TECHNOLOGY (AMRIT)

(A peer-reviewed open access multidisciplinary journal)

www.adtu.in/amrit

REVIEW ARTICLE

REPRODUCTION

Female Reproductive Health - Regulating Hormones and Phytosteroids as Alternative Modulator: A Review

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Article Chronicle: Received: 08/05/2023 Accepted: 29/05/2023 Published: 26/06/2023

Abstract

Female reproduction in mammal is a neuroendocrine regulated system governed by ovarian steroid hormones, hypothalamic-pituitary peptides and its target tissues. It is an integrated functional phenomenon of hypothalamus-pituitary, ovary and finally the nonendocrine uterine tissue. Adult female mammal undergoes reproductive cycle during which ovarian hormones and the uterine tissue work together in a coordinated manner for successful gestation. The ovarian steroids estrogen and progesterone plays the pivotal role in successful completion of pregnancy. Impaired ovarian steroid functions caused due to various reasons may lead to infertility as well as female reproductive health disorder. To overcome such health problems, phytosteroid could be used as an alternative steroid agonist and/ or antagonist as and when necessary. Phytosteroids could bind with the native ovarian steroid receptors and impart its effects on the target tissues. During last few decades a number of phytosteroids have been reported which may have the possibility of being used as hormone replacement therapy. Infine, phytosteroids could be alternative drug source for development of nonsteroidal contraceptive beneficial for women reproductive health.

Keywords: *Female Reproductive Health, Phytosteroids, Ovary, Estrogen, Progesterone*

1 Introduction

Reproductive health of women is determined by the feminine physiological condition that enables the individual to attain motherhood and well-being of the reproductive system and its functions. Throughout her life, women pass through many changes of physiological phases beginning with the attainment of puberty and ending with menopause through pregnancy. During the period, reproductive health encompasses proper functional integration of hypothalamus-pituitary gonadal interaction, ovarian function of oocyte maturation, ovulation, uterine cellular proliferation and internal biochemical milieu, healthy menstrual cycle maintenance and finally uptake of gestation. These entire phenomena are maintained under the integration of gonadal steroid hormones and its feed back to releasing and tropic hormones from hypothalamus and pituitary. Mothers' health during pregnancy is crucial for both pre and neonatal development and health of child. The female reproduction is maintained under the control of gonadal hormones, the estrogen and progesterone. The hormones estrogen and progesterone are endocrine chemical messengers; exert effect on target cells of different tissues elsewhere in the body. These two hormones are the prime regulators of the reproductive function. The modern contraceptive is based on the manipulation of status of these two hormones by introducing exogenous hormonal therapy as birth control device. One of the most popular birth control devices is the hormonal oral contraceptive used by the women all over the world. Yet, there are still numerous challenges in contraceptive development for fertility regulation and development of hormonal therapy with respect to reproductive health of women. Use of such hormonal therapies (steroids) was reported to invite unknown complications and side effects(1). Consequently, search for a new medicinal product still continues to improve and develop an effective and safe alternative to conventional hormonal therapy. Estrogen and progesterone- the two prime regulators of female reproduction are very often manipulated for reproduction regulation

process like contraception. At the same time alteration of synchronized balanced release of ovarian hormone may lead to reproductive disorder causing failure of implantation as well as other related problems. Some other problems related to the reproductive health of women are anomalies of hormonal functions in their target tissues. Imbalance of hormones causes physiological problems that affect directly or indirectly the women's health. The failure of the ovary to produce estrogen results in hot flashes, and/or sleep disturbances, accelerated bone loss, increased risk of colon cancer and weight gain. These effects have been accompanied by shifts in plasma lipoprotein, cholesterol profiles associated with a higher incidence of cardiovascular diseases(2), ovulation disorder, polycystic ovary syndrome (PCOS)(3), abnormal cervical mucus, premature menopause etc.(4). Failure of hormonal synchronization is tackled with conventional hormone replacement therapy (HRT) replacing estrogen(5). Phytotherapeutic management of endocrine dysfunctions allows hormone free choices for addressing conditions associated with PCOS(6), menopause(7), breast cancer(8), endometrial carcinoma etc.(7).

World Health Organisation (WHO) designed a draft strategy to the resolutions adopted by 55th World Health Assembly to improve reproductive health of women all over the world demanding reproductive health care and cure and prevention of sex related diseases (WHO, 2004). Understanding of the mechanism by which the plant-derived substance(s) affect the biological system will allow individuals with more hormone-free options that significantly impact quality of life and risk of diseases. Following this principle of hormone free options a growing number of women turned to use herbal remedies to solve their feminine problems(9)(9; 10). As desired, this specific drug should be effective enough to cause the purpose, physiologically safe with low toxicity without any side effects, reversible in action and easy to use. It has been speculated that herbs may fulfill the demand of such a safe and effective contraceptive and be the alternative to the synthetic hormonal therapy. Many plants have been evaluated to develop a safe novel drug to be used for replacing conventional hormonal therapy including the contraceptive medicine. The plant possesses a kind of compound(s) that shows similar action of ovarian hormone particularly the estrogen in the estrogen responsive tissues. These substances are termed as 'phytoestrogen', interact with the estrogen receptors in the way the ovarian estrogen does in the cells of estrogen responsive tissue of reproductive organs and exerts effect similar to the estrogen. The uterine endometrium is the estrogen responsive tissue undergoing proliferation and differentiation under the influence of the ovarian estrogen. Similarly, administration of phytoestrogen induces the proliferation and differentiation of the uterine endometrium. Several phytoestrogens have been isolated so far and evaluated its estrogenic effects on both animal models and human being. Genistein, pueranin, diadzein, coumestrol etc. are some of the phytoestrogens isolated from various plants in recent years. With the ability to alter the hormonal status of the estrogen responsive tissue, these phytosteroids may disrupt the normal function of the reproductive organs. In contrast, many phytoestrogens have beneficial effects on prevention of cancer, maintenance of menopausal symptoms and bone mineral density, cardiovascular disease, obesity etc.(11; 12)(11; 12). Discovery of such non steroidal compound(s) may lead to development of a new health friendly drug as an alternative conventional hormonal contraceptive and alternative of hormone replacement therapy.

2 Approaches to Non-Steroidal Drug Development for Reproduction Regulation

The changing interest of developed and developing countries in the natural resources have opened a new horizon of drug development on the basis of traditional knowledge with the perspective of safety and efficacy. Medicinal plants are traditionally used for the reproductive health problems either as profertility or antifertility drug by the people of different societies all over the world. The knowledge on medicinal system prevails for centuries among the folk people of different part of the world. Very often, this indigenous knowledge are available as oral literature, while in the country like India these knowledge were scripted in the form of valuable ancient literature e.g., Ayurveda. With the advancement of time and development of modern medical science, this traditional crude medicine of herbal origin has drawn attention of the scientific communities across the world. Various Governmental and non Governmental organizations all over the world initiated the process of documentation of these medicinal plants for human and animal welfare. In this regard the World Health Organization plays a pivotal role in exploration, utilization and protection of these traditional medicines exists among the people of various societies in different countries. The WHO's "Traditional Medicine Strategy 2002-2005" dramatically increased the pace of research on herbal products among the scientists of the world community. On the basis of WHO special programme in search of herbal solution for female reproductive problems, research has been carried out in many developed and developing countries including United States, South Korea, England, China, India, Indonesia, Brazil, South Africa etc. for finding a new lead of herbal derivatives. As a result, a multitude of fertility regulatory phytocompounds have been reported from various countries of the world to address the female reproductive health problems and contraceptive medicines. China, the most populous country of the world has been brought with for the discovery of some compounds for fertility regulation in female. 'Yuehchukene' (YCK), an indole alkaloid has been isolated from the root of Chinese medicinal plant *Murraya peniculata*. However, the YCK was failed to develop as a antifertility drug as it showed low level of estrogenicity reviewed by Fabricant and Farmsworth (13). Many other phytocompunds viz. 'Trichosanthin' and 'Yuanhuacine' having abortifacient properties have been isolated from Chinese medicinal plants *Murraya peniculata* and *Daphne genkwa* respectively(14). Studies in western medicinal system revealed use of plant products 'hyoscine' and 'ergometrine' having effects on uterus used for obstetrics and gynaecological problems(15). Around seventy traditionally used Ethiopian plants subjected to uterotonic and antiimplantation bioassays have been reported with antifertility activity(16). Similarly, *Pelago Indians* of Argentina have tradition of using herbal drugs with antireproductive activity(17). Two marine red algae viz., *Gelidiella acerosa* and *Gracilaria corticata* have been reported

as the useful source of potential postcoital contraceptive drugs from Sri Lanka(18; 19). Dried leaves of *Casia nigricans* is used for family planning by the 'Rukuba' community of 'Jos metropolis'(20).A folk medicine '*Pergularia daemia*' is used by the rural people of Bangladesh to induce abortion(21). The Ethiopian herb *Rumex steudelii*(22) and *Achyranthes aspera*(23) have been reported to possess antifertilty property in albino rats. An indigenous contraceptive herbal formulation consisting of a mixture of *Lepidagathis longifolia*, *Palaquium* sp. and *Phyllagathis rotundifolia* was used by the Temuan Aborigins of Malaysia(24). The uterolytic effect of traditional abortifacient medicine *Hypoxis hemerocallidea* of South Africa has been demonstrated(25). Caribbean folk medicines comprising a numbers of plants including *Achyranthes indica*, *Coleus aromaticus*, *Hibiscus rosa-sinensis*, and *Scoparia dulcis* with many other potent medicinal plants are used for curing reproductive problems in Trinidad and Tobago(26). The medicinal plant *Aspilia africana* has the reputation for contraception among the 'Mbaise' and most 'Igbo' speaking parts of Nigeria(27). Embryotoxic effect of *Cissus sicyoides*, popularly known by its antidiabetic action in Brazil has been reported to be embryotoxic in rats(28). Embryotoxic property of another plant *Acanthus montanus*, used in folk medicine of Cameroon was observed in albino rats. The aqueous extract caused appreciable preimplantation loss and delayed fetal growth(29). A group of European scientists has reported that *Rhaponticum carthomoides*, a perennial herb used for centuries in eastern part of Russia exert effects on reproduction and sexual function(30). These plants tested in various laboratories of the world as mentioned above have furnished a strong background of ethnomedicinal knowledge in terms of feminine problems. Screening of such medicinal plants may provide information regarding non-steroid estrogenic compound(s) with the capabilities to manipulate ovarian estrogen with safety and efficacy to be used as an alternative to conventional hormonal therapy.

3 Indian Medicinal Plant Research for Fertility Regulation

India harbors a rich diversity of plant species with huge varieties of medicinal plants. The scientists of Indian subcontinent have reported a number of medicinal plants for fertility regulation during twentieth century. A multitude of Indian plants for unspecified antireproductive activity has been documented and mentioned in different literature during last few decades(31; 32; 33; 34; 33; 35; 36; 37; 38). Antifertility properties of various plants like *Piper longum, Lawsonia inermis, Abrus precatorius, Curcuma longa, Embelia ribe, Plumbago rosea, Hibiscus rosa sinensis, Ferula jaeschkeana, Azadiracta indica, Carica papaya, Moringa oleifera* etc. have been reported by these authors. The dimension of this research has been increased and changed with the report of potential herbal derivatives and their target specific effects for fertility regulation by the beginning of 21st century. Aqueous extract of seeds of Indian plant '*Cassia fistula*' showed antiimplantation activity in female rats(39). The 'bark' of an Indian herb '*Alangium salvifolium*' showed antifertility effect in female wistar rats(40). A composite root extract of five plants viz. *Plumbago rosea, Dolichos lablab, Shorea robusta, Carica papaya* and *Cannabis sativa* has been found to induce reversible sterility in albino rats effecting the ovarian follicle and endometrial surface epithelium(41). The widely used rhizomes of turmeric *Curcuma longa* is a potential Indian traditional medicine for the development of a novel intravaginal contraceptive(42). The 'Curcumin' from the *Curcuma longa* has been reported to be a potential vaginal contraceptive(43).

Ethnomedicinal survey of the tribal areas of southern Rajasthan uncovered 53 plants belonging to 33 families which are used to cure sexual diseases and use for family planning(44). These studies illustrate the importance of different parts of the medicinal plants in curing reproductive health problems. The tribe 'Chenchus' living in the forest of Nnallamalais in Kurnool district of Andhra Pradesh, used the root of *Pentanema indicum* for abortion(45). Pregnancy interceptive property of root extract of *Melia azedarach*(46) and *Calotropis gigantea*(47) have shown in vivo in albino rats. Docking analysis of 'rohitokene' an alkaloid isolated from the active chloroform soluble fraction of bark of *Dysoxylum binecteriferum* showed contraceptive property. This study revealed that the 'rohitokine' with almost similar molecular size (MW 305kD) as estradiol-17β appears to fit ideally into the hydrophobic pocket of estrogen receptor(48). The plant *Wrightia tinctoria* with ethnomedicinal background for various ailments found in Madhya Pradesh, Rajasthan, Tamil nadu has been reported for promising antifertility activity. A series of fractions prepared with non polar and polar solvent of bark of *Wrightia tinctoria* showed 100% anti-implantation activity(48). India has the sufficient amount of information on the herbal contraceptive to define the status of herbal legacy in traditional knowledge system. There are still a large number of territory remained to be explored that may lead to discovery of new herbal solution for fertility regulation.

The north east region of India being one of the richest zones of biodiversity gifted with majestic Himalayan range harbouring wide varieties of flora, has exceptionally higher potentiality in the medicinal plant sector(49). The Government of India has set up the Traditional Knowledge Digital Library (TKDL) to protect Indian Traditional knowledge on various aspects including the Traditional Medicines. Data on 65,000 formulations in Ayurveda, 70,000 in Unani and 3,000 in Sidha had already been entered in TKDL. The North-East region of the Indian sub-continent is one of the Biodiversity Hotspots of the World enriched by large number of medicinal plants. Like many other population of different countries, the indigenous people of North-East India also practices a good number of herbs for therapeutic uses. Numerous indigenous tribal groups of the population inhabiting this region have their own traditional medicine system that uses the available plants in this Eastern-Himalayan Mega Biodiversity. It has been reported that around 300 plants are being used for treating various diseases in the traditional healthcare system of North-East Indian states (De, 2016). Among these plants, 65 have been reported from Meghalaya, 82 from Assam, 33 from Arunachal Pradesh, 38 from Manipur, 30 from Sikkim and 25 from Tripura. In Arunachal Pradesh, 60 numbers of plants have been used by the inhabitants of Lohit and Dibang Valley districts(50).

The use of 34 herbs by the Apatani tribe of Ziro Valley of Arunachal Pradesh has been reported by(51). One hundred seven plant species have been reported to be used by different tribes from the Cachar district of Assam(52). The study reveals the use of 50 plant species only for curing skin diseases in Assam(53). A survey by(54) reported the use of 51 plants by ethnic people of Tripura. In Assam and Arunachal Pradesh, the use of traditional herbal preparation for female reproduction regulation is an age-old practice among the indigenous people. It has been reported that oral administration of traditional herbal preparation can cause structural disorganization of the ovarian follicle and uterine endometrial epithelium(41; 55). Several plants have been used for the regulation of female reproduction in domestic animals(56).

4 Phytocompounds' Estrogenic Property

Phytoestrogens are a family of non-steroidal chemically diversified plant-derived compounds having the effect on mammalian tissues similar to that of the ovarian estrogen(57) . They may mimic or/and interact to the estrogen hormones in mammalian tissues. These groups of compounds are categorized on the basis of their structural resemblance with estrdiol-17β. Isoflavones, coumestans, Lignans, are the major phytoestrogens while there are many other phytoestrogens with structural diversity having estrogenic activity(12). Estrogenic effect of herbs in reproductive system was first reported with adverse effects on mammalian development and fertility from observations of animals consuming phytoestrogen-rich plants. Ewes grazing on estrogenic pasture rich in subterranean clover developed breeding problems in Western Australia(58). The traditional herbal medicines used for controlling reproduction have adverse estrogenic effects on target organs and application of such herbal medicines for desired women terminate pregnancy and may cause abortion. Estrogenic effects of such herbal medicines have been widely investigated to formulate new product with safety and efficacy to control reproduction and other feminine reproductive ailments like menopausal symptoms, menstrual disorder etc. Screening of such herbal medicines show the effect of such medicines on vaginal epithelial cyclicity, endometrial receptivity, implantation, follicular development etc. Very often these phytoestrogens exert their effects on vagina, uterus by acting as an endocrine disruptor. They exert estrogenic effect by binding to the estrogen receptor with varied affinity(59; 60). Most phytoestrogens bind to the estrogen receptors with lower affinity than estradiol-17β (61) and are weekly estrogenic. The genistein, daidzein, coumestrol are weak estrogen as compared to Estradiol-17β (62). These weak estrogens act as estrogen agonist and mimic ovarian estrogen inducing cellular proliferation, maturation, cornification in estrogen responsive tissues. An indigenous herb of Thailand '*Pueraria mirifica*' contains phytoestrogen 'deoxymiroestrol' and isoflavones such as daidzin, and genistein(63). Such isoflavones were also isolated from the red clover '*Trifolium pratense*' (64). Extract of Red clover *Trifolium pratense* increases the uterine weight dose-dependently and induce vaginal cornification showing estrogenic effect in Sprague-dawley rats(65). The effect of *Pueraria mirifica* was postulated to estrogenic on reproductive system in both sexes of rats(66). The ethanol extract of *Hibiscus rosa sinensis* showed estrogenicity in immature albino rats(67). Orally administered soy extract proliferates the uterus of ovariectomised rats(68) and soy rich diet shows higher maturation value of vaginal epithelial cells revealing the estrogenicity of the soy food(15).'Resveratrol' a phytoestrogen available in the grape, induce vaginal epithelial cell maturation in ovariectomized rat(69). An estrogenic compound isolated from the plant '*Humulus lupulus*' induced proliferation of vaginal and uterine mass of epithelial tissues and the compound has been identified as 8-prenylnaringenin(70). The phytoestrogens may have antiestrogenic effect; they may block or alter estrogen receptors binding affinity acting as estrogen antagonist(12). The balance between the estrogenicity and the antiestrogenicity is dependent on the hormonal milieu. For example, coumestrol rich diet induces onset of estrous cycle prepubertally in immature female, whereas same dose of diet inhibits ovarian cycle in adult female rats(71). These phytoestrogens with different binding affinity to the estrogen receptors (ER) compete with the ovarian estrogen (E2) and alters the normal functions of reproductive tissues such as ovarian follicles, uterine and vaginal epithelial tissues and may explain the fertility regulatory activity in mammals. The mechanism of action of phytoestrogen involves more than one aspect of molecular response. The phytoestrogen may elicit genomic estrogenic response by binding to the estrogen receptor (ER)(72). It may modulate epigenetic estrogenic response by influencing protein kinase A action and intracellular calcium (C2+) mobilization(73; 74). There are many evidences that phytoestrogens may disrupt the endocrine system and may act as endocrine disruptor both in animals and humans(75). Administration of 1000 mg of suspension of tuberous root powder of the *Pueraria mirifica* increased the levels of both FSH and LH after 1 weak of treatment in OVX female wistar rats(66). The 'coumestrol' has profound effect to inhibit Gn-RH-induced LH release in vivo and reveals a concomitant hypothalamic site of action(76). Dietary genistein exerts estrogenic effect involving hypothalamic-pituitary axis in rats(77) and can modulate the prostagland in production(78). The phytoestrogens have been proposed to have potentiality for prevention and treatment of vascular disease(79) and to cure menopausal symptoms(11). The researches on the estrogenic compounds and their biological effects on animal and human are still required to evaluate the beneficial effect of the phytoestrogens.

5 Phytoestrogens and Their Mechanism of Action

The mechanism of action of phytoestrogens has been already reviewed by various researchers(80; 81; 82; 83). It has been stated that various phytoestrogens can communicate the signals using different alternate pathways in tissue and cells. Phytoestrogens are able to interact with ERα and ERβ and can act either as agonists or antagonists depending on the presence or absence of 17β-estradiol(83).Numerous phytoestrogens are selective estrogen receptor modulators (SERMs) that are found to have a higher affinity for ERβ than ERα(82). Moreover, phytoestrogens also act via other signaling pathways that include non-genomic signal-

ing which is mediated by oxidative stress pathways, tyrosine kinases, nuclear factor-kappaB and extracellular signal-regulated kinases(84; 85). In addition, phytoestrogens also serve as the ligand to the peroxisome proliferator-activated receptors, the non-classical estrogen receptor GPER1 (previously GPR30), estrogen-related receptors and Aryl hydrocarbon receptor(86; 80; 87; 85). Phytoestrogens along with directly modulating signaling pathways can also alter the activities of DNA and histone methyltransferases, NAD-dependent histone deacetylases and other modifiers of chromatin structure(88; 81; 83). They can also competitively inhibit the production of 17β-Estradiol by aromatase(89; 83) leading to a low level of endogenous 17β-Estradiol. For the determination of the molecular pathway of action, one of the major problems has been the presence of these compounds as a mixture in the source that can act either through a single or multiple pathways. It has been found that when exposed to genistein the morphogenesis of oviduct in neonates were disrupted due to alteration in the hedgehog signaling pathway and expression of transcription factors like homeobox genes. This causes the oviduct to become posteriorized (expresses genes and proteins normally observed only in posterior regions of the reproductive tract (i.e cervix and vagina) and abnormal expression of genes like homeobox transcription factors, Pitx1 (Paired-like Homeodomain 1) and Six1 (Sineoculis homeobox homolog 1) have been observed. Microarray analysis of gene expression of oviduct on day 2 of pregnancy further showed that significant changes occurred in inflammatory response pathways pointing towards the alteration in the immune response of oviductal mucosa that can possibly impact survival and development of the embryo(90). Early vaginal opening and an initial increase in uterine wet weight during the time of treatment followed by decrease in adult uterine weight has been seen in coumestrol treated neonatal rats(91) and DES (Diethylstilbestrol)-treated neonatal mice(92). Administration of coumestrol during the postnatal period (Days 10 to 14) has shown lesser endometrial glands and reduced expression of estrogen receptor in adults(93; 91). It has been reported that exposure to DES in prenatal mice increases the similar changes in Hoxa10 methylation has been found in case of prenatal exposure of genistein and daidzein(94). High doses of genistein exposure to ovariectomized adult rats caused a decrease in methylation of the steroidogenic factor 1 promoter causing increased expression of this gene in the endometrium(95). These discussed observations decipher that brief exposure to phytoestrogens could induce effects on reproductive tissues' functions when exposed during the prenatal developmentally sensitive period.

6 Phytosteroids as Beneficial Effects or Endocrine Disrupter

The multi-faceted regulation of reproduction begins with the ovarian regulation. The estrogen released by the ovaries largely determines the reproductive system's preparedness to move to the next stage of fertility(96). For decades, the basic aspects regulating the female reproductive cycle have been broadly understood, including a regulation hierarchy incorporating the hypothalamic/anterior pituitary/ovarian axis. The hypothalamus stimulates anterior pituitary synthesis of gonadotropins- luteinizing hormone and follicle stimulating hormone, which operate on the ovaries to promote follicle development, ovulation, corpus luteum formation, and release of the sex steroid hormones estrogen and progesterone. These two gonadal steroid hormones have well-documented effects on the female reproductive tract. A balance of the gonadal steroid hormone negative and positive feedback regulation of gonadotropin secretion is at the core of the female reproductive cycle. Both estrogen and progesterone signaling pathways are linked to gonadotropin feedback control and female reproductive cycle regulation(97). Estradiol, as the primary estrogen, acts as a growth hormone for reproductive organ tissues, is involved in the development of secondary sex characteristics in females, and plays a significant role in bone structure maintenance. The female menstrual cycle is influenced by progesterone, the primary progestogen(98). Progesterone is essential for both creating a favourable endometrial environment for embryo implantation and promoting and maintaining pregnancy(99). Progesterone is a crucial reproductive hormone that operates on the estrogen-primed endometrium to produce favourable conditions for embryo implantation and pregnancy maintenance(100). The genomic actions of estrogen and progesterone in the target cells are mediated by interactions with distinct intracellular nuclear receptors. Steroid hormones binding to their receptors causes structural and functional changes in receptor, culminating in the interaction of ligand- receptor complexes with specific target genes to regulate their transcription(101). Steroid hormones are frontline regulators of diverse biological responses, both physiologically and clinically. Steroid hormones perform by way of their downstream effectors(101). Estrogen (E2) and Progesterone (P4) are chief regulators of female reproduction, the former induces the proliferation of the endometrial cells during the proliferative phase while the later is responsible for the differentiation of endometrial cells into the secretory phase(98). E2 and P4 have two receptor subtypes 'α', 'β' and 'A', 'B' respectively. During proliferative phase, the estrogen receptor α (ER-α) is expressed by endometrial epithelial and stromal cells whereas the expression of ER-β is limited to glandular epithelium cells. Similarly progesterone receptor A (PR-A) is expressed in the uterine stroma and epithelium during proliferative and secretory phases whereas the PR-B is expressed in glandular and stromal nuclei only during proliferative phase of the menstrual cycle. To acquire the receptive state of the uterus the maternal steroid hormones i.e E2 and P4 stimulate some specific temporal modification(100). In recent years, structure, origin and nature of phytosteroids have been researched in various laboratories through different angles across the globe. Various definition, route and mechanism of action in health issues in addition of reproductive health have been formulated. Infine, phytosteroids are some plant-derived non-steroidal compounds that show similar properties towards estrogen and progesterone by binding with their respective receptor molecules in cells called the phytosteroid. Some of these plants possess compounds that show similar actions towards ovarian hormones. These compounds mimic hormonal action with distinct characteristics and modulate different categories such as estrogenic, antiestrogenic, androgenic or antiandrogenic hormonal function(102). These molecules interact with the

estrogen and progesterone receptors with their respective responsive tissues. They work in metabolic pathways either blocking or mimicking the native hormones in the body. Phytosteroids bind with the steroid hormone receptor and form analog receptor complex (ARC) and mimic the function of the original hormone–receptor complex (HRC). Sometimes these hormone analogues bind with the receptor competitively and block the hormone binding sites and produce an antagonistic effect in the target cells. There are various routes through which a phytosteroid can enter our body, some are via food, skin or mucous membranes(103). The endocrine disruptors give the perception of the compounds being hazardous. The phytosteroids act as the modulators of the estrogen and progesterone receptors are not always harmful though they disrupt the ongoing endocrine function. There are large numbers of phytosteroids which have the ability to act as steroid hormones agonistically or antagonistically. As compared to other disruptors the phytosteroids have proved to have beneficial effects in different ailments. The compounds identified from plants are healthier alternative to the synthetic steroids prevailing in the market. These molecules present in ethno-medicinally important plants can be projected as the valuable medicines to help in treating various reproductive related diseases in women(104).

7 Conclusion

Phytosteroids are plant derived specialized chemicals that bind to steroid receptors in animals and can either activate or suppress downstream receptor-mediated signaling cascades. Phytosteroids have varied structures, often different from the endogenous steroid; yet, they can behave as agonists, antagonists, or frequently have mixed agonist/antagonist action for steroid receptors. Furthermore, certain phytosteroids interact with multiple steroid receptors or interfere with steroid metabolising enzymes, resulting in profound impacts on the endocrine system as well as the reproductive system(105). Phytosteroids can be natural endocrine disruptors having both endocrine disruptive and endocrine function modifying properties. Plants produce a variety of chemicals that are structurally and functionally comparable to vertebrate hormones. Animals exposed to these hormonally active photochemicals (HAPs) have a variety of consequences on their behaviour, physiology, and reproduction. Phytochemicals are one of the most varied families of molecules to which humans are constantly exposed. Phytoestrogens are plant-derived substances with estrogenic characteristics that work through estrogen receptor signaling pathways by mimicking or modifying estrogen receptors. Phytocompounds that act through the estrogen and progesterone hormone receptors can be either agonists or antagonists. There are many reports on the plant derived compounds that act on target cells of animals and mediate beneficial effects in treatment of various ailments by endocrine modulation(104).

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