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HERBAL CONTRACEPTIVES: EVALUATION OF ANTIFERTILITY POTENTIAL OF *HIBISCUS ROSA-SINENSIS* (LINN.)

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ABSTRACT

This review explores, evaluates, and analyzes the contraceptive potential of *Hibiscus rosa-sinensis* L. There are large numbers of synthetic contraceptives available in the market. These synthetic contraceptives are associated with many side effects ranging from user discomfort to toxicity. India is a land of traditional herbal medicines. People are finding and exploring the advantages associated with herbal contraceptives because of their lower side effects. Herbal contraceptives have lower cost of development as compared to modern medicine. This review explores the recent advances in development that offers many benefits for shifting the paradigm for herbal contraceptives. From times immemorial, references have been made for the plants that possess antifertility properties. This review explores the need for the development of herbal contraceptives from the plant *H. rosa-sinensis* L. *H. rosa-sinensis* L is reported to have antiovulatory activity. However, the need of the hour is to assess and carry out toxicological studies and initiate development activity for formulation development.

Keywords: Contraceptive, Herbal, *Hibiscus rosa-sinensis* L, Antifertility.

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INTRODUCTION

India being developing nation is still not able to cope up with the demerits of high population growth. There are a large number of devices, mechanisms, and techniques adopted for antifertility treatment. However, still people are very apprehensive to use synthetic chemicals and procedure because of long term after effects and side effects. Moreover, the procedures adopted to treat antifertility are irreversible in nature. Contraception is one of the proximate determinants of fertility and the most important predictor of fertility transition [1,2]. Family planning as a strategy for population stabilization received attention only after 1971 population census [3]. After the launch of the National Rural Health Mission (NRHM) in 2005, the official family planning program has been subsumed in the Reproductive and Child Health (RCH) component of the mission [4].

However, universal adoption of small family norm still remains a distant dream in India. During 2007–2008, only about 54% of the currently married women aged 15–49 years or their husbands were using a contraceptive method to regulate their fertility [5] and the contraceptive prevalence rate appears to have stagnated after 2004 [6]. Reproductive health is intricately linked to issues of women's and children's health, the spread of sexually transmitted diseases, poverty, education, gender equality, and human rights [7]. Improving access to reproductive health is thus central to the process of development, as reflected in sustainable development goal [8].

Investment on family planning has multiple returns: Demographic, health, social, and economic benefits at individual, familial, and societal levels. Improved access and use of family planning improves child survival, reduces unwanted pregnancies and abortion, and improves health of mother and children [9]. Despite strong benefit of contraception, the pattern and use of contraception vary largely across countries. In developing countries, though the use of any contraceptive method has increased from 44% in 1980 to 61% in 2009, the unmet need of contraception remains high, the method mix of contraception remains skewed, the quality of care of family planning services remained poor, and contraceptive discontinuation remained high [10-12]. To large extents, the unintended pregnancies are attributable to contraceptive discontinuation due to method failure and abandonment of contraception while being in the need [13]. In countries passing through demographic transition, a further decline in fertility depends on the consistent, correct, and effective use of contraception [14,15]. The contraceptive discontinuation varies greatly by the level of overall contraceptive use and by type of methods. The contraceptive discontinuation was lowest among intrauterine device (IUD), and implant users followed by injectable, condoms, and oral contraceptive users concluded that the method choice is endogenous to discontinuation [16-19]. The reasons associated with contraceptive discontinuation can be broadly categorized into four groups: Method-related reasons, contraceptive failure, reduced need, and non-method-related reasons. Among method-related reasons, health concerns and side effects were frequently cited by pill and IUD users, whereas accidental pregnancy was frequently cited among traditional method users [20,21]. The differentials in failure rates were largely due to differences in service delivery, user characteristics, and defining the failure rates [22]. In the United States, the failure rates for implants and IUDs were lowest, and it was highest for the traditional methods and spermicides [23]. Lack of adequate counseling and partner disapproved the use of method were more likely to discontinue a method [24].

India's demographic transition is of global significance due to its size (accounting 17% of global population) and large variation in demographic and health parameters within the country. Furthermore, the country has launched the largest flagship program, the NRHM, in 2005, to improve the utilization of RCH services in the country and achieve the demographic targets, and fertility trends are diverging across states and districts of India [25].

However, the use of modern spacing method has not increased in India. This is further confirmed by reduction in the use of modern contraceptive method in 10 of the 15 states for which the key indicators from the National Family Health Survey-3 have been recently released [26].

In a recent study on contraceptive use in India, 13 distinct groups that need programmatic attention to improve the family planning services and less focused on the post-adoption contraceptive behavior [27-32].

Shortly after the introduction of oral contraceptives, reports of adverse side effects associated with their use began to appear. Many of the side effects were found to be dose-dependent, and this led to the development of current low-dose preparations. Untoward effects of early hormonal

contraceptives fell into several major categories: Adverse cardiovascular effects, including hypertension, myocardial infarction, hemorrhagic or ischemic stroke, and venous thrombosis and

embolism; breast, hepatocellular, and cervical cancers; and a number of endocrine and metabolic effects [33].

There are various adverse effects associated with contraceptive pills and injectables including increased cholesterol levels, weight gain, headache, hypermenorrhea, depression, fatigue, and intermenorrheal bleeding. Since these are hormones, they also disbalance the metabolism of lipids, proteins, carbohydrates, enzymes, and vitamins [34]. The World Health Organization (WHO) suggested that effective, locally available plants be used as substitutes for drugs [35].

Although there are a large number of plants reported to have antifertility potential, even then, very few plants are explored for their long-term effects and therapeutically evaluated for toxicity analysis. The main problem lies in evaluating the active constituents in herbal extracts, batch-to-batch variations, and understanding their mode of action [36].

More than 35,000 plant species are being used in various human cultures around the world for medicinal purposes. Nearly 80% of the world populations rely on traditional medicines for primary health care, most of which involve the use of plant extracts [37,38].

From the advancement of reproductive biomedicine, several hormonal contraceptive pills have been developed but no one is free from different side effects for this purpose, the WHO has constituted a population control program, which includes studies having traditional medical practices. At present, global attempt has been taken to search out the effect of herbal product for contraceptive purposes [39].

Hence, there is a need for searching suitable product from indigenous medicinal plants that could be effectively used in the place of pills. All combination oral contraceptives contain both an estrogenic compound and a progestin. Over the years, the amounts and types of these components have changed in attempts to lower side effects and improve efficacy [40].

Herbal contraceptives are a category of herbs that have an antifertility effect. There are many different ways in which herbs can impair fertility. Some herbs may affect the ovary, while others act on the uterus, affect normal hormone production, or block certain hormones. For several of these, we do not really understand their action or how they got their reputation. Some herbs have the ability to interfere with implantation; these herbs can be taken on as needed basis and are used as an emergency contraceptive. There are also some herbs that have been found to interfere with normal sperm production or mobility. Each herb is used in its own way, so it is important to have some idea of how they are used or could be used [41].

Some herbal contraceptives have a cumulative effect in the body; they need to be taken regularly to maintain the contraceptive effect. Often needing a period of time to establish effectiveness, so a barrier method should be employed [42].

There is sufficient evidence in humans that combined oral estrogen-progesterone contraceptives are carcinogenic in nature. This assumption has made by increased risk for cancer of breast, cervical, and liver. However, experiments in animals have provided inadequate evidence for the carcinogenicity of progesterone, LNG, norgestrel, or progestin-derived contraceptive pills. These contraceptives act as LH receptor (LHR) and progesterone hormone receptor (PGR) inhibitors and thus in long-term usage interferes with the ovulation cycle which results in premature ovulation or delayed ovulation. However, herbal compounds have been found to work as partial inhibitors of LHR and PGR, and at the moment, they are being removed from the system, and the ovulation cycle is retained. Collectively, there is a need to work for herbal analogs of these contraceptives which can be effective as well as safe [43].

This review explores the antifertility potential of the plant *Hibiscus rosa-sinensis* L. The best advantage of having herbal resources is that their action is reversible and they do not possess side effects to the body which leads to better patient compliance. The present article focuses on the contraceptive potential of *H. rosa-sinensis,* for enhancing the research potential in the development and evaluation of a herbal contraceptive.

DESCRIPTION

H. rosa-sinensis (Family Malvaceae) is an ornamental plant. It grows as an evergreen herbaceous plant. It bears large flowers on the bushy hedges. These enormous flowers are usually red in color and are not usually fragrant. Different cultivators and hybrids have been produced and developed with flowers ranging in colors and other features. The flowers have been reported to possess antiimplantation and antispermatogenic activities. The flowers have been reported to possess antiimplantation and antispermatogenic activities. The pharmacological effects of different parts of the plant HIBISCUS ROSA-SINENSIS (LINN.) as reported in the literature is mentioned in Table 1.

In Ayurveda, *Hibiscus esculentus* L. fruits are considered tonic, astringent, and aphrodisiac. In Unani medicine, the fruits are considered emollient and useful for treating urinary disorders [44].

The leaves and roots of *Hibiscus manihot* L. are used as a poultice for boils, sprains, and sores, and the flowers are used to treat chronic bronchitis and toothache. The mucilage of the bark is considered to be an emmenagogue [45].

The seeds of *Hibiscus abelmoschus* L. are valued for their diuretic, demulcent, and stomachic properties and are considered stimulant, antiseptic, cooling, tonic, carminative, and aphrodisiac. The bark, flowers, and fruits of *Hibiscus bauiferus*. J.G. Froster are used externally for the treatment of skin diseases such as eczema, scabies, psoriasis, and ringworm. In Ayurvedic medicine, the bark is the official source of the drug "parisha," a reputed remedy for skin diseases.

According to the literature, many *Hibiscus* species have been investigated and found to contain many classes of secondary metabolites, including flavonoids, anthocyanins, terpenoids, steroids, polysaccharides, alkaloids, amino acids, lipids, sesquiterpene, quinones, and naphthalene groups. Some of these compounds have been shown to have antibacterial, anti-inflammatory, antihypertensive, antifertility, hypoglycemic, antifungal, and antioxidative activities [46-52].

Common name: Gudhal.

Family: Malvaceae.

Chemical constituents [77]: Steroids, tannins, saponins, and flavonoids [53].

Activities [77]: Antispermatogenic and antiandrogenic activity [54 56,77].

Extract used [77]: 50% ethanolic extract and benzene and benzene/ether extract of flowers were showed antifertility activity [53-55].

Animal models [77]: Rats [55], non-scrotal bat [54], and mice [56] used for assessing antifertility activity of *H. rosa-sinensis*.

Table 1: Pharmacological effects reported from different parts of the plant HIBISCUSROSA-SINENSIS (LINN.) (25)

Pharmacological effects	Extract	Part used	Dose
Abortifacient effect	Ethanol (95%), water, and petroleum ether extracts	Leaves, flowers, roots	200 mg/kg
Acid phosphatase stimulation	(50%) ethanolic and benzene extracts	Flowers	150 mg/kg
Alkaline phosphate inhibition	Benzene and ethanol/water (1:1) extracts	Flower	75.0 mg/kg
Analgesic activity	Ethanol extract (70%)	Dried leaves	125 mg/kg
Androgenic effect	Benzene and ethanol (95%) extracts	Dried flowers	250 mg/kg
Anticonvulsive effect	Ethanol extract	flower	-
Antifertility effect	Ethanol (95%) extract	Dried flowers	750 mg/kg
Antifungal activity	Ethanol/water (50%) extract	Dried leaves	-
Antigonadotropin effect	Benzene extract	Dried flower	250 mg/kg
Antiimplantation effect	Benzene extract	Dried flowers	250 mg/kg
Antipyretic activity	Ethanol (70%) extract	Dried leaves	100 mg/kg
Antispasmodic activity	Ethanol/water (1:1) extract	Ariel part	-
Antispermatogenic effect	Benzene extract dried	Dried flower	250 mg/kg
CNS depressant activity	Ethanol/water (1:1) extract	Ariel part	500 mg/kg
Anti-inflammatory activity	Ethanol (70%) extract	Dried leaves	100 mg/kg
Antiviral activity	(80%) ethanol extract	Freeze dried plant	-
Antiestrogenic effect	Benzene extract	Dried flowers	250 mg/kg

CHEMICAL CONSTITUENTS [78]

H. rosa-sinensis plant extracts contain alkaloids, glycosides, fatty materials, reducing sugars, resin, sterols, and the lack of tannins and saponins [78]. Isolation of β-sitosterol, taraxeryl acetate, and four uncharacterized compounds which included an alkaloid and three sterols has been reported in the leaves [78]. The leaves of *H. rosa-sinensis* were also investigated for their fatty alcohol, fatty acids, and hydrocarbon content [58]. Two cyclic acids, namely, malvalic and sterculic are also identified [57,78].

Flowers contain vitamins, flavonoids, ascorbic acid, niacin, riboflavin, thiamine, and cyaniding diglucoside [78]. Quercetin-3-diglucoside, cyanidin-3-sophoroside-5-glycosides, 3,7-diglucoside, cyanidin-3,5-diglucoside have been isolated from deep yellow flowers [58].

PREPARATION OF BENZENE EXTRACT

Preparation of extract

All the flowers were shade direct at room temperature and finely powdered with the help of mixer grinder. About 150 g of the powder was extracted with benzene. The extract was concentrated to a residue. The crude extract was used for further testing for its phytochemical compounds [59,79].

The benzene extract of *H. rosa-sinensis* flowers was administered intraperitoneally at the dose levels of 125 and 250 mg/kg body weight to adult mice and resulted in an irregular estrous cycle with prolonged estrus and metestrus [79]. An increase in the atretic follicles and the absence of corpora lutea indicate the antiovulatory effect of the extract [79]. The extract also showed estrogenic activity in immature mice by early opening of the vagina, premature cornification of the vaginal epithelium, and an increase in uterine weight [79]. Therefore, the antiovulatory effect may be due to an imbalance in the hormonal environment, as there may be an increase in the endogenous secretion of estrogen by atretic follicles and also to the estrogenicity of the flower extract [60,79,80].

Japakusuma **(***H. rosa-sinensis***)**

Alcoholic extract of flower exhibited significant 50–60% inhibition of pregnancy at 200 mg/kg dose [80]. Benzene extract (total) produced 100% antifertility effect in 250 mg/kg [61,80]. Alcoholic extract of leaves and branches caused 30% antifertility activity only [80]. Flowers of the plant caused abolition of regular estrus cycle in rats [80]. The ethanol extract of flower was devoid of antifertility effect, i.e. antispermatogenic, antiovulatory, antiimplantation, and abortifacient activity at 400 mg/kg, p.o. day. Benzene extract of flower of *H. rosa-sinensis* in 100 mg/kg exhibited post-coital antifertility effect in 80% of treated female rats [62,80].

The drug is having antifertility and antispermatogenic and antiestrogenic activities [63-67,80]. Benzene extract of flower in 250 mg/kg from day 1 to day 10 of pregnancy in rats was found most effective to prevent pregnancy.

THERAPEUTIC EVALUATION

Reproductive potential of *H. rosa-sinensis*

The effect of *H. rosa-sinensis* linn. on the estrous cycle and reproductive organs was studied in female albino rats [64]. Depending on the dose and duration of treatment, the benzene extract of the flowers disrupted the estrous cycle [64]. Treatment for 30 days resulted in a significant ($p<0.05$) reduction in the weight of the ovaries, uterus, and pituitary gland [64]. Ovarian follicular atresia and uterine atrophy were observed. Treatment resulted in degranulated gonadotrophs in the pituitary, with the extent of damage being dose-dependent [64]. Ancient literature mentions the use of a number of plants/preparations for fertility regulation [76]. Some local contraceptive agents have also been described in Ayurvedic and Unani texts [76]. Documented experiments or clinical data are, however, lacking [76]. Therefore, the present study was undertaken to explore the antifertility and estrogenic activity of ethanolic extract of the roots of *H. rosa-sinensis* linn. [76]. A strong antiimplantation (inhibition 100%) and uterotropic activity were observed at the dose level of 400mg/kg body weight [76]. Histological studies were carried out to confirm this effect [65,78].

Antispermatogenic and androgenic activities

The oral administration of benzene extract of *H. rosa-sinensis* flowers (250 mg/kg daily for 30, 45, and 60 days) was found to affect spermatogenesis as well as the endocrine function of the testis as studied by weight changes, histology, and biochemical estimations [78]. The effect of extract on spermatogenesis ranged from mild damage of germinal epithelium to nearly total sloughing depending on the duration of treatment. Similarly, reduction in weight of the testes, accessory sex organs, and pituitary was observed [78]. The alkaline phosphatase in ventral prostate, citric acid content in seminal vesicles, and dorsolateral prostate fructose concentration were also reduced [78]. The accessory reproductive organs showed loss of secretory activity while pituitary showed degranulation of gonadotrophs [78]. However, these effects were reversible after discontinuation of treatment. It seems probable that the effects of the drug are mediated through pituitary [66,76].

Antiovulatory and antiestrogenic activities

Japa flowers (*H. rosa-sinensis*) is to be given orally in the form of paste along with *kanji* (rice gruel) and 400-year-old *guda* (jaggery) in the dose one *pala* (48 g) for 3 consecutive days during menstruation [67]. Antiovulatory and antiestrogenic activity has also been discussed and described in Bhavaprakasa of bhavmisra Vidyotini hindi commentary by Brahmasanker misra.

In mouse, oral administration of the benzene extract of *H. rosa-sinensis* flowers at a dose level of 1 g/kg body weight/day from day 5 to 8 of gestation led to termination of pregnancy in about 92% of the animals [67]. The effect was associated with a significant fall in peripheral level of progesterone and increase in uterine acid phosphatase activity, as measured on day 10 [67]. The ovary exhibited signs of luteolysis, and the corpus luteal delta 5–3 beta-hydroxysteroid dehydrogenase activity decreased markedly [67]. The interceptive effect of the extract was prevented completely by exogenous progesterone (1 mg/mouse/day) or chorionic gonadotropin (1 I.U./mouse/day) and partially (62.5%) by exogenous prolactin (500 µg/mouse/day) [22]. In unilaterally pregnant mouse having trauma-induced deciduomata in the sterile horn, the extract caused resorption of the fetuses, and regression of the deciduomata accompanied by reduction in weight of the ovaries [67]. Luteolysis may be due to interference with the luteotropic influence, and a consequent fall in plasma level of progesterone has been suggested as the plausible cause of termination of pregnancy [67].

Antiimplantation activity

H. rosa-sinensis flowers have been shown to possess antifertility and abortifacient activity [68]. In this report, anti-implantation activity of water extract of leaves of *H. rosa-sinensis* was investigated [68]. Pregnant female mice were dosed with extract (100 mg/kg body weight) from days 1 to 6 of pregnancy [68]. No implantation sites were observed in treated animals when they were surgically opened on day 15 of pregnancy. Biochemical and biophysical alterations were observed in the endometrium in treated animals, especially on day 5, at 4:40 a.m., the day of implantation [68]. A sharp increase in superoxide anion radical and a sharp fall in superoxide dismutase (SOD) activity, as seen in the endometrium from control animals, were altered in treated animals [68]. The extract also exhibited antiestrogenic activity, as judged by increase in uterine weight [68]. The physiological alterations induced by water extract of *H. rosa-sinensis* are discussed [68].

Many plants are known to possess antifertility activity [68]. However, limited attempts have been made to scientifically evaluate these claims [68].

Therapeutic evaluation

There are also important new findings concerning the antiherpes simplex virus activity of Mangifera indica, the anti-Parkinson's activity of Mucuna pruriens, the antiviral activity in Phyllanthus niruri and Jatropha curcas, the hyperthyroid regulation properties of Moringa pterygosperma, and the antioxidant activity of Mangifera indica, Punica granatum, Psidium guajava, and Allium sativum. Allium sativum is highlighted for its treatment of unstable angina pectoris, sickle red blood cell dehydration inhibition, senescence ameliorative, chemoprotective, cardiovascular, antineoplastic, anticarcinogenic, and antiatherogenic effects.[70] In a clinical trial, treatment of 21 women at reproductive age group with ethanolic extract of H. rosa-sinensis flowers at 750 mg/kg body weight/ day in 3 doses, from 7th to 22nd day of menstrual cycle [72], 14 women did not have pregnancy for 4 years, whereas 7 women dropped out of the trial [71,72]. The trials were also conducted with Vidangadi yoga (a herbal preparation containing Embelia ribes seeds, H. rosa-sinensis flowers, and Ferula foetida oleo-gum resin) for antifertility activity, and the drug was found to be quite effective without any harmful effects [71].

Evaluation of the herbal medicinal plants has been in progress for several decades to identify effective and safe substances for fertility regulation. Several medicinal plant extract were investigated for their antifertility activity both in male and female animal models. [73]

Hibiscus rosa sinensis possess many properties and this plant may procured at large scale for providing herbal alternative to many diseases. The phytochemical screening on qualitative analysis shows that the plant is rich in alkaloids, terpenoids, flavonoids, glycosides, reducing sugar, Fatty materials, saponins, gums and mucilage. [74]

he benzene extract of Hibiscus rosa sinensis flowers was administered intraperitoneally at the dose levels of 125 and 250 mg/kg body weight to adult mice and resulted in an irregular estrous cycle with prolonged estrus and metestrus. An increase in the atretic follicles and the absence of corpora lutea indicate the antiovulatory effect of the extract. The extract also showed estrogenic activity in immature mice by early opening of the vagina, premature cornification of the vaginal epithelium and an increase in uterine weight. Therefore the antiovulatory effect may be due to an imbalance in the hormonal environment, as there may be an increase in the endogenous secretion of estrogen by atretic follicles, and also to the estrogenicity of the flower extract.[75].

For antifertility activity, the percentage fertility on female mice for control, 500 mg/kg and 1000 mg/kg were 100%, 20% and 33.33%, respectively. Histopathology study showed abnormality effects on ovaries for higher dose concentration and size decrease effects on fallopian tubes which are responsible for antiimplantation. These results indicate that *Sida cordifolia* produced mainly abortifacient activity and antiimplantation activity [79].

In a study carried out for the evaluation of antifertility potential of *Portulaca oleracea* L. in female albino rats, it was found that the weights of the ovary and uterus of both low and high doses increased when compared to control group. The increase in the wet weight of the ovary in the extract-treated animals compared to the control animals may indicate inhibition of ovulation through suppression of follicular-stimulating hormone [80].

TOXICITY ASSESSMENT

Treatment with ethanol/water (1:1) extract of the aerial parts, administered intraperitoneally to both sexes of mice, produced LD50 1.0 g/kg [72].

Why herbal contraceptives lagging behind the modern pill? This is an obvious question that comes in our mind. Several factors are responsible for this. One major factor is that it is impossible for us to say how effective they are as the information are remain scarce and fragmented and transmitted orally among ethnic people. The model animal-based scientific description of very little number of plants is available till now. Furthermore, very little is known about long-term side effects associated with these herbal preparations. Although many plants have birth controlling bioactive compound, standardization of these compounds as birth controlling drugs remains a challenging task. The concentration and potential of active constituents of a plant are variable according to the variation in season and biogeographical regions. Hence, the reliability of herbal contraceptive remains uncertain, and people do not show much interest in this "eco-friendly" birth control option [81].

CONCLUSION

This review summarizes the traditional values and antifertility activity of *H. rosa-sinensis*. Through the vast literature supports and researches, it is very clear that the plant possessive antiimplantation property. Since there is a huge scope of development of herbal contraceptives, these medicinal plants should be formulated and developed into herbal contraceptives which are easy to use, causes least discomfort and have no side effects. It is suggested to explore the detailed mechanism of action and effects on reproductive organs and the changes in hormone levels. It possesses a huge potential for the development of natural contraceptive which can be a great boon to the society.

The plant kingdom holds many species of plants containing substances of medicinal value that have yet to be discovered. A large number of plants are constantly being screened for their possible pharmacological value. The *Hibiscus* genus may prove to be a richer source of compounds with possible pharmacological value, but more investigations are necessary in this direction.

The reported biological studies of *Hibiscus* were carried out mostly on various extracts, but more attention is required to screen the phytoconstituents responsible for these activities.

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AUTHOR'S CONTRIBUTIONS

Ms. Shikha Baghel Chauhan has collected the data and compiled and drafted the article. Dr. Tanveer Naved has reviewed the article.

CONFLICTS OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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