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Review Article

A comprehensive review on reproductive toxicity of fenugreek and its bioactive component diosgenin: A review based on toxicological evidence

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ABSTRACT

Due to insufficient understanding and medication on the cause of the COVID-19 pandemic, attention toward the daily intake of dietary supplements and nutraceutical compounds has increased globally to improve health and resistance toward pathogens. Despite remarkable advances in the pharmacology industry to discover and formulate various new dietary ingredients in the form of health-boosting and antioxidant food products, fenugreek is one of the most popular herbs during the pandemic due to its strong antioxidant compound, diosgenin. Diosgenin is an active phytosteroid saponin found in fenugreek and known to exert several biological effects as well as promote health. Despite its beneficial health effects, several unwanted side effects are caused by the consumption of fenugreek seeds (whole seed/extract); however, these side effects may not be immediately visible. Recently, diosgenin has been shown to have reproductive toxicity, fetal toxicity, and teratogenicity at high doses and for long-term use. This review has highlighted and summarized research articles to outline the harmful impact and potential toxicity of steroidal compound (diosgenin) in fenugreek on male and female reproductive functions and its mechanism of action from previous to recent literature. In addition, we also discussed the possible challenges and awareness of using dietary herbal supplements for the prevention of diseases and disorders. We searched PubMed and Google Scholar and selected research and review articles that showed fenugreek (*Trigonella foenum-graceum*) toxicity, fenugreek reproductive toxicity, *Trigonella* reproductive toxicity, fenugreek side effects, fenugreek anti-fertility effects, fenugreek gestational and developmental toxicity, and fenugreek adverse health effects. Herein, we isolated previously published findings on fenugreek toxicity on reproduction, fetal development, and teratogenicity to better comprehend the fundamental idea of reproductive toxicity and established that steroidal saponin diosgenin has been associated with reproductive defects. This review outlines the comprehensive awareness on herbal medicine as it may inhibit fertility potential, therefore, consumption of fenugreek with limited doses is suggested. In addition, we have also discussed the underlying mechanism for reproductive toxicity induced by fenugreek's phytosteroid component, diosgenin.

Keywords: Dietary supplements, Antioxidant, Fenugreek, Diosgenin, Side effects, Reproductive toxicity

INTRODUCTION

The COVID-19 pandemic has become a global concern and brought various challenges for people who survived with medication or vaccines. In India, the lack and unavailability of efficient medicine and vaccines have increased anxiety and made people unsecured. Due to COVID-19 infection and vaccination against the virus, the incidence of cardiac dysfunction, such as heart stroke and inflammation, is reported in young and elderly people.[1-4] As a result of that, a large number of

people who have been infected with COVID-19 or not have shifted themselves toward their traditional known herbal supplements.[5] Many herbal and nutraceutical pharmaceutical companies took an advantage and approached forward and advertised their herbal formula as syrup, tablets, and dietary supplements and claimed as effective against COVID-19 infection by boosting the resistance against the virus. A report from Global Immune Health Supplements Market Share, Trends, Analysis, and Forecasts (2020–2030) has revealed and predicted on the basis of news from important trends, business strategies, research and development activities, supply chain analysis, competitive landscape, and market composition analysis, and the market for immune health supplements which was US $19 billion in 2020 is predicted to reach US$ 43.5 billion by 2031, with a compound annual growth rate of 7.7%. However, reports from the National Institute of Health's Office of Dietary Supplements[6] and the United States Food and Drug Administration[7] suggest that there is a dearth of information on the use and safety of any herbal and dietary supplements to elucidate its beneficial health impact against COVID-19 infection. The Covid-19 pandemic has raised awareness of the need to take herbal supplements daily to enhance immunity, which has led to an increase in unintended adverse effects. During the pandemic, one of the undesirable side effects that was noted was reproductive toxicity. In general, it is understood that a diet rich in antioxidants may enhance immunity and protect from various pathogens. However, there is less concern and no awareness of the safety of the consumption of high doses of antioxidants present in food or food supplements. The risks associated with high doses of antioxidants are linked to diarrhea, abdominal bloating, kidney problems, cardiac disturbances, and initiation of cancers.[8] Moreover, some kinds of antioxidants are known to interact with some therapeutic medicines and may alter their functioning. The majority of people who have consumed herbal supplements for longer duration during the pandemic in the form of tea, soup, and seed extract showed various side effects such as mouth ulcer, abdominal discomfort, and fertility disorders. Therefore, it is necessary to explore the side effects of known herbal supplements when consumed on a daily basis.

Fenugreek (*Trigonella foenum-graecum*) is one of the most popular herbs and is globally used as a dietary supplement during the COVID-19 pandemic. Conventionally, it has been used to treat disorders of fat and sugar, to relief menstrual cramps, and to enhance milk supply in lactating women.[9] Both fenugreek seeds and leaves are loaded with antioxidant compounds with medicinal properties and have been utilized for several therapeutic purposes. The nature of fenugreek seeds are mild laxative and diuretic. It has been used in the treatment of leprosy hemorrhoids, as a mouth spray, digestive complication, and in several kinds of infection.[10] Besides these, several other studies have reported fenugreek as anti-inflammatory and antipyretic,[11,12] anti-hyperglycemic, hypo-cholesterolemic,[13] antimicrobial,[14] and immunomodulatory.[15] The seeds contain its major active steroidal saponin diosgenin. Steroidal saponins (diosgenin) present in fenugreek are also known to exhibit estrogenic and anti-androgenic activities.[16-18] Moreover, reproductive dysfunction in adults and teratogenicity in fetuses have been observed due to fenugreek seed/extract.[19-22] In addition to that, gestational exposure to fenugreek not only affects fetal development but also caused alter neurobehavioral disorders in offspring.[21,23] Another research finding also revealed that fenugreek seed aqueous extract caused adverse effects on the male reproductive health and pregnancy outcome in Parkes mice.[24] Recently, Moreno *et al*. (2023) reported that fenugreek straw-intoxicated cattle have shown peripheral neuropathy.[25]

In India and other countries, due to the COVID-19 pandemic, the global daily intake of fenugreek in the form of seed and seed extract has tremendously increased due to its potent antioxidant compound, diosgenin. Diosgenin is a major phytosteroid saponin found in fenugreek and exerts various beneficial biological effects against cancer, inflammation, cardiovascular disease, metabolic syndromes, neurodegenerative, bone loss, aging, etc. Moreover, diosgenin is also used in the pharmaceutical industry for the synthetic production of sex hormones and other steroids, for skin care products, and as a functional food and health product.[23] However, the dearth of information on the safety of consumption of high doses of fenugreek for longer duration has caused many health irregularities.[26-28] A recent report from the Drugs and Lactation Database, National Institute of Child Health and Human Development (2023), has listed side effects after fenugreek consumption as digestive issues, nausea, lower potassium and sugar levels, liver toxicity, allergy, and internal hemorrhage.[29] Other side effects of fenugreek consumption are epidermal necrolysis, hormonal disorders, reproductive alterations, and poor fertility.[22,30] The Moroccan Centre of Pharmacovigilance reported that it received 8 cases of congenital malformations associated with the maternal ingestion of fenugreek seeds during pregnancy.[23] Diosgenin is a major phytosteroid saponin found in fenugreek and was found to be 0.28% and 0.92%,[31] 1.3% and 1.5%,[32] 0.42–0.75%,[33] and 1.57–4.03% mg/100 g[34] in fenugreek seed.

Besides its health-beneficial effects, diosgenin altered biochemical and physiological parameters and altered reproductive functions in healthy mice. Our recent study on pure compound diosgenin administration in both male and female experimental mice showed underactive gonads, hormonal imbalances, and poor fertility.[35] A similar effect was also observed with fenugreek seed extract, which caused degenerative changes in the testis histoarchitecture and reduced spermatogenesis in Parkes mice.[24] Although there are many published reports claiming fenugreek and its potentially harmful effects on gonads and other body organs, the cause and actual mechanism of such side effects

remain unclear. Incomplete information and lack of public awareness on fenugreek consumption (acute/chronic) have seriously affected fertility among adults. Therefore, in our last experiment, we decided to explore pure diosgenin treatment in healthy mice and their impact on reproductive function, and we found diosgenin as a reproductive toxicant. Hence, on the basis of our published report on diosgenin, we have collected and summarized all reproductive toxicity data and their mechanism of action with regard to diosgenin-rich fenugreek seed. This review will help to understand future studies assessing the actual cause and mode of dietary supplement-induced reproductive toxicity and the identification of bioactive plant compounds responsible for reproductive alterations.

MATERIAL AND METHODS

Based on earlier and recent literature surveys and search on PubMed and Google Scholar, we have segregated and selected the research and review articles showing fenugreek (*T. foenum-graceum)* toxicity, fenugreek reproductive toxicity, *Trigonella* reproductive toxicity, fenugreek side effects, fenugreek anti-fertility effects, fenugreek gestational and developmental toxicity, and fenugreek adverse effect on health. Furthermore, we have segregated and summarized the already published reports on fenugreek toxicity on reproduction, fetal development, and teratogenicity to better understand the basic concept of reproductive toxicity. In addition, we have also explained the mode and cause of reproductive toxicity of fenugreek due to its phytosteroid component, diosgenin [Figure 1]. The main objectives of this review are to gather the parameters used for reproductive toxicity and the cause and mode of underlying reproductive toxicity caused by the fenugreek compound diosgenin.

RESULTS

Herbal plants have been used to treat many conditions of diseases and many times misconception of being fit and healthy but have serious side effects which lead to deleterious effects for several systems in the body. Dietary supplements do not require extensive pre-marketing approval from the United States, Food and Drug Administration. Manufacturers are responsible for ensuring the safety but do not need to prove the safety and effectiveness of dietary supplements before they are marketed. Dietary supplements may contain multiple ingredients, and differences are often found between labeled and actual ingredients or their amounts. A manufacturer may contract with an independent organization to verify the quality of a product or its ingredients but does not certify the safety or effectiveness of a product. Because of the above issues, clinical testing results on one product may not be applicable to other products.

DISCUSSION

Male and female-related reproductive toxicity

Phytoestrogens are plant-based phyto-compounds with estrogenic/anti-estrogenic activity. Fenugreek seed contains a phytoestrogen compound, diosgenin, which exerts reproductive alterations in healthy mice.[35] Diosgenin is a functioning constituent of fenugreek and has been separated from the seed of fenugreek as a basic element required for the production of synthetic testosterone, estrogens, progesterone, and other steroid hormones in pharmaceutical industries. Keeping all these reports in view, fact encouraged us to take up fenugreek active compound, diosgenin, for detailed exploration, specifically on the reproductive function in male and female mice [Tables 1 and 2]. The acute and chronic administration of diosgenin as a pure compound severely damaged the testis and ovary and altered the fertility parameters in mice.[35] Interestingly, our observations were similar to earlier published reports on the anti-fertility effect of fenugreek.[19-22]

Anti-spermatogenic activity and related mechanism of action

Spermatozoa present in the testicular and epididymal lumen are the most sensitive cells in males and can be easily affected by a range of external and internal factors such as reactive oxygen species (ROS), variation in temperature, and insufficiency of nutritional factors and shortage of testosterone. Moreover, modifications in antioxidant status also may lead to malfunction of spermatogenesis, as shown by a noteworthy decrease in the number of different ages of germ cells at explicit stages in the spermatogenesis cycle. Likewise, it is naive to think that a single sperm measure in rats will be sufficient to detect reproductive toxicity from any chemical exposure. Different reproductive toxicants act by different mechanisms to produce an array of effects. Therefore, it is advantageous to consider all the evidence from sperm numbers, motility, and morphology as well as from reproductive organ histology, reproductive behavior, and fertility and to characterize the toxicity and estimate risk. Sperm motility, viability, and concentration are the most critical parameters of semen quality and can be a compensatory factor in males with low sperm. A report on a crude non-polar steroidal portion of fenugreek extract demonstrated complete infertility and severe decreases in reproductive organ weights, sperm counts, and motility.[36] Moreover, it is observed that fenugreek treatment in mice not only reduced sperm motility and count but also induced critical changes in the chromosomal structure.[21] Furthermore, fenugreek exposure in mice demonstrates an elevation in plasma estradiol and decreases in testosterone, which is known to influence sperm motility, viability, and concentration.[22,37] In another case, there was a change in the male reproductive hormones

Table 1: Effect of fenugreek on male reproductive toxicity parameters.

Treatment type	Species	Dosage level	Route and Duration	Major Findings	References
Crude non-polar steroidal fraction of fenugreek seed	Rats	100 mg/kg body weight/day	Oral, 60 days	Complete infertility, significant decreases in reproductive organ weights, sperm counts, and motility, and histopathological alterations in the testicular seminiferous tubules and cauda epididymis tubular epithelium	Kamal *et al.* [17]
Fenugreek seed diet form	Rabbit	30% fenugreek seeds	Oral, 90 days	Significant reduction in testis weight, sperm concentration, and circulating testosterone	Kassem *et al.*[19]
Fenugreek seed alcohol extract	Mice	100 mg/kg body weight/day	Oral, 90 days	Significant increase in sperm morphological abnormalities: swollen acrosomes, amorphous, microcephaly, megacephaly, rotated head, and flat head	Al-Ashban *et al.*[44]
Fenugreek seeds powder	Rats	200 mg/rat/day	Oral, 30 days	Significant decrease in circulating LH and testosterone levels, reduction in testis weight, degeneration of some spermatogenic cells, necrotic changes in the germinal cells, and prominent disruption of the interstitial stroma	Ibrahim and El-Tawill[38]
Fenugreek seed capsules	Mice	305 and 610 mg/kg body weight/day	Oral, 90 days	Significant reduction in fertility, decrease in motility, sperms count, and an increase in the proportion of abnormal sperms associated with DNA damage	Al-Yahya[22]
Fenugreek seed ethanolic extract	Rats and cocks	1 g\kg\day	Oral, 4 weeks	Reduced male fertility by reducing testosterone concentration and sperm concentration and inhibiting mass and individual motility of the sperms	Mohammed *et al.* [37]
Fenugreek seed aqueous extract	Parkes mice	600 mg/kg body weight/day	Oral, 28 and 56 days	Reduced sperm parameters, degenerative changes in the testis histoarchitecture, depletion in fertility indices	Singh *et al.*[24]
Fenugreek seed compound (pure diosgenin)	Mice	10, 50, 100 and 200 mg/kg body weight/day	Oral, 90 days	Poor sperm quality, disturbed homeostasis of the reproductive hormones, interrupted steroidogenesis, increased germ cell apoptosis, and decreased fertility potential	Khushboo *et al.*[35]

LH: Luteinizing hormone, DNA: Deoxyribonucleic acid

together with a diminished mass and motility of the sperm caused by *T. foenum-graecum* seeds extract.[38] Treatment with fenugreek seed extract caused declined sperm indices and low levels of sialic acid and fructose in the epididymis and seminal vesicle, respectively.[24] Furthermore, our recent study on diosgenin has shown its anti-spermatogenic nature resulted in poor sperm indices.[35] The anti-spermatogenic activity of fenugreek is possibly by aggregation of free radicals in the testis, triggered by its diosgenin constituent. It indicated comprehensive impacts of fenugreek on the male testis.

Sperm morphological alterations and related mechanism of action

Spermiation is a very sensitive phase during sperm development and maturation. Epididymal spermatozoa consist of a typical morphology and determine their fertility ability. There are various known/unknown pharmacological and dietary compounds that interfere in Sertoli cell signaling resulting in spermiation failure. Moreover, interference during spermiation induces abnormal production of reactive oxygen species (ROS), which can induce nucleic acid damage in the sperm and may produce defective or abnormal sperm.[39] A deformity such as detached/amorphous heads and abnormal tails of sperm is an indication of abnormal acrosomes or acrosomal degeneration due to irregularity during spermiation.[40] Earlier researcher also has shown that insufficiency of glutathione causes sperm distortion.[41,42] In addition, 90-day treatment of male mice with ethanolic extract of fenugreek at the dose of 100 mg/kg body weight/day has increased sperm DNA damage and morphological defects such as swollen acrosomes, amorphous, microcephaly, megacephaly, rotated, and flat head.[38,43] Furthermore, in experimental mice, prolonged treatment of fenugreek at the higher doses of 305 and 610 mg/kg body weight/day has significantly increased the production of defective sperm.[22] Our recent findings on

Table 2: Effect of fenugreek on female reproductive toxicity parameters.

Treatment type	Species	Dosage level	Route and duration	Major findings	References
Ethereal extract of fenugreek seeds	Rats	25 mg/kg body weight/day	Oral	Moderate anti-fertility effect	Khare *et al.*[45]
Petroleum extract of fenugreek	Rats	500–1250 mg/kg body weight/day	Oral, gestational exposure (1–10)	Anti-fertility effects	Adhikary *et al.*[50]
Fenugreek seed powder	Rats	175 mg/kg body weight/day	Oral, gestational exposure (1–10)	A decrease in fetal body weight and crown-rump length, gross anomalies, a slight increase in resorptions, and some abortifacient events	Sethi *et al.*[51]
Aqueous extract of fenugreek seed	Rats	800 mg/kg body weight/day	Oral, gestational exposure (1–6)	Decrease in number of total resorptions and number of dams with resorptions	Elbetieha *et al.*[52]
Diets containing steroidal extract of fenugreek	Rats	100 mg/day	Oral, 15 days	The reduction in uterine and ovarian weights	Sharma and Bhinda[48]
Fenugreek seed diet form	Rabbit	30% fenugreek seeds	Oral, 90 days	The levels of estrogen and progesterone decreased, while gestational progesterone levels significantly increased due to the proliferation of endometrial glands and abnormal development of the fetus.	Kassem *et al.*[19]
Fenugreek seeds	Humans	-	Oral, whole gestational	Congenital malformations such as hydrocephalus, anencephaly, cleft palate and spina bifida	Skalli[58]
Fenugreek leaves decoction	Rats	0.8, 1.6 and 3.2 g/kg	Intraperitoneal (single dose on the 10th day of gestation)	Decreased fetal size and increased fetal mortality rate	Araee *et al.*[55]
Fenugreek seeds powder	Rats	200 mg/kg body weight/day	Oral, 30 days	Hormonal levels dropped drastically, decreased ovarian weight, several follicles were destroyed, and an increase in inflammatory cells	Ibrahim and El-Tawill[38]
Ether, ethanol, and water seed extract of fenugreek, respectively	Rats and mice (immature and ovariectomized)	500 mg/kg body weight/day	Oral, gestational exposure (1–10)	Significant estrogenic and anti-implantation activity	Ahirwar *et al.*[46]
Fenugreek seed aqueous extract	Mice	500 and 100 mg/kg body weight/day	Oral, whole period of gestation	Decreased litter size and increase in pup mortality	Khalki *et al.*[23]
Saponin extract of fenugreek	Rats	200 mg/kg body weight/day	Oral, gestational exposure (1–7 and 1–14)	A dose-dependent anti-implantation response and abortifacient activity significant increase in uterine and diameter in immature ovariectomized rats	Dande and Patil[20]
Hydroalcoholic extract of fenugreek seeds	Balb/C mice	50,100, and 200 mg/kg body weight/day	Intraperitoneal, 20 days	Stopped folliculogenesis trend and destroyed ovary tissue	Modaresi *et al.*[47]
Fenugreek seed compound (pure diosgenin)	Mice	10, 50, 100 and 200 mg/kg body weight/day	Oral, 90 days	A considerable reduction in folliculogenesis, greater prevalence of atretic follicles, produces reproductive teratogenicity in fetus, and impairs sexual development in the F_1-generation pups	Khushboo *et al.*[35]

chronic treatment of diosgenin to male mice also have shown structural deformities in sperm,[35] hence suggesting that the changes in physical characteristics of sperm cells are possibly due to excessive generation of ROS leading to sperm damage.

Testicular dysfunction and related mechanism of action

Hypogonadism is a consequence of dysfunction of gonads due to an imbalance of reproductive hormones. Testis is the site for spermatogenesis and steroidogenesis, viewed as increasingly influenced by pressure due to its high metabolic necessities. The increase in oxidative stress and decrease in the level of antioxidants disturb the homeostasis of testicular tissue. This kind of imbalance in the testis induces apoptosis and loss in testicular volume. Previous results demonstrated that fenugreek seed extract fundamentally diminished testosterone levels in rabbits resulting in atrophy of the testis. A diet containing 30% fenugreek seeds altogether diminished testis weight and also male circulating testosterone.[19] Similarly, research done by Ibrahim and El-Tawill on fenugreek seed powder (200 mg/rodent/day) for 30 days in male rodents, have demonstrated underweight testicles alongside the huge decline in serum luteinizing hormone and testosterone hormones, indicated testicular toxicity.[38] Recently, chronic treatment of diosgenin in male mice caused atrophy of gonads and hormonal imbalances.[35] These findings showed a harmful effect of fenugreek seeds on testicular tissue. This lopsidedness of reproductive hormones caused by the disability of gonads and these weakened reproductive hormone systems are almost certainly bound to influence the procedure of spermatogenesis.

Impaired spermatogenesis and steroidogenesis and related mechanism of action

Spermatogenesis and steroidogenesis are two main essential functions of mammalian testis. Hypothalamic–pituitary–gonadal axis either directly or indirectly bound to influence spermatogenic events in the testis. Leydig's cell produces testosterone that determines the future of germ cell, and Sertoli cells are crucial for the maturation and release of spermatozoa. Any interruption in their signaling pathway may cause testicular atrophy and failure of spermatogenesis. Another factor that may trigger degeneration of cells of seminiferous tubules is the abnormal production of ROS, resulted in excessive apoptosis. Therefore, it is assumed that the mechanism by which anti-fertility herbs target sperm production is possibly oxidative stress and disruption in Leydig's and Sertoli cell signaling pathways. An earlier study reported huge modifications in testicular histopathology of seminiferous tubules in male rodents supplemented with fenugreek seed (100 mg/kg body weight/day) for 60 days.[17] Kassem *et al*. have reported that fenugreek supplementation for 3 months in male rabbits causes testicular toxicity (degeneration of seminiferous tubules) accompanied by low testicular weight.[19] Furthermore, more comprehensive research done by Al-Ashban *et al*.[44] and Al-Yahya[22] reported morphological abnormality of sperm due to impaired spermatogenesis. In addition, fenugreek seed extract treatment had a negative impact on oxidative status and germ cell dynamics in the testis and caused degenerative changes in the testis histoarchitecture.[24] In a recent report, diosgenin, an active phytochemical of fenugreek, causes testicular toxicity followed by degenerating germinal epithelia, along with sever necrotic changes, multinucleated giant cell arrangement, sloughing of immature germ cells from the seminiferous tubules, and vacuolization of Sertoli cells and prominent interruption of the interstitial stoma have been reported.[35]

Fertility disorder and related mechanism of action

One of the most significant activities of the anti-fertility herb is their impact on sperm physiology, that influences the capacitation of sperm responsible for fertilization. Furthermore, accessory sex organs nourish and provide the nutritional requirements for developing spermatozoa. Low testosterone, combined with low levels of sialic acid and fructose in the epididymis and seminal vesicle, alters sperm maturation and may reduce sperm fertilization capacity. Singh *et al*. found that mice treated with fenugreek had low levels of sialic acid and fructose in the epididymis and seminal vesicle, showing impaired fertility ability.[24] These reports demonstrated an adverse impact of fenugreek on sperm development and the inability of spermatozoa to undergo capacitation. A few examinations have demonstrated fenugreek to be a strong antifertility herb in a few imminent and animal model studies. Fenugreek treated male mice have shown lower acrosin activity and are required for prosperous fertilization.[38] Oxidative stress might be one of the fundamental mechanisms through which exposure to fenugreek can adversely influence sperm DNA functions and cause fertility issues. Supplementation of fenugreek seed for a time of 90 days at doses 305 and 610 mg/kg body weight/day in mice diminished fertility with noteworthy lessening of immotile sperms related to DNA damage.[22] In another study, fenugreek is accounted for as an anti-fertility agent in both male and female rabbits, causing complete infertility.[20,37] These outcomes are united with those of past report by Kamal *et al*.[17] and Kassem *et al*.,[19] who revealed testicular toxicity pursued by decreased circulating androgen and changed testicular histoarchitecture. Diosgenin is a claimed compound in fenugreek due to its structural similarity with estrogen. Based on the report claimed that fenugreek, an anti-fertility herb, we have supplemented male mice with pure diosgenin and found that the rate of fertility was significantly reduced in a dose-dependent-manner.[35] These findings showed an adverse impact of fenugreek on sperm function.

Failure of ovarian folliculogenesis, estrogenic activity, and related mechanism of action

Female mice normally show an abnormal range of 5–6-day reproductive cycles in which the estrus phase is known as the fertile phase. The duration and length of these phase types are determined by ovarian activity. First of all, Khare *et al.* reported fenugreek as a mild antifertility herb in female rats.[45] However, later on most conspicuous and comprehensive work done by Kassem *et al.* in female rabbits illuminated that 30% fenugreek seed administration for 30 days showed some proliferative changes associated with endometrial glands with hyperplastic changes and may interfere with implantation activity.[19] Moreover, Ibrahim and El-Tawill reported remarkable degeneration of some ovarian follicles after 30-day treatment of fenugreek in female mice.[38] These observations are comparable with the studies made by Ahirwar *et al.*[46] and Sreeja *et al.*,[18] who reported that fenugreek shows estrogenic activity that may affect ovarian folliculogenesis.[18,46] Another research work done by Modaresi *et al.* observed that stopped folliculogenesis trend and ovary tissue destruction in female Balb/C mice supplemented with fenugreek seed.[47] Diosgenin supplementation in female mice has shown degenerative changes in ovarian tissue and altered folliculogenesis.[35]

Imbalance of reproductive hormones, ovarian weight, and related mechanism of action

Attributions of ovarian weight and serum reproductive hormone in female are considered the most important characteristics for female fertility evaluation and ovarian toxicity since the ovary is responsible for folliculogenesis, and low folliculogenesis results in poor production of estradiol and progesterone. Several studies in female with fenugreek treatment revealed a decreased in uterine and ovarian weights together with significant depression in female hormone levels (estrogen and progesterone) and markedly increased uterine diameter in immature ovariectomized rats.[19,20,48,49]

Abortifacient activity and related mechanism of action

As previously known, fenugreek seeds contain diosgenin as a steroidal component and are precursor for steroid production. Several previous reports reveal fenugreek as mild anti-fertility.[45,50] A tremendous group of pre-clinical exploratory proof proposes that fenugreek seed powder to rodents during the initial 10 days of gestation leads to a diminish in fetal size and an expansion in fetal death rate.[51,52] In another report, ethanol extract of fenugreek administration in female rats and mouse exerts anti-implantation and abortifacient activity.[46] This study correlates with several works such as that of Dande and Patil who reported that fenugreek affects implantation activity and leads to resorption of the fetus (abortifacient activity).[20] Chronic administration of diosgenin to female mice at the doses of 10, 50, 100, and 200 mg/kg body weight showed a reduction in the length of the right uterine horn containing few embryos, atrophy of the uterine horn with asymmetrical distribution of fetuses and fewer implantation sites with multiple resorption sites,

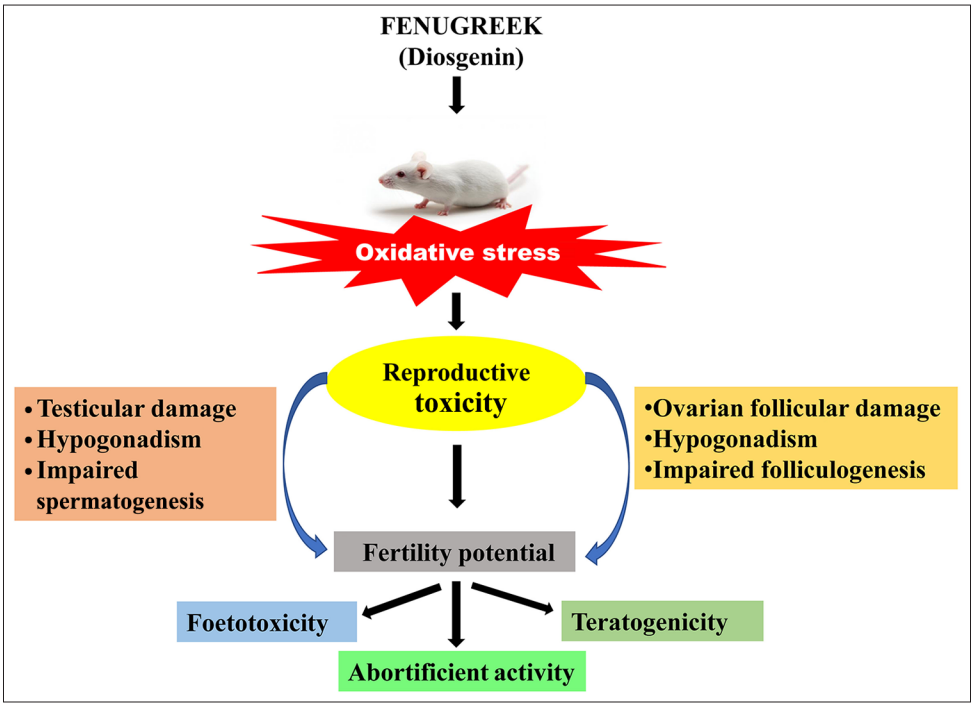

Figure 1: Possible mechanism of action of fenugreek-induced reproductive toxicity.

dead fetuses with complete resorption sites, and intensive bleeding in the uterine horns.[35] From the above findings, it seems that fenugreek alters hormonal homeostasis and interferes with implantation activity. However, in accordance with the findings and because of the complexities behind reproductive procedures, more investigations should be led. We can suggest that the fenugreek steroidal component (diosgenin) may be responsible for its abortifacient activity.

Teratogenicity and related mechanism of action

Numerous researches have been done to access the role of estrogenic compound present in various herbal foods during fetal development. Fenugreek exerts estrogenic effects through its active compound diosgenin, which may affect fetal development..[19,20,22] There has been a report that infants show atypical smell after maternal consumption of fenugreek just before delivery.[53,54] It is suggested that fenugreek containing estrogenic compound (diosgenin) may transported through the placental barrier, affecting the growth and physiology of the developing fetus.[18] Several clinical studies on the teratogenic effect of fenugreek addressing fetal deformities, increased mortality rate, marked decreases in fetal and placental weights, limb bone disorder, malformations such as arrangement of congenital fissure, and a knock-on head in infants alongside modified neurobehavioral issue increased in percentage of dead embryos.[22,51,54-57] Moreover, in human cases, maternal consumption of fenugreek seeds causes several distinct congenital deformities (hydrocephalus; anencephaly, cleft palate, and spina bifida).[58] The exact mechanism of fetal toxicity due to fenugreek steroid has not been specified. However, administration of diosgenin to pregnant mice has shown dead embryos with manifold body deformities such as hematoma, growth retardation, and total foot and tail loss.[35] These findings suggest that steroidal saponin might interfere with maternal physiology, affecting fetal development.

CONCLUSION

Fenugreek, a popular herbal supplement, is widely used as a traditional and therapeutic medicine worldwide. However, existing research has shown varied effects of fenugreek. The health status of the consumer/patient, dose amount, and duration determine the action of any supplement. It has been attributed that the antifertility impact of fenugreek seed may be because of its steroidal saponin and diosgenin. Diosgenin has been extensively used as a precursor to produce synthetic steroid requirements in the pharmacological industry. Overall, diosgenin may negatively affect the reproductive organs owing to its structural resemblance to estradiol. Herein, we have summarized the reproductive toxic effects of fenugreek and its active compound, diosgenin. Reproductive disorders are one of the major consequences of fenugreek supplementation, resulting in poor fertility. Consequently, this is insufficiently convincing, and the precise reaction mechanism is still required. Additional experimental evidence should be carried out to explore the reproductive toxic effects of other herbal supplements. In this review, we have summarized the antifertility property of fenugreek containing steroidal saponin (diosgenin) with possible mechanisms of action. In conclusion, the objective of this review is to present a comprehensive awareness of herbal medicine, being used in food habits and to improve health status, may inhibit male and female fertility potential. This review article outlines the harmful impacts of fenugreek steroidal compounds on fertility.

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