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AN OVERVIEW OF PLANTS CAUSING TERATOGENICITY: FENUGREEK (*TRIGONELLA FOENUM* GRAECUM)

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ABSTRACT

Some plants are toxic to living beings including humans, and are widely used all over the world in the treatment of various types of body ailments in traditional medicine, especially in the developing countries, due to theirs economic, social and cultural conditions. These plants are routinely taken for the nourishment of the pregnant women. This may cause the toxicity to the developing foetus, known as teratogenicity effect, and the plants are qualified as teratogens. Fenugreek is one of these plants, which has a wide range of medical applications, and wide use by ladies during pregnancy for different reasons. This Paper aims to present an overview of some existing studies and status of the teratogenic effect of fenugreek, to benefit from their results and conclusions.

INTRODUCTION: Throughout the world many pregnant women consume a great variety of herbs. Traditionaly, 12-59 % of women used herbal products during pregnancy for a variety of reasons, including pregnancy related conditions (nausea, vomiting, constipation), to prepare for labor, to induce abortion[1]. In developing countries, plant products are still routinely administered to women during pregnancy and childbirth.

In Morocco, Plants, especially fenugreek, are used in the treatment of various diseases, and are widely taken by women for the nourishment during pregnancy and for lactation after childbirth.

Fenugreek (*Trigonella foenum* graecum) is an old medicinal plant from Papilionaceae, Leguminosae family and it is cultivated in some countries such as Morocco, Egypt, India and some parts of England. Theirs benefits include stimulating the appetite and digestion, induce labour, promote the lactation for breast feeding, reduce menstrual discomfort, minimize symptoms of menopause, reduce cholesterol level, reduces cardiovascular risk, control diabetes, relief for sore throat, treat constipation and diarrhoea, prevent colon cancer, treat inflammation and renal insufficiency [2-5]. It was also reported that fenugreek seeds increase the bone marrow cell counts indicating its stimulatory effect on blood cells especially [6].

Fenugreek's seeds contain simple alkaloids consisting mainly of trigonelline (up to 0.13%), choline (0.05%), gentianine, and carpaine; much of the trigonelline is degraded during roasting to nicotinic acid and other pyridines and pyrroles, which probably account for much of the flavor of roasted fenugreek. Other constituents include saponins that yield on hydrolysis 0.6–1.7% steroid sapogenins consisting mainly of diosgenin and its isomer yamogenin usually in a 3:2 ratio, with tigogenin and neotigogenin also present; yamogenin tetrosides B and C have been reported to be two of the glycosides (saponins) present; flavonoids,

including vitexin, vitexin-7-glucoside, orientin arabinoside, homoorientin, saponaretin (isovitexin), vicenin-1, vicenin-2, quercetin, luteolin, and vitexin cinnamate; fixed oils (5–8%); considerable amount of a mucilage, which appears to be mostly a galactomannan; protein (23–25%), which is low in *S*-amino acids but high in lysine and tryptophan; free amino acids, including (2*S*, 3*R*, 4*R*)-4-hydroxyisoleucine, histidine, lysine, and arginine, with the first one isolated at 0.09% yield as the major component; vitamins, especially A, B_1, and C; minerals (especially calcium and iron); volatile components (more than 50), which include *n*-alkanes, sesqui-terpenes, and oxygenated compounds (undecane to hexadecane, elemenes, muurolenes, γ-nonalactone, 5-methyl-δ-caprolactone, etc.), coumarins and other constituents that might affect platelet aggregation [7-8].

Most of the medicinal properties of fenugreek are found in the seeds, which have been used for thousands of years in Greco-Arab and Islamic medicine as well as in Indian and Chinese medicine [9]. Some plants, taken in pregnancy, cause the toxicity to the developing foetus i.e. teratogenicity. Their toxicity includes neurotoxicity, cardiovascular toxicity, and cause diarrhoea, cramps, dermatitis, allergic reactions etc [10].

In this paper, we present an overview of the teratogenicity caused by plants, especially fenugreek.

Teratogenic Effect of Fenugreek: Plants toxin which cross the placenta at a high enough dose and are present at a specific time in gestation to exert its effect on the developing foetus, are considered as teratogens [11].

There are some plants species which are very toxic to living beings including humans, and having teratogenic potential [12-21].

To assess the teratogenic effect of the fenugreek, we distinguish two types of studies:

i) Experiment studies which test the teratogenicity using animal model systems (mouse, rat, dog…), based on exposing pregnant animals to fenugreek agent and observed the developing foetuses for gross visceral anomalies and malformations, and

ii) prospective studies that register women receiving the fenugreek during their pregnancy and record the outcome effect on their new born.

Several animal studies and preliminary trials in humans have found that fenugreek can reduce blood sugar and serum cholesterol levels in people with non-insulin-dependent diabetes [22].

The adverse effects of teratogens can be at both prenatal and postnatal stages of human development. It is observed that teratogens can be present in the woman's body before conception takes place and it can affect the unborn baby at birth during delivery or manifest later in the life of the individual child [10].

It is now suspected that toxic constituents of some commonly used plants may contribute to human birth defects [23]. Birth defects are known to occur in 3-5% of all newborns [10].

Anomalies and malformation associated with teratogenic exposures include various effects that range from infertility, prenatal onset growth restriction, structural defects, and functional CNS abnormalities to miscarriage or foetal death [24]. Altered function of nervous and endocrine systems or in postnatal function is the main concern for both experimental and human teratology. It was reported that teratogenic plants family (fenugreek, Veratum californicum…) is one of the main factors causing congenital defects [25-27].

An antifertility effect of fenugreek seeds in the female rabbits, and a significant reduction in foetuses developing due to the reductions of both foetal and placental weights at 20 days of gestation and litter size was demonstrated [28].

The effect of Fenugreek on foetal macroscopic diameters and microscopic bone marrow cell histological changes in its teratogenic dosages were investigated [20]. It was reported that fenugreek causes decrease bone marrow cell proliferation and increase foetal mortality rate in rats [20]. Fenugreek was dissolved in 1.5 milliliter distilled water and injected intraperitoneumly in three dosages of 0.8 g/kg, 1.6 g/kg, and 3.2 g/kg for three groups of Wistar female rats mated by Wistar male.

Only 1.5 milliliter distilled water was injected for a control group. LD50 for the measurement of teratogenic dosage of fenugreek was 4.1 and 3.5 g/kg in female and male rat, respectively.

The effect of fenugreek on the decrease of the foetal ear to ear diameter and increase of foetal mortality rate are proved in this study. However, the effects of Fenugreek on bone marrow proliferation and its effects on the normal histological pattern of bone marrow cell have not been clearly demonstrated.

There was a positive relation between the injected drug dosage and foetal mortality rate. Ear to ear diameter was decreased in groups received Fenugreek decoction. It was also observed that the severity of stem cell histological changes caused by 3.2 g/kg drug injection was lower than distilled water injection. Differences in the severity of histological changes of other cells across three groups with different drug dosages and control group were detected. Fenugreek in teratogenic dosages can decrease the severity of bone marrow cell proliferation and increase foetal mortality rate

Other studies demonstrate the impairment of peripheral conversion of thyroid hormones caused by the use Fenugreek seed extract, and that administration of Fenugreek, 0.11 g/kg daily for 15 days [29].

On the other hand, fenugreek administered at 2 and 8 g/kg dose orally significantly reduce the blood sugar both in normal and diabetic rats [30]. Take account of the directly dependence of the metabolism of bone marrow to glucose, decrease in glucose absorption in bone marrow may lead to metabolic disturbances of bone marrow cell and enzymatic dysfunction in bone marrow cell proliferation [20].

Trigonella foenum-graecum leaves aqueous extract (TGLE) on the organogenesis stage of Sprague-Dawley rat fetus was investigated [31]. TGLE was administered in pregnant rats by intra peritoneal injection at the dose levels of 0.8, 1.6 and 3.2 g/kg/day on the 10th day of gestation. Then all rats were sacrificed on the 20th day of gestation and foetuses were removed from their uterus.

It was observed that TGLE has toxic potential on pregnant rats at the highest dose level 3.2 g/kg/day. It showed that the extract has adverse effects on the development of hind limb long bone by disorder in the histology details of cell structure and growth into long bone during endochondral ossification. Furthermore, TGLE at the highest dose level, may cause severe adverse alterations in rat foetus.

It was reported that the use of dose of fenugreek aqueous extract (0.8, 1.6 and 3.2 g/kg) throughout 10th day of pregnancy, increased mortality rate in embryos in a dose-dependent manner and moderate malformation was noticed by microscopic examinations of embryos liver, suggesting that the aqueous extract of fenugreek, may have teratogenic effect on rat embryo hepatocytes [32].

In Morocco, cases of pronounced congenital malformations such as hydrocephalus, anencephaly and spina bifida were found among women who consumed fenugreek seeds during pregnancy [33-34]. Other study to evaluate the potential toxic effects of fenugreek seeds on pregnant mice and foetal development was conducted [35] and provides experimental evidence that aqueous seeds extract of *Trigonella foenum*-graecum affects reproduction in mice and shows teratogenic and foetotoxic effect. In this study, lyophilized aqueous extract from fenugreek seeds (LAE-FS) was administered to the mated female mice during the entire period of pregnancy, at doses of 500 and 1000 mg/kg daily.

Females were examined for standard parameters of reproductive performance, and foetuses were weighed and examined for externally visible malformations. It was reported that there is no death or treatment-related signs of abnormal behavioural changes were observed in the females. Developmental toxicity in offspring included an increase in the foetal death rate, a decrease in the litter size, and a reduction in the foetal body weight. And an increase in the incidence of morphological abnormalities was observed [35] 3 cases of external malformations: an aplasia of external ear, bump on the head and median cleft of the lower lip. This study concludes that fenugreek seeds extract may have deleterious toxic effects on reproductive performance and potential teratogenic effects in foetuses.

CONCLUSION: Pregnant women should be very careful when taking both prescription and non-prescription plant based drugs, especially fenugreek seeds which are traditionally and recommended for increasing milk production in nursing women, and widely used during pregnancy. Thus, a proper knowledge should be about teratogencity of the fenugreek.

On the other hand large sensitizing of the population about teratogenic effect of this plant is well desired. Given the prevalent use of the fenugreek by pregnant women in Morocco, clinical (epidemiological) research should be carried out to confirm the same activity in humans. Currently, a retrospective study following up the new born malformations registered in the Hospital of Children in Rabat is under development.

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