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Review

Toxicological properties of fenugreek (*Trigonella foenum graecum*)

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ABSTRACT

Fenugreek (Trigonella foenum graecum), used as traditional medicine and natural additive food, has been shown to exert significant antiatherogenic, antidiabetic, antianorexic, antioxidant, anticarcinogenic, antihyperlipidemic, galactogogue and anti-inflammatory effects in several human and animal models. Besides, several medicinal pharmaceutical and nutraceutical properties, fenugreek have toxic effects as well. The aim of this review is discuss the cumulative evidence, which suggests that consumption of fenugreek induced some serious toxicological side effects. In this review, many teratogenic effects of fenugreek, from congenital malformations to death, were reported in human, rodent, rabbit, and chick. Moreover, results obtained in rats, mice and rabbits show a testicular toxicity and anti-fertility effects in male associated with oxidative stress and DNA damage, as well as anti-fertility, antiimplantation and abortifacient activity in females related to saponin compound of fenugreek which suggest that fenugreek is not recommended for use during pregnancy. Indeed, the consumption of fenugreek should be avoided for persons having peanut and chickpeas allergy because of possible cross-reactivity as well as chronic asthma. Accumulating evidence suggest also that fenugreek may have neurodevelopmental, neurobehavioral and neuropathological side effects. It is suggested that future studies would be conducted to identify molecular and cellular mechanisms underlying the fenugreek toxicological properties.

Contents

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1. Introduction

Fenugreek (*Trigonella foenum graecum*) is one of the oldest traditional medicinal plants, cultivated in the Indian subcontinent, parts of west Asia, Middle East, North Africa, United Kingdom, Russia, Mediterranean Europe, Australia, US and Canada (Acharya et al., 2008). Fenugreek belongs to the family of Fabaceae and is used as a herb (dried or fresh leaves), spice (seeds), vegetable (fresh leaves) but also as a condiment in artificial flavoring of maple syrup or in the production of steroid and other hormones for the pharmaceutical, nutraceutical and functional food industries (Zandi et al., 2015). Fenugreek was traditionally recommended for increasing milk production in lactating women (Ghedira et al., 2010; Bukhari et al., 2008; Damanik et al., 2004) and, interestingly, as an appetite enhancer by Moroccan Saharawi women to increase their physical attractiveness (Rguibi and Belahsen, 2006). In recent years, research on fenugreek has identified a number of health benefits such as antidiabetic, hypocholesterolemic, antilipidemia, antioxidant, hepatoprotective, anti-inflammatory, antibacterial, antifungal, antiulcer, antilithigenic, anticarcinogenic and neuroprotective effects in both experimental animals as well as clinical trials in humans (for review: Neelakantan et al., 2014; Yadav and Baquer, 2014; Nathiya et al., 2014; Adedapo et al., 2014). Although beneficial properties of fenugreek have been reported by a large number of research groups, studies of its toxicological effects increase considerably.

Toxicity of fenugreek has been studied because of large antifertility and abortifacient effects as well as locomotor disorders reported after ingestion of fenugreek during the 1960s (Casey, 1960; Abdo and Al-Kafawi, 1969; Lustig, 1958; Adler et al., 1960, Adler and Egyed, 1961). Both previously published and new findings focusing on the evaluation of acute, sub-acute and subchronic toxicity of the fenugreek seeds and leaves are presented here to discuss the cumulative evidence, which suggests that consumption of fenugreek induced some serious toxicological side effects.

2. Methods

Electronic searches were performed in MEDLINE (PubMed), Scopus, Google Scholar, BIOSIS, Cochrane Trials Registry and Web of Science databases, using the following key words: Fenugreek, *Trigonella foenum graceum*, toxicity, teratogenicity, clinical toxicity, allergenicity, antigenicity, neurotoxicity, anti-fertility effect, genotoxicity, mutagenic, histopathology, cellular and molecular effects, to identify relevant articles in English and French. Searches were also performed from the references of the systematic review articles, Meta-Analysis, thesis, books, and conference presentation. When assessment of eligibility based on the title and abstract was insufficient, the full text of the articles was obtained. No time limit was established. The second screening of those full text articles was then performed. We identified 150 potentially relevant articles of which 116 were selected to compose the present review.

3. Results and discussions

3.1. Chemical composition

Fenugreek contains many active components such as flavonoids, alkaloids, amino acids, coumarins, vitamins, saponins and other antioxidants summarized in Table 1.

Saponins, a class of glycosylated triterpenes found to be 4.8% in seed with two major steroidal sapogenins compounds diosgenin and yamogenin, are known to exhibit antifertility activity and causing teratogenicity through their estrogenic and androgenic activities (Al-Yahya, 2013; Dande and Patil, 2012; Kassem et al., 2006). Fenugreek contains 35% alkaloids, primarily trigonelline with high therapeutic potential and low toxicity (Zhou et al., 2012). Trigonelline degraded to nicotinic acid and related pyridines during roasting is responsible for flavour of the seed (Naidu et al., 2011). Furthermore, alkaloid and volatiles of fenugreek seed cause bitter taste and bad odour due to which people try to avoid consumption of fenugreek seed and its products (Ahmad et al., 2016). Polyphenolic compounds, like flavonoids, represent more than 100 mg/g and have high antioxidant activity (Naidu et al., 2011). Since flavonoids readily cross the placenta, at higher doses, flavonoids may lead to the formation of reactive oxygen species, and ultimately DNA damage which may in turn increase the possible health risks in fetal development (Skibola and Smith, 2000). Several coumarin compounds in fenugreek seeds (e.g. lactone orthodihydroxy cinnamic acid and scopoletin) have been suggested to affect platelet aggregation which might increase the risk of bleeding and then might enhance the activity of other anticoagulants, including warfarin (Lambert and Cormier, 2001; Abebe, 2002). We noted also that some cases of hepatotoxicity have been reported from patients treated with coumarin (Abraham et al., 2010). Fenugreek seeds are also rich sources of vitamins, minerals and antioxidants. Other constituents of fenugreek include carbohydrates, mainly mucilaginous fiber (galactomannans), fixed oils (lipids), volatile oils, free amino acids, calcium and iron etc.

3.2. LD_{50} (half maximal lethal dose) of fenugreek

Several toxicological studies have focused on the evaluation of acute toxicity of the fenugreek seeds and leaves and have shown that LD_{50} for the measurement of teratogenic dosage of fenugreek is different between species and sex (Table 2).

3.2.1. Oral administration

Earlier investigations of toxic effects of fenugreek compound, trigonelline, orally administered to rats shows a LD_{50} at 5 g/kg bw (Mishkinsky et al., 1974). However, debitterized fenugreek powder in mice and rats administered intragastrically for both sexes failed to induce any symptom of toxicity or mortality up to a maximum practical dosage of 2 and 5 g/kg bw, respectively (Muralidhara et al., 1999).

It's interesting to mention that a novel water-soluble fenugreek seed extract enriched in >60% furostanolic saponins didn't induce any mortality or gross toxicity at a higher dose level of 5 g/kg bw in female rats (Swaroop et al., 2014). This study suggests that the acute