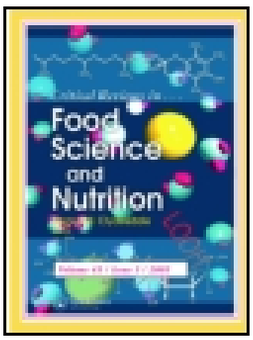

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REVIEW

Advances on application of fenugreek seeds as functional foods: Pharmacology, clinical application, products, patents and market

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ABSTRACT

Trigonella foenum-graecum L. (fenugreek) is one of the oldest applied medicinal herbs. Significant pharmacological and clinical evidence have highlighted the medicinal application of fenugreek. Explore the current knowledge regarding the bioactivity (animal aspects) and clinical application of fenugreek and its bioactive components, as well as the products, markets and patents related to fenugreek. This review highlights the phytochemicals, bioactivity (animal aspects) and clinical application of fenugreek from recent literatures and products, markets and patents from database. Until now, more than 100 phytochemicals have been isolated from fenugreek seeds, mainly including polysaccharides, saponins, alkaloids, phenolic acids, and flavonoids. Fenugreek extract and its bioactive compounds showed excellent antidiabetic activity and anti-obesity activity in animal and human study. Although the fenugreek seed has been used as TCM raw materials for a long time of period in China, China is lacking the research of fenugreek in both depth and width.

KEYWORDS

Fenugreek seeds; foods; bioactivity; clinical application; products; markets and patents

Introduction

Trigonella foenum-graecum L. (fenugreek), a spice bean crop, is one of the oldest applied medicinal herbs in history dating back to Hippocrates and ancient Egyptian times (Jensen 1992), and evidence showed that the fenugreek seeds acquire anti-oxidant potential in seeds and leaves of fenugreek. Fenugreek is originated in the Mediterranean region. Nowadays, India is the major producer of the fenugreek in the world with a production of 45,000–55,000 tons per year (Vikas 2003). Fenugreek has long time been used as a cooking material and a traditional medicine for its therapeutic properties (Basch et al. 2003).

The fenugreek seeds are traditionally applied for impotence, prolactin, lowering blood sugar, as well as the treatment for some symptoms like eczema, burns, gout, diarrhea, abdominal distension, stomach discomfort. In China, fenugreek seeds recorded in 'Jia You Medical Herbs' (1060 A.D.) have been used to warm and tonify kidney-yang, dissipate cold and relieve pain. Fenugreek seeds also have been used in Europe to treat temporary lack of appetite and skin inflammations (http://www.ema.europa.eu).

Significant pharmacological and clinical evidence have highlighted the medicinal application of fenugreek seeds as anti-diabetic activity, hypolipidemic activity, anti-obesity activity, anticancer activity, anti-inflammatory activity, antioxidant activity, antifungal activity, antibacterial activity, and so on. The benefits of fenugreek depended on its bioactive components.

Recently, several qualitative reviews on fenugreek seeds have been published. Fuller and Stephen (2015) discussed the mechanisms of actions 4-hydroxyisoleucine and fiber from Fenugreek on metabolic syndrome. Ouzir et al. (2016) described the toxicological side effects related to consumption of fenugreek. Venkata et al. (2017) summarized the potential of fenugreek for disease prevention and health improvement with special emphasis on cellular and molecular mechanisms. Żuk-Gołaszewska and Wierzbowska (2017) reviewed the botanical aspects of fenugreek including productivity, properties and applications. This review summarizes current knowledge regarding the pharmacology (animal aspects) and clinical application of fenugreek and its bioactive components, as well as the products, markets and patents related to fenugreek.

Bioactive components

Till now, more than 100 phytochemicals have been isolated and identified from fenugreek seeds, mainly including polysaccharides, saponins, alkaloids, polyphenols, and flavonoids

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(Taylor et al. 1997; Rayyan et al. 2010; Król-Kogus et al. 2014; Mandegary et al. 2012). Fenugreek seeds mostly contain soluble galactomannan (about 30%), insoluble fiber (about 20%), protein (20–30%), fat (5–10%), alkaloids, which are mainly composed of trigonelline (0.2–0.38%), diosgenin (0.6–1.7%) and yamogenin-based saponins (about 4.8%), 4-hydroxyisoleucine (about 0.09%), volatile oil (about 1.25%) and *C*-glycosylflavones of apigenin and luteolin (about 0.10%).

Quality control

Chinese Pharmacopeia and EU Pharmacopeia identified fenugreek seeds by the Thin Layer Chromatography (TLC) method. Chinese pharmacopeia defined the content of trigonelline in raw material should higher than 0.45% (HPLC). SEC-MALS can be used to quantitatively analyze the soluble polysaccharide such as galactomannan. HPLC and HP-TLC can accurately analyze saponins, flavonoids, diosgenin and yamogenin.

Bioactivity (animal aspects)

Modern pharmacological studies confirmed that fenugreek seeds have anti-diabetic activity, hypolipidemic activity, anti-obesity activity, improvement of sexual function, anti-ulcer activity, anti-analgesic activity, antioxidant activity and anti-inflammatory activity. The indications for fenugreek seeds in the European herbal monograph published by European Medicines Agency (EMA) are temporary loss of appetite and mild inflammation of the skin.

Anti-diabetic activity

The natural products are proven to be effective anti-diabetic agents (Cao et al. 2018; Zhao et al. 2018a, 2018b, 2019). Early in 1986, fenugreek seeds, defat fenugreek seeds, fenugreek gum and ripe fenugreek were found to effectively lower the blood sugar level in diabetics and improve the insulin response (Sharma 1986). Fenugreek seeds contained a large amount of soluble dietary fiber (galactomannan), diosgenin, trigonelline, 4-hydroxyisoleucine, flavone *C*-glycosides and other ingredients that showed hypoglycemic activity on animals. The soluble dietary fiber, namely galactomannan, reduced the blood sugar level in diabetic objectives by delaying gastric emptying of carbohydrates, inhibiting digestive enzymes, increasing bowel movements and regulating intestinal flora (Hamden et al. 2010; Zentek et al. 2013). Diosgenin can protect pancreatic islet β-cells, up-regulate hepatic glucose kinase, down-regulate hepatic glucose heteroplasia, and enhance the anti-oxidase activity (Fuller and Stephen 2015). Diosgenin also improved the symptoms of diabetes by force the differentiation of adipose cell and anti-inflammation (Kiasalari et al. 2017).

Trigonelline showed anti-diabetic activity by improvement of insulin signaling pathway (Aldakinah et al. 2017), attenuation of endoplasmic reticulum stress and oxidative stress in type 2 diabetic rats (Mayakrishnan et al. 2015), affecting the regeneration of pancreatic islet β-cells, the secretion of insulin, and glucose metabolizing enzymes (Zhou et al. 2012). Flavone *C*-glycosides can inhibit digestive enzymes, activate insulin signaling, and reduce the formation of advanced glycation end products (Xiao et al. 2016) and 4-hydroxyisoleucine can stimulate pancreas to secrete insulin. The essential oils from fenugreek seeds with ω-3 fatty acids can inhibit pancreas α-amylase and maltase activity in diabetic rats and protect pancreatic islet β-cells (Hamden et al. 2011).

The water extracts of fenugreek seeds (10:1) can prevent diabetic nephropathy in rats by lowering blood glucose, enhancing kidney function and inhibiting the accumulation of extracellular matrix (Jin et al. 2014). Fenugreek seeds extract (80% methanol, 5:1) attenuated endoplasmic reticulum stress and oxidative stress to show hepatoprotective effects in type 2 diabetic rats (Mayakrishnan et al. 2015). The powder fenugreek seeds normalized free radical metabolism in diabetic animals (Ravikumar and Anuradha 1999). Fenugreek added to rice and wheat diets can lower GI by delaying gastric emptying and increased intestinal transit time, decreasing glucose absorption, and inhibiting starch digestion due to soluble fiber and galactomannans (Sampath et al. 2011). Fenugreek seeds can alleviate oxidative stress-mediated nephropathy in streptozotocin-induced diabetic rats (Pradeep and Srinivasan 2018).

Anti-obesity activity

The dietary fibers such as galactomannan from fenugreek seeds appear significant anti-obesity function by forming a viscous gel in the intestine and inhibiting glucose and lipid absorption (Hamden et al. 2010). The water extract of fenugreek seeds (20:1) reduced fat accumulation induced by high-fat diet and improved dyslipidemia in rats via inhibiting fat digestion and absorption, improving metabolism of glucose and fat, enhancing insulin sensitivity, improving antioxidant capacity and reducing lipase (Kumar et al. 2014). The extract of fenugreek seeds and 4-hydroxyisoleucine can reduce plasma triglyceride levels in obese mice and lower the increasing body weight (Handa et al. 2005).

A 6-week double-blind randomized placebo-controlled parallel trial involving 39 overweight male volunteers found that the administration of a fenugreek seed extract decreased dietary fat consumption (Chevassus et al. 2010). Yamogenin inhibits lipid accumulation through the suppression of gene expression in fatty acid synthesis in hepatocytes (Moriwaki et al. 2014).

The water extract of fenugreek (20:1) (galactomannan, 32.5%; total polyphenols, 2.31%; total flavonoids, 0.255%) can inhibit fat accumulation and dyslipidemia by inhibition of impaired lipid digestion and absorption, improvement in glucose and lipid metabolism, enhancement of insulin sensitivity and activity, increased antioxidant defense, and down-regulation of lipogenic enzymes (Kumar et al. 2014; Kumar and Bhandari 2016).

Diosgenin from fenugreek can attenuate abnormal hepatic lipid metabolism *in vivo*, shrink diabetic rat's adipose

cells and raise the mRNA expression level of adipose tissue differentiate gene (Fuller and Stephen 2015). Trigonelline attenuated the adipocyte differentiation and lipid accumulation in 3T3-L1 cells (Ilavenil et al. 2014). In a single blind, randomized, crossover study, fenugreek fiber significantly increased satiety and reduced energy intake at lunch (Mathern et al. 2009).

Improve sexual function

Jiayou Materia remarked that fenugreek seeds can nourish kidney, clear damp and dispel cold inside the body. The water extract of fenugreek can enhances sperm motility and the expression of the cation sperm channel proteins in mice (Kim et al. 2015).

A 6-week clinical trial involving 60 healthy man aged between 25 and 52 years old indicated that standardized fenugreek seeds extract can enhance male's sexual desire, improve sexual life quality, and regulate orchidic hormone and lactogen level (Steels, Rao, and Vitetta 2011). A research with 80 healthy women aged between 20 and 49 years old found that the fenugreek standardize extract (33:1) may raise the level of free testosterone and estradiol and also increase sexual desire and excitement (Rao et al. 2015). A randomized controlled pilot study with 60 healthy young men revealed that the resistance training for 8 weeks and intake 600 mg fenugreek everyday enable to enhance the ability of synthetize and metabolize androgen (Wankhede, Mohan, and Thakurdesai 2016).

Galactogogue function

According to a 6-year investigation involving in 1,200 women, the administration of 2–3 fenugreek capsules (580 mg or 610 mg) 3 times per day makes most of experimental subjects to produce more breast milk in 24–72 hours (Huggins 1998).

The standardize extract of fenugreek seeds (76% trigoneoside and 15% vicenin) regulated anti-inflammatory factors, inhibited pulmonary fibrosis and decreased apoptosis to avoid pulmonary fibrosis (Kandhare et al. 2015). Specifically, the methanol extract of fenugreek seeds rich in alkaloids and flavonoids showed significantly antinociceptive activity and anti-inflammatory activity (Mandegary et al. 2012). Feed with 10% fenugreek powder and 2% freeze dried garlic powder for 8 weeks can improve heart tissue pathological change and regulate blood lipid in myocardial infraction rats (Mukthamba and Srinivasan 2015).

Improvement in learning and memory

Supplementation of fenugreek extract or/and choline with DHA to ovariectomized rats significantly improved learning and memory and decreased neural cell deficits (Anjaneyulu et al. 2018). Trigonelline mitigates lipopolysaccharide-induced learning and memory impairment in rats due to its anti-oxidative and anti-inflammatory effects (Khalili et al. 2018).

Reducing and healing liver's hepatotoxicity and genotoxicity

A polysaccharide extract from fenugreek seeds significantly reduced and healed in a dose-dependent manner in liver's hematological and genotoxic induced by thiamethoxam injuries (Feki et al. 2019).

Clinical application

Evidence from clinical and human studies showed that fenugreek seeds are helpful to control of blood glucose level in diabetics. A meta-analysis of 10 clinical studies indicates fenugreek seeds can significantly decrease the blood glucose level by 0.96 mmol/L and glycosylated hemoglobin level by 0.85% (Neelakantan et al. 2014). 60 NIDDM patients with fenugreek seeds treatment for 24 weeks (25 g powder before lunch and dinner per day) effectively decreased the cholesterol level, LDL-C level and triglyceride level whereas HDL-C level (Sharma et al. 1996). In a cross-sectional study involving 100 type 2 diabetic patients (6 %$<$ HbA1c $<$ 7%) administrated with 2 g fenugreek powder per day for 6 months, the level of glycosylated hemoglobin was decreased by 0.4% averagely, and the lost-weight was 5.5 kg on average (Jagannathan et al. 2015).

Thirty-eight T2DM patients treated with fenugreek powder for 2 months, the levels of blood sugar and triglyceride were significantly reduced (Geetha, Shivananda, and Manjula 2011). In a double blind placebo controlled study, 25 early T2DM patients administrated with the water extract of fenugreek seeds for 2 months (1 g/d), the blood sugar was controlled well and insulin resistance was inhibited distinctly (Gupta, Gupta, and Lal 2001). In another randomized controlled trial, 102 T2DM patients fed with 50 g fenugreek powder per day and medicine cure, the combined intervention is more effective in lowering glycosylated hemoglobin level than usual treatment (Ansari and Ansari 2011). A randomized controlled trial lasting 3 years with 140 early diabetic patients aged between 30 and 70 years old showed that intake of 5 g fenugreek twice per day can prevent or delay the development of diabetes with no side effects (Gaddam et al. 2015). Fenugreek seed consumption (15 g/day) significantly decreased in high-sensitivity C-reactive protein and increase in superoxide dismutase activity in T2DM patients (Tavakoly et al. 2018). In a randomized controlled clinical trial, fenugreek (2 g/day) significantly increased the fasting insulin level in T2DM patients (Najdi et al. 2019). In a 12-week, randomized, double-blind, placebo-controlled, multi-center study, the standardized fenugreek seed extract is a safe, effective, and well-tolerated add-on oral medication therapy in T2DM patients inadequately controlled with a sulfonylurea (Kandhare et al. 2018).

American *Cepham* Company developed Furocyst^{TM} capsule with fenugreek extract, which contains 40% furostanol saponins. Furocyst^{TM} capsule (1000 mg/d) can low ovarium volume effectively, increase the level of luteinizing hormone and follicle-stimulating hormone without any side effects (Swaroop et al. 2015). A randomized double-blind placebo trial in Australia involving in 120 healthy men aged between

Table 1. New products introduced into the global market.

Therapy	Name	Ingredients	Date	Country	Corporation
Hay fever, respiratory tract, infections, sinusitis	GARLIC VITC H/RAD	Althaea; ascorbic acid; fenugreek; garlic; horse radish	6/1/2000	New Zealand	HEALTHERIES
	ALLERGEZE	Ascorbic acid; bioflavonoids; fenugreek; garlic; horseradish	5/1/2006	Australia	GREENRIDGE
	B/G HAYFEVER&ALLGY	Ascorbic acid; fenugreek; garlic; horseradish; marsh mallow	8/1/2004	Australia	BIOGLAN LTD
	CONGEST-X	Ascorbic acid; fenugreek; garlic; horseradish; marshmallow; wasabi	11/1/2004	New Zealand	GOOD HEALTH
	ENERVITE SINUS & HAYFEVER	Ascorbic acid; fenugreek; horseradish; zinc chelate	9/1/2004	Australia	ENERVITE
	GARLIC CENOV	Fenugreek; garlic; horseradish; marshmallow; parsley; vitamin C	1/1/1997	Philippines	CENOVIS
	HORERADISH COMPLX	Arizona garlic; fenugreek; horseradish; marshmallow; thyme; vitamin A; vitamin C	8/1/1997	Australia	BIO ORGANICS
	HORSERAD GARLIX + C	Ascorbic acid; fenugreek; garlic; horseradish	9/1/2005	Singapore	BLACKMORES
	HORSERADISH/GARLIC	Ascorbic acid; fenugreek; garlic; horseradish	3/1/1999	New Zealand	BLACKMORES
	N/O GARL/VITC/HR	Ascorbic acid; fenugreek; garlic; horseradish; marsh mallow	5/1/2006	New Zealand	SYMBION HEALTH
	OLIVELIFE	Ascorbic acid; colecalciferol; lysine; fenugreek; olive leaf; rose hip	6/1/2004	Australia	HEALTH DIRECTION
	T/S SINUS/HAYFEVER	Fenugreek; garlic; golden seal; horseradish; marsh mallow	11/1/2001	New Zealand	THOMPSONS
Insufficient lactation	FENOLACT	Calcium carbonate; calcium caseinate; fenugreek	5/1/2005	Egypt	EL-OBOUR AVERRO.PH
	HERBANA	Caraway; dill; fennel; fenugreek	10/1/2003	Egypt	PHARMA CURE
	LACTOFLOW	Carvi; fenouil; fenugreek	3/1/2008	French	MEPACO
	LACTOMAX	Caraway; fennel; fenugreek; soya bean oil	10/1/2003	Egypt	MACRO INT.
	LACTO-TON	Calcium citrate; caraway; fennel; fenugreek	10/1/2005	Egypt	EGYPTIAN GROUP
	SEKEM MUMMY HERB	Aniseed; caraway; chamomile; fennel; fenugreek	3/1/1995	Egypt	SEKEM
Nutritional supplementation	APPETITO	Blackberry; fenugreek; ginger; honey; pollen; wheat germ	4/1/2003	Kuwait	PHARMALIFE
	BIO-NUTICARE	Barley; fenugreek; lupin; magnesium stearate; phytosterols; silicon dioxide; soya; sunflower	3/1/2007	South Africa	ENALENI PHARM
	GRD HORS & GARLIC	Ascorbic acid; betacarotene; fenugreek; garlic; horseradish; manganese; thyme; zinc	5/1/2000	New Zealand	GUARDIAN PHCY
	NEW PADIBU	Bee pollen; fenugreek; plantago major; *Talium paniculata*; tribulus terrestris; yohimbe	7/1/2004	Indonesia	KIMIA FARMA
	SIWA LACTO-OIL	Fenugreek	11/1/2007	Egypt	ARAB GELATIN
Improves glycemic control.	DIATONE	Fenugreek; ginkgo biloba; gymnema sylvestre; lecithin; minerals; vitamins	1/1/2008	Egypt	EGYPTIAN GROUP
	GLUCOFACTORS	Chromium; fenugreek; gymnema sylvestre; thioctic acid	1/1/2005	Australia	FIT SALES PTY LTD
	GYMNEMA&FENUGREEK	Bitter melon; fenugreek; gymnema; holy basil	6/1/2006	Malaysia	BIO-LIFE (MAL)
	N/W CARB STOP	Fenugreek; green tea; gymnema sylvestre; phaseolus vulgaris	4/1/2005	Australia	PHARMACARE
Aids	BILBERRY 3000 PLUS	Bilberry; eyebright; fenugreek; golden seal	5/1/2008	Australia	EAGLE
	GLUCOBALANCE	Bitter melon; fenugreek; ginkgo biloba; gymnema; thioctic acid	1/1/2006	Indonesia	KIMIA FARMA
	NUTRAC ENZYME PLUS	alpha galactosidase; amylase; cellulase; fenugreek; ginger; invertase; lipase; papaya; protease	4/1/2004	Indonesia	TOTAL C. NUTRACEUT
	ARKOG.FENUGREC	Fenugreek	3/1/1999	French West Africa	ARKOPHARMA
Digestive disorders	BOWEL&INTEST CLNSR	Fenugreek; ginger; inulin; psyllium	4/1/2004	Australia	NATURES OWN
	NEFROMEX	Fenugreek; orthosiphonis; phyllanthus; sericocalysis	8/1/2008	Indonesia	KONIMEX
Kidney stones	BILBERRY 3000 PLUS	Bilberry; eyebright; fenugreek; golden seal	5/1/2008	Australia	EAGLE

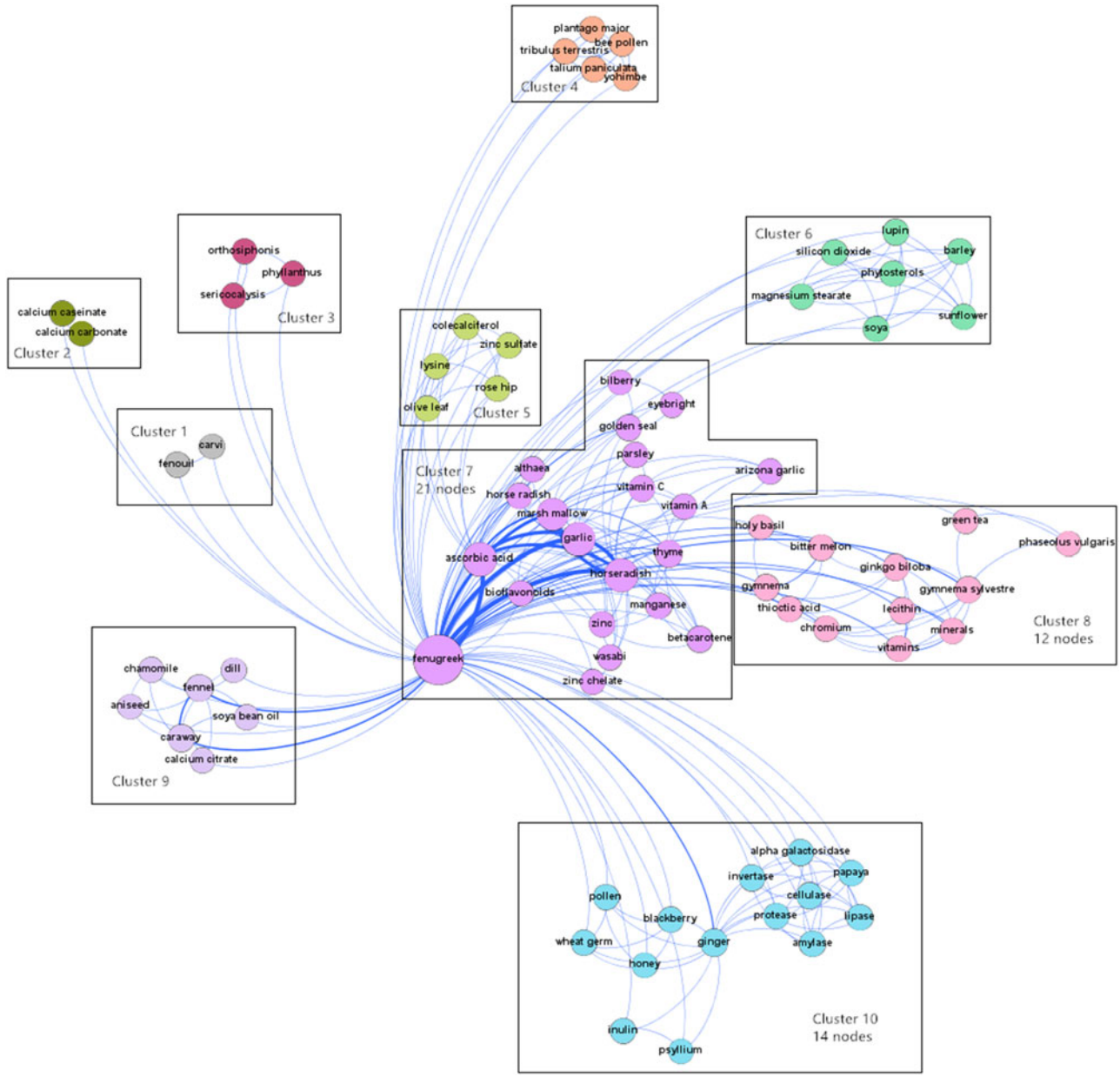

Figure 1. The combinational network of 35 fenugreek-relevant medicines.

43 and 70 years old, taking standardized fenugreek seeds extract (600 mg/d) for 12 weeks can reduce age-related symptoms of androgen decrease, increase testosterone levels and improve sexual function (Rao et al. 2016). In a double blind trial with placebo effect, fenugreek can significantly increase in quality of the life and lung function tests and IL-4 levels in mild asthma (Emtiazy et al. 2018).

Toxicity and safety

Fenugreek seed is a GRAS (generally recognized as a safe food additive) ingredient approved by FDA. Fenugreek seeds showed very low toxicity *in vivo* without any side effects and serious adverse events. Allergic reactions including bronchospasm, asthma, diarrhea, flatulence, and dizziness were rarely reported. The acute toxicity tests showed that fenugreek seed is nontoxic for animals, and the maximum dose was 5 g/Kg weight. However, due to its potential stimulation on the uterus, fenugreek seeds are forbidden for women during pregnancy. After fed with fenugreek seeds for 12 weeks, loss of appetite and diarrhea were observed in Sprague-Dawley rats (Muraki et al. 2011). The acute and subacute toxicity tests of oral standardized fenugreek seed extracts (76% trigoneoside Ib and 15% vicenin 1) for 28 days showed that the oral dose of 250 mg/Kg has no histopathologic or toxicological effects on the weight, organ, appetite, behavior, hematological index, blood biochemistry and urine routine in laboratory mice (Kandhare et al. 2016).

Marketed medicines related to fenugreek seeds

IMS LifeCycle was used to identify the fenugreek products worldwide. For each product, IMS identifies its ingredients, country, launch date, and its corporation. 35 New products related to fenugreek seeds were found to be introduced into 7 therapeutic areas around the global market by 32 different

firms between 1995 and 2008 (Table 1). However, there are no any medicines and drugs found in CFDA database.

Fenugreek drugs data distribution

The medical treatment is not completely separated, in fact, some of these are crossed. For example, N/W CARB STOP not only can prevent Prophylaxis of hyperglycemia, but also has better effect to hypertriglyceridemia. GLUCOBALANCE is helpful in treating diabetes mellitus. And the indications of GARLIC CENOV are a temporary relief of colds, influenza, a protection against ischemic heart disease and a lipid-lowering effect.

There are only two products singly containing fenugreek seeds. One is used to against digestive disorders, and depressive disorders; another is used for nutritional supplementation. Other products are composed of more than three ingredients. It is suggested that fenugreek seeds are commonly combined with other herbs in application.

Fenugreek medicines' ingredients network

As shown in IMS data, the results can predict the trend of product development in the future. Here, the components in the existing 35 medicines were analyzed using the Gephi to draw a network to explore their relationship (Figure 1). It reflects a positive role in this research and the application in the new drug research and development areas.

The complex network approach was utilized to propose the combinational relationships of 78 components in 35 fenugreek-relevant drugs. The nodes indicate the components of fenugreek drugs, and the edges represent the combinational relationships between ingredients with the weight as combinational frequency. Further, the nodes were divided into 10 clusters through modularity algorithm (Newman 2006). The combinational network was analyzed and visualized by *Gephi* (Bastian, Heymann, and Jacomy 2009). As shown in Figure 1, ascorbic acid, garlic, horseradish, and marshmallow are top components, which are frequently combined with fenugreek seeds through network analysis. Meanwhile, the nodes of same cluster provide a significant clue to investigate new combinations of components for exploring potential new drugs of fenugreek.

Patents related to fenugreek seeds

The global existing patents of fenugreek offer the present research status of fenugreek. Based on 1204 patents recorded in the database of the incoPat, 213 patents involved in human medicines, dietary supplement and cosmetics. The detailed information of these patents is summarized in Table 2, and the histogram excluding China is shown in Figure 2. These patents were classified into six groups based

Table 2. Patents related to fenugreek seeds for medicines and dietary supplements.

	A	B	D	AB	AD	BC	BD	CD	E	F	ABD	ACD	ABCD	Total
AT			1							1				2
AU					2					1				3
CH											2			2
CN	12	23		4	37		4		2	1	22	2	7	114
DE					2		1			9				12
DE,CH	1													1
DK				3										3
FR			6							1				7
FR,IL		1												1
GB	1													1
GB,AU,IL											1			1
HU										1				1
IN	5	3		4	7	2	3	1			9			34
JP		4								1				5
KR	1													1
KY										1				1
MH		1		1	1								2	5
NL		1	2		1									4
PT	1													1
CN-TW	1	1												2
US	3	2			5					1	1			12
Total	25	36	9	12	55	2	8	1	2	17	35	2	9	213

Country code corresponding to the country: AT = Austria; AU = Australia; CH = Switzerland; DE = Germany; DK = Denmark; FR = France; IL = Israel; GB = England; HU = Hungary; IN = India; JP = Japan; KR = Korea; KY = Cayman Islands; MH = Marshall Islands; NL = Netherlands; PT = Portugal; US = America.

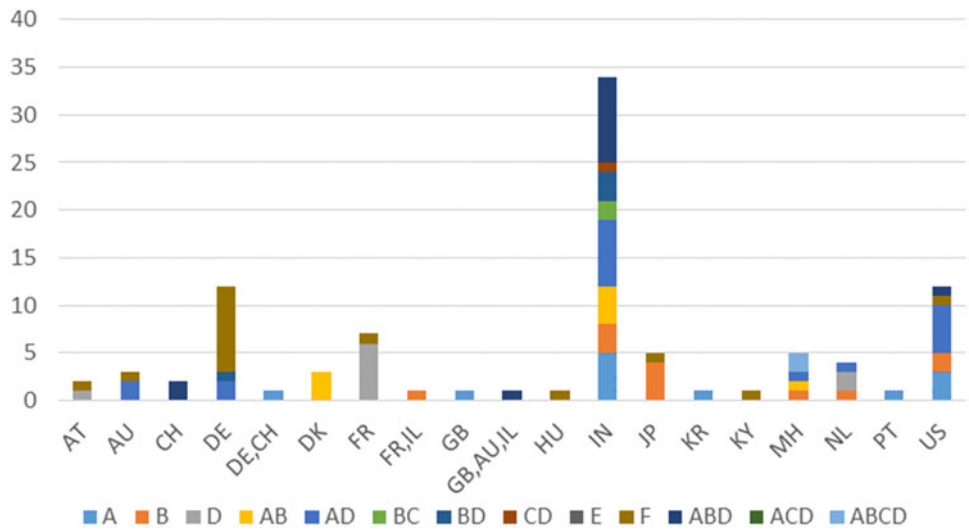

Figure 2. Patent information of fenugreek seeds for drugs and dietary supplement. (A = Compounds; B = Technological; C = Pharmaceutical form; D = Therapeutic application; E = Design; F = Cosmetic.) In addition, patents with multiple protection objects are assorted as mixed-categories. (AB, AD, BC etc.).

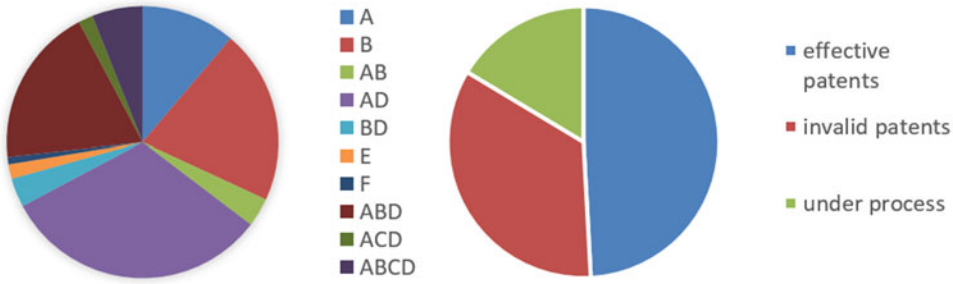

Figure 3. Patent information of fenugreek for human drugs and dietary supplement in China. (A = Compounds; B = Technological; C = Pharmaceutical form; D = Therapeutic application; E = Design; F = Cosmetic.) In addition, patents with multiple protection objects are assorted as mixed-categories. (AB, AD, BC etc.).

on the objects claimed of patents. (A = Compounds; B = Technological; C = Pharmaceutical form; D = Therapeutic application; E = Design; F = Cosmetic.) In addition, patents with multiple protection objects are assorted as mixed-categories. (AB, AD, BC etc.)

The reason why the histogram excluded China is that among the 213 patents worldwide from 22 countries and regions, China including Taiwan has the most patents consisting of 57 effective patents, 40 invalid patents and 19 patents, which are under processing (Figure 3). A high proportion of invalid patents in China patents applications is not strict, which made the enormous difference in patent quality larger (Hu and Jefferson 2009). In other words, the large number of fenugreek patents issued by China is more a measure of the value of the Chinese market than a measure of patent value. In these 116 patents, 37 of those protect both compounds and therapeutic application, and there are 24 patents protecting technological innovation. Besides, 22 patents protect compounds, technological innovation and therapeutic areas at the same time. In other countries, India has the most patents, because India is the origin of the fenugreek. Furthermore, the United States and Germany have more fenugreek products, as well as more fenugreek patents.

The production and market of fenugreek seeds

Fenugreek seeds production and export

Although the number of spices has been recorded from time immemorial, only few dozens are important – black pepper, ginger, turmeric, cumin fennel and fenugreek. By comparing the current spice market and application worldwide, a huge differentiation has been found in the Chinese fenugreek seeds comparing with others. Therefore, this review focused on the fenugreek, although problems frequently arise with production and trade statistics since spice products are frequently combined under one heading (Edison 1995).

The fenugreek agriculture had undergone a substantial improvement after the Agricultural machinery was widely applied. However, the global fenugreek seeds production pattern has not been rapidly changed by far. Fenugreek or fenugreek seeds as a spice or medical raw material were still predominantly cultivated in India. India as an agriculture based country, spice remain an important role in its only culture. Also as the world largest spice producer and exporter, Indian government offered annual spice statistic report to investigate the global spice trends. Previews record demonstrates the fenugreek cultivation area and total production value remain in a stabilized level with alternative increasing rate achieved by the cultivation improvement from 1970s to 1990s. However, the export value exhibited a relatively high increasing trend over the years. The export increased from 1,549 tons (1975) to 15,135 tons (1995), which reflects an enhanced global fenugreek trade. The major fenugreek import regions include Europe, Middle East and North American. Major fenugreek applications in those regions are flavor spice, dietary supplement raw material and mixed tea ingredients. These recorded statics is lack of accuracy- all three forms of traded fenugreek are often aggregated with other seeds, spices or extracts in trade statistics thus impeding the exact calculation of fenugreek traded volume (Petropoulos 2002). Alternatively, a predictable total amount was given by adding 30% more over the statistic record. On the other hand, the recent Indian annual export performance report (from 2006 to 2014) has been published by spice board of Indian. Figure 4 exhibited Indian total fenugreek production and cultivation area remain in an overall increase trend from 2006 to 2014. The export number exhibited rapid increasing from 11,100 tons (2007) to 21,000 tons (2009). This growth of export value could be attributed by the newly added import country-Yemen Republic. Fenugreek export exhibited a highest growth rate of 395.30% and 484.16%, respectively in case of Yemen (Solanki 2015). In numbers, from 2007 to 2009, Yemen imported 8,919 tons out of total 52,850 tons. Other major countries to which Indian fenugreek products are mostly exported are United Arab Emirates (UAE), Sudan and USA. Of those most fenugreek imported countries, only USA imported fenugreek as a raw material mostly for making dietary supplements and relative functional groceries. In UAE and Sudan, fenugreek was primarily used as the cooking ingredient-often used as flavor ingredient in different curry. Fenugreek exported to the US was largely increased from 313 tons (2009) to 1,648 tons (2015). Ancient Chinese believed that fenugreek have many benefits; it's been applied in many traditional Chinese medical recipes. However, no record reported China import any fenugreek from India exhibit a possible self-sufficient fenugreek market in China (Figure 5).

Supplement product and market of fenugreek seeds

Fenugreek has been widely used as an important dietary supplement in USA. In addition, fenugreek health food has

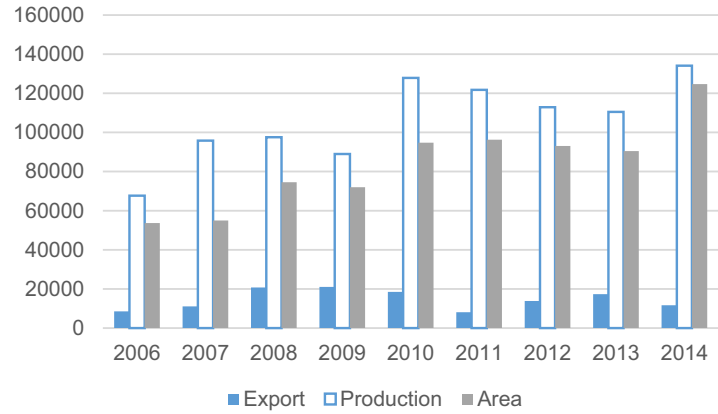

Figure 4. Total area, production and export of fenugreek from India from 2006 to 2014. Data Scouse: India Spice Board.

Figure 5. Map of the global fenugreek research major area trend and density.

Table 3. Ranked top sale single compound herb supplement in Amazon US online store.

Items	Total result
Ginseng	12,587
Turmeric	5907
Black Seed	5534
Saw Palmetto	4137
Cinnamon Bark	2568
Basil Leaf	2403
Fenugreek	2159
Hops	1408
Black Raspberry	1305
Horsetail	952
Catnip	499
Lung tonic	232
Skullcap	112

been launched in several developed countries, such as UK, Germany, France, Spain, Japan, etc. Fenugreek products mainly use its raw powder, extracts and active compounds, whose main dosage form is capsule. Its seeds are the most valuable plant part (Olang et al. 2012). Hence, most supplements are made from fenugreek seed or seed extracts. Regard of accessibility and reliability, USA fenugreek seeds market was analyzed through data collection from amazon. Data were collected and assorted by sale values and trends. The overall herb dietary supplements result ranked by total sale numbers were listed in Table 3.

Searching results from fenugreek supplements are matched with some other popular dietary supplements. Respectively, fenugreek dietary products played important roles in the USA dietary supplement trade. Fenugreek supplements were further categorized by function and form. Over 200 products were screened by ranking custom review. Seventy-six products were chosen, associated with three form-tea, capsule and raw material. Statistically, capsule is the most commonly supplement form, and 58 out of 76 is formulated as capsule. In terms of flavoring-raw seeds are golden in color with maple flavor but bitter in taste (Basch et al. 2003). With its unique flavor, the fenugreek seeds are also added as functional and flavor ingredients in tea (12 out of 76 are formulated as tea). Only small portion (6 out of 76) of the total product were raw seeds and concentrated extract with specific purpose. Concentrated extract labeled with sleep promotion purple with partial customer is reported that the concentration does promote their sleep quality, although there was not any experiential evidence to support this clam. In terms of functionality, sport supplement contains fenugreek often labeled with improving overall male health, energy booster and improving testosterone level. Recent studies on fenugreek seeds extracts support their effectiveness in promoting lean body mass, and lowering cholesterol (Basch et al. 2003). These effects are purported to be mediated through an aromatase and 5α reductase inhibition, thereby increasing total testosterone levels by blocking its conversion to estrogen and dihydrotestosterone, respectively (Wilborn et al. 2010). In addition, more fenugreek studies demonstrated the benefits in both female and male health performance. The oral intake of ethyl acetate extract of fenugreek seeds has been tested to reduce triglycerides and low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol (HDL-C); hence had a noteworthy antioxidant and

hypocholesterolemic effects (Belguith-Hadriche et al. 2013). Moreover, their optimal consumption may lower triglycerides and cholesterol concentrations in the blood (Afef et al. 2000). On the other hand, fenugreek seeds contain trigonelline, choline, prolamin, sapogenin, alkaloid and mucilage fibers. Sapogenins in fenugreek seeds such as diosgenin and yamogenin have estrogen properties (Heydar 2010). Their exact mechanism of action is unknown. Researchers believe the breast glands are improved sweat glands and fenugreek increases milk production through increase of sweat production (Patisaul and Jefferson 2010). With enough research evident, fenugreek has been widely used for breast milk promotion. In total, 38 out of 76 supplements are labeled with breast-feeding with partial product clam to have clinical evident.

Although there is no statistical data to directly compare the current fenugreek seeds online sale numbers in China and USA. It's still possible to make comparison by categorizing online fenugreek product. Based on the Chinese online store researching result from Taobao, fenugreek seeds are majorly sold as raw material in the form of seeds and processed powers. Most of the raw materials are label as traditional Chinese spice without function specified. There are no domestic fenugreek supplements on the market yet. Whilst, fenugreek seeds' supplement claiming breast milk promotion is the best sold one among fenugreek functional products on Taobao web. Apparently, this comparison exhibit online Chinese fenugreek supplement market is completely overwhelming by imports suggests that the potential of domestic fenugreek supplement is underestimated in China.

Research trend of fenugreek seeds

To demonstrate the global fenugreek research trend, the heat spot density map was drawn by collecting geographic data from papers related to 'fenugreek' on web of science from 2006 to 2016. In total, 500 articles were selected from total of 1024 articles (from 2006 to 2016 web of science 'fenugreek' core collection data base) by trend, resulted in 20 high research density area with total of 1331 research rows. India as the predominant fenugreek producer consists of more than 45% of total research rows and 8 high research density area, followed by USA with roughly 20% of total research rows with 3 high research density area. In contrast, China had less than 5% of total research rows with no high research density area.

Astragalus mongholicus, *Codonopsis pilosula*, and *Lycium chinense* are the three top sales of TCM in the Chinese market in 2015 (the Report on the Analysis of Key Varieties of Traditional Chinese Medicine published by the Department of Market Supervision, Ministry of Commerce of the People's Republic of China). In order to find the current research status of fenugreek in China, this review compared the number of articles between fenugreek and *A. mongholicus*, *C. pilosula*, *L. chinense* published on the China National Knowledge Infrastructure (CNKI). This review used four TCM as the key words to search in the database separately, collecting all the research articles from 2006 to 2016. The results indicated that there are total 26,889 articles of *A. mongholicus*, 7788 of *L. chinense* and 6019 of *C. pilosula*, while the article number of fenugreek is only 439.

Results show that although the fenugreek seeds, as mentioned above, have been used as TCM raw material for a long time of period, with the data collected from recent years, it is noticed that China is lacking the research of fenugreek seeds in both depth and width.

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Abbreviations

CNKI	China National Knowledge Infrastructure
EMA	European Medicines Agency
GRAS	generally recognized as a safe food additive
HDL-C	high-density lipoproteins-cholesterol
HPLC	high performance liquid chromatography
LDL-C	low-density lipoproteins-cholesterol
NIDDM	non-insulin-dependent diabetes mellitus
TLC	thin layer chromatography

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