JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 53, Number 1, 2021; 78-86
http://dx.doi.org/10.19106/JMedSci005301202108

Potential role of fenugreek (*Trigonella foenum-graecum*) in the prevention of skin aging

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Submited: 2019-11-22
Accepted : 2020-04-07

ABSTRACT

Skin aging is a process influenced by several factors, including estrogen. Estrogen modulates the physiology of the skin, and its deficiency in postmenopausal women accelerates skin aging. Administration of estrogen can delay the skin aging process. Phytoestrogens are estrogen-like compounds derived from plants that administered via oral as well astopical routes. *Trigonella foenum-graecum*, commonly known as fenugreek, is one plants containing phytoestrogens. Several studies have been conducted on the phytoestregonic activity of fenugreek. Fenugreek extract exhibits estrogenic activity, as observed in the study of mouse and rat reproductive organs. Fenugreek exhibits estrogenic activity in the reproductive organs of a rat, as well as demonstrates positive effects on the skin by topical administration. This review explored the fenugreek as the source of phytoestrogens and its role in delaying skin aging.

ABSTRAK

Penuaan kulit merupakan suatu proses yang dipengaruhi oleh berbagai faktor, salah satunya estrogen. Estrogen merupakan salah satu modulator fungsi kulit, sehingga pada perempuan pasca menopause defisiensi estrogen mempercepat penuaan pada kulit. Pemberian esterogen dapat memperlambat proses penuaan pada kulit. Fitoestrogen, senyawa tanaman yang secara kimiawi serupa dengan estrogen, yang diberikan secara oral maupun topikal untuk memperlambat penuaan pada kulit. *Trigonella foenum-graecumgraecum*, atau klabet, adalah salah satu fitoestrogen yang banyak diteliti. Ekstrak klabet menunjukkan aktivitas estrogenik pada organ reproduksi tikus serta menunjukkan efek positif saat diaplikasikan secara topikal pada kulit. Tinjauan pustaka ini mengeksplorasi klabet sebagai sumber fitoestrogen dan fungsinya dalam memperlambat penuaan kulit.

Keywords:
fenugreek;
phytoestrogen;
skin aging;
postmenopausal women;
herbal;

INTRODUCTION

Skin aging is a complex biological process involving both intrinsic and extrinsic factors. Intrinsic aging is affected by genetic and hormonal factors, while extrinsic aging is affected mainly by environmental factors.[1] Skin aging is accelerated following menopause in women. Estrogen has significant roles in modulating skin physiology, affecting keratinocytes, fibroblasts, melanocytes, hair follicles, and sebaceous glands. Estrogen also enhances angiogenesis, wound healing, and immune responses. A study reported that the estrogen receptor-α (ERα) and the estrogen-receptor-β (ERβ) are expressed in dermal fibroblasts of human skin tissue.[2] Another study reported that the estradiol accelerates the process of wound healing by stimulating the production of TGF-β1 and TGF-β2. Both cytokines are related to the proliferation of dermal fibroblasts and secretion of extracellular matrix (ECM). Matrix metalloproteinase I (MMP 1) is an enzyme that takes responsibility

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in collagen degradation process and ECM down regulation.[3]

Hypoestrogenism in postmenopausal women leads to physiological changes in the skin, including hypoestrogenism in postmenopausal women leads to physiological changes in the skin, including decreased thickness due to less collagen and elasticity, increased wrinkles and dryness, as well as reduced vascularity.[4,5] Administration of estrogen significantly delays the process of skin aging.[4] This article reviewed the potential role of phytoestrogen contained in *T. foenum-graecum* in decelerating skin aging.

DISCUSSION

Phytoestrogens

Phytoestrogens are non-steroidal polyphenolic compounds produced naturally in plants.[6] Phytoestrogens are similar in structure to 17 β-estradiol, which enables them to bind with ERα and ERβ.[7,8] The effect of phytoestrogens also depends on the level of endogenous estradiol. It may cause antiestrogenic activity if there is a high level of endogenous estrogens by occupying part of the ERs. However, in a state with a low level of endogenous estrogens, phytoestrogens may express estrogenic activity. It can be classified as selective estrogen receptor modulators (SERMs).[8,9]

Due to its estrogenic activity, phytoestrogen has a potential role in delaying skin aging. Phytoestrogen can either be administered by oral or topical.[10] The classification and source of phytoestrogen compounds is presented in TABLE 1.

TABLE 1. Classification and source of phytoestrogen compounds

Classification	Chemical compounds	Sources
Flavon	Apigenin, quercetin, chrysin, vitexin, 7-hydroxyflavone	Red or yellow colored fruits and vegetables
Flavonon	Flavanon, naringenin, 8-prenilnaringenin	Cytrus and hops
Isoflavon	Genistein, biochanin A, daidzein, formononetin, glisetein	Legumes, especially soy and red clover
Koumestan	Koumesterol	Bean shoots, alfalfa, clover, sunflower seeds, seeds
Lignan	Enterolacton, enterodiol, matairesinol	Cereals, fruits, vegetables
Stilbena	Resveratrol	Grape skin and red wine
Sapogenin steroid	Diosgenin, yamogenin, tigogenin, dammarane	Fenugreek seeds, ginseng, wild yam

Oral Phytoestrogens

A double-blinded randomized clinical trial was conducted to evaluate the efficacy of oral intake of soy isoflavone aglycone in aging skin treatment of adult women. Thirteen participants received oral intake of 40 mg isoflavones per day for 12 weeks. The experimental group showed significant improvement in skin wrinkles and elasticity with minimal side effects.[11]

Another study was conducted to investigate the effect of oral isoflavonoids on skin thickness. Thirty postmenopausal women received oral intake of 100 mg isoflavonoid per day for 6 months. They reported that the epidermis thickness increased by 9.46% at the end of the study. They

also observed significant increases in collagen, elastin, dermis vascularity, and skin moisture at the end of the study.[12]

Topical Phytoestrogens

Topical phytoestrogens are used in skin problem treatment, including hyperpigmentation and wrinkles. The side effects of topical phytoestrogens usually include photosensitivity, skin irritation, erythema, and contact dermatitis. Skin hydration status, lipid structure in the stratum corneum, and dermal glycosaminoglycan have significant roles in skin water retention capacity. One study reported that the application of phytoestrogen molecules from 1% w/v *P. candollei var. mirifica* extract and 1% w/v *Aspergillus oryzae-Glycinemax* fermentation extract at 200 µg/cm^2 increase the water retention capacity in the dermis of mice that underwent ovariectomy. The skin elasticity of the mice, measured with Cutometer®, also increased within 4 weeks and 12 weeks after application.[13] Another study reported that the application of gel containing isoflavone extract (4% genistein) from seeds of *G.max* increased the thickness of the epidermis by 20% in postmenopausal women. Significant improvement is found in skin collagen content and vascularity of the dermis.[14]

Trigonella foenum-graecum **(fenugreek)**

Trigonellafoenum-graecum, known as fenugreek, is a plant commonly found around the Mediterranean and Western Asia regions. It has been used for centuries as a medical and culinary plant. In Indonesia, fenugreek is popular as herbs, spices, and food additives.[15]

FIGURE 1. Illustration of *Trigonella foenum-graecum*[16]

Geographical Distribution of *T. foenum - graecum*

*Trigonella foenum-graecum*is is a plant in the Fabaceae family, commonly known as fenugreek. *Trigonella foenum-graecum* is believed to be native to southern Europe and the Mediterranean region. It has been cultivated for centuries in Greek, Egypt, and several other countries. In Indonesia, fenugreek is cultivated on Java Island, specifically the Lembang region, 1200 m above sea level. *Trigonella foenum-graecum* grows up to 30-60 cm in height and has round leaves with a length 8-10 cm. The flower petals are bright yellow in color. The fruit is bitter in taste and contains approximately 10-20 seeds.[17,18]

Phytochemistry of *T. foenum-graecum*

Fenugreek leaves and seeds are often used for medicinal and culinary purposes. The leaves of fenugreeks contain 86.1% moisture, 4.4% protein, 0.9% fat, 1.5% mineral, 1.1% fiber, and 6% carbohydrates. It also contains various minerals and vitamins, including calcium, zinc, iron, phosphorous, riboflavin, carotene, thiamine, niacin, and vitamin C.[19] Fresh leaves of fenugreek contain 220.97 mg ascorbic acid per 100 g of leaves and 19 mg β-carotene per 100 g of leaves. It was also reported that sun exposure would reduce the ascorbic acid content by 84.94%, while over-drying would reduce it by 83.79%.[20] There was better retention of nutrients in the fresh leaves of fenugreek.

Fenugreek seeds contain 20-30% protein, 20-30% galactomannan, 20-25% insoluble fiber, 7-9% lipid, 5-7% saponin, and 3-4% ash. Another component contained inside fenugreek seeds is 0.2-0.36% trigonelline and 0.015% essential oil. Fenugreek seeds have distinct smells caused by 3-hydroxy-4.5-dimethyl-2(5H)-furanone (sotolon) and 3-hydroxy-4-methyl-2 (5H) - furanone.[13] Fenugreek seeds also contain polyphenol, diosgenin, galactomannan, flavonoid, protodioscin, trigoneoside, and yamogenin.[21]

Fenugreek seeds have a hard center and yellow embryos surrounded by a corneus and endosperm. The endosperm had the highest saponin content (4.63 g/100 g) and protein content (43.8 g/100 g). Extracts of endosperm husk and fenugreek seeds at 200 μg concentration showed that it has antioxidant activity of 72%, 64%, and 56% by the free-radical scavenging method.[19,22]

Fenugreek seeds have estrogenic properties because of their diosgenin content (in the form of 0.8-2.2% free base). Diosgenin (FIGURE 2) is a precursor of several hormones, including sex hormones. Fenugreek seeds also contain isomers of diosgenin (yamogenin, gitogenin, tiogenin, and trigoneoside) and also flavonoids (vitexin, isovitexin, orientin, isoorientin, kuersetin, and luteolin).

Fenugreek seeds can be used as an antioxidant (flavonoids, flavon, and polyphenol), anti-inflammatory (galactomannan and flavonoid), anti-ulcerogenic, and immunomodulator. The antioxidant activity of fenugreek varies between its components. Fenugreek husk displays the most significant free-radical scavenging activity, followed by fenugreek seed and endosperm extract. This was proposed to be directly related to the polyphenol contents of the different fenugreek fractions.[22]

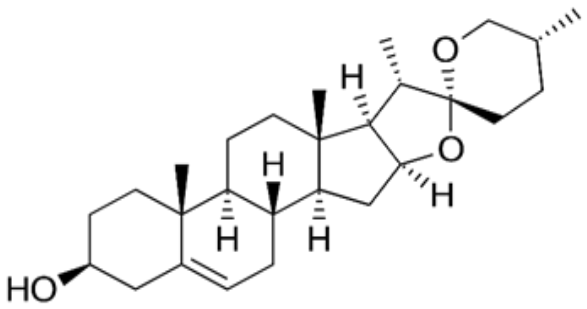

FIGURE 2. Chemical structures of diosgenin[19]

A study conducted by administering aqueous extract of fenugreek at three doses (50, 100, and 200 mg/kg body weight or BW) for ten days has been shown to stimulate an immunomodulatory effect on the immune system of Swiss albino mice.[23] Due to its antioxidant activity and rich fiber content, fenugreek seeds have emollient properties as well. The chemical contents of fenugreek is presented in TABLE 2.

TABLE 2. Chemical contents of fenugreek[19]

Classification	Chemical constituents
Alkaloids	Trimethylamine, neurin, trigonelline, choline, gentianine, carpaine, and betain
Amino acids	Isoleucine, 4-Hydroxyisoleucine, histidine, leucine, lysine, L-tryptophan, arginine
Saponins	Graecunins, fenugrin B, fenugreekine, trigofoenosides A-G
Steroidal sapinogens	Yamogenin, diosgenin, smilagenin, sarsasapogenin, tigogenin, neotigogenin, gitogenin, neogitogenin, yuccagenin, saponaretin
Flavonoids	Quercetin, rutin, vitexin, isovitexin
Fibers	Gum, neutral detergent fiber
Lipids	Triacylglycerols, diacylglycerols, monoacylglycerols, phosphatidylinositol, free fatty acids
Other	Coumarin, lipids, vitamins, minerals, 28% mucilage, 22% proteins, 5% of stronger swelling, bitter fixed oil

Application of *T. foenum-graecum*in Skin Aging prevention

Adouble-blinded RCTs were conducted on 11 subjects aged 25-35 years old. Fenugreek water in oil (W/O) cream with 4% fenugreek seed extract was applied every night before sleep on both cheeks for 8 weeks. The participants were followed up every week to examine their skin condition. The examined parameters included melanin and erythema (measured using a mexameter), skin moisture (measured using a corneometer), sebum (measured using a sebumeter), and trans-epidermal water loss (measured using a tewameter). Melanin levels

increased in the first 2 weeks but declined steadily in the following each week. Erythema increased in the first 3 weeks but decreased in the following each week. The sebum level increased gradually every week. The changes in melanin, erythema, and sebum levels were not statistically significant. There was an increase in the humidity level of the skin, while trans-epidermal water loss increased in the first 3 weeks and then gradually decreased.[24]

An *in vitro* effect of the administration of fenugreek seed extract towards collagen type I alpha I (COL1A1) and collagen type III alpha I (CO3A1) on postmenopausal women's fibroblasts was observed by administering 0.5-2 µg/mL fenugreek seed extract to old human dermal fibroblasts (HDFs) that were obtained from the leftover tissue of blepharoplasty in a 60-year-old woman and young HDFs from the preputium. An optimal concentration of 2 µg/mL was found to significantly increase COL1A1 and COL3A1 secretion in both old HDF and young HDF by COL1A1/COL3A1 ratios of 1:1.5-2 and 1:1, respectively. Fenugreek extract was also shown to stimulate collagen secretion better than 5 nM estradiol.[25]

Another *in vitro* study was conducted to observe the effect of fenugreek extract on MCF-7 breast cancer cell culture. The results showed that fenugreek extract bound to the estrogen receptor and inhibited estradiol activity in the dose-dependent manner. Fenugreek extract acts as a competitive inhibitor of estradiol.[26]

A study was conducted to observe the estrogenic activity of fenugreek extract on the uterus and breast of female white mice that had already undergone ovariectomy and prepubertal female white mice. Both mice were administered with fenugreek seed extract (120 mg/200g BW). The prepubertal mouse group showed an increase in estradiol and FSH levels, an increase in vaginal lubrication, and an increase in uterus weight, diameter, and endometrial thickness. The other group did not show a significant increase in estradiol levels; however, there was a decrease in FSH levels and an increase in uterus weight, although there was no significant change in uterus development or endometrial thickness. The results showed that although there were no specific hormonal changes, the administration of fenugreek extract to both mice still affected their vaginal lubrication and uterus weight. It is suspected that fenugreek extract works in the genomic pathway.[27]

Tada *et al*.[28] conducted a study on diosgenin from *Discorea composita* (yam). They reported that diosgenin increased the synthesis of DNA and stimulated the proliferation of keratinocytes because of its similar structure to endogenous estrogen (E2) through a different mechanism, which is the activation of cAMP signaling without estrogen receptor involvement.

Side Effects of *T. foenum-graecum*

One study observed the acute and subchronic toxicity of fenugreeks. Adult house mice and adult brown rats were used to examine acute toxicity. The house mice and brown rats were given debitterized fenugreek via the intragrastic route, 0.25-2 g/kgBW for the adult house mice, and 1-5 g/kgBW for the brown rats. There was no acute toxicity found in this study, like changes in organ weight and histopathological changes in several organs such as the liver, lungs, kidney, and spleen in either the house mouse or brown rat that were given the maximal dose (2 g/kgBW for adult house mice and 5 g/kgBW for adult brown rats). Markedly, there was no mortality observed in these mice and rat groups. A subchronic toxicity study was conducted on weaning male and female rats. Both the male and female rats

were given food containing 0, 1, 5, and 10% debitterized fenugreek for 90 days. There were no observed signs of toxicity, weight changes, food intake changes, histopathological changes, laboratory parameter changes (routine blood test, SGOT/SGPT, ALP, cholesterol, ureum, and creatinine), or mortality in any dosage group.[29]

Another study was conducted on chickens by giving saponin fractions from fenugreek seeds at 50 mg/kgBW via the intraperitoneal route and 500 mg/kgBW via the oral route. Both groups showed a decrease in body mass, an increase in liver enzymes, and organ changes, including hepatocyte necrosis, necrotic degeneration of renal tubules, catarrhal enteritis, and peritonitis.[30]

CONCLUSION

In recent years, the use of medicinal plants in the cosmetic field has been increasing. Phytoestrogens, estradiol-like substances derived from plants, can be used as selective estrogen receptor modulators. *Trigonella foenum-graecum* (fenugreek) seeds can be used as phytoestrogen sources. Based on several studies, fenugreek has estrogenic activity, and its application revealed improvement of the skin, a part of this may be due to its antioxidant and emollient properties. Further researchs to exploprethe application of *T. foenum-graecum* extract on human skin and its side effects are required.

ACKNOWLEDGEMENT

I would like to thank all those who gave their hands and support to complete this article review.

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