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Djream

Product Information Sheet

Djream contains phytotherapeutic extracts of **Trigonella foenum graecum, Nelumbo nucifera*, Peganum harmala, Boswellia sacra, Curcuma longa,*** and ***Cinnamomium vera*.** Using advanced laboratory extraction apparatus & proprietary production protocols, these phytochemicals are known for their neuroplasticity and neuromodulated properties which have been observed by changes in excitability, disinhibition, and enabled neuroplasticity.

Trigonella foenum graecum is a synergist of Oxytocin - a hypothalamic neuropeptide known for peripheral actions regulating uterine contraction during parturition and milk letdown during nursing. However, oxytocin also acts within the brain to coordinate a suite of social behaviors, including maternal nurturing, mother-infant bonding, social recognition, and pair-bonding. The neural mechanisms of oxytocin regulation of social behaviors have enhanced our understanding of these cellular and synaptic mechanisms.

Oxytocin is a nine amino acid–long cyclical peptide that is synthesized in hypothalamic neurons, packaged into dense-core vesicles, and transported into dendrites and axons for release. Oxytocin is synthesized in the paraventricular nucleus (PVN), supraoptic nucleus (SON), and accessory magnocellular hypothalamic nuclei. Most oxytocin is secreted into the bloodstream via axonal release from the posterior pituitary. Regulation of synaptic inhibition seems to be a major, if not the most common, mode of oxytocinergic modulation in the brain, although specific effects vary across regions. Oxytocin activates inhibitory cell types in other cortical, subcortical, and peripheral regions

Oxytocin acts in many brain areas to recruit local inhibitory circuits. Modulation of inhibitory circuits enables more selective signal enhancement for specific cell types, synapses, and sensory inputs than does the direct excitation of principal cells (Froemke & Schreiner 2015). These observations underscore the importance of examining spontaneous and evoked patterns of synaptic transmission to determine local circuit effects of neuromodulation. There are potentially many biological processes by which oxytocin receptor signaling can indirectly influence gene expression, excitability, synaptic transmission, and neural computations (Jurek & Neumann 2018).

Through widespread direct and indirect effects on neural excitability, oxytocin also affects perception and cognition. Long-term synaptic plasticity can serve as a mechanism for enhancing and stabilizing neural representations of important sensory stimuli related to social interactions. Oxytocin acts as a neuromodulator to amplify incoming signals, increasing the salience of sensory input and leading to refinement of subsequent behaviors via mechanisms of long-term plasticity. Growing evidence has shown that oxytocin has a large number of effects on neurons in the central nervous system. A consistent finding is that oxytocin increases excitability and enables synaptic plasticity.

In traditional medicine, *P. harmala* has been used among societies to treat some nervous system disorders such as Parkinson's disease, in psychiatric conditions such as nervosity, and to relieve rigorous pain. The alkaloid content of *P. harmala* is shown to be psychoactive and various *in vitro* and *in vivo* studies indicate a wide range of effects produced by *P. harmala* and its active alkaloids on both central and peripheral nervous system including, analgesia, hallucination, excitation, and anti-depressant effect. Beta-carbolines present in *P. harmala* strongly inhibit monoamine oxidase enzyme that is the main factor in degradation and reuptake of monoamines like serotonin and norepinephrine.

Nelumbo nucifera, also known as sacred lotus has demonstrated neuroprotective activity. It attenuates brain damage, improves memory and learning abilities, and has antidepressant action. Neferine a component of sacred lotus, reduced seizure severity, exerted neuroprotective effects, and ameliorated neuroinflammation in the hippocampi of KA-treated rats, possibly by inhibiting NLRP3 inflammasome activation and decreasing inflammatory cytokine secretion.

Boswellia sacra, known as Olibanum-tree or Frankincense, is a small deciduous tree that is native to the Arabian Peninsula and northeastern Africa, and is one of the plants known to produce olibanum. Previous chemical investigations on the gum resin from B. sacra have reported the isolation of a number of cembranoids with neuroprotective, hepatoprotective, anti-inflammatory and anti-depression activities.

Trigonella foenum graecum – Constituents include flavonoids, alkaloids, coumarins and saponins; the most prevalent alkaloid is trigonelline and coumarins include cinnamic acid and scopoletin.
Nelumbo nucifera, also known as **sacred lotus**, **Laxmi lotus**, **Indian lotus**, or simply **lotus**. Neferine is a bisbenzylisoquinoline alkaloid, a major component from the seed embryos of N. nucifera. Neferine is effective in the treatment of high fevers and hyposomnia, as well as arrhythmia, platelet aggregation, occlusion, and obesity. Neferine has been found to have a variety of therapeutic effects such as anti-inflammatory, antioxidant, anti-hypertensive, anti-arrhythmic, anti-platelet, anti-thrombotic, anti-amnesic, and negative inotropic. Neferine also exhibited anti-anxiety effects.
Peganum harmala*,* *Peganum harmala* seeds have been used as a substitute for *Banisteriopsis caapi* in ayahuasca analogs, as they contain monoamine oxidase inhibitors that enable DMT to be orally active
Elitaria cardamomum, the highest sources of plant-based zinc. extracts of cardamom may be effective against a variety of bacterial strains that contribute to fungal infections.
Curcuma longa, anti-aging, antioxidant, anti-inflammatory, anti-arthritic, and anti-cancer effects and increases BDNF (Brain-derived Neurotropic Factor).
Boswellia sacra Its anti-inflammatory effects mean that it may help with inflammatory conditions, such as rheumatoid arthritis, inflammatory bowel disease, and asthma. It is used as a rejuvenating medicine and treats menstrual pain, mouth problems, wounds, sores, ulcers, carbuncles, hemorrhoids, inflammation, and throat problems. Analgesic Effects. &e analgesic effects of crude extracts and fractions of Omani frankincense obtained from B. sacra. Anti-Alzheimer Effect. &e genus Boswellia has been suggested to cure or prevent neurodegenerative disorders through anti-inflammatory, antioxidative, antiamyloidogenic, and antiapoptotic effects [50]. Evaluating the effect of essential oil obtained from resins of B. sacra showed that frankincense essential oil can significantly inhibit the acetylcholinesterase enzyme (AChE). Inhibition of AChE leads to increased acetylcholine levels in the brain and improves memory in Alzheimer's disease patients.
***Cinnamomium vera* -** Contains antioxidants, including polyphenols, phenolic acid and flavonoids. These compounds work to fight oxidative stress in the body and aid in the prevention of chronic disease.

molecules

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Review

Natural Products Inhibitors of Monoamine Oxidases—Potential New Drug Leads for Neuroprotection, Neurological Disorders, and Neuroblastoma

Narayan D. Chaurasiya [1,*], Francisco Leon [2,*], Ilias Muhammad [3,*] and Babu L. Tekwani [1,*]

[1] Scientific Platforms, Southern Research, Birmingham, AL 35205, USA
[2] Department of Drug Discovery and Biomedical Sciences, College of Pharmacy, University of South Carolina, Columbia, SC 29208, USA
[3] National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, USA
* Correspondence: nchaurasiya@southernresearch.org (N.D.C.); jleon@mailbox.sc.edu (F.L.); milias@olemiss.edu (I.M.); btekwani@southernresearch.org (B.L.T.); Tel.: +1-205-581-2026 (N.D.C.); +1-803-576-6082 (F.L.); +1-662-915-1051 (I.M.); +1-205-581-2205 (B.L.T.)

Abstract: Monoamine oxidase inhibitors (MAOIs) are an important class of drugs prescribed for treatment of depression and other neurological disorders. Evidence has suggested that patients with atypical depression preferentially respond to natural product MAOIs. This review presents a comprehensive survey of the natural products, predominantly from plant sources, as potential new MAOI drug leads. The psychoactive properties of several traditionally used plants and herbal formulations were attributed to their MAOI constituents. MAO inhibitory constituents may also be responsible for neuroprotective effects of natural products. Different classes of MAOIs were identified from the natural product sources with non-selective as well as selective inhibition of MAO-A and -B. Selective reversible natural product MAOIs may be safer alternatives to the conventional MAOI drugs. Characterization of MAO inhibitory constituents of natural products traditionally used as psychoactive preparations or for treatment of neurological disorders may help in understanding the mechanism of action, optimization of these preparations for desired bioactive properties, and improvement of the therapeutic potential. Potential therapeutic application of natural product MAOIs for treatment of neuroblastoma is also discussed.

Keywords: natural products; monoamine oxidases (MAO-A and -B); antidepressant; monoamine oxidase inhibitors; neurological disorders; neuroprotection; Parkinson's disease; neuroblastoma

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1. Introduction

Amine oxidases are a heterogenous group of enzymes that metabolize various monoamines, diamines, and polyamines produced endogenously for physiological functions or exogenous xenobiotic substances absorbed through dietary intake [1]. The amine oxidases are distinguished by their co-factor requirements and substrate specificities [2]. The flavin adenine dinucleotide (FAD)-dependent amine oxidases include mitochondrial monoamine oxidase A (MAO-A), monoamine oxidase B (MAO-B), and cytosolic polyamine oxidases (PAOs). Copper and topoquinone (TPQ)-dependent amine oxidases include plasma and tissue enzymes, also referred to as semicarbazide-sensitive amine oxidases (SSAOs) [3] (Figure 1). This review primarily focused on MAO-A and MAO-B due to their predominant role in oxidative deamination of endogenous neurotransmitter biogenic monoamines such as dopamine, epinephrine (EPI), and norepinephrine (NE) [4]. Changes in the physiological levels of these monoamines have been implicated in the pathophysiology of several neurological disorders.

Differential localization of MAO-A and -B in tissues determines their physiological functions. MAO-A and -B play an important role in deamination of biogenic amines in

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Oxytocin, Neural Plasticity, and Social Behavior

Robert C. Froemke[1,2], **Larry J. Young**[3,4,5]

[1]Skirball Institute, Neuroscience Institute, and Departments of Otolaryngology and Neuroscience and Physiology, New York University School of Medicine, New York, NY 10016, USA

[2]Center for Neural Science, New York University, New York, NY 10003, USA

[3]Silvio O. Conte Center for Oxytocin and Social Cognition, Center for Translational Social Neuroscience, and Yerkes National Primate Research Center, Emory University, Atlanta, Georgia 30329, USA

[4]Center for Social Neural Networks, Faculty of Human Sciences, University of Tsukuba, Tsukuba 305-8577, Japan

[5]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322, USA

Abstract

Oxytocin regulates parturition, lactation, parental nurturing, and many other social behaviors in both sexes. The circuit mechanisms by which oxytocin modulates social behavior are receiving increasing attention. Here, we review recent studies on oxytocin modulation of neural circuit function and social behavior, largely enabled by new methods of monitoring and manipulating oxytocin or oxytocin receptor neurons in vivo. These studies indicate that oxytocin can enhance the salience of social stimuli and increase signal-to-noise ratios by modulating spiking and synaptic plasticity in the context of circuits and networks. We highlight oxytocin effects on social behavior in nontraditional organisms such as prairie voles and discuss opportunities to enhance the utility of these organisms for studying circuit-level modulation of social behaviors. We then discuss recent insights into oxytocin neuron activity during social interactions. We conclude by discussing some of the major questions and opportunities in the field ahead.

Keywords

hypothalamus; maternal care; neural circuits; neuromodulation; social bonding; social behavior

robert.froemke@med.nyu.edu .

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PHCOG REV. PLANT REVIEW

Pharmacological and therapeutic effects of *Peganum harmala* and its main alkaloids

Milad Moloudizargari, Peyman Mikaili[1], Shahin Aghajanshakeri, Mohammad Hossein Asghari, Jalal Shayegh[2]

Student of Veterinary Medicine, Faculty of Veterinary Medicine, Urmia University, [1]Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, [2]Veterinary Medicine, Faculty of Agriculture and Veterinary, Shabestar Branch, Islamic Azad University, Shabestar, Iran

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ABSTRACT

Wild Syrian rue (*Peganum harmala* L. family Zygophyllaceae) is well-known in Iran and various parts of this plant including, its seeds, bark, and root have been used as folk medicine. Recent years of research has demonstrated different pharmacological and therapeutic effects of *P. harmala* and its active alkaloids, especially harmine and harmaline. Analytical studies on the chemical composition of the plant show that the most important constituents of this plant are beta-carboline alkaloids such as harmalol, harmaline, and harmine. Harmine is the most studied among these naturally occurring alkaloids. In addition to *P. harmala* (Syrian rue), these beta-carbolines are present in many other plants such as *Banisteria caapi* and are used for the treatment of different diseases. This article reviews the traditional uses and pharmacological effects of total extract and individual active alkaloids of *P. harmala* (Syrian rue).

Key words: Harmine, harmaline, *peganum harmala*, pharmacological effects, wild syrian rue

INTRODUCTION

Harmal[1] (*Peganum harmala* L. family *Zygophyllaceae*) is a perennial, glabrous plant which grows spontaneously in semi-arid conditions, steppe areas and sandy soils, native to eastern Mediterranean region. It is a shrub, 0.3-0.8 m tall with short creeping roots, white flowers and round seed capsules carrying more than 50 seeds. The plant is well-known in Iran and is widely distributed and used as a medicinal plant in Central Asia, North Africa and Middle East.[2-5] It has also been introduced in America and Australia. Dried capsules – mixed with other ingredients – are burnt as a charm against "the evil eye" among Iranians.[2] This plant is known as "Espand" in Iran, "Harmel" in North Africa and "African rue," "Mexican rue" or "Turkish rue" in the United States.[6] Various parts of *P. harmala* including its seeds, fruits, root, and bark, have been used as folk medicine for a long time in Iran and other countries [Table 1]. Many pharmacological surveys have shown different effects of *P. harmala* [Table 4] and/or its active alkaloids (particularly harmaline) [Table 5].

Studies carried out on the chemical composition of the extracts show that beta-carboline and quinazoline alkaloids are important compounds of this plant [Figure 1]. In one study, the concentration of harmaline in different parts of the plant including seeds, fruits, and capsule walls was determined by Reverse phase high-performance liquid chromatography (RP-HPLC) as 56.0 mg/g, 4.55 mg/g and 0.54 mg/g, respectively.[7] Although, harmaline and harmine are the most important alkaloids that are generally responsible for their beneficial effects, numerous studies show that other alkaloids present in *P. harmala* also have some roles in the pharmacological effects of the plant.[8] Harmaline ($C_{13}H_{15}ON_2$) was first isolated by Göbel from the seeds and roots of *P. harmala* and is the major alkaloid of this plant.[6] In addition to *P. harmala* (Harmal), beta-carboline alkaloids are present in many other plants such as *Banisteriopsis caapi* (*Malpighiaceae*). They are also constituents of Ayahuasca, a hallucinogenic beverage ingested in rituals by the Amazonian tribes.[7] This article completely reviews the pharmacological effects of *P. harmala* [Table 2] and its active ingredients [Table 3].[6,7]

Address for correspondence:
Mr. Milad Moloudizargari, Veterinary School, Urmia University, Urmia, Iran.
E-mail: miladmoludi@gmail.com

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REVIEW ARTICLE

Pharmacological effects of *Trigonella foenum-graecum* L. in health and disease

Umesh C. S. Yadav[1] and Najma Z. Baquer[2]

[1]*Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, TX, USA and* [2]*School of Life Sciences, Jawaharlal Nehru University, New Delhi, India*

Abstract

Context: The health benefits and medicinal properties of herbal food products are known since antiquity. Fenugreek [*Trigonella foenum-graecum* Linn. (Fabaceae)], a seed spice used to enhance flavor, color and texture of food, is employed for medicinal purposes in many traditional systems. A number of epidemiological studies and laboratory research have unraveled the biological actions of fenugreek.
Objective: Research on fenugreek in recent years has identified a number of health benefits and physiological attributes in both experimental animals as well as clinical trials in humans. In this study we have reviewed the available scientific literature on fenugreek.
Methods: This review article summarizes and reviews published experimental studies and scientific literature from the databases including PubMed, Google and local library searches.
Results: The information available in the literature on the health benefits and pharmaceutical effects of *Trigonella* accounts for its known medicinal properties and adds new therapeutic effects in newer indications. Besides its known medicinal properties such as carminative, gastric stimulant, antidiabetic and galactogogue (lactation-inducer) effects, newer research has identified hypocholesterolemic, antilipidemia, antioxidant, hepatoprotective, anti-inflammatory, antibacterial, antifungal, antiulcer, antilithigenic, anticarcinogenic and other miscellaneous medicinal effects of fenugreek. Although most of these studies have used whole seed powder or different forms of extracts, some have identified active constituents from seeds and attributed them medicinal values for different indications.
Conclusion: The resarch on *Trigonella* exhibits its health benefits and potential medicinal properties in various indications and has little or no side effects, suggesting its pharmaceutical, therapeutic and nutritional potential.

Keywords

4-Hydroxyisoleucine, anticarcinogenic, anti-cholesterolemic, antidiabetic, anti-inflammatory, antioxidant, diosgenin, fenugreek, trigonelline

History

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Introduction

Use of plant-derived medicinal compounds has been in practice since antiquity in many cultural systems including India, China, Egypt and Middle Eastern countries. In recent times, plant-derived medicinal compounds are being widely used and are suggested by doctors to be used in a number of ailments due to their minimal side effects and numerous positive effects on human health. Out of many such medicinal plants, fenugreek [*Trigonella foenum-graecum* Linn (Fabaceae)] has recently attracted the attention of scientists from across the globe. Fenugreek is native to Eastern Europe and parts of Asia but now widely cultivated almost all over the world for its leaves and seeds, which are commonly used as leafy vegetables and condiments, respectively (Anonymous, 1998; Rastogi & Mehrotra, 1990; Srinivasan, 2006). Fenugreek plant is an erect annual herb with trifoliate leaves reaching a height of 0.3–0.8 m. The plants bear white or yellow flowers, which give rise to long, slender, yellow to brown pods. At maturity the pods contain hard brown seeds of fenugreek, which is known and utilized for its medicinal use. While the green leaves are used as a vegetable in many societies, the dried leaves are an excellent additive in many food preparations in the Indian subcontinent.

In the ancient Indian traditional system of medicine, Ayurveda, fenugreek has been suggested as an important medicine to treat a variety of digestive and mucosal conditions (Escot, 1994/95; Passano, 1995). The fenugreek seed has traditionally been used as a carminative, demulcent, expectorant, laxative and stomachic agent. The mature fenugreek seed has many other active components such as amino acids, fatty acids, vitamins and saponins such as disogenin, gitogenin, neogitogenin, homorientin saponaretin, neogigogenin and trigogenin, fibers, flavonoids, polysaccharides, fixed oils and some identified alkaloids, that is, trigonelline and choline (Jayaweera, 1981; Yoshikawa et al., 1997). The

Correspondence: Umesh C. S. Yadav, Department of Biochemistry & Molecular Biology, The University of Texas Medical Branch, 6.644 Basic Science Building, 301 University Blvd., Galveston, TX 77555, USA. Tel: 001 409 772 3776. Fax: 001 409 772 9679. E-mail: ucyadav@utmb.edu

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genes

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Article

Fenugreek Stimulates the Expression of Genes Involved in Milk Synthesis and Milk Flow through Modulation of Insulin/GH/IGF-1 Axis and Oxytocin Secretion

Thomas Sevrin [1,2], Clair-Yves Boquien [2], Alexis Gandon [2], Isabelle Grit [2], Pierre de Coppet [2], Dominique Darmaun [2,3] and Marie-Cécile Alexandre-Gouabau [2,*]

1 FRANCE Bébé Nutrition (FBN) Laboratory, 53000 Laval, France; thomas.sevrin@etu.univ-nantes.fr
2 Mixed Research Unit 1280 Pathophysiology of Nutritional adaptations (UMR 1280 PhAN) Nantes University, Research Center in Human Nutrition-West (CRNH-O), Institute of Digestive Tract Diseases (IMAD), French National Research Institute for Agriculture, Food and Environment (INRAE), F-44000 Nantes, France; clair-yves.boquien@univ-nantes.fr (C.-Y.B.); alexis.gandon@univ-nantes.fr (A.G.); isabelle.grit@univ-nantes.fr (I.G.); Pierre.De-Coppet@univ-nantes.fr (P.d.C.); dominique.darmaun@univ-nantes.fr (D.D.)
3 Nantes University Hospital (CHU) Nantes, F-44000 Nantes, France
* Correspondence: Marie-Cecile.Alexandre-Gouabau@univ-nantes.fr; Tel.: +33-(0)2-53-48-20-12

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Abstract: We previously demonstrated galactagogue effect of fenugreek in a rat model of lactation challenge, foreshadowing its use in women's breastfeeding management. To assess longitudinal molecular mechanisms involved in milk synthesis/secretion in dams submitted to fenugreek supplementation, inguinal mammary, pituitary glands and plasma were isolated in forty-three rats nursing large 12 pups-litters and assigned to either a control (CTL) or a fenugreek-supplemented (FEN) diet during lactation. RT-PCR were performed at days 12 and 18 of lactation (L12 and L18) and the first day of involution (Inv1) to measure the relative expression of genes related to both milk synthesis and its regulation in the mammary gland and lactogenic hormones in the pituitary gland. Plasma hormone concentrations were measured by ELISA. FEN diet induced 2- to 3-times higher fold change in relative expression of several genes related to macronutrient synthesis (*Fasn*, *Acaca*, *Fabp3*, *B4galt1*, *Lalba* and *Csn2*) and energy metabolism (*Cpt1a*, *Acads*) and in IGF-1 receptor in mammary gland, mainly at L12. Pituitary oxytocin expression and plasma insulin concentration (+77.1%) were also significantly increased. Altogether, these findings suggest fenugreek might extend duration of peak milk synthesis through modulation of the insulin/GH/IGF-1 axis and increase milk ejection by activation of oxytocin secretion.

Keywords: fenugreek; galactagogue; milk synthesis; gene expression; lactating mammary gland; pituitary gland; insulin; oxytocin

1. Introduction

The World Health Organization (WHO) recommends exclusive breastfeeding for infants up to 6 months of age, based on evidence of its clear health benefits on mother–infant dyad [1–3]. Yet, 6 months after delivery, less than 40% of mothers are still breastfeeding in several high-income countries of North America and Europe [4]. Although the early cessation of breastfeeding is multifactorial [5], the perception that their milk secretion is insufficient to support adequate infant growth is reported by about 35% of lactating women [6,7]. Though perceived milk insufficiency due to psychological

plants

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Review

Revisiting *Trigonella foenum-graecum* L.: Pharmacology and Therapeutic Potentialities

Theysshana Visuvanathan [1,2], Leslie Thian Lung Than [1], Johnson Stanslas [3], Shu Yih Chew [1] and Shalini Vellasamy [2,*]

[1] Department of Medical Microbiology, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang 43400, Malaysia; theyshu_89@hotmail.com (T.V.); leslie@upm.edu.my (L.T.L.T.); chewshuyih@upm.edu.my (S.Y.C.)
[2] Department of Microbiology and Parasitology, School of Medicine, Faculty of Medicine, Bioscience and Nursing, MAHSA University, Jenjarom 42610, Malaysia
[3] Department of Medicine, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang 43400, Malaysia; rcxjs@upm.edu.my
* Correspondence: shalini.v@mahsa.edu.my

Abstract: Fenugreek (*Trigonella foenum-graecum* L.) is a medicinal plant that has been used as a food condiment as well as for its multiple therapeutic characteristics since ancient times. Fenugreek plant grows up to 60 cm in height, and its seeds are golden-yellow rhomboidal-shaped. Though fenugreek is more commonly known for its seeds, the leaves and stem have also been reported to have medicinal uses. These properties exhibited are due to the content of the secondary metabolites, also known as phytochemicals, in the fenugreek plant. Such metabolites are alkaloids, saponins, tannins, phenols, and many others. Fenugreek has been used traditionally for numerous indications, such as aid in labour, lactation stimulant, and laxatives. In modern research, there have been several animal and clinical studies that have shown therapeutic effects of fenugreek when taken orally. Fenugreek is a suitable plant candidate with a high prospect of being used as a credible medicinal plant to derive new drugs. This review aims to summarize the physical and chemical properties of fenugreek and its bioactive compounds that have been isolated for medicinal purposes and discusses the traditional and pharmacological uses of fenugreek.

Keywords: alkaloids; fenugreek; pharmacological potential; phytochemicals; *trigonella foenum-graecum*; saponins

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1. Introduction

Despite the incredible advances in medicine development, herbal crops are still widely used for treating and preventing a variety of diseases due to their medicinal and nutraceutical characteristics. *Trigonella foenum-graecum* L., or also commonly known as fenugreek, is known to be one of the plants with these traits. It is from the family of Fabaceae and is a self-pollinating annual herbaceous aromatic crop, also known as bird's foot, Greek hayseed, halba, and methi [1]. Its origin is India and Northern Africa; however, it is now widely cultivated in Northern Africa, Europe, South Asia, Argentina, and Australia. Fenugreek is mainly produced in India, which accounts for 80% of the total world production [2]. Fenugreek seeds and leaves are used as a spice and ingredient in culinary preparation in several countries. It is used as a functional and traditional food, as well as in nutraceuticals and physiological application. Because of its high fibre, protein, and gum content, fenugreek has recently been utilized as a food stabilizer and emulsifying agent.

Fenugreek is known to be one of the world's most ancient medicinal herbs, in relation to which the seeds and leaves are used as a treatment in various ailments [3]. The leaves and seeds of *T. foenum-graecum* are extensively utilized to make extracts and powder for

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Review Article

Taxonomical Investigation, Chemical Composition, Traditional Use in Medicine, and Pharmacological Activities of *Boswellia sacra* Flueck

Mansour Miran,[1] **Keyvan Amirshahrokhi**,[2] **Yousef Ajanii**,[3] **Reza Zadali**,[4] **Maxwell W. Rutter**,[5] **Ayesheh Enayati**,[6] **and Farahnaz Movahedzadeh**[7,8]

[1]*Department of Pharmacognosy, School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran*
[2]*Department of Pharmacology, School of Pharmacy, Ardabil University of Medical Science, Ardabil, Iran*
[3]*Botany Division, Research Institute of Forests and Rangelands, Agricultural Research Education and Extension Organization (AREEO), Tehran, Iran*
[4]*Department of Pharmacognosy, Faculty of Pharmacy, Islamic Azad University-Damghan Branch, Iran*
[5]*Hollingbery & Son, Inc, Yakima, WA 98902, USA*
[6]*Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran*
[7]*Institute for Tuberculosis Research, University of Illinois at Chicago, Chicago, IL, USA*
[8]*Department of Pharmaceutical Sciences, University of Illinois at Chicago, Chicago, IL, USA*

Correspondence should be addressed to Mansour Miran; mansour.miran@gmail.com

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Aromatic oleo-gum-resin secreted from *B. sacra*, reputed as frankincense, is widely used in traditional medicine to treat Alzheimer's disease, gastric disorders, hepatic disorders, etc. Frankincense is also used in the cosmetic, perfume, and beverage and food industries. Frankincense is a rich resource for bioactive compounds, especially boswellic acids and derivatives. Although several reports have described frankincense's constituents and pharmacological activities, there is no comprehensive study that covers the valuable information on this species. Therefore, the current review will focus on the phytochemistry, traditional uses, and pharmacological activities of *B. sacra*.

1. Introduction

Boswellia sacra Flueck is a perennial plant belonging to the family Burseraceae. Aromatic oleo-gum-resin extracted from *B. sacra*, known as frankincense or olibanum (Figure 1), is used as a home remedy, especially in Middle East countries [1]. Frankincense is harvested by making shallow incisions into the tree trunk [2]. Frankincense is used in many industries such as cosmetic, pharmaceutical, beverage, food, detergents, and perfume industries [3, 4]. The oleo-gum resin of *B. sacra* has many uses for the human body, including analgesic, hepatoprotective, anticoagulant, antioxidant, tumor-suppressive, anti-inflammatory, cardioprotective, Alzheimer's disease, gastric, hepatic, and skin disorders [5, 6]. *B. sacra* is an important source of bioactive compounds, including terpenoids which have a wide range of biological activities [6]. The most important compounds found in resin from *Boswellia sacra* are boswellic acids and their derivatives, which are responsible for a number of medicinal properties belonging to the plant.

Accordingly, this review introduces *B. sacra* as a valuable herbal source in different industries such as pharmacy and food.

2. Genus *Boswellia* Roxb. Ex. Colebr

The genus *Boswellia* belongs to the family Burseraceae. It comprises 20–25 species of trees and shrubs widely distributed in dry areas of northeast Africa, Arabia, and India

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Article

Neferine, an Alkaloid from Lotus Seed Embryos, Exerts Antiseizure and Neuroprotective Effects in a Kainic Acid-Induced Seizure Model in Rats

Tzu-Yu Lin [1,2], Chih-Yu Hung [3], Kuan-Ming Chiu [4,5], Ming-Yi Lee [4], Cheng-Wei Lu [1,2,*] and Su-Jane Wang [3,6,*]

1 Department of Anesthesiology, Far-Eastern Memorial Hospital, New Taipei City 22060, Taiwan; drlin1971@gmail.com
2 Department of Mechanical Engineering, Yuan Ze University, Taoyuan 32003, Taiwan
3 School of Medicine, Fu Jen Catholic University, New Taipei City 24205, Taiwan; h.chihyu@gmail.com
4 Cardiovascular Center, Division of Cardiovascular Surgery, Far-Eastern Memorial Hospital, New Taipei 22060, Taiwan; chiu9101018@gmail.com (K.-M.C.); mingyi.lee@gmail.com (M.-Y.L.)
5 Department of Electrical Engineering, Yuan Ze University, Taoyuan 32003, Taiwan
6 Research Center for Chinese Herbal Medicine, College of Human Ecology, Chang Gung University of Science and Technology, Taoyuan 33303, Taiwan
* Correspondence: drluchengwei@gmail.com (C.-W.L.); med0003@mail.fju.edu.tw (S.-J.W.)

Abstract: Current anti-seizure drugs fail to control approximately 30% of epilepsies. Therefore, there is a need to develop more effective anti-seizure drugs, and medicinal plants provide an attractive source for new compounds. This study aimed to evaluate the possible anti-seizure and neuroprotective effects of neferine, an alkaloid from the lotus seed embryos of *Nelumbo nucifera*, in a kainic acid (KA)-induced seizure rat model and its underlying mechanisms. Rats were intraperitoneally (i.p.) administrated neferine (10 and 50 mg/kg) 30 min before KA injection (15 mg/kg, i.p.). Neferine pretreatment increased seizure latency and reduced seizure scores, prevented glutamate elevation and neuronal loss, and increased presynaptic protein synaptophysin and postsynaptic density protein 95 expression in the hippocampi of rats with KA. Neferine pretreatment also decreased glial cell activation and proinflammatory cytokine (interleukin-1β, interleukin-6, tumor necrosis factor-α) expression in the hippocampi of rats with KA. In addition, NOD-like receptor 3 (NLRP3) inflammasome, caspase-1, and interleukin-18 expression levels were decreased in the hippocampi of seizure rats pretreated with neferine. These results indicated that neferine reduced seizure severity, exerted neuroprotective effects, and ameliorated neuroinflammation in the hippocampi of KA-treated rats, possibly by inhibiting NLRP3 inflammasome activation and decreasing inflammatory cytokine secretion. Our findings highlight the potential of neferine as a therapeutic option in the treatment of epilepsy.

Keywords: neferine; anti-seizure; neuroprotection; antiinflammation; NLRP3 inflammasome; kainic acid; hippocampus

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1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, spontaneous, and unpredictable seizures and affects up to 70 million people worldwide [1]. Currently available anti-seizure drugs (ASDs), which are the main treatment for epilepsy, mainly act by blocking Na^+ channels, inhibiting glutamatergic transmission, or enhancing GABAergic transmission [2]. However, long-term treatment with these ASDs is often accompanied by many side effects, and approximately 30% of patients with epilepsy do not respond to these drugs [3,4]. Therefore, there is still a need to search for new, more effective and safer anti-seizure medications. In this context, medicinal plants can potentially play an

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Research Article

Neferine Protects against Hypoxic-Ischemic Brain Damage in Neonatal Rats by Suppressing NLRP3-Mediated Inflammasome Activation

Jin-jin Zhu,[1] **Bin-yuan Yu**,[1] **Xiao-kai Huang**,[2] **Min-zhi He**,[1] **Bin-wen Chen**,[1] **Ting-ting Chen**,[1] **Huang-yi Fang**,[1] **Shang-qin Chen**,[1] **Xiao-qin Fu**,[1] **Pei-jun Li**,[1] **Zhen-lang Lin**,[1] **and Jiang-hu Zhu**[1]

[1]*Department of Neonatology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325027, China*
[2]*Department of Hematology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325027, China*

Correspondence should be addressed to Jiang-hu Zhu; zhujianghu2005@163.com

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Hypoxic-ischemic encephalopathy (HIE) is recognized as the main cause of neonatal death, and efficient treatment strategies remain limited. Given the prevalence of HIE and the associated fatality, further studies on its pathogenesis are warranted. Oxidative stress and neuroinflammatory injury are two important factors leading to brain tissue injury and nerve cell loss in HIE. Neferine, an alkaloid extracted from lotus seed embryo, exerts considerable effects against several diseases such as cancers and myocardial injury. In this study, we demonstrated the neuroprotective effect of neferine on HIE and hypothesized that it involves the inhibition of neuronal pyroptosis, thereby ameliorating neurological inflammation and oxidative stress. We demonstrated that the mRNA levels of proteins associated with pyroptosis including caspase-1, the caspase adaptor ASC, gasdermin D, interleukin- (IL-) 18, IL-1β, and some inflammatory factors were significantly increased in neonatal HIBD model rats compared to those in the control group. The increase in these factors was significantly suppressed by treatment with neferine. We stimulated PC12 cells with $CoCl_2$ to induce neuronal HIBD *in vitro* and investigated the relationship between neferine and pyroptosis by altering the expression of the NLRP3 inflammasome. The overexpression of NLRP3 partially reversed the neuroprotective effect of neferine on HIBD, whereas NLRP3 knockdown further inhibited caspase-1 activation and IL-1β and IL18 expression. In addition, simultaneous alteration of NLRP3 expression induced changes in intracellular oxidative stress levels after HIBD. These findings indicate that neferine ameliorates neuroinflammation and oxidative stress injury by inhibiting pyroptosis after HIBD. Our study provides valuable information for future studies on neferine with respect to neuroinflammation and pyroptosis.

1. Introduction

Hypoxic-ischemic encephalopathy (HIE) is the most common cause of death and disability among neonates, with a reported incidence of 2–3 cases per 1000 live births in developed countries and approximately 26 cases per 1000 live births in underdeveloped countries [1, 2]. In recent years, increased preemptive and neonatal care and improved critical care techniques have improved patient survival but they do not prevent neurological disorders, resulting in an increase in the incidence of such disorders in the adult population [3]. Surviving patients with HIE have lifelong neurological deficits, including cerebral palsy (10%–20%), auditory and visual problems (~40%), and motor and behavioral impairments, such as epilepsy, global developmental delay, and autism [2, 4, 5]. Therapeutic hypothermia has been established as a standard clinical treatment for newborns with moderate to severe HIE; however, it is only partially