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RECENT PROGRESS IN MEDICINAL PLANTS:
Series Editors: J.N. Govil and V.K. Singh

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Eds. Amani S. Awaad, V.K. Singh & J.N. Govil

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Eds. J.N. Govil, V.K. Singh & N.K. Goyal

Vol. 30: Drug Plants IV (2010)
Eds. V.K. Singh & J.N. Govil
Medicinal plants are value added for the content and chemical composition of their active components. Therefore, the demand on plant based therapeutics has increased many fold in both developing and developed countries due to the growing recognition that they are natural products, being non-narcotic, having no side-effects, easily available at affordable prices. In a wider context, there is a growing demand for plant-based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. International market of medicinal plants is over US $ 60 billion per year, which is growing at the rate of 7% and expected to be US $ 5 trillion by 2050. Herbal remedies would become increasingly important especially in developing countries.

Progress in medicinal plants research has undergone a phenomenal growth during last two decades. The input of biochemistry to pharmacology has grown. Molecular pharmacology puts more emphasis on the mode of action of drugs. Worldwide trend towards the utilization of natural plant remedies has created an enormous need for information about the properties and uses of the medicinal plants. Based on this rationale, the present series Recent Progress in Medicinal Plants brought out eight volumes, in the first phase, providing edited information from over 225 original and review papers by eminent scientists and researchers from India and abroad on a wide range of topics in the areas of Ethnomedicine, Pharmacognosy, Phytochemistry, Pharmacology, Aesthetics, Biotechnology, Genetic Engineering, Crop Improvement, Production Technology, Trade and Commerce, Diseases and their Management etc. In continuation to these foregone efforts, further eight volumes (9-16) viz., Plant Bioactives in Traditional Medicine; Phytotherapeutics; Drug Development from New Molecules; Globalisation of Herbal Health; Search for Natural Drugs; Biopharmaceuticals; Natural Products; Phytomedicines, providing recent research data in the areas of medicinal plants investigations, aimed at discovering new drugs of plants origin, were presented.

Continuing with the ongoing efforts and over-whelming response, the Series editors have been hard pressed to bring out further nine volumes (Vols: 17-25) of the series on herbal drugs containing recent researches on bioactive components based on their phytochemistry and phytopharmacology in order to discover potential drugs coupled with their therapeutic values. In this direction, nine volumes (17-25) on Phytochemistry and Pharmacology III, Natural Products II, Phytopharmacology and Therapeutic Values I, II, III, IV & V, Standardization of Herbal/Ayurvedic Formulations and Chemistry and Medicinal Value were published.

Thus the publication of 25 volumes of “Recent Progress in Medicinal Plants” (2002-2009) provides a comprehensive account of nearly 1800
important medicinal plants for producing drugs, cosmetics, perfumery etc. Hence, it was felt that there is an urgent need to document these 25 volumes in a more condensed form for scientist’s desk reference in day to day research activity. Considering the importance of such a resource book, it was planned to bring out Vol. 26 containing the abstracts of papers published in 25 volume-set of Recent Progress in Medicinal Plants. The Vol. 26- "Cumulative Index to Abstracts, Vols. 1-25"- provides information on some 1282 abstracts of original and review papers published in the aforesaid volumes.

Considering the fact that many traditional remedies are back to therapeutic use, including plants as such, or extracts prepared in accordance with the pharmacopoeia of the country where they are used. These medicinal plants are increasingly used as (i) source of direct therapeutic agents; (ii) as a raw material base for the elaboration of more complex semi-synthetic chemical compounds; (iii) as models for new synthetic compounds; and, (iv) as taxonomic markers for the discovery of new compounds. In addition to these applications in developed countries, naturally, the medicinal plants will continue to be used increasingly in developing countries, where they are a traditional source of medicine for generations. This has created renewed interest of scientists in medicinal plants and research is at phenomenal rate. We have received excellent studies for publication. It was, therefore, felt desirable to bring out further four Volumes 27-30 of the series, covering recent global updates in medicinal plants researches.

It is hoped these volumes will open new vistas of knowledge and the information presented will lead to further research in the discovery of new drugs of natural origin and serve as good source of material for future work.

J.N. Govil and V.K. Singh
Recent Progress in Medicinal Plants

Foreword

"Save plants to save lives" was the call given by the World Health Organisation a few years ago to stress the role of medicinal plants in achieving the goal of "health for all". Unfortunately, a high percentage of plant species used in the Indian Systems of Medicine like Ayurveda, Unnani and Siddha are still being collected from forests and from natural vegetation. With a rapid rise in the national and global understanding of the importance of herbal medicines in preventive and curative medicine, the pace of exploitation of medicinal plants from the wild state has increased. Consequently, several important medicinal plant species occurring in forest canopies are being threatened with extinction and are being listed in the Red Data books of IUCN and the Botanical Survey of India. Our first task is to bring about a paradigm shift from collection to cultivation. Species occurring in the wild should be domesticated and cultivated in accordance with market demand. Conservation, sustainable use and equitable sharing of benefits are all vital for developing a sustainable medicinal plant industry. At the same time, we should accelerate our efforts in the areas of validation and identification of the biomolecules responsible for specific medicinal properties. Medicinal plants are equally important in veterinary medicine and our vast livestock wealth can be made more productive only by attending to their health and nutrition.

Dr. J.N. Govil and Dr. V.K. Singh deserve our gratitude for their painstaking efforts to compile 28 volumes containing a wealth of information on all aspects of medicinal plants with particular reference to the formulation of both traditional and novel drugs. Volumes 13 to 28 in the series *Recent Progress in Medicinal Plants* contain valuable ideas on the botanical, biochemical and pharmaceutical aspects of herbal drugs. Volume 16 deals with recent work on medicinal plants, including information on bioprospecting. This timely series of books reinforce the views expressed by
Charaka centuries ago that there are no useless plants in our planet. We must preserve our heritage in herbal medicine and also add to scientific knowledge relating to their properties and active principles. Dr. J.N. Govil, Principal Scientist, Indian Agricultural Research Institute, New Delhi and Dr. V.K. Singh, Assistant Director (Botany), Central Council for Research in Unani Medicine, New Delhi, have rendered valuable service in drawing attention to the vast scope in medicinal plants research and drug development.

I hope these books will be widely read and used by all interested in promoting sustainable health security.

(M.S. Swaminathan)

New Delhi
Dated: 4th October, 2005
Foreword to Volume

Medicinal plants represent a primary source for the pharmaceutical industry. Large quantities of these plants are used in the preparation of drugs of traditional origin in India and elsewhere. A sizeable number of these plants are used in the preparation of a wide spectrum of derivatives ranging from active constituents to chemically pure products, the latter being used directly as medicaments or as precursors for the synthesis of other therapeutic agents. The growing demand for herbal products has led to a quantum jump in the number of medicinal plant species and their volumes traded within and across the countries. Developed countries in Europe and America of late have been showing keen interests in the use of herbal medicines because these are supposed to have no side-effects compared to allopathic medicines obtained through chemical process, besides treating diseases considered chronic and incurable. In view of the tremendous demands of the plants throughout the world in medicine, phytochemicals, nutraceuticals, cosmetics and other products, they have become a major sector of trade and commerce. According to WHO estimates, the International market of herbal products is estimated to be US $ 62 billion per year poised to grow to US $ 5 trillion by the year 2050.

Further, medicinal plants produce and contain a variety of chemical substances that act upon the specific organ or on the body as a whole. These plant derived substances remain the basis for a large proportion of the commercial medications used today for the treatment of several challenging diseases like, heart problems, high blood pressure, pain, asthma, and other ailments. The efficacy of a number of phytopharmaceuticals derived from plants such as atropine (pupil dilator), berberine (gastrointestinal disorders), caffeine (stimulant), camptothecin (antitumour), digitoxin (cardiotonic), emetine (antiamoebic), ephedrine (antiasthmatic), forskoline (hypotensive and antispasmodic), morphine (analgesic), papain (protein digestant and anthelmintic), quinine (antimalarial), reserpine (tranquillizer), vinblastine and vincristine (antileukemic) have been discovered. And, continuing with the ongoing world-wide efforts of scientists,
there have been many advances in the strategies for discovery and evaluation of drugs, in recent years, particularly from natural sources. The input of biochemistry to pharmacology has grown. Molecular pharmacology puts more emphasis on the mode of action of drugs, albeit it becomes clear that the activities of most drugs are not confined to one single mode of action. This has generated a lot of research data encompassing different disciplines of science aimed at discovering new drugs of plant origin, and there is, therefore, a need for effective exchange of such information on properties and uses of medicinal plants for wider application of scientific community, globally. The present volume **28 : Drug Plants II** of the series **Recent Progress in Medicinal Plants** is an endeavour in this direction and presents 27 research and review papers containing recent research data in the areas of phytochemistry, pharmacology, microbiology, clinical research, agrotechniques and related sciences on wide range of topics. The studies included amply demonstrate medicinal potential of many species investigated *viz.*, Fennel (*Foeniculum vulgare Mill*), Ginseng (*Panax ginseng Mayer*), Garlic (*Allium sativum L.*), Carqueja (*Baccharis trimera (Less) DC.*), Birch (*Betula spp.*), Evening Primrose (*Oenothera biennis* L.), Horse chestnut (*Aesculus hippocastanum L.*), Khat (*Catha edulis Forsk.*), Winged bean (*Psophocarpus tetragonolobus (L) DC*), Three leaves carper (*Crataeva nurrvala* Buch.-Ham), Bhringa Raja (*Eclipta alba (L.) Hassk*), St. John Wort (*Hypericum perforatum L.*), Rakta Kovindra (*Bauhinia variegata L.*), *Lippia sidoides* Cham., Palash (*Butea monosperma L.*), Milk Thistle (*Silybum marianum L.*), *Bidens pilosa* auct. non L., *Alisma orientale* (Sam.) Juzep, *Cinnamomum tamala* Nees and Eberm, *Ulmus davidiana* Planch var. *japonica* and *Conyza canadensis* (L). Cronq. Thus, advanced scientific investigations on a number of medicinal herbs included in this volume have amply demonstrated their medical efficacy in combating many of the common and chronic diseases and conditions, owing to their innate medicinal properties and action.

The contributions are from far and wide including **Brazil, China, Egypt, Estonia, Hongkong, India, Italy, Kenya, Malaysia, Poland, South Korea, Spain, Sweden** and **Turkey**.

I feel extremely honoured to prepare this foreword and congratulate the editors Dr. Amani S. Awaad, Professor of Pharmacognosy, Chemistry Department, Faculty of Sciences, King Saud University, Riyadh, KSA, Dr. V.K. Singh, formerly Deputy Director (Botany), CCRUM, New Delhi and Dr. J.N. Govil, formerly Principal Scientist, IARI, New Delhi, for their painstaking efforts in producing this commendable work. The findings could serve as new leads of research particularly for those engaged in the discovery of new therapeutics of plant origin.

September 25, 2009

( Dr. G.S. Lavekar)

Director General
Preface

Recent investigations in specialized areas of biological activity have nevertheless confirmed that plants are a reservoir of chemical agents with therapeutic potential. Since new diseases of known pathogens continue to emerge, the search for novel compounds from drug plants is ongoing process and there still would be many potential pharmaceutical compounds yet to be discovered. In the past more than 180 potential plant species have been identified to obtain bioactive molecules of therapeutic and agricultural applicability. In terms of modern research endeavours, drug development from plants must necessarily imply a multidisciplinary approach. Therefore, focused R&D efforts have been directed globally through modern science and technology to discover a number of active principles and biological activities in plants generating enormous data on properties and uses of medicinal plants and there is a need for exchange of this vital data for wider application by the scientific community. Based on this rationale, the present volume 28 : Drug Plants II of the series Recent Progress in Medicinal Plants has been prepared. The volume presents 27 research and review papers contributed by eminent scientists from India and abroad.

Some interesting studies included in this work are Ginseng, *Panax gingseng* Meyer; *Peganum harmala* L., A potential traditional plant and House of natural leads; *Astragalus membranaceus* (Fisch.) Bge; *Baccharis trimera* (Less.) DC; Evening Primrose (*Oenothera biennis* L.); Horse Chestnut (*Aesculus hippocastanum* L.); Winged bean *Psophocarpus tetragonolobus* (L.) DC – An edible plant with multiple medicinal and pharmacological uses; Botany, chemistry, pharmacology and medicinal uses of *Eclipta alba* (L.) Hassk; St. John’s wort (*Hypericum perforatum* L.); Soy isoflavones and their effect on menopause symptoms; The traditional uses, chemical constituents and biological activities of *Lippia sidoides*; *Butea monosperma* L. – Chemistry, technological aspects and medicinal properties; Milk Thistle, *Silybum marianum*; *Alisma orientale* (Sam.) Juzep : A common traditional Chinese medicinal plant as a diuretic agent; Biological activities of *Ulmus davidiana* Planch var. *Japonica*; Biological properties of *Conyza canadensis* (L.) Cronq; Current progress on medicinal plants and their biological properties in contemporary China; Impact of medicinal plants on sensitivity of *Candida* strains to antifungal drugs. These studies amply demonstrate that medicinal species investigated exhibit wide array of biological attributes viz., antimicrobial, anti-inflammatory, antioxidant, antitumor, antiviral, adaptogenic, antidiabetic, antifungal, antibacterial, amoebicidal, abortifacient, antinociceptive, anticomplement, anthelmintic, antigoitrogenic, antihypertensive, antispasmodic, anti-stress, antidiarrhoeal, aphrodisiac, anti-arthritic, antiestrogenic, analgesic, antiestrogenic, antihepatotoxic, antiimplantation, antiprotozoan, carminative,
gerontological, hypolipidemic, immunoregulatory, stimulant gastroprotective, larvicidal, vermifuge etc. which are responsible to combat many of the common and chronic diseases and conditions.

The contributions are from far and wide including Brazil, China, Egypt, Estonia, Hongkong, India, Italty, Kenya, Malaysia, Poland, South Korea, Spain, Sweden and Turkey.

It is hoped the volume will open new vistas of knowledge and prove to be an excellent exposition of current research efforts of scientists in India and abroad in the area of medicinal plants investigations. The findings presented are likely to contribute valuable material for further research leading to the development of new drugs of plant origin. The volume will be useful to researchers in the discipline of phytochemistry, ethnobotany, pharmacology, microbiology, biochemistry, medical sciences and allied disciplines engaged in the search of new drugs of plant origin.

We extend our sincere thanks to all the contributors from India and abroad for their timely response, excellent and updated contributions and consistent cooperation that has enabled us to prepare this volume. We also thank our publishers, Studium Press LLC, Texas – 27707, USA, for a timely and expeditious job, rendering the manuscript press-ready.

- Editors
About the Editors

Dr. V.K. Singh (b. 1948): Formerly, Deputy Director (Botany) at Headquarters Office of the CCRUM, is responsible for execution of projects on ethnobotanical surveys, medicinal plants cultivation, development of herbal gardens, and pharmacognostic studies of crude drugs. Dr. Singh received his Ph.D. in plant taxonomy (1971). He has been a plant explorer, ethnobotanist and conservationist and has taken a series of medicinal plants collection trips in different tribal areas, particularly in North India, for over 27 years (1971-1997). Based on his studies, he has to his credit over 85 research papers published in various scientific journals in India and abroad, 26 books dealing with medicinal plants and folk medicines of India including edited volumes. Of recent, Dr. Singh has been conferred CCRUM Award (2005) and received first prize from Union Minister of Health & Family Welfare, Govt. of India, for his outstanding research contributions in the area of Survey and Cultivation of Medicinal Plants including development of Herb Gardens. Earlier, Dr. Singh was adjudged for “Award for Medical Research (1972)” from erstwhile Central Council for Research in Indian Medicine and Homeopathy (CCRIMH) for his contribution to the botanical identity of controversial Ayurvedic drugs. Nominated as Referee for various scientific journals on medicinal plants, and also on the panel of experts committee on WHO studies on indigenous drugs in India. Recently, Dr. Singh was nominated by department of AYUSH, Govt. of India to participate and present his paper in an international symposium on medicinal and nutraceutical plants held at Georgia, USA, during March 2007. Between 2001-2002, Dr. V.K. Singh served in the National Medicinal Plants Board, Government of India, New Delhi and was actively associated in the policy formulations and guidelines for promotion & development of medicinal plants sector in the country. He contributed in a book on agrotechniques of medicinal plants entitled “Cultivation Practices of Some Commercially Important Medicinal Plants”. During 2002-2007, Dr. Singh headed a Project “Awareness, Training and Cultivation of Medicinal Plants in Western U.P.” Dr. V.K. Singh happens to be the pioneer in giving the concept of medicinal plants cultivation and marketing among the farmers of Western U.P. districts in India. E-mail: VKS_CCRUM@yahoo.co.in

Dr. Amani Shafiq Awaad was born on 25th August in 1963 in Cairo, Egypt. She completed her B.Sc and M. Sc in Pharmaceutical Science from the College of Pharmacy, King Saud University, Riyadh and Ph.D. in Pharmacognosy from College of Pharmacy, Cairo University, Cairo in 1995. She started her professional career as Assistant Researcher of Pharmacognosy (1994-1996 & 1999-2001) and worked as Head of Natural Products Unit (2000-2006) at the Aromatic and Medicinal Plants Department, Desert Research Centre, Cairo. She also worked as Post Doctoral Researcher (1997-1998) at School of Pharmacy and Biomedical Science, Portsmouth University, U.K. and Post Doctoral Associate Professor
(2003-2004) at Bradford University, U.K. in between. She has been working as Professor of Pharmacognosy since 2006 at Chemistry Department, Faculty of Sciences, King Saud University, Riyadh, Kingdom of Saudi Arabia. She has been actively involved in Teaching and Research Guidance of students. She has handled several research projects. She is serving as Member of several important committees of the University and referee/editor for many journals of repute. She is also a member of several Professional Societies at National and International level. She is widely traveled and has attended several International Conferences. She has more than 30 research papers published in research journals of national and international repute and two technical bulletins to her credit. She has received several national and international awards for outstanding contribution in the field Aromatic and Medicinal Plants.

**Dr. J.N. Govil (b. 1945):** Obtained his Masters and Doctorate degrees from Agra University, Agra, India. In his career span of 41 years research experience at the Indian Agricultural Research Institute, New Delhi, Dr. Govil has been involved in the breeding of cross-pollinated, often cross-pollinated, and self-pollinated crops. His research is mainly focussed on breeding for better quality, disease resistance, and for higher productivity in *Pennisetum, Sorghum,* maize, chickpea, and pigeonpea. Dr. Govil has been well exposed to the international scientific community through various training programmes. He took his training in “Plant exploration and collection techniques” through IBPGR in 1982. He was also awarded the prestigious FAO/IBPGR Fellowship in “Genetic resources, evaluation, and data preparation and management” at the University of Birmingham, UK. In 1983, he made visits to gene banks located in Europe. He also participated in various international seminars and conferences, including “Food and Legume Improvement for Asian Farming Systems” in Thailand in 1986. Dr. Govil is credited with more than eighty research papers in various journals of national and international repute in various aspects of genetics, crop breeding, and topics on general agriculture. He has written and edited a number of books on medicinal Plants (2 Vols each of two Titles) and other books with international authors. A new series “Recent Progress in Medicinal Plants” has been published by Studium Press, LLC, USA in 25 volumes under Dr. Govil’s Chief Editorship. Dr. Govil has been Editor-in-Chief of the Journals, New Botanist (An International Journal of Plant Research) and Glimpses in Plant Research, since 1988. He has also guided more than a dozen post-graduate students. Dr. J.N. Govil was actively engaged through his leadership on pigeonpea breeding with special emphasis on “Breeding short duration pigeonpea varieties for improved management and low input conditions.” Through his intensive efforts over the last 20 years, nine varieties of early pigeonpea in arhar-wheat rotation have been released at national level. Currently, Dr. Govil has retired from ICAR and has joined as Publishing Director and Managing Editor with Studium Press LLC, USA. E-mail: jngovil@gmail.com
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Abstract

The common fennel (Foeniculum vulgare Mill.) from family Apiaceae is a plant yielding fruit that is traditionally used as a carminative and mild expectorant. The pharmaceutical importance have two varieties: F. vulgare Mill., subsp. vulgare var. dulce (Mill.) Thellung (sweet fennel) and F. vulgare Mill. subsp. vulgare var. vulgare (bitter fennel). The fruit is rich in essential oil, which’s the main constituent – the phenylpropene (E)-anethole. Other constituents are (+)-fenchone, limonene, α-pinene and estragole. Besides, fennel fruit stilbene trimers - derivatives of cis-miyabenol C, monoterpenoid glycosides and phenolic compounds - are identified. Investigations of extracts and essential oil as well as isolated compounds from fennel showed their broad pharmacological activity, among other activities are estrogen-like, antimicrobial, anti-inflammatory, antioxidant, hepatoprotective and antiplatelet. Fennel is considered to be rather safe drug with rare side effects and contraindications.

Key words: Foeniculum vulgare, Essential oil, Phenylpropene (E)-anethole, (+)-fenchone, Limonene, α-pinene, Estragole, Antimicrobial, Anti-inflammatory, Antioxidant, Hepatoprotective, Antiplatelet

Introduction

The common fennel is a tall, erect, glabrous, herbaceous plant with glaucous, striate branching stems. Plant may grow to over 2 m. The leaves are alternate and about 30 cm long, ovate to deltoid in outline, and pinnately dissected into many filiform divisions. The leaf stems are conspicuously sheathed at the base. The yellow, small flowers are arranged in compound
umbels with 15-40 unequal rays. The fruit is a cremocarp. In temperate climate it is biennial but in tropical climate it is perennial plant.

Fennel is originally native to the Mediterranean region, now cultivated in central Europe, Asia, parts of Africa and South America and much is imported from India, China and Egypt. The plant is common on dry slopes and ridges, in openings, by the sides of roads, trails, streambeds, in fields and waste places (Wichtl, 2004).

The species *Foeniculum vulgare* Mill. is divided in two subspecies, subsp. *vulgare* and subsp. *piperitum*. Subspecies *vulgare* is subdivided in four varieties: var. *azoricum* with characteristic hypertrophied sheaf of the basal leaves used as a vegetable, var. *dulce*, sweet fennel, its cultivar ‘Bronze’, which is a horticultural variety of fennel and var. *vulgare*, bitter fennel (Muckensturm *et al.*, 1997).

The pharmaceutical importance have both the varieties: *F. vulgare* Mill., subsp. *vulgare* var. *dulce* (Mill.) Thellung, which’s fruits are richer in anethole and have a sweet and aromatic taste and *F. vulgare* Mill. subsp. *vulgare* var. *vulgare*, which is rich in fenchone, resulting in a bitter taste of fruits. From those plants for medical purpose two sources are used: *Foeniculi dulcis fructus* and *Foeniculi amari fructus*. Their monographs in pharmacopoeias of most of the countries are featured. Sweet fennel is pale green or pale yellowish-brown, bitter fennel is greenish-brown, brown or green. The two varieties are nearly impossible to distinguish macroscopically or microscopically. The commercial drug consists partly of whole cremocarps, some of which have the pedicel attached and partly of isolated mericarps. A cremocarp is of almost cylindrical shape with a rounded base and a narrower summit crowded with a large stylopod. It is 3 to 12 mM long and 3 to 4 mM wide. A mericarp is glabrous and bears five prominent slightly carenated ridges. The most important diagnostic characters of the powdered fruit are yellow fragments of wide secretory canals, frequently associated with a layer of thin-walled transversely elongated cells having a parquetry arrangement. The powdered plant source possesses characteristic aromatic odor and strongly aromatic taste (European Pharmacopoeia 5, 2005).

**Chemical Composition of Fennel Fruit**

The most important compound, considered to be responsible for more pharmacological properties of fennel, is essential oil. This is a colorless or pale yellow liquid. The composition of volatile fraction is changing, dependent from variety, climatic conditions, the time of gathering and the method of isolation. According to Ph. Eur., sweet fennel fruit contains 1.5-3% and not less than 2.0% of essential oil with (E)-anethole as the main constituent (80-95%, not less than 80%), but with very little amount of fenchone, about 1% (according to Ph. Eur., not more than 7.5%). The content of estragole (= methylchavicol) is not more than 10%. Monoterpenes, α-pinene, limonene, α-phellandrene, α-thujene, sabinene are the
removing constituents of essential oil. In small amounts is detected anisaldehyde, the artificial oxidation product of anethole forming during storage and distillation of the oil.

Bitter fennel fruit contains of 2-6% volatile oil, according to Ph. Eur., not less than 4%, composed of (E)-anethole (50-70%, not less than 60%), fenchone (12-25%, not less than 15%) and estragole (2-8%, not more than 5.0% of the oil). Other constituents are monoterpenes, α-pinene (1-2%), limonene (1-2%) and cis-ocimene. The essential oil contains also small amounts of anisaldehyde (European Pharmacopoeia, 2005; Wichtl, 2004). The content of the main constituents of essential oil is presented in Table 1.

![Fig 1. The main components of fennel essential oil](image)

There are a number of literature reports on composition of volatile oil in sources indigenous to various countries. In all cases trans-anethole, estragole and fenchone are the main constituents, although a high variability was found among percentages of individual components and by the reason of this, several chemotypes were distinguished (Barazani et al., 1999; Garcia-Jimenez et al., 2000; Barazani et al., 2002, Piccaglia & Marotti, 2001; Diaz-Maroto et al., 2006; Cosge et al., 2008). Among bitter fennel (F. vulgare Mill. var. vulgare) populations of different origins, based on the cluster analysis of the fruit oil, three chemotypes (ct.) were separated: ct. anethole (anethole > 60%), ct. fenchone (fenchone > 30%), ct. methylchavicol (methylchavicol > 30%) (Bernath, 1996). In bitter fennel fruit oil from France, high concentration of methylchavicol was detected, therefore chemotype estragole (60% methylchavicol) and ct. estragole/anethole (50% methylchavicol and 10% trans-anethole) were distinguished (Muckensturm et al., 1997).

The method of distillation and the degree of fruits grinding shows the influence on the efficiency of the distillation process and quantitative composition of the essential oil (Marotti, 1992). In comparison to essential...
oil obtained by hydrodistillation, the extract prepared by extraction with supercritical CO$_2$ contained more trans-anethole, more fenchone and less methylchavicol. The extract possessed also more intense fennel aroma (Damjanoviæ et al., 2005). Also other new, simple and effective methods of isolation and analysis of volatile compounds from fennel fruit, such as direct thermal desorption coupled to gas chromatography-mass spectrometry (Diaz-Maroto et al., 2006), headspace solvent microextraction-gas chromatography-mass spectrometry (HSME-GC-MS) and solid phase microextraction-gas chromatography-mass spectrometry (SPME-GC-MS) (Fang et al., 2006) were utilized.

The Phytochemical Composition of the Non-volatile Fraction of Fennel Fruit

From the methanolic extract of fruit of F. vulgare stilbene trimers: miyabenol C (form trans), cis-miyabenol C (Fig 2) and its mono- and diglucosides: foeniculoses I-IV (Ono et al., 1995) and foeniculoses X and XI, together with stilbene trans-resveratrol 3-O-β-D-glucopyranoside and benzoisofuranone derivative (32R)-5-hydroxy-3-(32-hydroxybutyl)-isobenzofuran-1(3H)-one (Fig 3) (De Marino, 2007).

From the water-soluble fraction of methanolic extract of fennel various compounds were isolated. Among them dihydroxy-1,8-cineole monoglucosides named foeniculoses V-IX (Ono et al., 1996), 1,8-cineole glucosides, stereoisomers of 2-hydroxy-1,8-cineole glucoside and dihydroxy-1,8-cineoles (Ishikawa et al., 1998c) were recognized.

Many aromatic and monoterpenoid compounds were isolated: threo- and erythro-anethole glycol (Ono et al., 1996), erythro-anethole glycol monoglucosides and p-hydroxyphenylpropylene glycol glycosides (Kitajima et al., 1998b), fenchan-type monoterpenoid glycosides (Ishikawa et al., 1998a), menthane-type monoterpenoids in free and glycosyl form (Ishikawa et al., 1998b) and acyclic monoterpenoids in free and glycosyl form (Ishikawa et al., 1998d). Additionally benzyl alcohol glycosides: zizybeoside I and icaviside A$_4$, syringing and its 4-O-β-glucoside, sinapyl alcohol glucoside and 1,32-di-O-β-D-glucoside (Ono et al., 1996; De Marino et al., 2007), methylsyringin, isosalicin, phenylpropanoid glycosides, benzyl alcohol derivative glycosides, phenylethanoid and its glycoside (Kitajima

<table>
<thead>
<tr>
<th>Bitter fennel (%)</th>
<th>Sweet fennel (%)</th>
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<tbody>
<tr>
<td>(E)-anethole</td>
<td>60 - 75</td>
</tr>
<tr>
<td>(+)-fenchone</td>
<td>12 - 22</td>
</tr>
<tr>
<td>limonene</td>
<td>1.5 - 2.5</td>
</tr>
<tr>
<td>(+)-α-pinene</td>
<td>1.8 - 4.7</td>
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simple alkyl glycoside derivatives (ethyl, propyl, butyl and isopentyl glycosides) (Kitajima et al., 1998c) were obtained. As well as lipophilic compounds oleanolic acid, 7α-hydroxycampesterol, (3β, 5α, 8α, 22E)-5,8-epidioxy-ergosta-6,22-dien-3-ol and a monoacylglycerol: 2,3-dihydropropylheptadec-5-enoate were isolated (De Marino et al., 2007). Fennel fruit contains also coumarins (scopoletin) and furocoumarins (bergapten, psoralen) as well as neutral constituent-fatty oil (10-20%), proteins (20-30%) and carbohydrates (4-5%) (Sticher, 1999; Wichtl, 2004).

**Traditional Use of Fennel**

The fruit is primary carminative but also mild expectorant. Fennel tea is much used to treat colic, dyspepsia and diarrhoea. It provides a carminative effect that reduces flatulence and eases intestinal spasms. Additionally fennel makes an excellent flavor corrective of the preparations. In folk medicine fennel fruit is used as a lactagogue for nursing mothers. Sometimes fennel is used to treat inflammatory conditions of the external eye, *e.g.* blepharitis and conjunctivitis with swelling of the lids. Compresses with fennel water or fennel tea are used also to treat general weakness of vision (Schulz et al., 1998; Weiss, 2001; Wichtl, 2004).
The essential oil from fennel has a variety of applications in the food and pharmaceutical industries. Bitter fennel oil is used mainly to improve aromatic character of foods (confectionery, bakery products and marinades), liquors and oral hygiene products and medicinal uses in carminatives, diuretic agents, mouth and throat preparations, bronchological agents and expectorants. Sweet fennel oil is used mainly to improve the aromatic character of liquors and similar alcoholic beverages (Steiglich et al., 2000).

Pharmacological Effects and Clinical Efficacy

Traditional use of fennel fruit was confirmed in various investigations and new activities were also recognized. Fennel is the most frequently recommended to relieve infantile colic. The effectiveness of 0.1% stable emulsion of fennel seed essential oil in water in a randomized, placebo-controlled study was examined. The preparation significantly reduced the intensity of infantile colic in the comparison with placebo. In this study daily consumption of fennel oil was approximately 400 times lower than LD_{50} (Alexandrovich et al., 2003). Secretolytic and expectorant effectiveness of infusion from bitter fennel was observed in isolated ciliated epithelium from the frog oesophagus (ESCOP, 2003).

Oral administration of an acetone extract from fennel fruit to adult female ovariectomized rats in dose 0.5-2.5 mg/kg body weight caused dose-dependent estrogenic effects. Whereas moderate dose caused increase in weight of mammary glands, higher dose increased the weight of the endometrium, cervix and vagina (Malini et al., 1985). Estrogen-like activity of (E)-anethole was demonstrated using the yeast estrogen screen assay. The assay utilizes recombinant yeast cells expressing the human estrogenic receptor alpha. (E)-anethole showed activity with an EC_{50} of 625 μg/ml, relative estrogenic potency of 8.6 × 10^{-8} compared to 17β-estradiol and a percent maximal response of 54.5% (Tabanca et al., 2004).

Some study concerned the ability of essential oil from fennel to relieve painful menstruation. It was demonstrated that fennel essential oil can inhibit contraction of isolated uterus that was induced by oxytocin and prostaglandin PGE_{2}. The essential oil also reduced the frequency of contractions induced by PGE_{2} but not with oxytocin (Ostad et al., 2001). A randomized, double blind study, comparing oral administration of 1% and 2% solutions of essential oil with placebo, showed that the efficacy
of 2% essential oil in pain relief is 67.4% and is comparable with efficacy of non-steroidal anti-inflammatory drugs. The mechanism of action may be related to direct effect on uterine muscle (Khorshidi et al., 2003). The essential oil from sweet fennel with 2% concentration in oral drop form was effective in primary dysmenorrhea, however, in comparison to mefenamic acid, showed lower activity (Namavar Jahromi et al., 2003). The estrogenic activity of essential oil components involved also anti-osteoporotic action, which was demonstrated in ovariectomized rat osteoporosis model. Intraperitoneal injections of essential oil increased bone mineral density and uterine weight in a dose dependent manner. Protective effect on bone loss at the dose 1 g/kg was even more than estradiol but also more toxic than other doses (Jaffary et al., 2006).

The ethanolic extract of the dried, ripe fruit was active against Staphylococcus aureus and Bacillus subtilis. The minimum inhibitory concentration (1 mg/ml) was found to be similar for both microorganisms (Tanira et al., 1996). Methanolic extract from fennel fruit possess activity against Helicobacter pylori with minimum inhibitory concentration at 50 μg/ml (Mahady et al., 2005). In vitro study showed that the essential oil of F. vulgare fruit was more active than the herb essential oil against bacteria and fungi and exhibited the highest activity against C. albicans comparable to nystatin (Minija & Thoppil, 2002). Bioassay with 12 various fungi demonstrated that fennel oil possesses a strong antifungal activity, which can be attributed to the main compound, (E)-anethole. It may be used in the food industry for preventing infection with Aspergillus species and mycotoxin contamination, as well as against fungal infections of the skin, hair and nails caused by dermatophytes (Mimica-Dukic et al., 2003).

Pharmacological studies of the ethanol extract of fennel fruit in animals have found fennel to possess diuretic and choleretic (increase in production of bile) actions. The diuresis lasted for 24 h and the induced increase in the urinary output was not accompanied by a corresponding increase in either sodium or potassium excretion indicating an osmotic mechanism of action. The extract showed also pain-reducing and fever-reducing actions. The analgesic effect of the plant extract was observed later than antipyretic response. It suggests that the two actions are independent of each other pointing to the possibility of being caused by two different constituents (Tanira et al., 1996).

Anti-inflammatory activity of methanol extract was evaluated by carrageenan-induced paw edema, arachidonic acid-induced ear edema and formaldehyde-induced arthritis. For the acute inflammation, fennel extract administrated per oral at dose of 200 mg/kg caused a significant inhibition of paw edema (69%) as compared to the control group 3 h after carrageenan injection. It also inhibited by approximately 70% the ear-edema induced by arachidonic acid in mice. The results suggest that the extract from fennel may act on both the cyclooxygenase and lipoxygenase pathways. In the inflammation induced by formaldehyde after administration of
fennel extract the level of serum alanine aminotransferase was significantly lower than that of control group (Choi & Hwang, 2004). In the model of carrageenan induced rat paw edema, essential oil from fennel fruit administrated intraperitonelly (0.2 ml/kg) demonstrated moderate anti-inflammatory activity. This effect is probably due to limonene and α- and β-pinene (Özbek, 2005).

Anti-allergic activity (in type IV allergic reactions) of fennel methanolic extract, tested using 2,4-dinitrofluorobenzene-induced contact hypersensitivity reaction, was observed after oral administration of 200 mg/kg of extract once a day for 7 days. The inhibitory effect on immunologically induced swelling suggests the possible immunosuppressive properties of investigated extract. Fennel extract in the same dose show also analgesic activity, but mechanism of action is unclear (Choi & Hwang, 2004).

In vitro examination of the aqueous and ethanolic extracts of F. vulgare fruit showed their strong antioxidant activity through reducing power, free radical, superoxide anion radical and hydrogen peroxide scavenging and metal chelating ability (Oktay et al., 2003). After 3 weeks of oral administration of 200 mg/kg per day of methanolic extract to rats, superoxide dismutase and catalase (plasma antioxidant enzymes) activities were significantly increased while lipid peroxidation was significantly decreased (Choi & Hwang, 2004). Reach in polyphenols butanolic crude extract and isolated phenolic compounds foeniculoside X, cis-miyabenol, trans-miyabenol, sinapyl glucoside and syringin 4-O-β-glucoside showed a moderate activity in the lipid peroxidation assay. The aqueous residue, obtained after extraction, also exhibited some radical scavenging activity. It was observed that pure compounds showed higher antioxidant activity then the crude extracts, but were weaker than quercetin used as a standard (De Marino et al., 2007).

The essential oil from fennel fruit administrated i.p. to rats with carbon tetrachloride (CCl₄) induced acute and chronic liver injury showed, in both cases, decrease of the level of serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin. It suggested that the essential oil of fennel possess hepatoprotective activity (Özbek et al., 2003; Özbek et al., 2004). The level of hepatic enzymes was decreasing also after i.p. application of fixed oil obtained from fennel fruits by diethyl ether extraction (Özbek et al., 2006).

In experiment on the rat isolated phrenic nerve diaphragm preparation and on field-stimulated guinea-pig ileum preparations, fennel essential oil produced a spasmogenic effect on smooth muscle and had a similar effect whether the skeletal muscle was stimulated directly or through the nerve. It suggests that the oil made more calcium available within the muscle cell, possibly by releasing it from the endoplasmic reticulum (Lis-Balchin & Hart, 1997).

Fennel oil demonstrated inhibitory activity in aggregation of platelets induced by ADP, collagen, tromboxane A₂ (agonist or arachidonic acid)
with the same effectiveness but with broader antiplatelet spectrum as aspirin. For anti-platelet aggregation activity anethole was mainly responsible (Yoshioka & Tamada, 2005; Tognolini et al., 2006). Study of fennel oil and anethole (at antiplatelet concentrations) on isolated rat aorta rings showed, regardless of the presence of endothelium (NO-independent), vasorelaxant properties. In this case vasodilatation was likely unrelated to inhibition of α-adrenoreceptors since it was present also in KCl-induced vasospasm. Both, essential oil and anethole, after oral administration, in a subacute treatment to mice in dose 30 mg/kg/day for 5 days, showed significant antithrombotic activity without prohemorrhagic and gastrolesive side effects. Additionally gastroprotective activity was observed (Tognolini et al., 2007).

Cytotoxic effect of anethole in Ehrlich ascites tumor cells in the paw of mice was demonstrated (Al-Harbi et al., 1995). This compound inhibits TNF-induced cellular responses, which may explain its role in suppression of inflammation and carcinogenesis (Chainy et al., 2000). The ethanol extract from fennel fruit showed apoptotic effect on various human leukaemia cell lines (Bogucka-Kocka et al., 2008). Fennel seeds, added to food in concentration 4% and 6%, exhibited reduction in the tumor incidence and tumor multiplicity in case induced skin papillomagenesis and forestomach papillomagenesis. Additionally a significant increase in the components of cytochrome P450 was observed, what suggests that fennel seeds in diet the metabolism of carcinogens might enhance. Chemopreventive activity of fennel might be also due to its influence on enzymes taking the part in anti-oxidative processes (Singh & Kale, 2008).

In double-blind placebo controlled study antihirsutism activity of ethanolic extract from fennel fruit was examined. The duration of treatment was 12 weeks. Topical use of cream containing 1% and 2% of fennel extract caused reduction of hair diameters. No adverse effect in topical application was observed. The authors suggested that the presence of trans-anethole in extract is responsible for the activity (Javidnia et al., 2003).

Aqueous extract from fennel fruit at concentration of 0.6% (w/v) showed significant oculohypotensive activity in rabbits comparable to that of timolol. However, the onset of action of plant extract was slower and duration of action was shorter than that of timolol (Agarwal et al., 2008).

In vivo in the rabbit conjunctival reflex test and in rat phrenic nerve-hemidiaphragm technique, remarkable local anesthetic activity of trans-anethole, comparable with procaine, was evaluated (Ghelardini et al., 2001).

**Dosages and Route of Administration Including Dosage Forms**

*Fennel and its preparations are used orally as:* dried fruit infusion, for adult and adolescents over 12 years of age, single dose is 1.5-2.5 g of