Practitioner Information

Botanical Monograph

Artemisia annua

Chinese Wormwood, Qinghao, Sweet Wormwood, Sweet Annie, Sweet Sagewort, Annual Wormwood

Handroanthus impetiginosus

Pau d'arco, Tabebuia species, Taheebo, Lapacho, Ipe roxo, Peuva

Foeniculum vulgare

Fennel seed, Fennel fruit, Fenchel, Bitterfenchel, Aneth fenouil, Finocchio, Xian Hui Xiang

Artemisia annua

Artemisia annua

Botany

Artemisia annua belongs to the Asteraceae family. It is a sweetly pungent, bushy annual growing between 1/2 to 3 metres tall. The leaves are saw toothed and vivid green. *Artemisia annua* is native to Eurasia, and is found in areas from Europe through to China, Japan, Siberia, Korea, India and West Asia. It has now become a weed found throughout the world although commercial cultivation of the plant has commenced in China and the USA. It is harvested in summer before flowering. The leaves and aerial parts are used.

Active Constituents

The main active ingredient is artemisinin (also known as qinghaosu), a sesquiterpene lactone with a peroxide group.[1] There has been extensive research on artemisinin as it has been found to have antimalarial activity and has been shown to be effective in treating cases of drug resistant malaria.

Artemisinin was isolated by Chinese researchers in the early 1970s. In the last two decades, artemisinin and its semisynthetic derivatives artemether and artesunate have been established as safe and effective antimalarials.[2]

The other major constituents are essential oils, coumarins and flavonoids.[1, 3]

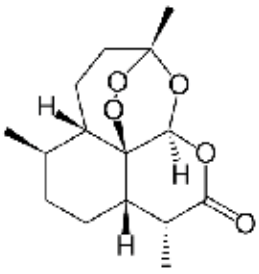

Figure 1: Artemisinin

Actions

Anthelmintic, antibacterial, antidiarrhoeal, antiemetic, antifungal, antimalarial, antiprotozoal, antioxidant, antipyretic, antiseptic, bitter, carminative, digestive.[7]

Traditional Use

Artemisia annua has a broad and extensive history of traditional use, both in Asia and Europe. It has been used in Traditional Chinese Medicine (TCM) for thousands of years, primarily as a general antipyretic.[4]

Reference to the medicinal use of *Artemisia annua* has been found in the earliest recorded Traditional Chinese Medicine text the Wu Shi Er Bing Fang *Prescriptions for Fifty-two Disease* which was compiled between 1065 and 771BC, where it was recommended for the treatment of haemorrhoids.[5] The Zhou Hou Bei Ji Fang text *Handbook of Prescriptions for Emergency Treatments* dated approximately 341AD, is the earliest written record suggesting *Artemisia annua* as a treatment for malarial fevers.

Additional sources document the traditional use of an infusion of *Artemisia annua* leaves used internally for colds and flu, fever, dysentery and diarrhoea. The seeds have been used for flatulence, indigestion, night sweats, dyspepsia and consumption (tuberculosis).[6] *Artemisia annua* has additional traditional use as an antibacterial and antifungal.[7]

Modern use

Artemisia annua or Qinghao is used today in TCM to dispel heat, cool the blood, remove fever and prevent Qi from being 'consumed' by summer heat syndrome (characterised by headache, dry mouth, fever, profuse sweating and irritability).[8] According to the Pharmacopoeia of the People's Republic of China, *Artemisia annua* is indicated for 'fever caused by summer-heat; afternoon fever in deficiency of yin or in consumptive diseases; malaria with chills and fever; jaundice'.[9] *Artemisia annua* is used as a broad spectrum, antiparasitic, antifungal, bitter and diaphoretic.[10] Its active constituent artemisinin is used as an antimalarial agent.[11]

Pharmacology

Antimalarial Activity

Artemisia annuas' principle active constituent, artemisinin, has been widely researched due to its potential for use in the treatment of malaria. The peroxide bridge in artemisinin and its derivatives is essential for the antimalarial activity. Such compounds are thought to cause free-radical damage to parasite membranes systems, and are considered to be effective schizontocides. [1, 11]

The exact mechanism of action of artemisinin is unclear. There are several schools of thought as to its action. The most widely accepted mode of action is a two-step mechanism proposed by Meschnick et al. which suggests that once artemisinin is absorbed into the parasite, the endoperoxide bridge of artemisinin is cleaved by iron or heme, generating free radicals. The second step called

alkylation involves the artemisinin-derived free radicals forming co-valent bonds with the parasite proteins causing irreversible damage to the parasite and rapid death.[12, 13]

Other research suggests a three step mechanism of action. Haemoglobin is utilised as a major source of amino acids by malarial parasites – a by-product of haemoglobin digestion is free heme which is toxic to the parasite. The parasite converts free heme into hemozoin- a form of nontoxic heme. This process is called heme polymerization and is specific to malarial parasites. Artemisinin interferes with this pathway by firstly, inhibiting the digestive proteases thereby preventing haemoglobin breakdown, secondly, by binding to free heme and forming covalent complexes preventing it from being converted to hemozoin thereby causing toxicity, and thirdly, initiating the breakdown of hemozoin back to heme, causing additional toxicity.[14]

Antiparasitic, Antibacterial and Antiprotozoal Action

Protozoa, parasites and bacteria cause a range of ailments. Symptoms such as diarrhoea, fever, vomiting, abdominal cramping and inflammatory bowel conditions and other gastrointestinal disturbances are common. Overseas travellers, particularly those visiting the tropics and areas such as Asia, Middle East, Africa and Latin America, are vulnerable through exposure to contaminated food, water and insect bites. [15, 16]

Artemisia annua has been shown to be effective against the following pathogens:

PARASITES	BACTERIA
• *Clonorchis sinensis* [1,3]	• *Enterococcus hirae* [21]
• *Plasmodium falciparum, P vivax* and multiple drug resistant malaria [1,3]	• *Escherichia coli* [22]
• *Pneumocystis carinii* [17]	• *Klebsiella spp* [22]
• *Leishmania major* [18]	• *Proteus spp* [22]
• *Schistosoma spp* [3,19]	• *Serratia marcescens* [22]
• *Toxoplasma gondii* [20]	• *Shigella dysenteriaw* [22]
	• *Staphylococcus aureus* [22]
	• *Streptococcus faecali* [22]

Immunological Activity

Artemisinin and its derivatives have been extensively studied for their immunological activity. The results of these investigations are sometimes contradictory which makes it difficult to draw any definite conclusions. Most research would indicate artemisinin and its derivatives have an immunosuppressive action; either by inhibition of T lymphocytes[23] stimulation of suppressor T cell activity,[24] or suppression of humoral responses. [25]

However, other studies have shown artemisinin to be immunostimulating. One study showed artemisinin accelerated immune function recovery in mice after bone marrow transplantation.[26] Another report showed artemisinin enhanced macrophage phagocytosis in mice.[2] Lin PY et al suggest that artemisinin and its derivatives have both immunosuppressive and immunostimulating activities; that artesunate suppressed humoral immune response but enhanced cell mediated immunity.[27] It has been proposed that the effects of artemisinin are dose dependant and low doses are immunostimulating whilst high doses are immunosuppressive, although again, there is contradictory evidence for this statement. [25, 26, 28]

Clinical Studies

Malaria

Artemisinin has been shown in several studies to be active against several forms of malaria including drug resistant strains. A Cochrane review of 41 trials involving over 5000 patients concluded that "compared with standard antimalarial treatments, artemisinin drugs showed fast parasite clearance and high cure rates at follow-up" and "malaria parasites have so far not developed resistance to artemisinin drugs. The review shows that artemisinin drugs clear malaria parasites from the blood more effectively than standard treatment drugs." [28]

Three clinical trials in the Congo involving 48, 91 and 21 patients used a tea made from 1 litre of boiling water to 5gms dried leaves of *Artemisia annua*. The tea was drunk in four portions in the course of the day for 5-7 days. The results of the three trials showed that 92%, 95% and 91% of patients experienced blood free of parasites by the end of the trial. There were several complaints of minor side effects being experienced but all adverse symptoms resolved within a few days of completing treatment.[2]

Systemic Lupus Erythematosus (SLE)

Artemisia annua has a long history of use in the treatment of SLE, and it is thought its benefit in this condition is due to its immune modulating effects. Studies have shown that it improves T-cell activity by promoting suppressor cells, thereby reducing the hyperactivation of the T cells that promote autoantibody production.[28]

In a study of 7 cases of SLE and 4 cases of discoid lupus erythematosus remission of various degrees were achieved in all the patients within 50 days on a treatment of 100ml artemisinin (approximately 16.5g *Artemisia annua* herb) twice a day for the first month, three times a day for the second month and four times a day for the third month.[19]

Toxicity

Artemisia annua is considered a safe herb to use; acute toxicity is low. Artemisinin has been shown to be far less toxic than other antimalarial drugs, with fewer adverse effects being associated with use. Caution is recommended for patients who are pregnant, taking angiogenic agents, or recovering from surgery or other wounds, as Chinese Wormwood may inhibit angiogenesis.[30] *Artemisia annua* is not recommended for use during pregnancy, although studies using artemisinin or derivatives to treat malaria in pregnant women in the second or third trimester have shown that it is the most effective and safest treatment available. Due to lack of evidence it is not recommended for use in the first trimester. Artemisinin and its derivatives do not exhibit mutagenic or teratogenic activity; however there is evidence of foetal resorption in rodents even at relatively low dose.[31]

Therapeutic Dose

Equivalent of 3g to 20g per day of the dried herb or 20 to 40mL per day of a 1:2 fluid extract has been recorded for a therapeutic effect.

Handroanthus impetiginosus

Formally known as *Tabebuia avellanedae*

Handroanthus impetiginosus

Botany

Handroanthus species is commonly called taheebo or Pau d'arco, and is a genus of tropical plants native to the rain forests of Central and South America. Pau d'arco is a tropical tree growing up to 38m high, with opposite, long-petiolate leaves with entire or toothed leaflets. The flower is large in terminal cymes or panicles, with

tubular or campanulate calyx, four stamens, corolla tube ampiate. The capsule is slender-cylindrical and the seeds are broadly winged. Preparations from the bark (specifically the inner bark) are used.[32]

Active constituents

Naphthoquinones of the 1, 4 type (including lapachol, beta-lapachone, xyloidone, deoxylapachol, alpha-lapachone and deyhdro-alpha-lapachone). Anthroquinones (which rarely occur in other plants containing naphthoquinones). Benzoic acid derivatives, benzaldehyde derivatives, iridoids, coumarins, flavonoids and carnosol.[32]

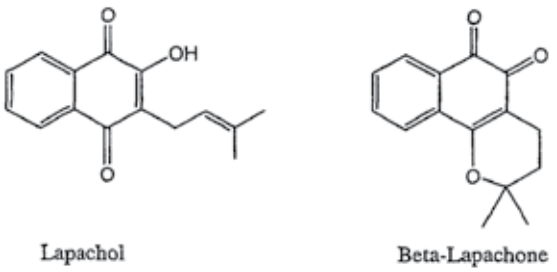

Figure 2: Lapachol and Beta-Lapachone

Actions

Immune enhancing, antitumour, antimicrobial, antiparasitic, depurative.[32]

Traditional use

The indigenous peoples of the South American rain forest have used Pau d'arco medicinally for hundreds of years. The traditional use of Pau d'arco may predate the Incan civilization. Traditional herbal actions include immune tonic, antimicrobial, antifungal, antineoplastic and antiviral.[33]

Pau d'arco has traditionally been used as a folk medicine to treat bacterial infection, blood coagulation, cancer, cutaneous infections, fevers, inflammatory diseases, malaria, peptic ulcers, stomach disorders and syphilis. Interestingly, tribes located hundreds of miles apart used Pau d'arco for the same purposes primarily for its antimicrobial properties.[34, 35]

Specific regional uses include coughs, colds and influenza in Amazonia; diarrhoea and urinary tract infections in Argentina; cancer, colds, fever and snakebites in Costa Rica.[36] In Brazil this herb is used for a great number of conditions including immune system disorders, upper respiratory infections, inflammatory conditions, women's health and as an analgesic.[37]

Modern use

In modern herbal medicine, the bark is used mainly to treat candida, fungal and parasitic infections, bacterial infections, chronic venereal diseases and as a supportive treatment in cancer.[38, 39, 40] Pau d'arco is used for viral respiratory infections including the common cold and flu, and swine flu.[41]

Pharmacology

Napthoquinones contained in extracts of Pau d'arco bark demonstrate definite antibacterial, antifungal, antiviral and anti-parasitic properties.[38]

Antibacterial

Pereira et al. researched the antibacterial activity, toxicity and in dermal irritability in vivo of lapachol extracted from *Handroanthus impetiginosus*. Results demonstrated antibacterial activity for three compounds with minimal inhibitory concentrations of 8, 4/8 and 64/128mcg/mL for beta-lapachone, 3 hydroxy-beta-N-lapachone, and alpha-lapachone, respectively.[42]

Park et al. investigated the activity of *Handroanthus impetiginosus* bark against *Helicobacter pylori* in vitro. Isolated compounds from *Handroanthus impetiginosus* bark were compared with amoxicillin, metronidazole and tetracycline antibiotics. Inhibitory activity of all isolated compounds were more active than metronidazole, but less active than amoxicillin and tetracycline antibiotics.[43]

This effectiveness of napthoquinone analogues from Pau d'arco has been confirmed against *methicillin-resistant Staphylococcus aureus* (MRSA), *methicillin-susceptible Staphylococcus aureus* (MSSA), *Staphylococcus epidermis* and *Staphylococcus haemolyticus* strains in animal in vitro studies.[44, 45] Additionally lapachol possesses potent growth inhibition of *Streptococcus, Enterococcus, Bacillus* and *Clostridium*.[45, 46]

Antifungal

Lapachol has also been shown to have an antifungal activity similar to amphotericin B against *C.albicans, C.tropicalis* and *C.neoformans. Handroanthus impetiginosus* bark significantly inhibits *A.fumigatus, M.gypseum, P.purpurogenum, S.cerevisiae* and *T.mentagrophytes.*[39, 47]

The antifungal activity of lapachol is postulated to be due to its interaction with the cellular membrane[39, 45] A study by Howland reported that this mechanism may involve uncoupling oxidative phosphorylation and/or inhibition of cell electron transport.[48]

Antiparasitic Activity

Handroanthus impetiginosus and its constituents, including lapachol are active against various tropical parasites. In original animal studies by Wedel using naphthoquinones against malarial parasites on ducks, researchers found that the compounds inhibit oxygen uptake of parasitised cells at more than 100 times the concentration required to inhibit respiration in normal cells.[49] Further studies confirmed these results and proposed that lapachol and other napthoquinones act like cyanide in inhibiting the main respiration pathway.[32]

Phenazines from lapachol, beta lapachol and its derivatives demonstrated anti-malarial activity and were effective against *Plasmodium falciparum* and *Plasmodium berghei*, especially those resistant to chloroquine.[40]

Lapachol has been used as a chemoprophylactic against *Schistosoma mansoni* (a tropical fluke) cercarial penetration and infection. Studies by Austin showed that 0.8% lapachol in the diet of mice reduced infections by 97% after 3 days feeding. The study further demonstrated that lapachol is secreted onto the skin where it forms a barrier to penetration.[32,5]. Lapachol and lapachol analogues isolapachol and dihydrolapachol, showed significant activity against *Leishmaniasis amazonensis* and *L.braziliensis* in vitro. Isolapachol acetate was the most active and also displayed activity in vivo when assessed.[50,51]

Antitumour Effects

Much of the scientific in vitro and animal research conducted to date has demonstrated a number of antineoplastic effects, including antiangiogenic, antimetastatic, anti-invasive, apoptotic, antiproliferative, and antimyelosuppressive properties attributed to *Handroanthus impetiginosu*s and its constituents, especially lapachol and beta-lapachone. However, human clinical trials remain lacking in the available data.

Various researchers have reported on the apoptotic effects of beta-lapachone, a quinone derived from the bark of the lapacho tree (*Handroanthus impetiginosus*). Lee et al. studied the in vitro molecular mechanism of apoptosis of human bladder carcinoma cells. Results showed that beta-lapachone in micro molar concentrations inhibited the viability of T24 human bladder carcinoma cells by inducing apoptosis, as evidenced by the formation of apoptotic bodies and DNA fragmentation.[52] Woo et al demonstrated that beta-lapachone induced apoptosis in HepG2 human hepatoma cells, as evidenced by the formation of apoptotic bodies and DNA fragmentation. Induced apoptosis was associated with proteolytic activation of caspase-3 and -9 and degradation of poly (ADP-ribose) polymerase (PARP), a main regulator of the DNA damage response pathway.[53]

Flick et al. demonstrated that beta-lapachone exhibited an uncompetitive inhibitory profile against indoleamine 2,3-dioxygenase 1 (IDO1), through an enzyme kinetics-based analysis. Results showed that beta-lapachone inhibited IDO1, an immunoregulatory enzyme that catabolises tryptophan to kynurenine, which allows tumour cells to escape immune detection. Beta-lapachone appears to have promising applications due to its classical tumour directed mechanism of action integrated with the chemoimmunotherapeutic capability to inhibit IDO1.[54]

Clinical Studies

Inflammatory diseases

By using the experimental autoimmune encephalomyelitis (EAE) animal model for mutliple sclerosis (MS), Xu et al. demonstrated in mice that beta-lapachone suppresses the production of IL-12 and IL-23 by microglia and dendritic cells, and IL-17 expression by T cells. In this study, beta-lapachone suppressed EAE, and this suppression is associated with decreased expression of molecules critical to IL-23, IL-17 and MyD88 (gene) dependant signalling. These results indicate that beta-lapachone may be effective in inflammatory diseases such as MS.[55]

Byun et al. studied the effect of beta-lapachone on human endothelial cells (ECV304) in vitro to investigate the potential cytoprotective and anti-inflammtory effects of AMP-activated protein kinase. Beta-lapachone was shown to induce endothelial anti-inflammatory heme oxygenase (HO)-1 expression by enhancing AMP- activated protein kinase (AMPK) activation via NADH oxidation by increasing NAD(P)H: quinone oxidoreductase 1 (NQO1) activity. It also demonstrated that AMPK activation by beta-lapachone and subsequent HO-1 expression provides cytoprotection against TNF-α induced endothelial cell death, indicating a potential application in cardiovascular disease.[56]

Beta-lapachone has been shown to activate Sirt1 by acting as a NAD+ donor. Sirt1 has been shown to repress the onset of diet-induced obesity by promoting mitochondrial fatty acid oxidation through activating peroxisome proliferator-activated receptor alpha. In a 2014 study, Jeong et al. studied the effects of beta-lapachone, and its ability to activate Sirt1 through elevation of the intracellular NAD+ level, on acyl CoA synthase (ACS) transgenic (Tg) mice with lipotoxic cardiomyopathy. This study demonstrated that the beta-lapachone treated mice had a lower heart weight/body weight ratio, reduced left ventricular dilation and lower contractile dysfunction compared to control mice. Jeong et al. also showed that the mitochondrial area in the hearts of the beta-lapachone treated mice were larger, and that treatment with beta-lapachone completely restored reduced AMPK activity.[57]

Wound Healing

Kung et al. investigated the effects and mechanism of action of beta lapachone, extracted from the bark of the lapacho tree (*Handroanthus impetiginosus*), on wound healing. In vitro tests showed low concentrations of beta-lapachone promoted both cell proliferation and accelerated scrape-wound healing in both mouse fibroblasts and human endothelial cells. Beta-lapachone was also shown to facilitate the migration of mouse fibroblasts and human endothelial cells through activation of ERK, p38 and JNK pathways. These pathways all play critical roles in the regulation of cell proliferation, differentiation, and apoptosis. Application of ointment with or without beta-lapachone to a punched wound on normal and diabetic mice showed faster healing in those mice treated with the ointment containing beta-lapachone.[58]

Candida albicans

Dichloromethane and methanol extracts of *Tabebuia avellanedae* (*Handroanthus impetiginosus*) were tested in vitro against *Candida* species through analysis of Minimum Inhibitory Concentration (MIC). The *Candida* species tested were *Candida albicans, C. dubliniensis, C. parapsilosis, C. tropicalis, C. guilliermondii, C. ulilis, C. krusei, C. lusitaniae, C. glabrata, C. rugosa*. The results revealed a strong activity by the *Tabebuia avellanedae* methanol extract, while the dichloromethane extract showed activity for only *C. krusei*.[59]

Toxicity

There is no evidence to suggest that long term use of Pau d'arco causes toxicity and therefore is generally regarded as safe.[32] Based on animal studies, lapachol, a compound isolated from the *Handroanthus impetiginosus* tree, has fetal toxic and abortifacient effects. [60, 61] Therefore, Pau d'arco is contraindicated in pregnancy and lactation, with a caution for women wishing to conceive. Use with anticoagulant therapy with caution, due to the warfarin-like action of the naphthoquinones at high doses.[32]

Therapeutic Dosage

1.5 to 3.5g per day or 3 to 7mL per day of a 1:2 extract in 45% ethanol or equivalent doses in tincture, tablets or capsules.

Foeniculum vulgare

Foeniculum vulgare

Botany

Fennel is a tall perennial herb and culinary vegetable. Fennel is native to the Mediterranean region and is popularly used in the cuisine of that region.[62] It has a mild liquorice flavour and celery like texture. Preparations from the seeds are used for medicinal purposes. Fennel seed consists of dried, ripe fruits. The seeds contain at least 4% essential oil with not more than 5% estragole.[63] According to the European Pharmacopoeia, the official fennel oil is derived from bitter fennel (*vulgare*) as opposed to sweet fennel (*dulce*).

Active Constituents

Fennel seeds can contain at least 4% essential oil, which contain over 60% trans-anthenole, over 15% fenchone.[64] Additional constituents found in fennel include fixed oil, flavonoids, organic acids, plant sterols including beta-sitosterol.[64] Fennel contains varied amounts of phenols and isoflavonoids. Major phenolic compounds present in fennel include 3-O-caffeoylquinic acid (3-CQA), chlorogenic acid, 4-O-caffeoylquinic acid (4-CQA), eriocitrin, rutin, miquelianin, 1,3-O-dicaffeoylquinic acid (1,3-diCQA), 1,5-O-dicaffeoylquinic acid (1,5-diCQA), 1,4-O-dicaffeoylquinic acid (1,4-diCQA) and rosmarinic acid.[62]

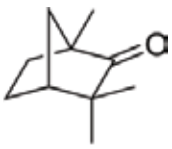

Figure 3: Fenchone

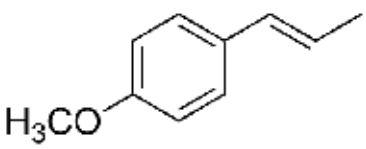

Figure 4: Anthenole

Actions

Carminative, spasmolytic, galagtagogue, aromatic, anti-inflammatory, antimicrobial, diuretic, expectorant.[64, 65]

Traditional Use

For centuries, fennel seed, also known as fennel fruit, has been used as traditional herbal medicine in Europe and China. Fennel seed has been used traditionally for digestive disorders including windy colic in infants, flatulent colic, griping pain, irritable bowel, bloating, nausea, vomiting, dyspepsia, lower abdominal pain and gastrointestinal spasm.[41] Fennel is also traditionally used for decreased appetite, dysmenorrhoea, upper respiratory tract infections, respiratory catarrh, coughs, bronchitis and to increase milk production in nursing mothers.[64]

Modern Use

Modern use indicated the use of fennel for the treatment of infantile colic, griping pain and irritable bowel. Its administration as a carminative is practiced in infant care in private homes and in maternity clinics, where it is appreciated for its mild flavour and good tolerance. Fennel seed is also indicated for modern use in dysmenorrhea.[64]

The Commission E approved the internal use of fennel seed preparations for dyspepsia such as mild, spastic gastrointestinal afflictions, fullness, and flatulence. It is also approved for catarrh of the upper respiratory tract. Fennel syrup and fennel honey are used for catarrh of the upper respiratory tract in children. The Commission E reported that fennel seed promotes gastrointestinal motility and in higher concentrations acts as an antispasmodic.[66] ESCOP lists fennel seed for dyspeptic complaints such as mild, spasmodic gastrointestinal complaints, bloating, and flatulence, and for catarrh of the upper respiratory tract.

Pharmacology

The active constituent anethole, a phenolic ether, resembles the catecholamines adrenaline (epinephrine), noradrenaline (norepinephrine) and dopamine. This structural similarity appears to be responsible for the various sympathomimetic activity of *Foeniculum vulgare.*[67]

Mucociliary, Bronchodilatory and Expectorant

The constituent's anethole and fenchone reduce upper respiratory tract secretions. Some evidence suggests the aqueous fennel extract might also increase mucociliary activity.[41]

Fennel ethanolic extract and essential oil showed exhibited bronchodilatory activity on contracted tracheal chains of the guinea pig.[67]

Spasmolytic and Carminative

Fennel oil and alcoholic extracts of fennel demonstrated significant spasmolytic activity on several in vitro models using isolates of both uterine and gastrointestinal smooth muscle.[64]

This anti-spasmodic action is proposed to be due to direct local activity on smooth muscle, namely its effect on calcium metabolism in the smooth muscle cells, and stimulation of the sympathetic nervous system.[64] Fennel extracts produce a reduction in acetylcholine-induced contraction and decreases maximum possible contractility.[62]

Ostad et al demonstrated that fennel oil reduced the frequency of prostaglandin E2 induced uterine contractions, and significantly reduced the intensity of both oxytocin and prostaglandin E2 induced uterine contractions in vitro.[67, 68]

Antimicrobial and Antifungal activity

Antifungal and antibacterial activity of fennel oil was attributed largely to the chemical constituent E-anethole.[69, 70]

Fennel essential oil possesses antifungal activity against different fungal species including *Candida albicans, Aspergillus* species and dermatophytes.[67] Essential oil of fennel and bitter fennel has been found to exert varying levels of antifungal effects against *Alternaria alternata, Fusarium oxysporum, Botrytis cinerea, Rhizoctonia solani* and *Sclerotinia sclerotiorum*.[62]

Antibacterial action of fennel essential oil was exhibited in vitro against food borne pathogens including *Escherichia coli, Listeria monocytogenes, Salmonella typhimurium* and *Staphlococcus aureus*.[62, 67] Remarkable antibacterial action was recorded in vitro against *Helicobacter pylori* and *Camphylobacter jejuni*.[71] A study performed by Jazani et al evaluated the antibacterial activity of fennel essential oil on 48 isolates of *Acinetobacter baumannii*, a bacteria involved in hospital infections. Fennel essential oil displayed antibacterial activity against all 48 isolates tested.[72]

A study conducted by Camacho-Corona et al concluded fennel displayed antibacterial effects against drug resistant *Mycobacterium tuberculosis* isolates.[73]

Digestive stimulant

In one study, a single oral dose of fennel seed (250 mg/kg) enhanced the activity of amylase in pancreatic tissue and lipase in the small intestine. Fennel at 0.5% of diet over 6 weeks shortened food transit time in rats by 12%.[74] Fennel fruit extract caused an increase of (33%) of collected bile after oral administration (500mg/kg) to rats. The bilirubin content of the bile was similar in both treated and control groups.[64]

In an experimental model, oral administration of fennel fruit extract caused significant increase in collected bile when compared to controls.[75] Fennel seed relaxes sphincters, increases gastrointestinal motility and acts as an antispasmodic at high doses.[41]

Clinical Studies

Irritable Bowel Syndrome (IBS)

In one open pilot study, five patients with irritable bowel syndrome (IBS) who had unsuccessful response to various therapies were given sugar coated fennel fruits after meals for 1 week. The dose increased from 4-12 fruits three times daily. Significant improvements were seen after 2 weeks of therapy with fewer abdominal cramps and improved recovery.[76]

Infantile Colic

Emulsion of fennel essential oil was better than placebo in decreasing the intensity of infantile colic. In this placebo-controlled, randomised trial, parents administered a minimum of 5mL and a maximum of 20mL of either a water emulsion of 0.1% fennel fruit essential oil or placebo up to four times a day. Elimination of colic occurred in 65% of the cases in the treatment group compared to 23.7% in the placebo group.[64, 77]

Upper respiratory catarrh

The volume and thickness of expelled respiratory tract fluid (RTF) was measured after administration of anethole and fenchone in various doses to rabbits. A dose-dependent increase in RTF volume was observed for fenchone, with the maximum response at 9mg/kg. Thickness of RTF was reduced in a dose-dependent manner, with minimal occurring at 9 to 27mg/kg.[64]

Dysmenorrhoea

A study in Kerman, Islamic Republic of Iran in 2002 compared the effectiveness of fennel and mefenamic acid on pain relief in primary dysmenorrhoea. Two groups of high-school girls (mean age 13 years) suffering dysmenorrhoea were randomised to receive fennel extract (n = 55) or mefenamic acid (n = 55) for 2 months. 80% of girls in the fennel group, and 73% of girls in the mefenamic acid group showed complete pain relief or pain decrease, while 80% in the fennel group and 62% in the mefenamic acid group no longer needed to rest. There was no significant difference between the 2 groups in the level of pain relief.[78]

In 2012, Omidvar et al conducted a study with the aim to determine the clinical effect of *Foeniculum vulgare* on primary dysmenorrhoea. Sixty virgin girls with complaints of dysmenorrhoea were enrolled in this study, out of which 50 cases were completed the course of treatment and were divided in two groups (study and placebo) and were under treatment for two cycles. In the study group, a capsule of 30 mg fennel extract, four times a day for three days from start of their menstrual period and in placebo a capsule containing wheat flour in same dose was administered. Intensity of pain was reported by using a 10 - point linear analogue technique. In study group the mean age of menarche was 13.1 ± 0.1 and onset age of dysmenorrhoea was 14.5 ± 0.1 years. Both groups were relieved

but there was significant difference between study and placebo group. Study group shown more effective results than placebo in pain relief (P`0.05). Based on the observations, it can be concluded that, fennel is an effective herbal drug for menstrual pain.[79]

Toxicity

Fennel seed extract is not recommended for use in pregnancy, or when a known allergy/hypersensitivity exists to fennel or other members of the Apiaceae family, including anise, carrot, celery, and mugwort. Caution is recommended for oral use of fennel seed extract in patients with clotting disorders, or those taking anticoagulants, antidiabetic agents, ciprofloxacin, hormone therapy and diuretics.[62, 80]

Therapeutic Dose

5-7g equivalent crushed seeds for tea or compounded for tincture. 900 to 1800mg per day of the dried fruit or as an infusion. 3 to 6 mL per day of 1:2 liquid extract, 7-14mL per day of 1:5 tincture or equivalent in tablet or capsule form.

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InterClinical Laboratories Pty Limited
Unit 6, 10 Bradford Street Alexandria NSW 2015
PO Box 6474 Alexandria 2015 Australia
Phone: (02) 9693 2888 **Fax:** (02) 9693 1888
Email: lab@interclinical.com.au

www.interclinical.com.au

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