

20 July 2020
EMA/HMPC/271393/2022
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, *aetheroleum*

Draft – Revision 1

The European Medicines Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.

Abdollahi NG, Mirghafourvand M, Mollazadeh S. The effects of fennel on menstrual bleeding: A systematic review and meta-analysis. *J Complement Integr Med* 2018. Available at:
15(3):/j/jcim.2018.15.issue-3/jcim-2017-0154/jcim-2017-0154.xml

Abraham K. Anti-genotoxicity of *trans-anethole* and eugenol in mice. *Food Chem Toxicol* 2001, 39:493-498

Afiat M, Amini E, Ghazanfarpour M, Nouri B, Mousavi MS, Babakhanian M, et al. The Effect of Short-term Treatment with Fennel on Lipid Profile in Postmenopausal Women: A Randomized Controlled Trial. *J Menopausal Med* 2018a, 24(1):29-33

Afiat M, Dizavandi FR, Kargarfard L, mosavi Vahed SH, Ghazanfarpour M. Effect of *Foeniculum Vulgare* (Fennel) on Sleep Quality of Menopausal Women: A Double-blinded, Randomized Placebo-controlled Trial. *J Menopausal Med* 2018b, 24(3):204-209

Afzal H, Akhtar MS. Preliminary studies on the antibacterial properties of essential oil extracts from five folk medicines. *J Pak Med Assoc* 1981, 31:230-232

Akhbari N, Kord R, Nodooshan SJ, Hamed S. Analysis and evaluation of the antimicrobial and anticancer activities of the essential oil isolated from *Foeniculum vulgare* from Hamedan, Iran. *Nat Prod Res* 2019, 33(11):1629-1632

Albano SM, Lima AS, Miguel MG, Pedro LG, Barroso JG, Figueiredo AC. Antioxidant, Anti-5-lipoxygenase and Antiacetylcholinesterase Activities of Essential Oils and Decoction Waters of Some Aromatic Plants. *Rec Nat Prod* 2012, 6(1):35-48

Albert-Puleo M. Fennel and anise as estrogenic agent. *J Ethnopharmacology* 1980, 2:337-344

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova, T. Shushunov S. The effect of fennel (*Foeniculum vulgare*) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *Alternative therapies* 2003, 9:58-61

Al-Harbi MM, Qureshi S, Raza M, Ahmed MM, Giangreco AB, Shah AH. Influence of anethole treatment on the tumour induced by Ehrlich ascites carcinoma cells in paw of Swiss albino mice. *Eur J Cancer Prev* 1995, 4:307-318

Andersen KE. Contact allergy to toothpaste flavours. *Contact Dermatitis* 1978, 4:195-198

Aprotozoiae AC, Costache II, Miron A. Anethole and Its Role in Chronic Diseases. *Adv Exp Med Biol* 2016, 929:247-267

Arantes S, Piçarra A, Candeias F, Caldeira AT, Martins MR. Antioxidant activity and cholinesterase inhibition studies of four flavouring herbs from Alentejo. *Nat Prod Res* 2017, 31(18):2183-2187

Arikan D, Alp H, Gözüm S, Orbak Z, Çifçi EK. Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic. *J Clin Nurs* 2008, 17(13):1754-1761

Asano T, Aida S, Suemasu S, Mizushima T. Anethole restores delayed gastric emptying and impaired gastric accommodation in rodents. *Biochem Biophys Res Commun* 2016, 472(1):125-30

Biagioli E, Tarasco V, Lingua C, Moja L, Savino F. Pain-relieving agents for infantile colic (Review). *Cochrane Database Syst Rev* 2016, 9(9):CD009999

Blumenthal M, Busse WR, Goldberg A, et al., editors. The Complete German Commission E Monographs. 1st ed. American Botanical Council, Austin Texas 1998

Blumenthal M, Goldberg A, Brinckmann J, editors. Herbal Medicine. Expanded Commission E Monographs. 1st ed. Integrated Medicine Communications, Newton, MA 2000

Bokaei M, Farajkhoda T, Enjezab B, Khoshbin A, Zarchi Mojgan K. Oral fennel (*Foeniculum vulgare*) drop effect on primary dysmenorrhea: Effectiveness of herbal drug. *Iran J Nurs Midwifery Res* 2013 March, 18(2):128-32

Borghesan F, Mistrello G, Amato S, Giuffrida MG, Villalta D, Asero R. Mugwort-fennel-allergy-syndrome associated with sensitization to an allergen homologous to Api g 5. *Eur Ann Allergy Clin Immunol* 2013 45(4):130-137

Bounds SVJ and Caldwell J. Pathways of Metabolism of (1'-¹⁴C)*trans*-anethole in the rat and mouse. *Drug Metabolism and Disposition* 1996, 24:717-724

Boyd EM, Sheppard EP. An autumn-enhanced mucotropic action of inhaled terpenes and related volatile agents. *Pharmacology* 1971, 6:65-80

Brand N. *Foeniculum*. In: Hansel R, Keller K, Rimpler H, Schneider G, editors. Hagers Handbuch der Pharmazeutischen Praxis, 5th ed. Volume 5: Drogen E-O. Springer-Verlag, Berlin-Heidelberg-New York-London 1993, 156-181

Bristol DW. NTP 3-month toxicity studies of estragole (CAS No. 140-67-0) administered by gavage to F344/N rats and B6C3F1 mice. *Toxic Rep Ser* 2011, 82:1-111

Caldwell J. Perspective on the usefulness of the mouse lymphoma assay as an indicator of a genotoxic carcinogen: ten compounds which are positive in the test but are not genotoxic carcinogens. *Teratogenesis, Carcinogenensis and Mutagenesis* 1993, 13:185-190

Caldwell J, Sutton JD. Influence of dose size on the disposition of *trans*-[methoxy-¹⁴C] anethole in human volunteers. *Food Chem Toxicol* 1988, 26:87-91

Chainy GBN, Manna SK, Chaturvedi MM, Aggarwal BB. Anethole blocks both early and late cellular responses transduced by tumor necrosis factor: effect on NF-κB, AP-1, JNK, MAPKK and apoptosis. *Oncogene* 2000, 19:2943-2950

Chaudhary SK, Maity N, Nema NK, Bhadra S, Saha BP, Mukherjee PK. Angiotensin Converting Enzyme Inhibition Activity of Fennel and Coriander Oils from India. *Natural Product Communications* 2013, 8(5):671-672

Ciganda L, Laborde A. Herbal infusions used for induced abortions. *J Toxicol Clin Toxicol* 2001, 39:318-319

Czygan FC, Hiller K. Foeniculi amari fructus - Bitterer Fenchel, Foeniculi dulcis fructus - Süßer Fenchel. In: Teedrogen und Phytopharmaka. Ein Handbuch für die Praxis auf wissenschaftlicher Grundlage. 4th ed. Wissenschaftliche Verlagsgesellschaft, Stuttgart 2002, 212-215

Dadalioglu I, Evrendilek GA. Chemical composition and antibacterial effects of essential oils of Turkish oregano (*Origanum minutiflorum*), bay laurel (*Laurus nobilis*), spanish lavender (*Lavandula stoechas* L.) and fennel (*Foeniculum vulgare*) on common foodborne pathogens. *J Agric Food Chem* 2004, 52:8255-8260

De-Oliveira AC, Ribeiro-Pinto LF, Otto SS, Goncalves A, Paumgartten FJ. Induction of liver monooxygenase by beta-myrcene. *Toxicology* 1997, 26(124):135-140

Denaxa D, Arkwright PD. Fennel as a cause of immediate hypersensitivity to toothpaste. *Ann Allergy Asthma Immunol* 2020, 125(1):99-100

Dhar SK. Anti-fertility activity and hormonal profile of *trans*-anethole in rats. *Indian J Physiol Pharmacol* 1995, 39:63-67

Drinkwater NR, Miller EC, Miller JA, Pitot HC. Hepatocarcinogenicity of estragole (1-allyl-4-methoxybenzene) and 1'-hydroxyestragole in the mouse and mutagenicity of 1'-acetoxyestragole in bacteria. *J Natl Cancer Inst* 1976, 57:1323-1331

EMA/HMPC Public statement on the use of herbal medicinal products containing estragole. (EMA/HMPC/137212/2005 rev 1)

European Pharmacopoeia 10th ed. Fennel, Bitter - Foeniculi amari fructus. Council of Europe. 04/2013: 0824

European Pharmacopoeia 10th ed. Fennel, Sweet - Foeniculi dulcis fructus. Council of Europe. 04/2011: 0825

European Pharmacopoeia 6th ed. Bitter Fennel fruit oil - Foeniculi amari fructus aetheroleum. Council of Europe. 1/2008: 1826

ESCOP (European Scientific Cooperative on Phytotherapy). Foeniculi aetheroleum. Online series, ISBN 978-1-901964-63-9. Notaries House, Exeter UK 2019

Ezzat SM. *In vitro* inhibition of *Candida albicans* growth by plant extracts and essential oils. *World J Microbiol Biotechnol* 2001, 17:757-759

Farag R, Daw Z, Abo-Raya S. Influence of some spice essential oils on *A. parasiticus* growth and production of aflatoxins in a synthetic medium. *J Food Sci* 1989, 54:74-76

Foong SC, Tan ML, Foong WC, Marasco LA, Ho JJ, Ong JH. Oral galactagogues (natural therapies or drugs) for increasing breast milk production in mothers of non-hospitalised term infants (Review). *Cochrane Database Syst Rev* 2020, 5(5):CD011505

Franks A. Contact allergy to anethole in toothpaste associated with loss of taste. *Contact Dermatitis* 1998, 38:354

Friedman M., Henika PR, Mandrell RE. Bacterial activities of plant essential oils and some of their isolated constituents against *Campylobacter jejuni*, *Escherichia coli*, *Listeria monocytogenes* and *Salmonella enterica*. *J Food Prot* 2002, 65:1545-1560

Garcia Gonzalez JJ, Bartolomè Zavala B, Fernandez Meléndez S, Barcelò-Munoz JM, Pàez AM, Carmona-Bueno MJH, et al. Occupational rinoconjunctivitis and food allergy because of aniseed sensitization. *Ann Allergy, Asthma Immunol* 2002, 88:518-522

Ghasemian A, Al-Marzoqi AH, Mostafavi SKS, Alghanimi YK, Teimouri M. Chemical Composition and Antimicrobial and Cytotoxic Activities of *Foeniculum vulgare* Mill Essential Oils. *J Gastrointest Cancer* 2020, 51(1):260-266

Ghavi F, Taghizadeh M, Taebi M, Abdolahian S. Effect of *Foeniculum vulgare* essence on symptoms of polycystic ovarian syndrome (PCOS): A randomized double-blind, placebo-controlled trial. *Journal of Herbal Medicine* 2019, 17-18:100277

Ghazanfarpour M, Mohammadzadeh F, Shokrollahi P, Khadivzadeh T, Najafi MN, Hajirezaee H, et al. Effect of *Foeniculum vulgare* (fennel) on symptoms of depression and anxiety in postmenopausal women: a double-blind randomised controlled trial. *J Obstet Gynaecol* 2018, 38(1):121-126

Ghazanfarpour M, Shokrollahi P, Khadivzadeh T, Sharghi NB, Najmabadi KM, Babakhanian M, et al. Effect of *Foeniculum vulgare* (fennel) on vaginal atrophy in postmenopausal women: A double-blind, randomized, placebo-controlled trial. *Post Reprod Health* 2017a, 23(4):171-176

Ghazanfarpour M, Amini E, Khadivzadeh T, Babakhanian M, Nouri B, Rakhshandeh H, et al. The Effect of Short-term Treatment with Fennel on Bone Density in Postmenopausal Women: A Randomized Controlled Trial. *J Menopausal Med* 2017b, 23(2):124-130

Gorelick NJ. Genotoxicity of *trans*-anethole *in vitro*. *Mutation Res* 1995, 326:199-209

Hagan EC, Hansen WH, Fitzhugh OG, Jenner PM, Jones W, Taylor JM, et al. Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Food Cosmet Toxicol* 1967, 5:141-157

Hammer KA, Carson CF, Riley TV. Antimicrobial activity of essential oils and other plant extracts. *J Applied Microbiol* 1999, 86:985-990

Hare HA, Caspary C, Rusby HH. The National Standard Dispensatory. Lea & Febiger 1916

Hasan H.A.H., Inhibition of mycoflora and zearalenone on rice by selected essential oils. *Pakistan Journal of Scientific and Industrial Research* 1994, 37:471-473

Hausner H, Bredie WLP, Mølgaard C, Petersen Mam, Møller P. Differential transfer of dietary flavour compounds into human breast milk. *Physiol Behav* 2008, 95(1-2):118-124

Heck JD, Vollmuth TA, Cifone MA, Jagannath DR, Mhyr B, Curren RD. Evaluation of food flavouring ingredients in a genetic toxicity screening battery. *Toxicologist* 1989, 9:257

Howes AJ, Chan VSW, Caldwell J. Structure-specificity of the genotoxicity of some naturally occurring alkenylbenzenes determined by the unscheduled DNA synthesis assay in rat hepatocytes. *Food Chemical Toxicol* 1990, 28:537-542

Howes MJ, Houghton PJ, Barlow DJ, Pocock VJ, Milligan SR. Assessment of estrogenic activity in some common essential oil constituents. *J Pharm Pharmacol* 2002, 54(11):1521-1528

Hsia MTS, Adamovics JA, Kreamer BL. Microbial studies of insect growth regulators and other potential insecticidal compounds in *Salmonella typhimurium*. *Chemosphere* 1979, 8:521-529

Imaseki I, Kitabatake Y. Yakugku Zasshi. Studies on effect of essential oils and their components on the isolated intestines of mice. *Jpn J Pharmacol* 1962, 82:1326-1328

Ishidate M, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, et al. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem Toxicol* 1984, 22:623-636

Jensen-Jarolim E, Leitner A, Hirschwehr R, Kraft D, Wüthrich B, Scheiner O, et al. Characterization of allergens in Apiaceae spices: anise, fennel, coriander and cumin. *Clin Exp Allergy* 1997, 27(11):1299-1306

Jeurissen SMF, Punt A, Boersma MG, Bogaards JJP, Fiamegos YC, Schilter B, et al. Human cytochrome p450 enzyme specificity for the bioactivation of estragole and related alkenylbenzenes. *Chem Res Toxicol* 2007, 20(5):798-806

Joint FAO/WHO Expert Committee on Food Additives (JECFA) safety evaluation of certain food additives. Trans-anethole. World Health Organization. Geneva 1999

Kalleli F, Rebey IB, Wannes WA, Boughalleb F, Hammami M, Tounsi MS, et al. Chemical composition and antioxidant potential of essential oil and methanol extract from Tunisian and French fennel (*Foeniculum vulgare* Mill.) seeds. *J Food Biochem* 2019, 43(8):e12935

Keller K. *Foeniculum vulgare*. In: De Smet PAGM, Keller K, Hansel R, Chandler RF, editors. Adverse effects of herbal drugs. Vol.1. Springer-Verlag, Berlin-Heidelberg-New York 1992, 135-142

Kwon YS, Choi WG, Kim WJ, Kim WK, Kim MJ, Kang WH, et al. Antimicrobial constituents of *Foeniculum vulgare*. *Arch Pharm Res* 2002, 25:154-157

Langhammer AJ, Nilsen OG. *In vitro* Inhibition of Human CYP1A2, CYP2D6, and CYP3A4 by Six Herbs Commonly Used in Pregnancy. *Phytother Res* 10 July 2013, in press, doi 10.1002/ptr.5037. [Epub ahead of print] PubMed PMID:23843424

Leclerc H. Fenouil. In: Précis de Phytothérapie – Essai de thérapeutique par les plantes françaises. Masson, Paris 1983, 162-163

Lee JH, Lee DU, Kim YS, Kim HP. 5-Lipoxygenase Inhibition of the Fructus of *Foeniculum vulgare* and Its Constituents. *Biomol Ther* (Seoul) 2012, 20(1):113-117

Lee HS, Kang P, Kim KY, Seol GH. *Foeniculum vulgare* Mill. Protects against Lipopolysaccharide-induced Acute Lung Injury in Mice through ERK-dependent NF- κ B Activation. *Korean J Physiol Pharmacol* 2015, 19(2):183-189

Levorato S, Dominici L, Fatigoni C, Zadra C, Pagiotti R, Moretti M, et al. *In vitro* toxicity evaluation of estragole-containing preparations derived from *Foeniculum vulgare* Mill. (fennel) on HepG2 cells. *Food and Chemical Toxicology* 2018, 111:616-622

Levy SB. Bronchial asthma due to ingestion of fennel and fennel seed. *Ann Allergy* 1948, 6:415-416

Lin FSD. *Trans-anethole*. In: Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series 28. World Health Organization. Geneva 1991, 135-152

Lis-Balchin M, Hart S. A preliminary study of the effect of essential oils on skeletal and smooth muscle *in vitro*. *J Ethnopharmacol* 1997, 58:183-187

Lo Cantore P, Jacobellis NS, De Marco A, Capasso F, Senatore F. Antibacterial activity of *Coriandrum sativum* L. and *Foeniculum vulgare* Miller var. *vulgare* (Miller) essential oils. *J Agric Food Chem* 2004, 52:7862-7866

Madaus G. Lehrbuch der biologischen Heilmittel. Bd. 3, Thieme-Verlag, 1. Aufl., Leipzig 1938

Madaus G. *Foeniculum*. In: Lehrbuch der biologischen Heilmittel. Vol. 2. Georg Olms ed. Hildesheim-New York 1976, 1354-1361

Marcus C, Lichtenstein EP. Interactions of naturally occurring food plant components with insecticides and pentobarbital in rats and mice. *J Agric Food Chem* 1982, 30:563-568

Marshall AD, Caldwell J. Lack of influence of modulators of epoxide metabolism on the genotoxicity of *trans-anethole* in freshly isolated rat hepatocytes assessed with the unscheduled DNA synthesis assay. *Food Chem Toxicol* 1996, 34(4):337-45

Marzin D. Recherche d'une action mutagène par le test du micronucleus chez la souris (unpublished). Département Recherche et Essais Biologiques Stallergnes 1979

Mazaheri S, Nematbakhsh M, Bahadorani M, Pezeshki Z, Talebi A, Ghannadi AR, et al. Effects of Fennel Essential Oil on Cisplatin-induced Nephrotoxicity in Ovariectomized Rats. *Toxicol Int* 2013, 20(2):138-145

Merkes K. Drogen mit ätherischem Ö1 (XVI): *Foeniculum vulgare* Miller - Fenchel. *PTA-Repetitorium* 1980, 12:45-48

Miller EC, Swanson AB, Philips DH, Fletcher L, Liem A, Miller JA. Structure-activity studies of the carcinogenities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Res* 1983, 43:1124-1134

Mills, et al., editors. Principles and practice of Phytotherapie. Churchill Livingstone, Edinburgh 2000, 374-378

Minas A, Najafi G, Jalali AS, Razi M. Fennel induces cytotoxic effects against testicular germ cells in mice; evidences for suppressed pre-implantation embryo development. *Environ Toxicol* 2018 (Online ahead of print)

Miraldi E. Comparison of the essential oils from ten *Foeniculum vulgare* Miller samples of fruits of different origin. *Flavour Fragrance J* 1999, 14:379-382

Mohebbi-kian E, Mohammad-Alizadeh-Charandabi S, Bekhradi R. Efficacy of fennel and combined oral contraceptive on depot medroxyprogesterone acetate-induced amenorrhea: a randomized placebo-controlled trial. *Contraception* 2014, 90(4):440-446

Monien BH, Sachse B, Niederwieser B, Abraham K. Detection of N-Acetyl-S-[3' -(4-methoxyphenyl)allyl]-L-Cys (AMPAC) in Human Urine Samples after Controlled Exposure to Fennel Tea: A New Metabolite of Estragole and *trans-Anethole*. *Chem Res Toxicol* 2019, 32(11):2260-2267

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. Salmonella mutagenicity tests: II.

Results from the testing of 270 chemicals. *Environ Mutagen* 1986, 6(7):1-119

Mostafa DM, El-Alim SHA, Asfour MH, Al-Okbi SY, Mohamed DA, Awad G. Transdermal nanoemulsions of *Foeniculum vulgare* Mill. essential oil: Preparation, characterization and evaluation of antidiabetic potential. *Journal of Drug Delivery Science and Technology* 2015, 29:99-106

Muller L, Kasper P, Muller-Tegethoff K, Petr T. The genotoxic potential *in vitro* and *in vivo* of the alkylbenzene etheric oils estragole, basil oil and *trans*-anethole. *Mutat Res* 1994, 325:129-136

Müller-Limmroth W, Fröhlich H-H. Wirkungsnachweis einiger phytotherapeutischer Expektorantien auf den mukoziliären Transport. *Fortschr Med* 1980, 98:95-101

Nestmann ER, Lee EGH. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. *Mutation Res* 1983, 119:273-280

Nestmann ER, Lee EGH, Matula TI, Douglas GR, Meuller JC. Mutagenicity of constituents of pulp and paper mill effluent using the salmonella/mammalian-microsome assay. *Mutat Res* 1980, 79:203-212

Newberne PM, Carlton WW, Brown WR. Histopathological evaluation of proliferative lesions in rats fed *trans*-anethole in chronic studies. *Food Chem Toxicol* 1989, 27:21-26

Newberne P, Smith RL, Doull J, Goodman JI, Munro IC, Portoghese PS, et al. The FEMA GRAS assessment of *trans*-anethole used as a flavouring substance. Flavour and Extract Manufacturer's Association. *Food Chem Toxicol* 1999, 37:789-811

Nico A, Vacca M, Bellotti A, Di Giacomo M, Gilberti L, Lotti A, et al. Fennel (*Phoeniculum vulgare*) allergy. *Allergy* 2014, 69(99):326-453 (only abstract)

Niiho Y, Takayanagi I, Takagi K. Effects of a combined stomachic and its ingredients on rabbit stomach motility *in situ*. *Japan J Pharmacol* 1977, 27:177-179

Opdyke DLJ. Monographs on fragrance raw materials: fennel oil, bitter. *Food Cosmet Toxicol* 1976, 14:309

Opdyke DLL. Monographs on fragrance raw materials: fennel oil. *Food Cosmet Toxicol* 1974, 12:879-880

Ostad SN, Khakinejad B, Sabzevari O. Evaluation of teratogenicity of fennel essential oil (FEO) on the rat embryo limb buds culture. *Toxicology in vitro* 2004, 18:623-627

Ostad SN, Soodi M, Shariffzadeh M, Khorshidi N, Marzban H. The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea; pharmacology and toxicology study. *J Ethnopharmacol* 2001, 76:299-304

Ozbek H. Investigation of the level of the lethal dose 50 and the hypoglycemic effect of *Foeniculum vulgare* Mill. Fruit essential oil extract in healthy and diabetic mice. *Van Tip Dergisi* 2002, 9:98-103

Ozbek H, Ugras S, Ozturk M, Bayram I, Citoglu GS. Hypoglycemic and hepatoprotective effects of *Foeniculum vulgare* Miller seeds fixed oil extract in mice and rats. *Eastern J Medicine* 2003b, 8:35-40

Ozbek H, Ugras S, Bayram I, Uygan I, Erdogan E, Ozturk A, et al. Hepatoprotective effect of *Foeniculum vulgare* essential oil: A carbon-tetrachloride induced liver fibrosis model in rats. *Scand J Lab Anim Sci* 2004, 31:9-17

Ozbek H, Ugras S, Dulger H, Bayram I, Tunur I, Ozturk G, et al. Hepatoprotective effect of *Foeniculum vulgare* essential oil. *Fitoterapia* 2003a, 74:317-319

Ozbek H. The anti-inflammatory activity of the *Foeniculum vulgare* L. essential oil and investigation of its median lethal dose in rats and mice. *Int J Pharmacol* 2005, 1(4):329-331

Parfitt K. Martindale. The extra Pharmacopoeia. 31th Edition. London 1993

Park JS, Baek HH, Bai DH, Oh TK, Lee CH. Antibacterial activity of fennel (*Foeniculum vulgare* Mill.) seed essential oil against the growth of *Streptococcus mutans*. *Food Sci Biotechnol* 2004, 13:581-585

Pattanittum P, Kunyanone N, Brown J, Sangkomkamhang US, Barnes J, Seyfoddin V, et al. Dietary supplements for dysmenorrhoea (Review). *Cochrane Database Syst Rev* 2016, 3(3):CD002124

Phillips DH, Reddy MV, Randerath K. 32-P-post labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes.II. Newborn male B6C3F1 mice. *Carcinogenesis* 1984, 5:1623-1628

Plant OH, Miller GH. J. Effects of carminative volatile oils on the muscular activity of the stomach and colon. *Exp Pharmacol Ther* 1926, 27:149-164

Punt A, Paini A, Boersma MG, Freidig AP, Delatour T, Scholz G, et al. Use of physiologically based biokinetic (PBBK) modeling to study estragole bioactivation and detoxification in humans as compared with male rats. *Toxicol Sci* 2009, 110(2):255-269

Raal A, Orav A, Arak E. Essential oil composition of *Foeniculum vulgare* Mill. fruits from pharmacies in different countries. *Nat Prod Res* 2012, 26(13):1173-1178

Rabeh NM, Aboraya AO. Hepatoprotective Effect of Dill (*Anethum graveolens* L.) and Fennel (*Foeniculum vulgare*) Oil on Hepatotoxic Rats. *Pak J Nut* 2014, 13(6):303-309

Rahimikian F, Rahimi R, Golzareh P, Bekhradi R, Merhan A. Effect of *Foeniculum vulgare* Mill. (fennel) on menopausal symptoms in postmenopausal women: a randomized, triple-blind, placebo-controlled trial. *Menopause* 2017, 24(9):1017-1021

Ramadan FM, El-Zanfaly RT, El-Wakeil FA, Alian AM. On the antibacterial effects of some essential oils. I. Use of agar diffusion method. *Chem Mikrobiol Technol Lebensm* 1972, 2:51-55

Reed PM, Caldwell J. Induction of hepatic cytochrome P450 and related activities following dietary administration of trans-anethole in SD-CD rats. *Hum. Experimen. Toxicol* 1992, 11:580-581

Reicks MM, Crankshaw D. Effects of D-limonene on hepatic microsomal monooxygenase activity and paracetamol-induced glutathione depletion in mouse. *Xenobiotica* 1993, 23:809-819

Reiter M, Brandt W. Relaxant effects on tracheal and ileal smooth muscles of the guinea-pig. *Arzneimittelforschung/Drug Res* 1985, 35:408-414

Rezayat SM, Dehpour AR, Motamed SM, Yazdanparast M, Chamanara M, Sahebgharani M, et al. *Foeniculum vulgare* essential oil ameliorates acetic acid-induced colitis in rats through the inhibition of NF- κ B pathway. *Inflammopharmacology* 2018, 26(3):851-859

Ruberto G, Baratta MT, Deans SG, Dorman HJD. Antioxidant and antimicrobial activity of *Foeniculum vulgare* and *Crithmum maritimum* essential oils. *Planta Med* 2000, 66:687-93

Sangster SA, Caldwell J, Hutt AJ, Anthony A. Smith RL. The metabolic disposition of [methoxy-¹⁴C]-labelled *trans*-anethole, estragole and *p*-propylanisole in human volunteers. *Xenobiotica* 1987, 17:1223-1232

Sangster SA, Caldwell J, Smith RL, Farmer PB. Metabolism of anethole. I. Pathways of metabolism in the

rat and mouse. *Food Chem Toxicol* 1984a, 22:695-706

Sangster SA, Caldwell J, Smith RL. Metabolism of anethole. II. Influence of dose size on the route of metabolism of *trans*-anethole in the rat and mouse. *Food Chem Toxicol* 1984b, 22:707-713

Savino F, Cresi F, Castagno E, Silvestro L, Oggero R. A randomized double-blind placebo-controlled trial of a standardized extract of *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* (ColiMil) in the treatment of breastfed colicky infants. *Phytother Res* 2005, 19:335-340

Schilcher H. Ätherische Öle - Wirkungen und Nebenwirkungen *Dtsch Apoth Ztg* 1984, 124:1433-1442

Schilcher H. Pharmakologie und Toxikologie ätherischer Öle. *Therapiewoche* 1986, 36:1100-1112

Schulz V, Hansel R, Tyler VE. Rational Phytotherapy. A Physician's Guide to Herbal Medicine. Springer, New York, NY 1998, 159-160

Schwartz HJ, Jones RT, Rojas AR, Squillace DL, Yunginger JW. Occupational allergic rhinoconjunctivitis and asthma due to fennel seed. *Ann Allergy Asthma Immunol* 1997, 78:37-40

Sekizawa J, Shibamoto T. Genotoxicity of safrole related chemicals in microbial test systems. *Mutat Res* 1982, 101:127-140

Shahat AA, Ibrahim AY, Hendawy SF, Omer EA, Hammouda FM, Abdel-Rahman FH, et al. Chemical Composition, Antimicrobial and Antioxidant Activities of Essential Oils from Organically Cultivated Fennel Cultivars. *Molecules* 2011, 16(2):1366-1377

Sharopov F, Valiev A, Satyal P, Gulmurodov I, Yusufi S, Setzer WN, et al. Cytotoxicity of the Essential Oil of Fennel (*Foeniculum vulgare*) from Tajikistan. *Foods* 2017, 6(9):73

Singh G, Kapoor IP, Pandey SK, Singh UK, Singh RK. Studies on essential oils: Part 10; Antibacterial activity of volatile oils of some spices. *Phytother Res* 2002, 16:680-682

Soher EA. Prevention of the growth and aflatoxin production of *Apergillus flavus* by some spice essential oils. *Minufiya J Agric Res* 1999, 24:563-576

Shlosberg A, Egyed M. Experimental *Ferula communis* (giant fennel) toxicosis in sheep. *Zentralbl Veterinarmed A* 1985, 32:778-784

Skalli S, Bencheikh RS. Epileptic seizure induced by fennel essential oil. *Epileptic Disord* 2011, 13(3):345-347

Soliman KM, Badeaa RI. Effect of oil extracted from some medicinal plants on different mycotoxigenic fungi. *Food Chem Toxicol* 2002, 40:1669-1675

Stäger J, Wüthrich B, Johansson S. Spice allergy in celery-sensitive patients. *Allergy* 1991, 46:475-478

Suzuki Y, Umemura T, Hibi D, Inoue T, Jin M, Ishii Y, et al. Possible involvement of genotoxic mechanisms in estragole-induced hepatocarcinogenesis in rats. *Arch Toxicol* 2012, 86:1593-1601

Swanson AB, Chambliss DD, Blomquist JC, Miller EC, Miller JA. The mutagenicities of safrole, estragole, eugenol, *trans*-anethole and some of their known or possible metabolites for *Salmonella typhimurium* mutants. *Mutat Res* 1979, 60:143-153

Teuscher E, Anton R, Lobstein A. Plantes aromatiques. Editions Tec&Doc, Paris 2005, 236-241

To LP, Hunt TP, Andersen ME. Mutagenicity of *trans*-anethole, estragole, eugenol and safrole in the Ames *Salmonella typhimurium* assay. *Bull Environ Contam Toxicol* 1982, 28:647-654

Trabace L, Tucci P, Ciuffreda L, Matteo M, Fortunato F, Campolongo P, et al. "Natural" relief of pregnancy-related symptoms and neonatal outcomes: above all do no harm. *J Ethnopharmacol* 2015, 174:396-402

Tripathi P, Tripathi R, Patel RK, Pancholi SS. Investigation of antimutagenic potential of *Foeniculum vulgare* essential oil on cyclophosphamide induced genotoxicity and oxidative stress in mice. *Drug Chem Toxicol* 2013, 36(1):35-41

Trokoudes D, McFadden J. Cheilitis secondary to limonene contained in toothpaste. *Contact Dermatitis* 2016, 75(1):60-106 (only abstract)

Truhaut R, Le Bourhis B, Attia M, Glomot R, Newman J, Caldwell J. Chronic toxicity/carcinogenicity of trans-anethole in rats. *Food Chem Toxicol* 1989, 27:11-20

Türkyilmaz Z, Karabulut R, Sönmez K, Başaklar AC. A striking and frequent cause of premature thelarche in children: *Foeniculum vulgare*. *J Pediatr Surg* 2008, 43(11):2109-2111

Valnet J. Fenouil. In: Aromathérapie - Traitement des maladies par les essences de plantes. Maloine, Paris 1990

Von Skramlik E. On the toxicity and tolerance of ethereal oils. *Pharmazie* 1959, 14:435-45

Weiss RF. In: Lehrbuch der Phytotherapie, 8th ed. Hippokrates, Stuttgart 1997, 82-83, 443 and 463

Weizman Z, Alkrinawi S, Goldfarb D, Biltran C. Efficacy of herbal tea preparation in infantile colic. *J Pediatric* 1993, 22:650-652

Wiseman RW, Fennell TR, Miller JA, Miller EC. Further characterization of the DNA adducts formed by electrophilic esters of the hepatocarcinogens 1'-hydroxysafrole and 1'-hydroxyestragole *in vitro* and in mouse liver *in vivo*, including new adducts at C-8 and N-7 of guanine residues. *Cancer Res* 1985, 45:3096-3105

Wiseman RW, Miller EC, Miller JA, Liem A. Structure-activity studies of the hepatocarcinogenicities of alkenylbenzene derivatives related to estragole and safrole on administration to preweaning male C57BL/6J x C3H/HeJ F1 mice. *Cancer Res* 1987, 47:2275-2283

Yancu D, Vaillancourt C, Sanderson JT. Evaluating the effects on steroidogenesis of estragole and trans-anethole in a feto-placental co-culture model. *Mol Cell Endocrinol* 2019, 498:110583

Yancu D, Sanderson T. Essential oils disrupt steroidogenesis in a feto-placental co-culture model. *Reprod Toxicol* 2019, 90:33-43

Zargari A. Medicinal plants. Tehran University Publication. Tehran, Iran 1992, 32-37

Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ Mutagen* 1987, 9(9):1-110

Zhang S, Chen X, Devshilt I, Yun Q, Huang C, An L, Dorjbat S, et al. Fennel main constituent, trans-anethole treatment against LPS-induced acute lung injury by regulation of Th17/Treg function. *Mol Med Rep* 2018, 18(2):1369-1376

Zhu M, Wong PY, Li RC. Effect of oral administration of fennel (*Foeniculum vulgare*) on ciprofloxacin absorption and disposition in the rat. *J Pharm Pharmacol* 1999, 51:1391-1396