



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2024
EMA/HMPC/372844/2016
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, fructus and *Foeniculum vulgare* Miller subsp. *vulgare* var. *dulce* (Mill.) Batt. & Trab., fructus

Final – 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.

Abd-alsalam Alsalame HA, Al-Aameli MH, Al-Tae RAM, Al-Bazii WGM. Protective role of alcoholic extract of fennel seeds in nephrotoxicity induced by cisplatin in male rabbits. *Biochem Cell Arch* 2018, 18(1):1239-1244

Abdel-Wahab A, Abdel-Razik AH, Aziz RLA. Rescue effects of aqueous seed extracts of *Foeniculum vulgare* and *Carum carvi* against cadmium-induced hepatic, renal and gonadal damage in female albino rats. *Asian Pac J Trop Med* 2017, 10(12):1123-1133

Abdel-Wahhab KG, Fawzi H, Mannaa FA. Paraoxonase-1 (PON1) inhibition by tienilic acid produces hepatic injury: Antioxidant protection by fennel extract and whey protein concentrate. *Pathophysiology* 2016, 23:19–25

Abdollahi NG, Mirghafourvand M, Mollazadeh S. The effects of fennel on menstrual bleeding: A systematic review and meta-analysis. *J Complement Integr Med* 2018; 15(3):20170154

Abedi P, Najafian M, Yaralizadeh M, Namjoyan F. Effect of fennel vaginal cream on sexual function in postmenopausal women: A double blind randomized controlled trial. *J Med Life* 2018; 11(1):24–28

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

Akha O, et al. The effect of fennel (*Foeniculum vulgare*) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism, A randomized placebo controlled clinical trial. *Caspian J Intern Med* 2014, 5(1):26-29

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



- 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
- Al-Mofleh I, et al. Fennel "*Foeniculum vulgare*" treatment protects the gastric mucosa of rats against chemically-induced histological lesions. *International Journal of Pharmacology* 2013, 9(3):182-189
- 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
- Andersen KE. Contact allergy to toothpaste flavours. *Contact Dermatitis* 1978, 4: 195-198
- Aprotosoiaie AC, Costache II, Miron A. Anethole and Its Role in Chronic Diseases. *Adv Exp Med Biol*, 2016, 929:247-267
- Arikan D, Alp H, Gözümlü 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
- Avesina A. Law in medicine, 2nd ed., Vol 2, Soroush, Teheran, Press 1985, 187
- Azam H, Shirin Y, Majid A, Fariba S, Massood E. Ovarian protection in cyclophosphamide-treated mice by fennel. *Toxicology Reports*, 2017, 4:160-164
- Bano S, Jafri A, Ahmad N, Sharma AK, Arshad M. A Comparative Antibacterial Activity of Three Common Spices Extract and their Anti-Proliferative and Apoptotic Effectiveness against Human Breast Adenocarcinoma Cells. *Pharmacogn J* 2019; 11(1):88-93
- 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
- Bilia AR, Flamini G, Taglioli V, Morelli I, Vincieri FF. GC-MS Analysis of essential oil of some commercial fennel teas. *Food Chem* 2002, 76; 307-310
- Blumenthal M, Busse WR, Goldberg A *et al.* (eds): The Complete German Commission E Monographs, 1st ed. American Botanical Council, Austin, TX. 1998
- Blumenthal M, Goldberg A, Brinckmann J (eds): Herbal Medicine, Expanded Commission E Monographs, 1st ed. Integrated Medicine Communications, Newton, MA. 2000
- Bokaie 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 Mar, 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, 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. Berlin-Heidelberg-New York-London: Springer-Verlag 1993, 156-181

British Herbal Pharmacopoeia. British Herbal Medicine Association, West Yorks 1983, 92-93

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, Carcinogenesis 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- κ B, AP-1, JNK, MAPKK and apoptosis. *Oncogene* 2000, 19:2943-2950

Chatterjee S, et al. In Vitro Inhibition of Cholera Toxin Production in *Vibrio cholerae* by Methanol Extract of Sweet Fennel Seeds and Its Components. *Jpn J Infect Dis* 2016, 69:384-389

Chinese Herbal Medicine (Liu Gongwang Ed.). Xiaohuixiang. Hua Xia Publishing House 1999, 203-204 and 444-445 and 503

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

Council of Europe. Plants in Cosmetics 2002; Vol. II; 65-69

Czygan FC. Fenchel. In: Teedrogen (2nd ed.). Wichtl M. (Ed). Stuttgart: *Wissenschaftliche Verlagsgesellschaft* 1989, 2:171-173

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

Delaram M, Kheiri S, Hodjati MR. Comparing the Effects of *Echinophora platyloba*, Fennel and Placebo on Pre-menstrual Syndrome. *J Reprod Infertil* 2011, 12(3):221-226

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

Diaz-Maroto MC, Diaz Maroto Hidalgo IJ, Sanchez-Palomo E., Perez-Coello MS. Volatile components and key odorants of fennel (*Foeniculum vulgare*) and thyme (*Thymus vulgaris*) oil extracts obtained by simultaneous distillation-extraction and supercritical fluid extraction. *J Agric Food Chem* 2005, 53:5385-5389

Dua A, Ashwani M, Sanjeev G, Mahajan R. Bioreactive compounds and antioxidant properties of methanolic extract of fennel (*Foeniculum vulgare* Miller). *Int Res J Pharm* 2013, 4(5):241-245

El Bardai S, Lyoussi B, Wibo M, Morel N. Pharmacological evidence of hypotensive activity of *Marrubium vulgare* and *Foeniculum vulgare* in spontaneously hypertensive rats. *Clin Exper Hypertension* 2001, 23:329-343

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

European Food Safety Authority (EFSA), 2009a. ESCO working group on botanicals and botanical preparations. Advice on the EFSA guidance document for the safety assessment of botanicals and botanical preparations intended for use as food supplements, based on real case studies. The *EFSA J*, 7(9):280

European Food Safety Authority (EFSA), 2012. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. The *EFSA J*, 10(3):2579

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

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

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

Forster HB, Niklas H, Lutz S. Antispasmodic effects of some medicinal plants. *Planta Med* 1980; 40:309-319

Forster HB. Spasmolytische Wirkung pflanzlicher Carminativa. Tierexperimentelle Untersuchungen. *Z Allg Med* 1983, 59:1327-1333

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

Garcia Gonzalez JJ, et al. Occupational riginioconjunctivitis and food allergy because of aniseed sensitization. *Ann. Allergy, Asthma Immunol* 2002, 88:518-522

Ghasemi V, Kheirkhah M, Samani LN, Vahedi M. The Effect of Herbal Tea Containing Fennel Seed on Breast Milk Sufficiency Signs and Growth Parameters of Iranian Infants. *Shiraz E-Med J* 2014, 15(4):e22262

Ghods Z, Asltooghi M. The Effect of Fennel on Pain Quality, Symptoms, and Menstrual Duration in Primary Dysmenorrhea. *J Pediatr Adolesc Gynecol* 2014, 27(5):283-286

Godavari A, Amutha K, Moorthi NM. In-vitro hypoglycemic effect of *Foeniculum vulgare* Mill. Seeds on the carbohydrate hydrolyzing enzymes, α -amylase and α -glucosidase. *IJPSR* 2018, 9(10):4441-4445

Golian Tehrani S, Mirmohammadali M, Soltani Moghadam A, Mehran A, Taghi Zadeh M, Baleghi M. The Comparison of Fennel and Mefenamic Acid Effects on Post-Partum after Pain. *J Babol Univ Med Sci* 2015, 17(8):7-13

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

Hagan EC, et al. Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Food Cosmet Toxicol* 1967, 5:141-157

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

- He W, Huang B. A review of chemistry and bioactivities of a medicinal spice: *Foeniculum vulgare*. *J Med Plant Res*, 2011, 5(16):3595-3600
- 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
- L'Italia Agricola. Piante medicinali e aromatiche. Reda ed. 1989, 182-183
- Ivanov SA, Aitzemüller K. Untersuchungen über die Tocopherol- und Tocotrienolzusammensetzung der Samenöle einiger Vertreter der Familie Apiaceae. *European Journal of Lipid Science and Technology* 1995, 97(1):24-29
- Jahromi BN, Tartifzadeh A, Knabnadideh S. Comparison of fennel and mefenamic acid for the treatment of primary dysmenorrhea. *Int J Gynecol Obstet* 2003, 80:153-157
- Jayakumar R, Kanthimathi MS. Dietary spices protect against hydrogen peroxide-induced DNA damage and inhibit nicotine-induced cancer cell migration. *Food Chem* 2012, 134(3):1580-1584
- Javidnia K, Dastgheib L, Samani Mohammadi S, Naisri A. Antihirsutism activity of fennel (fruits of *Foeniculum vulgare*) extract. Double-blind placebo controlled study. *Phytomedicine* 2003, 10: 455-458.
- Jensen-Jarolim E, et al. Characterization of allergens in *Apiaceae* spices: anise, fennel, coriander and cumin. *Clin Exp Allergy* 1997, 27(11):1299-1306
- Jeurissen SMF, 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, 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, Volume 1. Berlin-Heidelberg-New York: Springer-Verlag 1992, 135-142
- Khazaei M, Montaseri A, Khazaei MR, Khanahmadi M. Study of *Foeniculum vulgare* Effect on Folliculogenesis in Female Mice. *Int J Fertil Steril* 2011, 5(3):122-127
- Khorshidi N, Ostad SN, Mosaddegh M, Soodi M. Clinical Effects of Fennel Essential oil on Primary Dysmenorrhea. *IJPR* 2003, 2:89-93

- Kim IS, Yang MR, Lee OH, Kang SN. Antioxidant Activities of Hot Water Extracts from Various Spices. *Int J Mol Sci* 2011, 12:4120-4131
- Kim TH, Kim HJ, Lee SH, Kim SY. Potent inhibitory effect of *Foeniculum vulgare* Miller extract on osteoclast differentiation and ovariectomy-induced bone loss. *Int J Mol Med* 2012, 29(6):1053-1059
- Kitajima J, Ishikawa T, Tanaka Y. Water-soluble constituents of fennel. I. Alkyl glycosides. *Chem Pharm Bull* 1998a, 46(10):1643-1646
- Kitajima J, Ishikawa T, Tanaka Y. Water-soluble constituents of fennel. II. Four *erythro*-anethole glycol glycosides and two p-hydroxyphenyl propylene glycol glycosides. *Chem Pharm Bull* 1998b, 46:1591-1594
- Kitajima J, Ishikawa T, Tanaka Y, Ono M, Ito Y, Nohara T. Water-soluble constituents of fennel. V. Glycosides of aromatic compounds. *Chem Pharm Bull* 1998c, 46:1587-1590
- Kunzemann J, Herrmann K. Isolierung and Identifizierung der Flavon(ol)-O-glykoside in Kiimmel (*Carum carvi* L.), Fenchel (*Foeniculum vulgare* Mill.), Anis (*Pimpinella anisum* L.) and Koriander (*Coriandrum sativum* L.) and von Flavon-C-Glykosiden im Anis. *Z Lebensm Unters-Forsch* 1977, 164:194-200
- Kwon YS, 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* 2014, 28(4):603-610 [doi: 10.1002/ptr.5037. Epub 2013 Jul 10. PMID: 23843424]
- Langhammer AJ, Nilsen OG. Fennel and Raspberry Leaf as Possible Inhibitors of Acetaminophen Oxidation. *Phytother Res* 2014, 28(10):1573-1576
- Leclerc H. Fenouil. In: Précis de Phytothérapie – Essai de thérapeutique par les plantes françaises. Paris: Masson 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, 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. Geneva: World Health Organization 1991, 135-152
- Liu Gan Zhong, Xu Qiu Ping, Wang Tai. The Essentials of Traditional Chinese Herbal Medicine. Foreign Language Press, Beijing 2003
- Madaus G. *Foeniculum*. In: Lehrbuch der biologischen Heilmittel. Volume II. 2 Georg Olms ed. Hildesheim-New York 1976, 1354-1361
- Mahdavi S, Alizad M, Sajjadi P, Baleghi M. A Study of the Antioxidant and Antimicrobial Effects of Ethanolic Extract of Fennel (*Foeniculum vulgare* Mill) Seeds. *Journal of Babol University of Medical*

Sciences 2017, 19(5):32-38

Malini T, Vanithakumari G, Megala N, Anusya S, Devi K, Elango V. Effect of *Foeniculum vulgare* Mill. seed extract on the genital organs of male and female rats. *Indian J Physiol Pharmacol* 1985, 29:21-26

Mansouri E, et al. Anti-fertility effect of hydro-alcoholic extract of fennel (*Foeniculum vulgare* Mill) seed in male Wistar rats. *Journal of Veterinary Research* 2016, 60:357-363

Marabini L, Galli CL, van den Berg SJPL, Marinovich M. In vitro evaluation of the genotoxic potential of plant food supplements (PFS) containing alkenylbenzene compounds. *Toxicology Letters* 2014, 229:S178-S179 (only abstract available)

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

Maruzzella JC, Freundlich M. Antimicrobial substances from seeds. *American Pharmaceutical Association* 1959, 48:356-358

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

Mascolo N, Autore G, Capasso F, Menghini A, Fasulo MP. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytother Res* 1987, 1:28-31

Mehralikhani A, Movahedi M, Larypoor M, Golab F. Evaluation of the Effect of *Foeniculum vulgare* on the Expression of E-Cadherin, Dysadherin and Ki-67 in BALB/C Mice with 4T1 Model of Breast Cancer. *Nutr Cancer* 2020, 73(2):318-328

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

Mihats D, Pilsbacher L, Gaberning R, Routil M, Gutternigg M, Langer R. Levels of estragole in fennel teas marketed in Austria and assessment of dietary exposure. *Int J Food Sci Nutr* 2016, 68(5):569-576

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(3):1124-1134

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

Mohamad RH, et al. Antioxidant and Anticarcinogenic Effects of Methanolic Extract and Volatile Oil of Fennel Seeds (*Foeniculum vulgare*). *J Med Food* 2011, 14(9):986-1001

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

Morimoto I, Watanabe F, Osawa T, Okitsu T, Kada T. Mutagenicity screening of crude drugs with *Bacillus subtilis* rec-assay and *Salmonella*/microsome reversion assay. *Mutat Res* 1982, 97:81-102

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 (suppl.7):1-119
- 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 mukoziliaren Transport. *Fortschr Med* 1980, 98:95-101
- Nasehi M, Sehhatie F, Zamanzadeh V, Delazar A, Javadzadeh Y, Chongheralu BM. Comparison of the effectiveness of combination of fennel extract/vitamin E with ibuprofen on the pain intensity in students with primary dysmenorrhea. *Iran J Nurs Midwifery Res* 2013, 18(5):355-359
- Nestmann ER, Lee EGH. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. *Mutat 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, Cartlton 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, 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
- Nguyen S, et al. Antimicrobial and P450 Inhibitory Properties of Common Functional Foods. *J Pharm Pharm Sci* 2014, 17(2):254-265
- Nico A, et al. Fennel (*Phoeniculum vulgare*) allergy. *Allergy* 2014, 69(99):326-453 (only abstract)
- Niesel S. Untersuchungen zum Freisetungsverhalten und zur Stabilität ausgewählter wertbestimmender Pflanzeninhaltsstoffe unter besonderer Berücksichtigung moderner phytochemischer Analysenverfahren. Dissertation, Freien Universität Berlin 1992
- 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
- Okdemir D, Hatipoglu N, Kurtoglu S, Akin L, Kendirci M. Premature thelarche related to fennel tea consumption? *J Pediatr Endocrinol Metab* 2014, 27:175-179
- Oktay M, Gulcin, I, Kufrevioglu I. Determination of *in vitro* antioxidant activity of fennel (*Foeniculum vulgare*) seed extracts. *Lebensmittel-Wissenschaft Technologie* 2003, 36:263-271
- Ono M, Masuoko C, Ito Y, Niiho Y, Kinjo J, Nohara T. Antioxidative and antihyaluronidase activities of some constituents from *Foeniculi fructus*. *Food Science and Technology International* 1997, 3:53-55
- Orosi G. *Farmacologia Teorica e Pratica*. Vincenzo Mausi Ed. 1851, Vol. I. 40
- Osman NN, Jambi EJ, Aseri NH. Assessment of antidiabetic and antioxidant activities of *Cassia angustifolia* and *Foeniculum vulgare* in diabetic rats. *Int J Pharm Res AlliedSci* 2017, 6(2):149-162
- Ostad SN, Shariffzadeh M, Soodi M. Evaluation of toxicity of *Foeniculum vulgare* variety *dulce* and its LD₅₀. *Barij Essence Pamphlet* 2000, 1:24-26
- Parandin R, Yousofvand N. *Foeniculum vulgare* (Fennel) Effects on Puberty Timing, Reproductive Function and Behaviour in Adult Female Mice Following Neonatal Exposure. *J Adv Med Biomed Res* 2019, 27(121):16-22

- Parfitt K. Martindale. The extra Pharmacopoeia. 31th ed. London, 1993
- Pattanittum P, et al. Dietary supplements for dysmenorrhoea (Review). *Cochrane Database Syst Rev* 2016, 3(3):CD002124
- Pazoki H, Bolouri G, Farokhi F, Azerbayjani MA. Comparing the effects of aerobic exercise and *Foeniculum vulgare* on pre-menstrual syndrome. *Middle East Fertility Society Journal* 2016, 21(1):61–64
- Pharmacopoeia of the People's Republic of China. Vol. I 73-74. English ed. Xiaohuixiang 2000
- 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
- Platel K, Srinivasan K. Studies on the influence of dietary spices on food transit time in experimental rats. *Nutr Res* 2001, 21:1309-1314
- Poojar B, Ommuragan B, Adiga S, Thomas H. Evaluation of antiurolithiatic property of ethanolic extract of fennel seeds in male Wistar albino rats. *Asian J Pharm Clin Res* 2017, 10(8):313-316
- Pourjafari F, Haghpanah T, Sharififar F, Nematollahi-Mahani SN, Afgar A, Karam GA. Protective effects of hydro-alcoholic extract of *foeniculum vulgare* and *linum usitatissimum* on ovarian follicle reserve in the first-generation mouse pups. *Heliyon* 2019, 5(10):e02540
- Punt A, 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
- Raffo A, Nicoli S, Leclercq C. Quantification of estragole in fennel herbal teas: implications on the assessment of dietary exposure to estragole. *Food Chem Toxicol* 2011, 49:370-375
- Rani MU, Meena R. Comparative Study on Antioxidant Potential and Phytochemical Composition of Cumin and Fennel. *Journal of Herbs, Spices & Medicinal Plants* 2014, 20:245–255
- 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* 1985, 35(1A):408-414
- Sadrefozalayi S, Farokhi F. Effect of the aqueous extract of *Foeniculum vulgare* (fennel) on the kidney in experimental PCOS female rats. *Avicenna J Phytomed* 2014, 4(2):110-7
- Sait K. The chemosensitizing effect of aqueous extract of sweet fennel on cisplatin treated HeLa cells. *Clin Exp Obstet Gynecol* 2016, 43(3):358-64 (only abstract available)
- 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
- Satyanarayana S, Sushruta K, Sarma GS, Srinivas N, Subba Rayu GV. Antioxidant activity of the aqueous extract of spicy food additives-evaluation and comparison with ascorbic acid in *in vitro* systems. *J Herb Pharmacother* 2004, 4:1-10
- 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
- Setyaningsih EP, Saputri FC, Mun'im A. The Antidiabetic Effectivity of Indonesian Plants Extracts via DPP-IV Inhibitory Mechanism. *J Young Pharm* 2019, 11(2):161-164
- Shah AH, Qureshi S, Ageel AM. Toxicity studies in mice of ethanol extracts of *Foeniculum vulgare* fruit and *Ruta chalepensis* aerial parts. *J Ethnopharmacol* 1991, 34:167-72
- Shayan M, et al. Teratogenic effect of the aqueous extract of the *Foeniculum vulgare* (fennel) on fetal development in mice. *J Contemp Med Sci* 2019, 5(5):258-263
- Shlosberg A, Egyed M. Experimental *Ferula communis* (giant fennel) toxicosis in sheep. *Zentralbl Veterinarmed A*. 1985, 32:778-784
- Stäger J, Wüthrich B, Johansson S. Spice allergy in celery-sensitive patients. *Allergy* 1991, 46:475-478
- Sulemain WB. In vitro estimation of superfluid critical extracts of some plants for their antimicrobial potential, phytochemistry, and GC-MS analyses. *Ann Clin Microbiol Antimicrob* 2020, 19(1):29
- 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
- Telci I, Dirican A, Elmastas M, Akşit H, Demirtas I. Chemical diversity of wild fennel populations from Turkey. *Journal of Applied Research on Medicinal and Aromatic Plants* 2019, 13:100201
- 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, Trezza V, Cuomo V. "Natural" relief of pregnancy-related symptoms and neonatal outcomes: above all do no harm. *J Ethnopharmacol* 2015, 174:396-402
- 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
- Van den Berg SJPL, Alhusainy W, Restani P, Rietjens IMCM. Chemical analysis of estragole in fennel based teas and associated safety assessment using the Margin of Exposure (MOE) approach. *Food Chem Toxicol* 2014, 65:147-154
- Vasudevan K, Vembar S, Veeraraghavan K, Haranath PS. Influence of intragastric perfusion of aqueous spice extracts on acid secretion in anesthetized albino rats. *Indian J Gastroenterol* 2000, 19:53-56
- Weiss RF. In: Lehrbuch der Phytotherapie. 8th ed. Hippokrates, Stuttgart 1997, 82-83, 443, 463
- Weizman Z, Alkrinawi S, Goldfarb D, Biltran C. Efficacy of herbal tea preparation in infantile colic. *The Journal of Pediatrics* 1993, 22:650-652
- WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS). World Health Organization. France 2010, 127-140
- Yamamoto H, Mizutani T, Nomura H. Studies on the mutagenicity of crude drug extracts. I. *Yakugaku Zasshi* 1982, 102:596-601
- 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* 2019a, 498:110583
- Yaralizadeh M, Abedi P, Najar Z, Namjoyan F. Effect of *Foeniculum vulgare* (fennel) vaginal cream on vaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled trial. *Maturitas* 2016, 84:75-80
- Zargari A. Medicinal plants. Tehran University Publication. Tehran, Iran 1992, 32-37
- Zeller A, Rychlik M. Character Impact Odorants of Fennel Fruits and Fennel Tea. *J. Agric. Food Chem* 2006, 54:3686-3692
- Zengin S, Oktay MM, Kamalak M, Al B, Yildirim C, Büyükaslan H. Acute Hepatitis Associated with The Use of Herbal Tea (Fennel and Cumin). *Journal of Clinical and Analytical Medicine* 2014, 6(102):781-783
- Zhang 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

Zlatanov M. Untersuchungen iiber die Phospholipidzusammensetzung der Glyceridole einiger Vertreter der Familie Apiaceae. *Fat Sci Technol* 1994, 96, N.12, 456-457