Revista de Ciências
Farmacêuticas
Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

Rev Ciênc Farm Básica Apl., 2009;30(3):235-239
ISSN 1808-4532

Potential pharmacological and toxicological basis of the essential oil from *Mentha* spp

Peixoto, I.T.A.[1]; Furlanetti, V.F.[1]; Anibal, P.C.[1]; Duarte, M.C.T.[2] ; Höfling, J.F.[1]

[1]Department of Oral Diagnosis, Piracicaba Dental School, State University of Campinas, UNICAMP.
[2]Pluridisciplinary Center for Chemical, Biological, and Agricultural Research (CPQBA), Microbiology Division.

Recebido 22/07/2009 / Aceito 12/02/2010

ABSTRACT

During the past few years, interest in the potential clinical and pharmacological basis of the efficacy and safety of herbal medicines has increased greatly, due to widespread domestic self-medication with these agents. Some authors have analyzed the use of *Mentha* ssp. in the pharmacological industry. The essential oil from *Mentha* spp. is used to treat discomfort of the gastro-intestinal tract, irritable bowel syndrome, myalgia and neuralgia, as well as oral mucosal inflammation, and also as an expectorant, an antimicrobial and an ingredient in many analgesic creams. The essential oil also contains chemical compounds that are associated with side effects such as nausea, vomiting, allergic reactions, flushing and headaches. Therefore, the purpose of the present review was to examine the literature on the efficacy and safety of the possible clinical and pharmacological uses of the essential oil from *Mentha* spp. in human beings.
Keywords: Mentha spp., Antimicrobial activity; Essential oil.

INTRODUCTION

Empirical knowledge of the properties of medicinal plants is the basis for their use as home remedies. However, scientific interest in the potential clinical and pharmacological basis for the efficacy and safety of herbal medicines has increased greatly in recent years, in view of the common occurrence of domestic self-medication with these agents (Rodriguez-Fragoso et al., 2007). Among the great diversity of plants in question, species of *Mentha* have been assessed by several authors (Nair, 2001; McKay & Blumberg, 2006; Gurib-Fakin, 2006; Bush et al., 2007; Hur et al., 2007), with respect to their use in the pharmacology (Oumzil et al., 2002; McKay & Blumberg, 2006), and cosmetology industries (Bhatia et al., 2008).

Autor correspondente: José Francisco Höfling - Piracicaba Dental School - State University of Campinas.- P.O. Box 52. - 13414-903 - Piracicaba - SP - Brazil
Phone: 55 19 21065322 - e-mail:hofling@fop.unicamp.br

The essential oil from *Mentha* spp. is used as an expectorant and against conditions such as discomfort of the gastrointestinal tract and upper bile ducts, irritation of the colon or irritable bowel syndrome, myalgia and neuralgia, as well as oral mucosal inflammation (McKay & Blumberg, 2006).

Although some health care professionals believe that herbal medicines, such as the essential oil from *Mentha* spp., are relatively safe as they are "natural", recent publications have highlighted the potentially severe consequences of side effects (Gurib-Fakin, 2006; Bush et al., 2007).

Therefore, the purpose of this review is to examine what has been published on the possible clinical and pharmacological uses of essential oils of *Mentha* spp. and their effective and safe utilization in human beings. This article, based on the existing literature, elucidates the benefits and risks of species of *Mentha* spp.

The history of *Mentha* spp

Throughout history, a number of mint species have been used around the globe for their various properties, both medicinal and culinary. Peppermint oil is one of the world's oldest herbal medicines. The gathering of dried peppermint dates back to at least 1000 BC. In Chinese traditional medicine, peppermint is called "bo he", and its use can be found documented in ancient Egypt, Greece and Rome. Peppermint (*Mentha* piperita) was not officially described until 1696, when the English botanist John Ray (1628-1705) first discovered the pepper-flavored mint. Entering the London Pharmacopoeia in 1721, peppermint has since been cultivated for its essential oil throughout Asia, Europe and North America (Middleton et al., 2000; Spirling & Daniels, 2001).

After the Second World War, some of the Japanese manufacturers shifted their manufacturing operations from Japan to Brazil. In 1987, India became an exporter of menthol, presently holding approximately 70% of the world menthol market. In Brazil, mint was available in the dense forest, where it grew wild. When it was harvested, the field could be left as it was, to grow back later. Brazil became one of the main sources of menthol in the world (Nanda et al., 2004). The oil is obtained by distillation from the freshly ground leaves and ranges from colorless to greenish-yellow (Spirling & Daniels, 2001).

Peppermint oil is the most studied form of mint oil and menthol, one of the main constituents of peppermint, is a key ingredient in many commercial remedies, in addition to the huge commercial sales of mint-flavored sweet products. With the growing popularity of herbal remedies, among both the public and medical practitioners, it would seem that now is an opportune time to consider further what peppermint has to offer the world of medicine (Spirling & Daniels, 2001).

Pharmacognoxy of *Mentha* spp essential oil

Purified constituents are necessary in order to characterize plants chemically and to assess, in preclinical studies, their medical efficacy as well as toxicity, before determining if they have biological activity in human clinical trials (Rodriguez-Fragoso et al., 2007). Several articles have been published, listing the essential oil constituents of diverse species of *Mentha* (Pitter & Ernest, 1998; Furahata et al., 2000; Iscan et al., 2002; Xu et al., 2003; Rodriguez-Fragoso et al., 2007).

The chemical composition of the oil from *Mentha* spp. varies according to the age of the plant, variety of species, geographic region and conditions of processing (Xu et al., 2003). The plant is sensitive to latitude and climate and grows principally in the mid-Western states of the USA where 75% of the world's fresh supply originates (Spirling & Daniels, 2001).

The main elements identified in the volatile essential oil of *Mentha* spp. are menthol (33-60%), menthone (15-32%), isomenthone (2-8%), 1.8 cineol (eucalyptol) (5-13%), menthyl acetate (2-11%) menthofuran (1-10%), limonene (1-7%), β-myrcene (0.1-1.7%), β-caryophyllene (2-4%), pulegone (0.5-1.6%) and carvone (1%) (Pitter & Ernest, 1998). The main active component of peppermint oil is menthol, which is responsible for its medicinal properties, whilst esters, such as menthyl acetate, provide the familiar minty taste and associated aroma (Spirling & Daniels, 2001).

The concept of several active principles acting in synergy in herbal remedies may be somewhat unusual for pharmaceutical scientists who are accustomed to monotherapy with single therapeutic agents (Rodriguez-Fragoso et al., 2007). An example of this phenomenon may be seen in the essential oils of *Mentha* spp., which have various active constituents. However, there are species that carry potential health risks among their constituents (Xu et al., 2003). The essential oil of *Mentha* piperita contains chemical compounds that are associated with side effects such as heartburn, nausea, vomiting, allergic reactions, flushing and headaches (Maniacal & Wanwimolruk, 2001; Akdogan et al., 2004; Bush et al., 2007). These effects will be discussed in "Clinical uses of the essential oil from *Mentha* spp".

Antimicrobial activity of the essential oil from *Mentha* spp

Several studies in the literature show the efficacy of antifungals and antibacterials obtained from the essential oils of various species of *Mentha*. Thus, these essential oils showed antimicrobial activity against bacteria, including Escherichia coli, Staphylococcus aureus, Salmonella choleraesuis (Sivropoulou et al., 1995; Sartoratto et al., 2004; Duarte et al., 2005; Yadegarinia et al., 2006; Fazlara et al., 2008), Streptococcus mutans and S. pyogenes (Rasooli et al., 2008), and other microorganisms, such as yeasts and periodontopathogens (Sartoratto et al., 2004; Tampieri et al., 2005; Lee et al., 2007).

Two of the main compounds, menthol and menthone, have been highlighted in several studies for their antimicrobial activity, which varies not only with the origin of the *Mentha* specimen, but also with different strains of the same bacterial species (Sivropoulou et al., 1995; Mahady et al., 2005).

Comparing menthol and menthone, Furahata et al. (2000) and Iscan et al. (2002) suggest, in a study conducted in vitro, that menthol is responsible for the antimicrobial activity of these oils. On the other hand, Mahady et al. (2005) tested the bactericidal effect of menthone on 15 strains of E. coli and demonstrated that they were susceptible.

Menthol, menthone, and the essential oil of *Mentha* were found to have antibacterial activity against Enterobacter aerogenes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus, Listeria monocytogenes, Escherichia coli, Staphylococcus epidermidis and Saccharomyces cerevisiae (Iscan et al., 2002; Schelz et al., 2006).

The essential oil of *Mentha* piperita is also capable of exerting a direct virucidal effect on the herpes simplex virus type 1 (HSV-1). The oil was active against an acyclovir-resistant strain of HSV-1, and plaque formation was reduced by a significant 99% (Schuhmacher et al., 2003). Preliminary evidence suggests that the main peppermint oil component, menthol, may protect against herpes simplex (Melzer et al., 2004).

The action of certain species of *Mentha* against the yeast Candida albicans and some periodontopathogens has already been tested (Oumzil et al., 2002; Sartoratto et al., 2004; Tampieri et al., 2005). Several studies prove their effectiveness as antifungal agents against Candida spp. (Oumzil et al., 2002; Freitas et al., 2004; Sartoratto et al., 2004; Duarte et al., 2005; Tampieri et al., 2005; Lee et al., 2007; Sokovic et al., 2009).

The essential oil from *Mentha* spp. may be considered a safe ingredient for the development of antibiofilm agents that could find a role in the pharmaceutical industry (Rasooli et al., 2008). This is especially relevant at a time when there is increasing interest in finding more natural alternatives to many existing preservatives (Fazlara et al., 2008).

Clinical uses of the essential oil from *Mentha* spp

Peppermint is probably best known in the field of medicine for its role in the suppression of the symptoms of indigestion; hence the eating of mint sweets after meals. Peppermint oil acts both to reduce spasms of the intestinal tract and to reduce fermentation of undigested food, by encouraging a balance between oral and intestinal microorganisms (Spirling & Daniels, 2001).

It has been observed that peppermint relaxes the lower esophageal sphincter and is useful as an antispasmodic agent for double-contrast barium meal examination, and in patients with dyspepsia (Melzer et al., 2004; Mizuno

et al., 2006). Menthol, a calcium channel antagonist, is thought to inhibit contraction of smooth muscle cells by blocking the inward flux of calcium ions. It is also believed to have an effect on the histamine, hydroxytryptamine and cholinergic systems of the gut; the end result of these effects is to reduce gastroduodenal motility by decreasing the number and amplitude of contractions during the migrating motor complex (Beesley et al., 1996). Peppermint oil alters the physiology of the gastrointestinal tract and is used in clinical trials for the treatment of barium enema-related colonic spasm, dyspepsia, irritable bowel syndrome (Melzer et al., 2004; Mizuno et al., 2006) and mouth malodor in intensive care patients (Hur et al., 2007). Peppermint provides a convenient and cheaper alternative to intravenous spasmolytics such as hyoscine N-butyl bromide (Buscopan), which can sometimes cause systemic upsets and anticholinergic side effects (Spirling & Daniels, 2001). Tate (1997) reported that gynecological patients given peppermint oil to inhale had a reduced prevalence of postoperative nausea. As an explanation of this phenomenon, there is physiological evidence that peppermint oil acts as an antagonist at sensory receptors involved in emesis (Spirling & Daniels, 2001).

Peppermint was found to inhibit spontaneous peristaltic activity; this reduces total gastrointestinal transit or gastric emptying, decreases the basal tone in the gastrointestinal tract, reduces the slow wave frequency in the esophagus and small intestine (slowing peristaltic movements) and inhibits potassium depolarization-induced responses in the intestine (Melzer et al., 2004; Mizuno et al., 2006).

Approved for internal use, the oil from *Mentha* spp. is also used to treat bile duct discomfort, myalgia and neuralgia, inflammation of the oral mucosa (McKay & Blumberg, 2006), discomfort from menstrual cramps (Spirling & Daniels, 2001) and diverticulitis, and as an anti-inflammatory and expectorant (Kingham, 1995).

Mentha spp. oil has a pain-soothing action and is used clinically as an ingredient in many analgesic creams and in the treatment of arthritis and other musculoskeletal conditions. Menthol relieves discomfort by gating afferent pain impulses, as part of an astringent effect (Buckle, 1999), and exciting those nerves that recognize the sensation of coldness. This not only causes a dulling of pain, but also encourages blood flow to the treated body part (McKay & Blumberg, 2006). The warm sensation produced by topical application around the affected body part or joint serves to distract attention from the original deeper tissue discomfort (Buckle, 1999). Peppermint can help soothe headaches; moreover, applied to the gums of teething babies it can help relieve distress and clean teeth (Spirling & Daniels, 2001).

Potential health risks of *Mentha* spp essential oil

Many dangerous and lethal side effects have been reported in relation to herbal products. These side effects may occur by several different mechanisms, including direct toxicity, contamination and interactions with drugs or other herbs (Rodriguez-Fragoso et al., 2007).

Side effects may be due to contaminants in herbal products, such as toxic heavy metals and metalloids, including lead, mercury and arsenic; undeclared pharmaceuticals, intentionally and illegally added to the herbs to produce a desired effect (Gagnier et al., 2006); microorganisms and microbial toxins, and genetic factors. These plants are capable of synthesizing a vast array of secondary metabolites as defense mechanisms to protect themselves against plant pathogens (Rodriguez-Fragoso et al., 2007).

The essential oil from peppermint is associated with side effects such as heartburn, nausea, vomiting, allergic reactions, flushing and headaches (Maniacal & Wanwimolruk, 2001; Akdogan et al., 2004; Bush et al., 2007). When taken together with "conventional" medicine, pharmacokinetic interactions may occur if the oil affects the absorption, distribution, metabolism or excretion of the drug, or there are pharmacodynamic interactions. Preliminary evidence suggests that peppermint oil might interact with cytochrome P450 isoforms (CYP1A2, CYP2C19, CYP2C9, CYP3A4) and therefore might modify the levels of drugs metabolized by those cytochromes (Maniacal & Wanwimolruk, 2001; Unger & Frank, 2004). This interaction is of great importance in clinical practice, given that: (1) CYP isoenzymes metabolize a large number of structurally diverse drugs and chemicals, both natural and synthetic; (2) there are important genetic polymorphisms in drug disposition among different populations, and (3) the variability in potency and complexity of herbal medicine preparations is hard to assess (Rodriguez-Fragoso et al., 2007).

As to suitability for application in cosmetic formulations, Nair (2001) reported that the topical application of the essential oil from *Mentha* spp. also deserved investigation, as its use might not always be safe; for example, pulegone, a component of this oil and recognized hepatotoxin, should be limited to a concentration of 1%, being toxic at higher concentrations. Repeated intradermal dosing with peppermint oil produced moderate and severe reactions in rabbits, although peppermint oil did not appear to be phototoxic. Peppermint oil was negative in the Ames test and a mouse lymphoma mutagenesis assay, but rendered equivocal results in a Chinese hamster fibroblast cell chromosome aberration assay (Nair, 2001).

Additionally, in a carcinogenicity study of toothpaste components, no apparent differences were noted between mice treated with peppermint oil and those treated with the toothpaste base (Nair, 2001).

Despite the low toxicity of *Mentha* spp., a few cases have demonstrated topical sensitivity (Bonamonte et al., 2001; Pérez-Calderon et al., 2007). A study carried out by Kanerva et al. (2001) in 4000 patients, however, found no cases of skin irritation or allergy.

Exacerbation of asthma has also been associated with the use of peppermint-containing toothpaste (Spurlock & Dailey, 1990) and, when taken in a non-capsulate form, the oil may precipitate heartburn (Wilkinson & Beck, 1994).

Thus, further scientific studies are needed to assess the safety and efficacy of the use of the essential oil from *Mentha* ssp in human beings (McKay & Blumberg, 2006).

Efforts to elucidate the health benefits and risks of essential oils from the diverse species of *Mentha* should be intensified.

Additional research is required for a biological evaluation of the medicinal properties of the essential oil from *Mentha* spp., so that formulations containing the essential oil can be used effectively for the treatment of diseases that affect human beings.

RESUMO

Bases farmacológicas e toxicológicas potenciais do óleo essencial de *Mentha* spp

Nas últimas décadas, houve um aumento crescente no interesse sobre as bases clínicas e farmacológicas potenciais em relação à eficácia e a segurança das drogas produzidas de plantas medicinais, devido à automedicação destes agentes. Diversos autores avaliaram o óleo essencial de *Mentha* spp., devido a sua larga utilização na indústria farmacológica. O óleo essencial de *Mentha* spp. componente de muitos analgésicos e com atividade antimicrobiana, é usado para tratamentos nos desconfortos gastrintestinais e dutos biliares superiores, Síndrome de Bowel, expectorante, mialgia e neuralgia, bem como na inflamação oral da mucosa. No entanto, esse óleo contém compostos químicos que apresentam efeitos colaterais tais como náusea, vômito, reações alérgicas e dores de cabeça. O objetivo desta revisão atual foi avaliar dados da literatura específica sobre a possível utilização, eficácia e segurança clínica e farmacológica do óleo essencial de *Mentha* spp. em seres humanos.

Palavras-chave: *Mentha* spp. Atividade antimicrobiana. Óleo essencial.

ACKNOWLEDGEMENTS

The authors would like to thank FAPESP for financial support.

REFERENCES

Akdogan M, Ozugner M, Aydin G, Gokalp O. Investigantion of biochemical and histopathological effects of Peppermint piperita Labiatae and Peppermint spicata Labiatae on liver tissue in rats. Hum Exp Toxicol. 2004; 23:21-8.

Beesley A, Hardcastle J, Hardcastle PT, Taylor CJ. Influence of peppermint oil on absorptive and secretory processes in rat small intestine. Gut 1996; 39:214-9.

Bhatia SP, Letizia CS, Api AM. Fragrance material review on tricyclo[5.2.1.02,6]dec-4-en-8-yl acetate. Food Chem Toxicol. 2008 Sep 19; 46:Suppl 12:S100-1.

Bonamonte D, Mundo L, Daddabbo M, Fotti C. Allergic contact dermatitis from *Mentha* spicata (spearmint). Contact Derm. 2001; 45(5):298.

Buckle J. Use of aromatherapy as a complementary treatment for chronic pain. Altern Ther Health Med. 1999; 5(5):42-51.

Bush TM, Rayburn KS, Holloway SW, Sanchez-Yamamoto DS, Allen BL, Lam T, So BK, Tran de H, Greyber ER, Kantor S, et al. Adverse interactions between herbal and dietary substances and prescription medications: a clinical survey. Altern Ther Health Med. 2007; 13:30-5.

Duarte MCT, Figueira GM, Sartorato A, Rehder VLG, Delarmelina C. Anti-Candida activity of Brazilian medicinal plants. J Ethnopharmacol. 2005; 97(2):305-11.

Fazlara A, Najafzadeh H, Lak E. The potential application of plant essential oils as natural preservatives against Escherichia coli O157:H7. Pak J Biol Sci. 2008; 11(17):2054-61.

Freitas MSM, Martins MA, Vieira IJC. Produção e qualidade de óleos essenciais de *Mentha* arvensis em resposta à inoculação de fungos micorrízicos arbusculares. Pesqui Agropecu Bras. 2004; 39(9):887-94.

Furuhata K, Dogasaki C, Hara M, Fukuyama M. Antibacterial activities of several herbs on Legionella pneumophila. J Azabu Univ. 2000; 1/2:15-20.

Gagnier JJ, DeMelo J, Boom H, Rochon P, Bombardier C. Quality of reporting of randomized controlled trials of herbal medicine interventions. Am J Med. 2006; 119:1-11.

Gurib-Fakin A. Medicinal plants: tradition of yesterday and drugs of tomorrow. Mol Aspects Med. 2006; 27:1-93.

Hur MH, Park J, Maddock-Jennings W, Kim DO, Lee MS. Reduction of mouth malodor and volatile sulphur compounds in intensive care patients using an essential oil mouthwash. Phytoter Res. 2007; 21:641-3.

Iscan G, Kirimer N, Kurkcuoglu M, Baser KHC, Demirci F. Antimicrobial screening of *Mentha* piperita essential oils. J Agric Food Chem. 2002; 50:3943-6.

Kanerva L, et al. A multicenter study of patch test reactions with dental screening series. Am J Contact Dermat. 2001; 12:83-7.

Kingham JCC. Peppermint oil and colon spasm. Lancet. 1995; 346(8981):986.

Lee SB, Cha KH, Kim SN, Altantsetseg S, Shatar S, Sarangerel O, Nho CW. The antimicrobial activity of essential oil from Dracocephalum foetidum against pathogenic microorganisms. J Microbiol. 2007; 45(1):53-7.

Mahady GB, Pendland SL, Stoia A Hamill FA, Fabricant D, Dietz BM, Chadwick LR. In vitro susceptibility of Helicobacter pylori to botanical extracts used traditionally for the treatment of gastrointestinal disorders. Phytother Res. 2005; 19:988-91.

Maniacal PP, Wanwimolruk S. Effect of herbal teas on hepatic drug metabolizing enzymes in rats. J Pharm Pharmacol. 2001; 53:1323-9.

McKay DL, Bumberg JB. A review of the bioactivity and potential health benefits of peppermint tea (*Mentha* piperita L.). Phytother Res. 2006; 20:619-33.

Melzer J, Rösch W, Reichling J, Brigmoli R, Saller R. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). Aliment Pharmacol Ther. 2004; 20:1270-87.

Middleton EJr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev. 2000; 52:673-751.

Mizuno S, et al. Oral peppermint oil is a useful antispasmodic for double-contrast barium meal examination. Gastroenterol Hepatol. 2006; 21:1297-301.

Nair B. Final report on the safety assessment of *Mentha* Piperita (Peppermint) Oil, *Mentha* Piperita (Peppermint) Leaf Extract, *Mentha* Piperita (Peppermint) Leaf, and *Mentha* Piperita (Peppermint) Leaf Water. Int J Toxicol. 2001;20 Suppl 3:61-73.

Nanda S, Nanda A, Nanda A. 2004 *Mentha* & Allied Products Ltd. [cited 2008 Oct 10] Available from: http://www.*Mentha*allied.com/mint001.htm - 11k.

Oumzil H, Ghoulami S, Rhajaoui M, Ilidrissi A, Fkih-Tetouani, Faid M, Benjouad A. Antibacterial and antifungal activity of essential oils of *Mentha* suaveolens. Phytother Res. 2002; 16:727-31.

Pérez-Calderón R, Gonzalo-Garijo A, Bartolomé-Zavala B, Lamilla-Yerga A, Moreno-Gastón I. Occupational contact urticaria due to pennyroyal (*Mentha* pullegium). Contact Dermatitis 2007; 57:285-6.

Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. Am J Gastroenterol. 1998; 93:1131-5.

Rasooli I, Shayegh S, Taghizadeh M, Astaneh SD. Phytotherapeutic prevention of dental biofilm formation. Phytother Res. 2008; 22(9):1162-7.

Rodriguez-Fragoso L, Reyes-Esparza J, Burchiel SW, Herrera-Ruiz D, Torres E. Risks and benefits of commonly used herbal medicine in Mexico. Toxicol Appl Pharmacol. 2007; 227(1):125-35.

Sartoratto A, Machado ALM, Delarmelina C, Figueira GM, Duarte MCT, Rehder VLG. Composition and antimicrobial activity of essential oils from aromatic plants used in Brazil. Braz J Microbiol. 2004; 35:275-80.

Schelz Z, Molnar J, Hohmann J. Antimicrobial and antiplasmid activities of essential oils. Fitoterapia. 2006; 77(4):279-85.

Schuhmacher A, Reichling J, Schnitzler P. Virucidal effect of peppermint oil on the enveloped viruses herpes simplex virus type 1 and type 2 in vitro. Phytomedicine. 2003; 10 (6-7):504-10.

Sivropoulou A, Kokkimi S, Lanaras T, Arsenakis M. Antimicrobial activity of mint essential oils. J Agric Food Chem. 1995; 43:2384-8.

Soković MD, Vukojević J, Marin PD, Brkić DD, Vajs V, van Griensven LJ. Chemical composition of essential oils of Thymus and *Mentha* species and their antifungal activities. Molecules. 2009;14(1):238-49.

Spirling LI, Daniels IR. Botanical perspectives on health peppermint: more than just an after-dinner mint. J R Soc Health. 2001; 121(1):62-63.

Spurlock BW, Dailey TM. Shortness of (fresh) breath – toothpaste induced bronchospasm. N Engl J Med. 1990; 323:1845-6.

Tampieri MP, Galuppi R, Macchioni F Carelle MS, Falcioni L, Cioni PL, Morelli I. The inhibition of Candida albicans by selected essential oils and their major components. Mycopathologia 2005; 159:339-45.

Tate S. Peppermint oil: a treatment for postoperative nausea. J Adv Nur. 1997; 26(3):543-9.

Unger M, Frank A. Simultaneous determination of inhibitory potency of herbal extracts on the activity of six major cytochrome P 450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. Rapid Commun Mass Spectrom. 2004; 18:2273-81.

Xu P, Jia W, Bi L, Liu X, Zhao Y. Studies on components and quality of essential oil from *Mentha* piperita L. produced in Xinjiang, China. Chem Ind Forest Prod. 2003; 23:43-5.

Wilkinson SM, Beck MH. Allergic contact dermatitis from menthol in peppermint. Contact Dermatitis. 1994; 30(1):42-3.

Yadegarinia D, Gachkar L, Rezaei MB, Taghizadeh M, Astaneh SA, Rasooli I. Biochemical activities of Iranian *Mentha* piperita L. and Myrtus communis L. essential oils. Phytochemistry 2006; 67(12):1249-55.