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REVIEW ARTICLE

A Review of the Bioactivity and Potential Health Benefits of Peppermint Tea (*Mentha piperita* L.)

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Peppermint (*Mentha piperita* L.) is one of the most widely consumed single ingredient herbal teas, or tisanes. Peppermint tea, brewed from the plant leaves, and the essential oil of peppermint are used in traditional medicines. Evidence-based research regarding the bioactivity of this herb is reviewed. The phenolic constituents of the leaves include rosmarinic acid and several flavonoids, primarily eriocitrin, luteolin and hesperidin. The main volatile components of the essential oil are menthol and menthone. *In vitro*, peppermint has significant antimicrobial and antiviral activities, strong antioxidant and antitumor actions, and some antiallergenic potential. Animal model studies demonstrate a relaxation effect on gastrointestinal (GI) tissue, analgesic and anesthetic effects in the central and peripheral nervous system, immunomodulating actions and chemopreventive potential. Human studies on the GI, respiratory tract and analgesic effects of peppermint oil and its constituents have been reported. Several clinical trials examining the effects of peppermint oil on irritable bowel syndrome (IBS) symptoms have been conducted. However, human studies of peppermint leaf are limited and clinical trials of peppermint tea are absent. Adverse reactions to peppermint tea have not been reported, although caution has been urged for peppermint oil therapy in patients with GI reflux, hiatal hernia or kidney stones. Copyright © 2006 John Wiley & Sons, Ltd.

Keywords: Mentha piperita; peppermint oil; menthol; herbal tea; tisane; dyspepsia.

INTRODUCTION

About 80% of the world population currently relies on indigenous or traditional medicines for their primary health needs, and most of this therapy involves the use of plant extracts, often in aqueous solutions (Zhang, 2002). Of the plant-based foods used as medicines, none have received more attention as a group than herbal remedies (Dubick, 1996). The use of herbal preparations, typically prepared by steeping or heating crude plant material, has prevailed for centuries and healthcare providers in Europe and Asia today often prescribe herbal teas. However, such practices are largely based on folklore and schools of traditional medicine rather than evidence-based research.

Peppermint (*Mentha piperita* L.) is among the most popular single ingredient herbal teas. The list of purported benefits and uses of peppermint as a folk remedy or in complementary and alternative medical therapy include: biliary disorders, dyspepsia, enteritis, flatulence, gastritis, intestinal colic, and spasms of the bile duct, gallbladder and gastrointestinal (GI) tract. We review here the available scientific literature related closely or directly to the bioactivity and potential health benefits of infusions, or tisanes, prepared with peppermint leaves, and the effects of the essential oil and other components contained therein. Information regarding the phytochemical and nutrient content, *in vitro* experiments, animal models, and human studies available in the recent scientific literature is presented.

NOMENCLATURE

Peppermint (*Mentha piperita* L.) is a perennial herb native to Europe, naturalized in the northern USA and Canada, and cultivated in many parts of the world. A hybrid of spearmint (*M. spicata* L.) and water mint (*M. aquatica* L.), peppermint grows particularly well in areas with high water-holding capacity soil. Best known for its flavoring and fragrance properties, peppermint leaves (fresh and dried) and the essential oil extracted from the leaves are used in many food, cosmetic and pharmaceutical products.

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PHYTOCHEMICAL AND NUTRIENT CONTENT

The chemical components of peppermint leaves and oil vary with plant maturity, variety, geographical region and processing conditions (Clark and Menary, 1981; Maffei and Scannerini, 1992; Rohloff, 1999; Gherman *et al.*, 2000; Blanco *et al.*, 2002; Pino *et al.*, 2002; Ruiz del Castillo *et al.*, 2003; Xu *et al.*, 2003). The fatty acid composition of the non-polar lipid fraction of peppermint leaves is dominated by palmitic (16:0), linoleic (18:2) and linolenic (18:3) acids (Maffei and Scannerini, 1992). The main volatile components identified in the essential oil of peppermint are menthol (33–60%), menthone (15–32%), isomenthone (2–8%), 1,8-cineole (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%) (Clark and Menary, 1981; Sang, 1982; Pittler and Ernst, 1998; Dimandja *et al.*, 2000; Gherman *et al.*, 2000). The leaves contain 1.2–3.9% (v/w) essential oil (Picuric-Jovanovic *et al.*, 1997; Blumenthal *et al.*, 1998) (0.38% yield from fresh leaves) (Kaul *et al.*, 2001), while an infusion of dried leaves is reported to contain 21% of the original oil (25 mg/L). Proportions of the individual components found in oil were both higher and lower than those found in the infused tea (Duband *et al.*, 1992).

Studies regarding the mineral content of peppermint leaves are more comprehensive than those pertaining to the vitamin content. Fresh *M. piperita* leaves from Brazil were found to contain 940–1016 retinol equivalents (RE)/100 g β-carotene (de Almeida-Muradian *et al.*, 1998). The presence of other carotenoids and chlorophylls (Pilipenko *et al.*, 1998), as well as α- and γ-tocopherols (Blumenthal *et al.*, 1998) and ascorbic acid (Capecka *et al.*, 2005), has also been reported. The major minerals in dried peppermint leaves (as g/kg) include K (33), Ca (15.3), Mg (5.8) and lower amounts of Na, along with smaller amounts (as mg/kg) of Fe (239), Mn (188), Zn (51) and Cu (12). Trace amounts (as µg/g) of Cr (941), I (325) and Se (147) are also present (Zimna and Piekos, 1988; Lozak *et al.*, 2002). Concentrations of these minerals found in an infusion of dried leaves (prepared at 95 °C, 15 min) were approximately 8–60% of the amounts present in the leaves, i.e. Ca (2.9 g/kg), Mg (2.2 g/kg), Fe (20 mg/kg), Mn (27 mg/kg), Zn (6 mg/kg), Cu (3 mg/kg), Cr (390 µg/g), I (206 µg/g) and Se (87 µg/g) (Lozak *et al.*, 2002). According to Lozak *et al.* (2002), the most readily eluted elements of nutritional importance from the leaves are Se and I with Fe as the least eluted mineral. Muller *et al.* (1997) reported finding 477 µg/g Al in dried mint leaves, approximately half the amount present in black tea (899 µg/g); however, the transfer of Al into a peppermint tea infusion was very low (5%) compared with black tea (30%).

The total polyphenolic content of peppermint leaves is approximately 19–23% (total flavonoids 12%), which includes 59–67% eriocitrin and rosmarinic acid (combined), 7–12% luteolin 7-O-rutinoside, 6–10% hesperidin, and smaller quantities of 5,6-dihydroxy-7,8,3′,4′-tetramethoxyflavone, pebrellin, gardenin B and apigenin (Hoffmann and Lunder, 1984; Zakharov *et al.*, 1990; Samejima *et al.*, 1995; Areias *et al.*, 2001; Zheng and Wang, 2001). About 75% of the polyphenolic compounds present in the leaves are extracted in an infusion (750 mg/L) (Duband *et al.*, 1992).

The salicylic acid content of peppermint candies and tea was reportedly very high (7.7–75.8 mg/kg) in an early study by Swain *et al.* (1985); however, a more recent analysis using a more sensitive assay method by Venema *et al.* (1996) revealed <0.2 mg/kg.

IN VITRO STUDIES

Antioxidant capacity. The antioxidant capacity of peppermint has been determined using a number of different assay methods. The oxygen radical absorbance capacity (ORAC) value for an aqueous solution of previously frozen fresh *M. piperita* leaves (supernatant of 2.0 g homogenized in 15 mL buffer) was among the highest found in an analysis of popular medicinal herbs by Zheng and Wang (2001). At 15.84 ± 0.42 µmol Trolox equivalents (TE)/g fresh weight, the ORAC value for *M. piperita* was similar to *Hypericum perforatum* (16.77 ± 0.22 µmol TE/g) and *Valerian officinalis* (15.69 ± 0.37 µmol TE/g), slightly higher than *Salvia officinalis* (13.28 ± 0.40 µmol TE/g) and lower than *Thymus vulgaris* (19.49 ± 0.21 µmol TE/g). The ORAC values for the related *M. aquatica* and *M. spicata* were 19.80 ± 0.43 and 8.10 ± 0.26 µmol TE/g, respectively. In a study using the ferric reducing ability of plasma (FRAP) assay, Dragland *et al.* (2003) found the relative antioxidant value of dried *M. piperita* (78.5 mmol/g) to be lower than *S. officinalis* (91.2 mmol/g) and higher than *T. vulgaris* (74.6 mmol/g). FRAP values >75 mmol/g are indicative of high antioxidant concentrations. As with other compounds present in *M. piperita*, seasonal variations with regard to antioxidant activity have been observed (range 59.8–96.1 mmol/g) (Dragland *et al.*, 2003).

According to Mimica-Dukic *et al.* (2003), the free radical scavenging capacity of *M. piperita* oil was higher than that of either *M. aquatica* or *M. longifolia*. In their experiment, *M. piperita* reduced the radical generator 2,2-diphenyl-1-picrylhydrazyl (DPPH) by 50% (IC_{50} = 2.53 µg/mL) and inhibited the generation of the OH radical in the Fenton reaction by 24%. In an assay based upon the oxidation of homovanillic acid (HVA) to its fluorescent biphenyl dimer in the presence of H_2O_2 and peroxidase, the antioxidant capacities of aqueous solutions of peppermint (0.1, 0.5 and 1.0%), prepared with boiling water and incubated 10 min at 95 °C, were among the highest of the tea infusions tested by Pazdzioch-Czochra and Widenska (2002). The percent of fluorescence inhibition exhibited by a 0.5% peppermint infusion (closest approximation to an amount typically used) was ~67%; lower than comparable amounts of black (78%) and green (81%) teas, but higher than other herb teas including hibiscus (56%) and rooibos (52%). When the results were expressed as Trolox equivalents, these teas were ranked similarly, i.e. black tea (0.32 ± 0.05), green tea (0.31 ± 0.03), peppermint tea (0.27 ± 0.02), hibiscus tea (0.20 ± 0.02) and rooibos (0.17 ± 0.01). One limitation of this particular method includes the ability to estimate only the H_2O_2 scavenging ability of the tested herbs, and not the scavenging of other free radicals. In other studies, ethanol extracts of dried *M. piperata* were shown to stabilize

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the auto-oxidation of kinetically pure triacylglycerols of sunflower oil (Yanishlieva and Marinova, 1995), and natural sunflower oil (Marinova and Yanishlieva, 1997). Essential oil derived from peppermint exhibited an even greater antioxidant effect against sunflower oil peroxidation than butylated hydroxytoluene (BHT) (Gurdip *et al.*, 1998).

Antitumor activity. Ohara and Matsuhisa (2002) screened 120 edible plants for antitumor promoting activities against the non-12-O-tetradecanoylphorbol-13-acetate (TPA)-type promoter, okadaic acid (OA), which promotes tumor formation by inhibiting protein phosphatase-2A. Peppermint was one of only eight plants that showed strong activity (86–100%) in suppressing the effect of OA. Menthol derived from *M. piperita* appears to affect cytosolic arylamine N-acetyltransferase (NAT) activity in the human liver tumor cell line J5 differentially dependent on dose (Lin *et al.*, 2001); higher doses (32 and 3.2 mM) inhibited NAT, a more moderate dose (0.32 mM) had no effect, and lower doses (0.032 and 0.0032 mM) promoted NAT relative to controls.

Peppermint oil showed a genotoxic effect in human lymphocytes in a study by Lazutka *et al.* (2001). The frequency of chromosomal aberrations was highest ($16.0 \pm 2.3\%$) with 0.20 μL/mL peppermint oil (control = $2.0 \pm 0.6\%$) but was reduced at concentrations of 0.25 and 0.30 μL/mL (9.0 ± 1.6 and $6.0 \pm 1.4\%$, respectively). In this same experiment, peppermint oil showed weak sister chromatid exchange (SCE) activity, although the effect was not dose-dependent, and the oil inhibited mitotic activity at the lowest tested concentration (0.10 μL/mL). In contrast, using a Chinese hamster fibroblast cell chromosome aberration assay, the effects of peppermint oil were equivocal and, using a mouse lymphoma mutagenesis assay and the Ames test (using *Salmonella typhimurium*), no mutagenic activity was detected with peppermint oil (Andersen and Jensen, 1984; Anonymous, 2001); individual components of peppermint leaves and peppermint oil were also absent for evidence of genotoxicity. No significant chromosomal aberrations or changes in the frequency of SCE were observed in phytohemagglutinin-stimulated human lymphocyte cultures grown in the presence of 0.1, 1.0 or 10.0 mM menthol when compared with control samples (Murthy *et al.*, 1991). Similarly, menthol (200–700 μg/plate) and 1,8-cineole (1500–2500 μg/plate) did not increase the number of revertant colonies observed with and without addition of S9 rat hepatic microsomal enzymes in the *S. typhimurium* assay (Gomes-Carneiro *et al.*, 1998). An aqueous extract of peppermint also strongly suppressed the mutagenicity of 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), a human carcinogen formed in cooked meat, when evaluated in the *S. typhimurium* assay (Natake *et al.*, 1989). This effect was most likely due to the presence of the flavonoid luteolin (Samejima *et al.*, 1995).

Kim *et al.* (2002) tested the effects of the methanol extracts of ten herbs on L1210 cancer cells, and found that all of the herbs, including *M. piperita*, were cytotoxic. The addition of the herbs augmented the generation of superoxide ion and increased activities of superoxide dismutase and glutathione peroxidase, suggesting the cytotoxic mechanism may involve reactive oxygen species. Astrocytes, the most abundant glial cell type in the brain, may pathologically affect neuronal activities following exposure to environmental stress. Koo *et al.* (2001) heat-shock induced apoptosis in rat and human and astrocytes pretreated with peppermint oil and inhibited DNA fragmentation and condensation of nuclear chromatin. In the human cells, peppermint oil also inhibited caspase-3 activation and poly-ADP-ribose polymerase fragmentation.

In human liver microsomes, Dresser *et al.* (2002) determined that peppermint oil and two of its components were moderately effective, reversible, and partially mixed inhibitors of nifedipine metabolism. Metabolism of this calcium channel blocker is mediated by the cytochrome P450 isoform CYP34A. The effects of peppermint oil, menthol and menthyl acetate (K_i 35.9, 87.0, 124.0 μmol/L, respectively) were less potent than two other partially mixed reversible CYP3A4 inhibitors, buspirone (K_i 20.2 μmol/L) and propafenone (K_i 38.9 μmol/L), and non-significant when compared with irreversible, or mechanism-based inhibitors. These findings suggest that peppermint may affect the bioavailability of certain drugs that require CYP3A4 for their effective metabolism. Using a different assay method, Unger and Frank (2004) reported that peppermint oil moderately inhibited all CYP enzymes tested except for 3A4, which was only 20% inhibited at 500 μg/mL.

Antiallergenic activity. In rat peritoneal mast cells, Inoue *et al.* (2002) observed an antiallergenic activity among the flavonoid glycosides derived from *M. piperita*, including eriocitrin, narirutin, hesperidin, luteolin-7-O-rutinoside, isorhoifolin, diosmin, rosmarinic acid and 5, 7-dihydroxycromone-7-O-rutinoside. Of the compounds tested, only luteolin-7-O-rutinoside showed a potent inhibitory effect on histamine release induced by compound 48/80 and an antigen–antibody reaction. However, beyond the flavonoid activity in this assay, using lipopolysaccharide (LPS)-stimulated monocytes from healthy human subjects, Juergens *et al.* (1998a) found that menthol (0.1 μg/mL) significantly suppressed the production of the inflammatory mediating compounds leukotriene (LT) B4 (64.4%), prostaglandin (PG) E2 (56.6%) and interleukin (IL)-β2 (64.2%). Mint oil (0.1 μg/mL) had a similar effect on LTB4, PGE2 and IL-β2, but at lower concentrations (<0.01 μg/mL) there was a paradoxical increase in PGE2 production. Another peppermint constituent, 1,8-cineole, significantly inhibited the production of tumor necrosis factor (TNF)-α, IL-1β, LTB4 and thromboxane B2 in the same *in vitro* model (Juergens *et al.*, 1998b). In canine airway epithelial cells, menthol increased cytosolic calcium (Takeuchi *et al.*, 1994) and stimulated the secretion of Cl^- through a calcium-dependent mechanism (Chiyotani *et al.*, 1994). Using Caco-2 cells, Satsu *et al.* (2004) observed the increased secretion of IL-8 with an ethanol extract of peppermint, most likely attributable to the presence of the monocyclic sesquiterpene α-humulene.

Antiviral activity. Herrmann and Kucera (1967) found significant antiviral activity in aqueous extracts of peppermint leaves towards Influenza A, Newcastle disease virus, Herpes simplex virus (HSV) and Vaccinia virus in egg and cell-culture systems. An alcohol extract of *M. piperita* in combination with four other herbs (*Thymus serpyllum*, *Viscum album*, *Salvia officinalis* and

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Glycyrrhiza glabra) inhibited the reproduction of influenza viruses A/Gabrovo (H1N1), A/Hong Kong (H3N2) and A/PR/8 (H1N1) in tissue cultures and embryonated eggs, reducing their infectious titers by 3.5, 3.0 and 2.0 $\log_{10}$ inhibitory dose (ID)50/mL, respectively (Manolova *et al.*, 1995). Yamasaki *et al.* (1998) tested an aqueous extract of *M. piperita* and found potent anti-human immunodeficiency virus-1 (HIV)-1 activity at an effective dose of 16 μg/mL in MT-4 cells. Water-soluble polar substances in the extract also showed inhibitory activity against HIV-reverse transcriptase.

Minami *et al.* (2003) found peppermint essential oil (1%) suppressed the replicative ability of HSV-1 in Vero cells incubated at 4 °C for 24 h. As no viral activity was observed in Vero cells treated with essential oil either before or after viral adsorption, the investigators suggested a direct interaction between the oil and the HSV-1 virion. Similarly, Schuhmacher *et al.* (2003) found both HSV-1 and HSV-2 were significantly inhibited when the viruses were treated with peppermint oil prior to adsorption, but not after penetration into the host cell. The 50% inhibitory concentration (IC_{50}) of peppermint oil was 0.002% for HSV-1 and 0.0008% for HSV-2 in RC-37 cells using a plaque reduction assay. Peppermint oil also exhibited virucidal activity in viral suspension tests. Viral titers of HSV-1 were reduced by 82%, HSV-2 by 92% and plaque formation of an acyclovir resistant strain (HSV-1-ACV[res]) was reduced by 99%.

Antibacterial activity. Many studies have assessed the antibacterial activity of peppermint (Piccaglia *et al.*, 1993; Shapiro *et al.*, 1994; Larsen *et al.*, 1996; Pattnaik *et al.*, 1996; Nelson, 1997; Carvalho *et al.*, 1999; Tkachenko *et al.*, 1999; Furuhata *et al.*, 2000; Tassou *et al.*, 2000; Akin *et al.*, 2001; Imai *et al.*, 2001; Inouye *et al.*, 2001; Marino *et al.*, 2001; Montes Belmont and Flores Moctezuma, 2001; Aridogan *et al.*, 2002; Bonyadian and Karim, 2002; Iscan *et al.*, 2002; Azuma *et al.*, 2003) and antifungal (Sarbhoy *et al.*, 1978; Rai and Upadhyay, 1988; Pattnaik *et al.*, 1996; Zambonelli *et al.*, 1996; Carvalho *et al.*, 1999; Blaszczyk *et al.*, 2000; Ezzat, 2001; Karanika *et al.*, 2001; Giamperi *et al.*, 2002; Edris and Farrag, 2003; Mimica-Dukic *et al.*, 2003). For example, Iscan *et al.* (2002) tested peppermint oil and its components menthol and menthone against 21 human and plant pathogens and found moderate inhibitory activity against the human pathogens. *Staphylococcus aureus* was inhibited by 0.63 mg/mL (minimum inhibitory concentration (MIC) of oil, *Listeria monocytogenes* by 0.16–63 mg/mL, and *Staphylococcus epidermis* by 0.63–2.5 mg/mL. The oil showed stronger inhibition (0.07–1.25 mg/mL) against the *Pseudomonas* and *Xanthomonas* strains of plant pathogens. Pattnaik *et al.* (1996) found that peppermint oil was effective against 22 different bacterial strains, including Gram-positive cocci and rods and Gram-negative rods, with an MIC of 0.16–20 μl/mL. According to Tassou *et al.* (2000), the addition of 0.4–1.2% of peppermint oil to nutrient broth, either with or without glucose, reduced the total viable count of *Staphylococcus aureus* by 6–7 logs colony forming units (cfu), while 0.1–1.0% reduced *Salmonella enteritidis* by 3 log cfu. At a concentration of 0.1% (v/v), peppermint oil was also able to inhibit the production of *S. aureus* toxin by a factor of 100 000. In drug resistant *S. aureus* and *Enterococcus faecium*, Nelson (1997) determined the effective bacteriostatic and bactericidal dose of peppermint oil was 0.5–2.0%. Mimica-Dukic *et al.* (2003) found *M. piperita* oil was more effective against a multiresistant strain of *Shigella sonei* and *Micrococcus flavus* than oils from other *Mentha* species.

Inouye *et al.* (2001) reported the major respiratory tract pathogens, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*, were susceptible to peppermint oil and its components menthol and menthone, but not 1,8-cineole. Menthol was the most effective of the peppermint components with a MIC range of 0.04–0.08% (w/v), followed by peppermint oil at 0.08–0.32%. Another respiratory tract pathogen, *Legionella pneumophila*, was also found to be susceptible to peppermint (Furuhata *et al.*, 2000).

Azuma *et al.* (2003) demonstrated the effectiveness of menthol against the gastrointestinal bacteria *Helicobacter pylori* at 0.5 mM (MIC), but found no inhibition with 1,8-cineole tested at concentrations ≤4 mM. Mahady *et al.* (2005) reported a methanol extract of peppermint as weakly active against 15 strains of *H. pylori* with an MIC range of 25–100 μg/mL. The reported effects of peppermint oil on *Escherichia coli* are mixed, possibly reflecting a differential susceptibility of various strains used and/or testing conditions (Pattnaik *et al.*, 1995; Arakawa and Osawa, 2000; Inouye *et al.*, 2001; Aridogan *et al.*, 2002; Mimica-Dukic *et al.*, 2003).

Fungicidal and antimicrobial activity. The fungicidal activity of peppermint oil was demonstrated in 11 of 12 fungi tested by Pattnaik *et al.* (1996), including *Candida albicans*, *Trichophyton mentagrophytes*, *Aspergillus fumigatus* and *Cryptococcus neoformans*, at an MIC range of 0.25–10 μL/mL. Peppermint extracts were shown to have a moderate effect against these and other pathologically relevant fungi in other studies as well (Guerin and Reveillere, 1985; Rai and Upadhyay, 1988; Blaszczyk *et al.*, 2000; Ezzat, 2001; Duarte *et al.*, 2005; Tampieri *et al.*, 2005).

Peppermint oil has also been shown to be an effective antimicrobial and pest control agent in food crops and foodstuffs (Mabrouk and El-Shayeb, 1980; Tassou *et al.*, 1995; Damayanti *et al.*, 1996; Montes-Belmont and Carvajal, 1998; Hirazawa *et al.*, 2000; Karanika *et al.*, 2001; Montes Belmont and Flores Moctezuma, 2001; Lee *et al.*, 2002; Al-Abbadi and Nazer, 2003; Araujo *et al.*, 2003; Choi *et al.*, 2003; Guynot *et al.*, 2003).

ANIMAL MODEL STUDIES

Gastrointestinal actions. The effects of peppermint on the muscular actions and secretory processes of the gastrointestinal (GI) tract have been examined in many different animal models. Aqueous extracts of *M. piperita* showed a significant, dose-dependent relaxation effect on isolated rabbit duodenum in a study by Mahmood *et al.* (2003). The effect of dried leaf extract was greater than fresh leaf extract and a decrease in spontaneous activity was also observed. Acetylcholine-induced contraction of the muscle was only slightly modified in the presence of peppermint extract suggesting the mechanism of relaxation was most likely not due to cholinergic

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antagonism. Further, the occurrence of an extract-induced relaxation after the addition of barium chloride (to increase spontaneous activity of the duodenum) suggests the relaxation was not due to adrenergic agonism.

Experiments by Hawthorn *et al.* (1988) using other isolated muscle preparations, including guinea-pig ileal smooth muscle, found that both menthol and peppermint oil at 78 µg/mL competitively inhibited the binding of the labeled calcium channel blockers ^{3}H-nitrendipine and ^{3}H-PN 200-110. The mechanism of action on GI smooth muscle relaxation appears to involve calcium channel antagonism. In a set of patch clamp experiments performed on rabbit jejunum and guinea-pig colon by Hills and Aaronson (1991), a reduction in calcium influx was also observed with peppermint oil. The calcium channel blocking action of peppermint and its components may influence the transport and secretory activity of enterocytes lining the intestinal lumen according to Beesley *et al.* (1996). In their experiment using intestinal sheets of Wistar rat jejunum, peppermint oil (1 and 5 mg/mL) applied to the mucosal side significantly inhibited active sodium-dependent glucose absorption and active transport of the amino acid glycine, while serosal application (1 mg/mL) inhibited acetylcholine induced secretion.

Peppermint oil and menthol have been shown to effectively stimulate choleretic activity (bile flow) in rats at doses of 25–50 mg/kg administered i.v. (Trabace *et al.*, 1992; Trabace *et al.*, 1994). Vo *et al.* (2003) observed a significant increase of bile flow in rats treated with 830 µL/kg by gavage, but not at lower doses (83 or 8.3 µL/kg). One possible mechanism may involve the ability of menthol to inhibit the binding of β-D-glucuronide, a cholestatic compound, to rat liver plasma membranes (Takacs and Vore, 1987).

In the large intestine of pigs, the production of volatile sulfur compounds by the metabolism of intestinal bacteria was significantly reduced with peppermint (Ushid *et al.*, 2002). The digesta of pigs supplemented with peppermint extract and L-methionine (to enhance methanethiol (MeSH) production) were sampled at 24 h. While the number of volatile sulfur-producing bacteria remained similar in each group, peppermint significantly decreased hydrogen sulfide, MeSH and ammonia production, but had no effect on the production of short chain fatty acids. In a study by Ando *et al.* (2003) of peppermint-fed Holstein steers, the ammonia nitrogen concentrations were also lowered and the total numbers of protozoa, including *Entodinum*, *Isotrica* and *Diplodium*, in the rumen were reduced. The digestibility of nutrients also tended to be higher in the steers given peppermint than in controls. In a feeding study of 72 New Zealand White rabbits, Ibrahim *et al.* (2000) compared the effects of different herbs, including peppermint, sweet basil, oregano, thyme and catnip, on growth and metabolic changes. Changes in weight gain, feed intake and biochemical parameters (red blood cell count, hemoglobin, packed cell volume, blood glucose, total protein, liver aspartate aminotransferase and alanine aminotransferase, urea, creatinine and total lipids) were only slightly affected by peppermint compared with all of the other herbs tested. The concentration of the antioxidant compound 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (HTCA) was, however, significantly higher (2.39 mol/L) in the milk of Holstein cows fed 1 kg peppermint per day for 14 days compared with cows fed either basil (2.21 mol/L), lemongrass (2.05 mol/L) or a basal diet without the addition of herbs (1.40 mol/L) (Uegaki *et al.*, 2001). In a study of 48 rats, Akdogan *et al.* (2004a) found that replacing their drinking water with 20 g/L of *M. piperita* tea for 30 days inhibited iron absorption, significantly reduced serum iron and ferritin levels, and increased unsaturated iron-binding capacity.

Hepatic and renal actions. A study of female Wistar rats by Maliakal and Wanwimolruk (2001) demonstrated the modulatory effects of peppermint tea on selected hepatic phase I metabolizing enzymes. Pretreatment with a 2% tea solution for 4 weeks ($n = 5$) significantly decreased the activities of cytochrome P450 isoforms CYP1A2 (24%) and CYP2E (48%) compared with an equal sized control group given free access to water. Similarly, peppermint oil (50–100 mg/kg) was also shown to inhibit CYP3A after 24 h and consequently improve the oral bioavailability of cyclosporine in rats (Wacher *et al.*, 2002). Rats given daily oral doses of 83 µL/kg peppermint oil for 28 days had significantly increased alkaline phosphatase (ALP) levels (262 ± 21 U/L, $n = 6$) compared with controls (181 ± 18 U/L, $n = 5$), but no increase in bilirubin, glutamyl transpeptidase (GGT) or alanine aminotransferase (ALT) and no changes in liver histology (Vo *et al.*, 2003). In a study comparing the effects of *M. piperita* and *M. spicata* teas, Akdogan *et al.* (2003) found no evidence of nephrotoxicity from *M. piperita* in male Wistar albino rats. In this experiment, rats ($n = 48$) were given water, 20 g/L *M. piperita* tea, 20 or 40 g/L *M. spicata* tea as their sole source of drinking water for 30 days. *M. spicata* tea significantly increased plasma urea, creatinine and TBARS and decreased the activities of superoxide dismutase, glutathione peroxidase and catalase compared with water; in contrast, none of these parameters were significantly altered in rats administered *M. piperita*. Although histopathological changes were observed in groups given either type of tea, i.e. hydropic degeneration of tubular epithelial cells, epithelial cells with picnotic nuclei and eosinophilic cytoplasm, tubular dilation and enlargements in Bowman capsules, these changes in the *M. piperita* group were slight compared with the *M. spicata* group. Similarly, a later experiment showed only minimal hepatocyte degeneration with *M. piperita* compared with *M. spicata* (Akdogan *et al.*, 2004b).

Chemopreventive potential. Peppermint appears to prevent or reduce carcinogenesis induced by various agents in some animal models. A powdered tobacco mixture (15 g) without or with 15 g peppermint leaves was painted onto cheek pouches of Syrian golden hamsters 3 times/week for 20 weeks by Samman *et al.* (1998). At week 30, the number of animals showing morphological changes and frank tumors was recorded. Compared with animals treated with tobacco plus peppermint, the non-mint containing tobacco mixture increased mucosal thickening ($n = 20/22$ in non-mint group vs 9/15 in mint-containing group), leukoplakia (20/22 vs 3/15) and frank tumors (19/22 vs 0/15) in the oral cavity. Overall 86.3% of the animals treated with non-mint tobacco were tumor-bearing at week 30, while those treated with the mint-containing tobacco mix exhibited no tumors (0%). The effects of an aqueous

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peppermint suspension on papillomagenesis of the skin induced by 7,12-dimethylbenz (a) anthracene (DMBA) in mice were studied by Sameena and Ashok (2001). Mice treated with peppermint topically for 2 weeks prior to and 2 weeks after DMBA application (just before application of 1% Croton oil) and mice fed peppermint beginning 2 weeks after DMBA (at the time of Croton oil application) showed a significant reduction in the cumulative number of papillomas compared with mice either topically treated with peppermint during the 2 weeks between DMBA and Croton oil application or untreated mice. These results suggest that the chemopreventive effect of peppermint on skin papillomas is most active during the promotional stage of carcinogenesis.

Samarth *et al.* (2001a; 2001b; 2002a; 2002b; 2004) and Samarth and Kumar (2003) explored the modifying effects of peppermint extracts against sublethal and lethal doses of gamma radiation in Swiss albino mice in several studies. Pretreatment with an aqueous extract of peppermint prior to whole body gamma irradiation at 4, 6, 8 and 10 Gy significantly increased the spleen weight and the number of endogenous spleen colonies compared with irradiated mice without pretreatment (Samarth *et al.*, 2001a). A daily oral dose of 1 g/kg administered for 3 days prior to irradiation at 8 Gy significantly increased hematological parameters (erythrocytes, leukocytes, hemoglobin, hematocrit) and improved the survival rate compared with irradiated control animals at 10 days post-irradiation (Samarth *et al.*, 2001b). The same protocol using peppermint extract (1 g/kg) and peppermint oil (40 µL/animal) decreased serum acid phosphatase and increased serum alkaline phosphatase compared with controls after irradiation, but the levels returned to normal within 5 d (Samarth *et al.*, 2001a; 2002b). Significant alterations in the intestinal mucosa of mice treated daily with 1 g/kg peppermint extract were observed within 20 days post-irradiation at 8 Gy (Samarth *et al.*, 2002b). Compared with controls, peppermint pretreatment increased villus height, total number of cells and mitotic cells, and decreased the number of goblet and dead cells. A regression analysis of the survival data in irradiated mice revealed that mice pretreated with peppermint were able to withstand a 1.78-fold higher dose of radiation than untreated mice (Samarth and Kumar, 2003).

Antiallergenic and antiinflammatory actions. A 50% ethanol extract of *M. piperita* leaves and stems administered orally to rats with nasal symptoms (induced by antigen challenge in actively sensitized animals) significantly inhibited sneezing at a dose of 300 mg/kg and nasal rubbing at 1000 mg/kg (Kamei *et al.*, 2000; Inoue *et al.*, 2001). In a study of flavonoid glycosides derived from *M. piperita*, only the fraction containing luteolin-7-O-rutinoside caused a dose-related inhibition of an antigen-induced nasal response at 100 and 300 mg/kg (Inoue *et al.*, 2002). These results suggest that peppermint may be helpful in alleviating the nasal symptoms of allergic rhinitis.

The immunomodulating effects of *M. piperita* and its constituents have also been examined in animal models. Intraperitoneal administration of peppermint oil, l-menthol and 1,8-cineole to guinea-pigs suppressed homologous passive cutaneous anaphylaxis mediated by IgE antibodies (Arakawa *et al.*, 1992; Arakawa and Osawa, 2000). At doses of 200 and 400 mg/kg, an ethanol extract of dried *M. piperita* leaves injected into male Swiss mice ($n = 5$/group) 30 min prior to topical xylene-induced ear edema significantly inhibited acute inflammation by 49–50% (Atta and Alkofahi, 1998). At 400 mg/kg, the extract also significantly reduced the weight of cotton granuloma in rats ($n = 6$) indicating a potential effect of peppermint on chronic inflammatory processes as well.

Laude *et al.* (1994) demonstrated the antitussive effect of menthol in guinea-pigs. The frequency of coughing in animals ($n = 13$) treated with 10 and 30 µg/L menthol vapors 5 min prior to an aerosolized citric acid challenge was reduced 28 and 56%, respectively, when compared with air (placebo). Similarly, Wright *et al.* (1997; 1998) showed that menthol had a direct action on guinea-pig bronchial smooth muscle ($n = 13$) where the bronchoconstrictors capsaicin and neurokinin A (NKA) were used to increase airway resistance *in vivo* in the presence of either air or menthol vapor (7.5 µg/L); after the removal of bronchial rings and precontraction with KCl or acetylcholine, relaxation was measured. Menthol significantly reduced both capsaicin- (51.3%) and NKA- (41.0%) induced airway restriction *in vivo*, and relaxed the KCl- and acetylcholine-induced bronchi constriction *ex vivo*.

Nervous system actions. Peppermint has been shown to affect both central and peripheral nervous system activity. Atta and Alkofahi (1998) examined the analgesic effects of an ethanol extract of *M. piperita* on Swiss mice ($n = 10$/group). Employing 0.7% acetic acid injected i.p. to induce pain observed by writhing, mice were first treated for 30 min with an oral dose of 200 or 400 mg/kg of the peppermint extract. The writhing in peppermint-treated animals was significantly lower by 38–44% compared with saline-injected controls. Using a hot plate test ($n = 10$) 400 mg/kg peppermint increased the latency of response to thermal stimulation, though the onset of analgesia was delayed (45–60 min) and temporary (subsided by 75 min).

The local anesthetic effect of 30–100 µg/mL menthol was demonstrated in rabbits using a conjunctival reflex test where an increased number of stimuli were necessary to provoke the reflex in a dose-dependent fashi on (Galeotti *et al.*, 2001). Examining other central nervous system effects of *M. piperita*, Della Loggia *et al.* (1990) used a lyophilized infusion, initially prepared with 50 g dried leaves in 500 mL hot water for 10 min, for their series of experiments with male CD1 albino Swiss mice. A moderate increase (32% at 60 min) in the onset of barbiturate-induced sleep was seen with a dose of 300 mg/kg. The same dose diminished exploratory behavior at 60 and 90 min by 31% and 17%, respectively, and depressed motor activity during this period (after an initial excitatory period), but had no effect on motor coordination up to 3 h post treatment. In contrast, Umezu *et al.* (2001) found that 400–800 mg/kg of peppermint oil injected intraperitoneally in mice significantly increased their ambulatory activity 10–40 min after administration. The isolated peppermint constituents 1,8-cineole, menthone, isomenthone, menthol, pulegone, menthyl acetate and caryophyllene also significantly increased ambulatory behavior. Further studies examining the behavioral effects of menthol suggest that dopamine may mediate the

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Table 1. Human studies examining the effects of orally ingested peppermint leaves (*Mentha piperita*)[a]

Reference	Delivery method	Subjects	Dose	Duration	Outcome
Westphal *et al.*, 1996	Tablet	70 patients with chronic dyspepsia	2 tablets (containing 100 mg peppermint plus other herbs) 3 times/day or placebo	14 days	Relief of symptoms after 1 week in treatment group compared with baseline. No change in placebo group.
Madisch *et al.*, 2001	Encapsulated powder	60 patients with functional dyspepsia (25–70 years)	Daily consumption of herbal mixture containing peppermint or placebo	4 weeks	Improved GI symptom score
Uehleke *et al.*, 2002	Tablet	12 patients with idiopathic dyspepsia	3, 6, or 9 tablets (containing 100 mg peppermint plus other herbs) after a meal	1 time	3 tablets were sufficient to reduce acute GI symptoms

[a] Not including studies of peppermint oil preparations.

activity-enhancing effect of peppermint (Umezu, 2002; 2003).

HUMAN STUDIES AND POTENTIAL APPLICATIONS TO HEALTH AND DISEASE

In Germany, peppermint leaf is licensed for use as a standard medicinal tea to treat dyspepsia. The German Commission E has also approved the internal use of the leaf for spastic complaints of the GI tract, gallbladder and bile ducts (Blumenthal *et al.*, 1998). Peppermint oil is approved for internal use in the event of spastic discomfort of the upper GI tract and bile ducts, irritable colon or irritable bowel syndrome (IBS), catarrahs of the respiratory tract and inflammation of the oral mucosa. Externally, the use of peppermint oil is approved for myalgia and neuralgia. With the exception of peppermint oil and IBS, studies providing evidence to either support or refute the applicability of peppermint as a treatment for many of these conditions in humans is somewhat limited (Table 1).

Effect on drug and nutrient bioavailability/metabolism. Dresser *et al.* (2002) examined the effects of peppermint oil (660 μL) on the bioavailability of the calcium channel blocking drug felodipine in 12 healthy subjects (18–43 years). Subjects fasted for 10 h prior to testing, refrained from using alcohol or medications, and were given either grapefruit juice, peppermint oil, ascorbyl palmitate or water in a single dose, randomized, 4-way cross-over study at 1 week intervals. Peppermint oil significantly increased the plasma felodipine concentration over time (30 ± 4 nmol h L, area under the curve, AUC) and its inactive metabolite dehydrofelopidine (59 ± 6 nmol h/L), which is formed by the action of the P450 cytochrome CYP3A4. The effect of grapefruit juice on the AUC of felodipine (37 ± 4 nmol .h/L) and dehydrofelodipine (59 ± 5 nmol .h/L) was similar to that of peppermint. However, unlike grapefruit juice, peppermint oil had no effect on the ratio of dehydrofelodipine/felodipine indicating a lack of inhibition at the primary step of felodipine metabolism, i.e. CYP3A4. Thus, although peppermint oil increased the bioavailability of this felodipine, the exact mechanism may not be identical to that of grapefruit juice.

Hurrell *et al.* (1999) found that the bioavailability of non-heme iron was reduced by peppermint tea. Compared with water, all the beverages tested in this study (coffee, herbal teas, black tea, and cocoa) inhibited iron absorption from a bread meal in a dose-dependent manner as estimated by measuring the incorporation of radiolabeled Fe (^{55}Fe or ^{59}Fe) into erythrocytes of adult subjects. Inhibition by black tea was 79–94%, peppermint tea was comparable at 84% followed by pennyroyal at 73%, cocoa at 71%, vervain 59%, lime flower 52% and chamomile 47%. When concentrations of the beverages were adjusted so that each contained the same amount of total polyphenols, black tea and peppermint were equally effective and their inhibitory actions were higher than the other beverages.

Gastrointestinal actions. In a study of 12 subjects, Goerg and Spilker (2003) found that 90 mg peppermint oil (in 0.10 mL capsule) did not significantly affect gastric emptying time (assessed by ultrasonography and H_2 breath tests) compared with a placebo, but did cause a complete inhibition of gallbladder emptying and significantly increased gallbladder volume during the refilling phase. Transit time through the small intestine was also significantly delayed with peppermint oil (85.0 ± 7.8 min) compared with placebo (65.0 ± 6.1 min). In contrast, Dalvi *et al.* (1991) studied 26 subjects fed a radiolabeled test meal either with or without the addition of peppermint oil (0.2 mL in 25 mL water) and found the gastric emptying rate was accelerated after the peppermint treatment.

Tate (1997) tested the efficacy of peppermint oil inhalation at a treatment for postoperative naused in 18 patients who underwent major gynecological surgery in a British hospital and received either no treatment (control), a placebo containing peppermint essence but no effective volatile constituents or peppermint. Although patients retained control over the frequency of administration, most inhaled the treatment only when feeling nauseous. Using a standardized descriptive ordinal scale survey to assess their degree of nausea, the reported nausea rate for the control and placebo groups was 100%, compared with 66% in the peppermint oil group, but the results were not statistically significant.

Peppermint oil has been found to reduce painful muscle spasms in patients undergoing endoscopy of the

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upper and lower GI tract as well as in people subjected to barium enema. Leicester and Hunt (1982) observed that peppermint oil relieved colon spasm in 20 patients undergoing colonoscopy within 30 s of administration. In a study of 445 patients undergoing colonoscopy, Asao *et al.* (2001) found that intracolonic administration of a 0.8% peppermint oil solution reduced the spasmolytic effect inherent in this procedure by 88.5% in the treated group ($n = 409$) compared with a reduction of 33.3% in the control group ($n = 36$). In a randomized controlled trial of 100 patients undergoing endoscopy of the upper GI tract, Hiki *et al.* (2003) compared the antispasmodic effects of peppermint oil administered intraluminally with hyoscine-N-butylbromide administered intramuscularly. The opening ratio (percent change in diameter of the pyloric ring before and after treatment) was significantly higher in the peppermint oil group while the contraction ratio (percent change in diameter between the maximally and minimally opened pyloric ring) was significantly lower. In addition, the time required for the disappearance of the contraction rings in the gastric antrum was shorter in the peppermint group (97.1 ± 11.4 s) than in the hyoscine-N-butylbromide group (185.9 ± 10.1 s).

When added to a barium sulfate suspension, Sparks *et al.* (1995) found that peppermint oil eliminated residual spasm in 60% of patients ($n = 70$) undergoing a double contrast barium enema (DCBE) examination compared with 35% of patients ($n = 71$) in a control group. In a study of 383 patients subjected to DCBE, Asao *et al.* (2003) compared the effects of scopolamine ($n = 105$), an antispasmolytic agent, with peppermint oil delivered either via a barium solution ($n = 91$) or enema tube ($n = 90$). The presence of spasm was evaluated on a second series of spot films. Compared with the non-treated group ($n = 97$), patients given either the drug or peppermint had a significantly higher rate of non-spasm examinations (13.4% vs 37.8–41.8%, respectively). The effects of the peppermint oil in the transverse and descending colon were comparable to the drug treatment; however, in the cecum and ascending colon, the effect of the peppermint oil was significantly stronger.

Pimentel *et al.* (2001) observed that manometry readings of lower esophageal sphincter pressures and contractile pressures of both upper and lower esophagus in eight patients with diffuse esophageal spasm, recorded before and after ingestion of a solution containing 5 drops peppermint oil in 10 mL water, were no different. However, peppermint oil completely eliminated simultaneous esophageal contractions in all patients and improved the number of multiphasic, spontaneous and missed contractions. The variability of amplitude and duration of esophageal contractions improved after peppermint oil treatment as well. Micklefield *et al.* (2000) also found a decreased number of duodenal contractions and contraction amplitudes in six patients measured with a manometer after the administration of a capsule containing 90 mg peppermint oil plus 50 mg caraway oil. In a follow up study of 24 patients, a capsule containing 90 mg of peppermint oil alone was also able to reduce significantly the frequency and duration of duodenal contractions and the duration of contractions in the gastric corpus, producing smooth-muscle relaxation in the stomach and duodenum (Micklefield *et al.*, 2003).

Abdominal pain and dyspepsia have been found to respond well to treatment with either peppermint leaves (Table 1) or oil. An herbal preparation containing peppermint leaves (in combination with extracts from bitter candy tuft, chamomile, caraway, licorice, lemon balm, angelica, celandine, and milk thistle) significantly improved the GI symptom score of 60 patients (mean age 46.8 years) with functional dyspepsia after 2 and 4 weeks of treatment in a randomized controlled trial by Madisch *et al.* (2001). This formulation was later shown to be as effective as the antispasmodic drug cisapride in relieving GI symptoms among patients whose initial symptoms were reported as moderate to severe (Rosch *et al.*, 2002). Uehleke *et al.* (2002) also reported improvement in patients with acute and chronic symptoms of dyspepsia after the administration of peppermint leaves (100 mg) in combination with other herbs (caraway, fennel, gentian). Similarly, Westphal *et al.* (1996) found that an herbal preparation (100 mL) containing 9.26 g peppermint leaves along with fennel (8.13 g), caraway (3.78 g) and wormwood (1.92 g) diluted and administered 20 min prior to meals 3 times daily for 2 weeks was more effective in alleviating symptoms than the antispasmodic drug metoclopramide. Significantly fewer patients taking the peppermint containing preparation ($n = 17$) complained of pain, nausea, heartburn, gastrospasms, retching, sensation of pressure and belching than those taking the drug ($n = 27$).

Two preparations of peppermint oil (90 or 36 mg) combined with caraway oil (50 mg or 20 mg, respectively) both reduced pain intensity and frequency over baseline measures in 213 patients with dyspepsia in an experiment by Freise and Kohler (1999). Compared with the antispasmodic cisapride, Madisch *et al.* (1999) found in a 4 week randomized controlled trial of 120 patients with functional dyspepsia, the effects of a peppermint oil (90 mg) plus caraway oil (50 mg) preparation were comparable with regard to pain score reduction and reduced frequency of pain. In another randomized clinical trial of the same formulation (90 mg peppermint oil plus 50 mg caraway oil) administered twice daily for 28 days in 96 patients with functional dyspepsia, May *et al.* (2000) observed a significant 40% reduction in pain intensity, 43% reduction in the sensation of pressure, heaviness and fullness, and 67% global improvement compared with baseline assessments. The respective changes for these measures in the placebo group were 21–22% lower than baseline values. May *et al.* (1996) also instituted a 4 week trial of 45 non-ulcer dyspepsia patients with the same preparation administered 3 times daily and found significantly improved reports on pain intensity and measures of pain frequency, medical prognosis, and severity of the disorder according to the Clinical Global Impressions Scale when compared with a placebo. The efficacy of this preparation was reportedly unaffected by *Helicobacter pylori*, which is present in approximately 50% of patients suffering from functional dyspepsia (May *et al.*, 2003). In a systematic review of studies examining the efficacy of herbal products in treating dyspepsia, Thompson Coon and Ernst (2002) concluded that the effects of peppermint and caraway were similar or greater in magnitude to conventional therapies and that the safety profile of this combination was encouraging.

Peppermint oil has also found to be efficacious in relieving symptoms attributable to irritable bowel

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syndrome (IBS) in both adults and children. A summary of intervention studies in IBS patients is presented in Table 2. In their meta-analysis of eight randomized controlled trials using peppermint oil as a treatment for IBS symptoms, Pittler and Ernst (1998) found a significant positive effect compared with placebo in five of the studies. Although the earlier peppermint oil trials were criticized for design flaws and questionable statistical analyses, later studies were considered more robust.

Respiratory tract actions. Eccles *et al.* (1988) found that menthol, but neither of its isomers isomenthol nor neomenthol, had a specific pharmacological action on nasal sensory nerve endings that was not related to its peppermint aroma. In their experiment, the inhalation of menthol significantly enhanced the nasal sensation of airflow in 40 subjects. The same sensation also occurred after 5 min of exposure to menthol vapor in 31 subjects from a different experiment, but nasal airflow resistance was not decreased (Eccles and Jones, 1983). Inhalation of menthol caused a significant reduction in the sensation of respiratory discomfort during flow resistant loading and elastic loading in 11 healthy subjects, but had no effect on breathing pattern or ventilation (Nishino *et al.*, 1997). Oral administration of 11 mg menthol (lozenges) did not decrease nasal decongestion in a randomized, double-blind, placebo-controlled trial of 62 subjects diagnosed with the common cold (Eccles *et al.*, 1990), but did cause a marked change in nasal sensation of airflow with a subjective sensation of nasal decongestion. According to Naito *et al.* (1991; 1997), the effect of menthol on nasal airflow sensation is due to its stimulatory effect on the palantine nerve and the sensory nerve endings of the nasal mucosa, which do not influence airflow resistance. Compared with placebo (pine oil or air), menthol did reduce coughing induced by inhalation of 33 μmol citric acid in 20 healthy subjects when given 5 min prior to each citric acid challenge (Morice *et al.*, 1994), suggesting its effectiveness as an antitussive agent. In contrast, Tamaoki *et al.* (1995) found no significant differences in vital capacity, forced expiratory volume or change in peak flow rate in a 4 week randomized controlled trial of 23 individuals with mild asthma given either nebulized menthol (10 mg) or placebo twice daily. However, using a different approach, Juergens *et al.* (2003) found the oral administration of 200 mg 1,8-cineole thrice daily for 12 weeks enabled 32 patients with steroid-dependent bronchial asthma to tolerate a 36% reduction in their daily prednisolone therapy (mean: 3.75 mg, range: 2.5–10.0 mg) compared with a 7% reduction (mean: 0.91 mg, range: 2.5–5.0 mg) with placebo. The same dose of 1,8-cineole also significantly inhibited the production of the arachidonic acid metabolites leukotriene 4 (40.3–57.9%) and prostaglandin E2 (31.3–42.7%) within 4 days in an *ex vivo* experiment of monocytes from both asthma patients ($n = 10$) and healthy subjects ($n = 12$) (Juergens *et al.*, 1998c). These results suggest a potential anti-inflammatory effect of peppermint oil when ingested over a period of time.

Analgesic actions. The application of peppermint oil to the skin of the forehead produced an analgesic effect in a randomized controlled trial of 32 healthy men (25 ± 2.1 y) by Gobel *et al.* (1994; 1995). Each

Table 2. Summary of studies examining the effects of peppermint oil in IBS patients

Study	Design	Subjects (*n*)	Intervention	Outcome
Rees *et al.*, 1979	Double-blind, placebo-controlled	18	12 × 0.2 mL capsules, 3/day	Relieved abdominal symptoms; patients felt better
Dew *et al.*, 1984	Double-blind, crossover	29	12 × 0.2 mL capsules, 3/day	Improved daily symptoms; no effect on bowel actions
Nash *et al.*, 1986	Double-blind, placebo-controlled	41	2 × 0.2 mL capsules, 3/day for 4 weeks	No difference in symptoms or stool frequency
Wildgrube, 1988	Uncontrolled	40	14 day course	Prolonged intestinal transit time; improved bloating, abdominal pain
Lawson *et al.*, 1988	Double-blind, crossover	25	0.2–0.4 mL capsules, 3/day for 4 weeks	No change in global symptoms or severity; small increase in defecation frequency
Lech *et al.*, 1988	Double-blind, placebo-controlled	42	200 mg, 3/day for 4 weeks	Improved symptoms compared with placebo
Liu *et al.*, 1997	Double-blind, placebo-controlled	110	1 × 187 mg capsule[a], 3–4/day for 4 weeks	Improved symptoms compared with placebo
Kline *et al.*, 2001	Double-blind, placebo-controlled	42 (children)	1 or 2 × 187 mg capsules[a], 3/day for 2 weeks	Improved severity of symptoms, including pain

[a] Capsules were manufactured by Tillots of Switzerland under the trademark name Colpermin. Each capsule contained 187 mg or 0.2 mL peppermint oil.

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subject received one of four different 3 min treatments consisting of ethanol preparations of either 10% peppermint plus 5% eucalyptus oils, 10% peppermint oil alone, 5% eucalyptus oil alone or ethanol plus oil essences (placebo) applied with a small sponge to the forehead and temples; treatment were separated by a 48 h washout period. Measures of pericranial muscle tension were significantly reduced by 30.6% with the combination of peppermint and eucalyptus oils and 28.8% with peppermint oil alone; however, only the peppermint oil preparation significantly reduced measures of pain sensitivity after thermal (40.3%) and ischemic (27.0%) stimuli to the head. The intensity of pain experienced by 41 patients (age 18–65 years) with tension-type headaches was significantly reduced with either the application of 10% peppermint oil or ingestion of 1000 mg acetaminophen in a follow-up study (Gobel *et al.*, 1996). There were no significant differences between the efficacies of these treatments, although a non-significant additive effect of simultaneous treatment was observed. It may be relevant to note here the electroencephalographic (EEG) data collected by Miki *et al.* (1997) showed significantly increased alpha and decreased beta waves in 15 healthy males (22–39 years) after peppermint inhalation, suggesting an activation of cerebral white matter. Satoh and Sugawara (2003) also reported a significant decrease in the magnitude of beta waves after peppermint inhalation.

ADVERSE REACTIONS/TOXICITY

Toxicology studies of peppermint oil and its components have been performed in animals. Histopathological changes in the white matter of the cerebellum were seen in rats ($n = 20$) given peppermint oil at doses of 40 and 100 mg/kg orally for 28 days, but no adverse effects were observed at 10 mg/kg (Thorup *et al.*, 1983a). No adverse effects were observed at 10 mg/kg. In a comparable 90 day rat study ($n = 28$), cyst-like spaces in the white matter of the cerebellum and hyaline droplets in the proximal tubules of the kidneys were observed in the highest dose group only (Spindler and Madsen, 1992). Interestingly, the extension of the cyst-like spaces was not aggravated with prolonged dosing in this study. Menthol administered to rats by gavage at 200, 400 and 800 mg/kg for 28 days significantly increased absolute and relative liver weights and the vacuolization of hepatocytes at all doses, although no sign of encephalopathy was observed (Thorup *et al.*, 1983b). At 80 and 160 mg/kg, pulegone administered for 28 days induced atonia, decreased blood creatinine levels, lowered body weight and caused histopathological changes in the liver and white matter of the cerebellum (Thorup *et al.*, 1983b). No adverse effects were observed with 20 mg/kg pulegone. Menthone given orally to rats ($n = 20$) at 200, 400 and 800 mg/kg for 28 days decreased creatinine and increased alkaline phosphatase in a dose-dependent manner, increased bilirubin and liver and spleen weights, and also caused histopathological changes in the white matter of the cerebellum in the two highest dose groups (Madsen *et al.*, 1986). The accumulation of protein droplets containing $\alpha_{2\mu}$-globulin in proximal tubular epithelial cells of rats ($n = 10$/group) was observed after the administration of either 500–1000 mg/kg 1,8-cineole or 800–1600 mg/kg limonene for 28 days, however, no histopathological changes were observed in the brain (Kristiansen and Madsen, 1995).

A review on the use of *M. piperita* oil, leaf extract, leaf and leaf water in cosmetic formulations by Nair (2001) concluded that each are considered safe, although the concentration of pulegone in products containing these ingredients should be limited to 1%. Although the toxicity of menthol is considered to be low, it has the ability to enhance the penetration and absorption of other agents contained in some formulations, thereby increasing the effective dose of these agents at the indicated intake. A few case study reports have described contact sensitivities to peppermint oil and its components in topical and oral preparations (Dooms-Goossens *et al.*, 1977; Andersen, 1978; Morton *et al.*, 1995; Bonamonte *et al.*, 2001), but a patch test study of 4000 patients by Kanerva *et al.* (2001) found that menthol and peppermint oil provoked neither allergic nor irritant reactions.

Akdogan *et al.* (2004c) reported increased follicle-stimulating hormone and luteinizing hormone levels and decreased testosterone levels in rats given 20 g/L peppermint tea in place of their drinking water. As opposed to *M. spicata* tea, the only effect of *M. piperita* on testicular tissue was segmental maturation arrest in the semniferous tubules.

There are no chronic toxicity studies of peppermint in humans, although the German Commission E (Blumenthal *et al.*, 1998) reports that the use of peppermint oil is contraindicated in patients with bile duct, gallbladder and liver disorders. Caution is also recommended for the use of peppermint oil capsules in patients with GI reflux, hiatal hernia or kidney stones.

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