An Evidence-based Systematic Review of Peppermint (*Mentha piperita*)

Natural Standard Research Collaboration

1. NOMENCLATURE

A. Common name(s)

- Peppermint

B. Etymology

- Peppermint, like most species of mint, derives from the Latin *mentha*, meaning “mint,” which in turn originated from the Greek *Minthē*, the name of a nymph in ancient Greek mythology. The “pepper” component derives from the genus name *Piperita*, referring to the strong, peppery taste. *Piperita* originated from the Sanskrit *papali*, “pepper.”

C. Ethnic names

Arabic	eqama, nana, nana al-fulfuli
Bulgarian	djodjen, dzhodzhen, giozum, menta
Chinese	pak hom ho
Croatian	paprena metvica
Czech	máta, máta peprná, mentol
Danish	pebermynte
Dutch	pepermunt
Estonian	piparmünt
French	menthe anglaise, menthe poivrée, sentebon
German	edelminze, englische minze, minze, pfefferminze
Greek	diosmos, dyosmos, menta
Greek (Old)	hedyosmon, minthe
Hebrew	menta, menta harifa, na'na', nana
Hindi	podina, pudina
Hungarian	borsmenta, borsos menta, fodormenta, menta
Irish	milseán miontais, miontas, mismín
Italian	menta pepe, menta peperina, menta piperita
Japanese	hakka, midori-hakka, minto, oranda-hakka, pepaminto, seiyō-hakka, seiyo-hakka, supea-minto
Korean	bagha, heobu, hobu, mintu, pakha, pepeo-mintu, pepo-mintu, spio-mintu, supieo-mintu
Latin	caromenta, menta, mentastrum, puledium, puleium, sisimbrium

Lithuanian	mėta, pipirinė mėta, pipirmėtė
Norwegian	peppermynte
Polish	mieta pieprzowa
Portuguese	hortelã-pimenta
Russian	myata perechnaya
Slovak	mäta kučeravá, mäta pieporná
Spanish	hierbabuena, menta, piperita
Swahili	pereminde
Swedish	pepparmynta
Thai	bai saranai, peppeort-mint, saranae
Turkish	gercek nane, nane
Urdu	lana, pudina
Vietnamese	bac hà, húng dũi, húng giũi, húng nhũi, rau thom

D. Family name

- Lamiaceae (mint)

E. Genus name

- *Mentha*

F. Species names

Species name	Common name	Origin	Physical properties
Mentha piperita L. (Synonyms: *Mentha* × *piperita* L., *Mentha citrata* Ehrh., *Mentha lavanduliodora* ined., *Mentha* × *piperita* var. citrata (Ehrh.) Briq., *Mentha pyramidalis* Ten.)	Peppermint	central and southern Europe	Short, distinctly stalked leaves with purplish stems, growing 2-4 feet in height. The plant has reddish, clustered flowers and a distinct peppermint odor, with a pungent, burning taste.
Mentha x *piperita officinalis* L.	White peppermint	Europe	Perennial, growing to approximately three feet in height. Whole plant emits a pleasant odor and has a mild peppermint taste.
Mentha x *piperita vulgaris* L.	Black peppermint	Europe	Perennial, growing to approximately three feet in height. Leaves have a strong, pungent, peppermint aroma and flavor.

2. HISTORY/CULTURAL/CULINARY USES

A. History

- Peppermint (*Mentha* x *piperita* L.) is a sterile hybrid or cross of spearmint (*Mentha spicata*) and water mint (*Mentha aquatica*), which was first documented as sprouting in a field of spearmint growing in England in 1696. Since then, it has been intensively cultivated for its fragrant oil. It is a perennial herb, growing to the size of 1m along stream banks and wastelands throughout much of Europe and North America. Peppermint oil is obtained by steam distillation from the fresh aboveground parts of the flowering plant of *Mentha* x *piperita* L.
- The name peppermint comes from the Latin *piper*, meaning “pepper,” and *Minthē*, the name of a nymph in Greek or Roman mythology who was metamorphosed into a plant. Records from ancient Egypt, Greece, and Rome show that other members of the family, especially spearmint, have been used medicinally for centuries (1). Peppermint has been used traditionally for gastrointestinal disorders, including irritable bowel syndrome, indigestion, and nausea, as well as colds,

headache, and cramps (2). Peppermint is also a popular culinary ingredient, figuring prominently in a number of dishes around the world, many of which are desserts and confectionaries. Robert Bentley reiterated peppermint's use as a carminative, stimulant, antispasmodic, and relief from gastrointestinal disorders. Hildegard of Bingen, the 12th-Century German nun and herbalist, championed mint for digestive disorders, although the exact species is unclear. Dioscorides and Culpeper had different beliefs about the various merits of mint, although the exact species is unclear.

- Peppermint is used extensively as a flavoring agent (3-17). The largest consumers of peppermint oil are manufacturers of chewing gum, toothpaste, mouthwash, and pharmaceuticals. In dentistry, peppermint may also be used as a debonding agent (18; 19). Menthol, a secondary alcohol of peppermint, is widely employed in the food and pharmaceutical industries as a cooling or soothing compound and as an odorant (20).
- There has been clinical study on peppermint-containing products that were used as an antispasmodic and to treat irritable bowel syndrome (IBS), breast tenderness, dyspepsia, headache (topical), abdominal distention, abdominal pain, bad breath, cognitive improvement (in brain injury), common cold, dental plaque, hot flashes, mental performance and alertness, postherpetic neuralgia, postoperative nausea (inhalation), pruritus, stress, stroke recovery, tuberculosis, and urinary tract infection. According to the German Commission E monographs, peppermint oil (as well as peppermint leaf) has been used internally as an antispasmodic (upper gastrointestinal tract and bile ducts) and to treat irritable bowel syndrome, catarrh of the respiratory tract, and inflammation of the oral mucosa. Externally, peppermint oil has been used for myalgia and neuralgia. According to the German Commission E, peppermint oil may also act as a carminative, cholagogue, antibacterial, and secretolytic, and it has a cooling action.

B. **Culinary use by country/region**

i. North America

- **United States**: Peppermint leaves are used to add a minty flavor to many dessert foods, double mint tea, mint syrup, and peppermint cream, which goes well with hot chocolate. Peppermint candies are used to make cookies. Peppermint candies and gums get their minty taste from commercially available peppermint oils. Mint jelly is often an accompaniment to lamb dishes, particularly during the Christmas holiday season.
- **Mexico**: A Mexican soup with meatballs, called *albondigas*, may use mint for flavoring, although it is unclear which variety is used.

ii. South America

- **Brazil**: In Brazil, peppermint may be added to sauces, cracker, omelets, and meats. Mint jelly, referred to as *geléia de hortelã*, is traditionally served with meat cutlet or mutton dishes.

iii. Europe

- **Austria**: Fresh mint is a vital ingredient in *Kärntner Kasnudeln* in Southern Austria. *Kärntner Kasnudeln* are big dumplings stuffed with cheese, potatoes, and a mixture of herbs. The herb mix contains a particular variety of Carinthian mint with a scent similar to caraway.
- **England**: In Britain, as well as in the rest of Europe, true peppermint has been largely reserved for use in confectionaries and sweet liquors for its pungent and cooling properties, which purportedly serve to balance out the sweetness of the sugar. For these purposes, pure essential oil is employed instead of peppermint leaves, because the leaves may impart an astringent or bitter flavor. Mint leaves are commonly added to potato and pea dishes in England. Also, mint sauce is popular both hot and cold and served with meat dishes, such as lamb.
- **France**: In *haute cuisine*, peppermint is used as an ingredient in the recipe for *saumon à la Humbertier*, or poached salmon. The fish is poached in white wine and tarragon vinegar with bay leaf, thyme, onions, carrots, and salt. Peppermint is often used for confectionaries and desserts, including as an addition to *mousse au chocolat* (chocolate mousse).
- **Germany**: *Pfefferminzlikör* is a cordial that uses peppermint. Rumple Minze® is a brand of German liqueur best known for its peppermint schnapps. Peppermint schnapps is either served chilled (occasionally as a digestif) or may be used in cocktails. It may also be combined with chocolate.
- **Greece**: Although it is unclear which variety is employed, a pie dish called *hortopitta* that contains fillings such as spinach and rice typically includes mint. A cheese called *haloumi* also contains mint.
- **Italy**: The Romans purportedly used peppermint leaves as a condiment. An 18th-Century *salsa al tonagusto* recipe includes peppermint, along with chilies, oregano, garlic, fennel, and anchovies, pounded together with vinegar, oil, and lemon juice. This sauce may be served with olives. Around 1815, the liqueur *Amaro Felsina Ramazzotti* was invented, incorporating peppermint, gentian, and rhubarb, among other botanicals.
- **Scotland**: "Sweeties," such as white peppermint taffy Hawick balls, Berwick cockles (with pink stripes and shaped like shells), Jeddart snails (dark brown toffees), and cheugh (chewy) jeans, are made using peppermint flavor.

iv. Asia

- **China**: Young shoots of fresh peppermint are used in China as a spice or for tea.
- **India**: Fresh mint is usually added to chutney, which is a dip that is served with fried foods, such as *pakoras*, and stuffed pastry, such as *samosas*. Coconut chutney occasionally incorporates mint and may be used as a dip for *idlis* (steamed rice cakes). Dried mint is used in vegetable and meat cutlets called *koftas* and for seasoning in kebabs, too. Mint is often added to yogurt and vegetables, such as cucumber, to make the Indian dish *raita*.
- **Thailand**: Local mint varieties found in Thailand are generally milder than true European peppermint. Fresh mint leaves are used along with other fresh vegetables and herbs, such as coriander and basil, in the preparation of Thai meat salad, a dish that originated from the northeast region of the country.
- **Vietnam**: Fresh mint leaves are used to decorate virtually every Vietnamese dish to the extent that it has become a characteristic of Vietnamese food. Mint is commonly added to salads, which are served with most dishes in Vietnamese cuisine.

v. Middle East

- **Iran**: Iranian cuisine knows several highly sophisticated recipes employing mint; some of these were later transferred to northern India, e.g., *Mughal*-style *biryani*.

- **Lebanon**: Fresh mint leaves are often used in Turkish cooking together with yogurt; similar concoctions are in use in Lebanon and Israel. The exact type of mint used, however, is unclear.
- **Turkey**: Fresh mint leaves are often used in Turkish cooking together with yogurt. A yogurt and mint spread uses fresh peppermint, garlic, olive oil, yogurt, and salt, and it is served with bread.

vi. Africa

- **North Africa (general)**: Soups consisting of water, oil, tomatoes, garlic, eggs, peppermint, and bread may be served. Peppermint leaves may accompany tomatoes, peppers, cheese, olives, vinegar, and salt for salads. Falafel may be made with dill, peppermint, parsley, onions, beans, or peas, pressed with sesame seeds and fried.

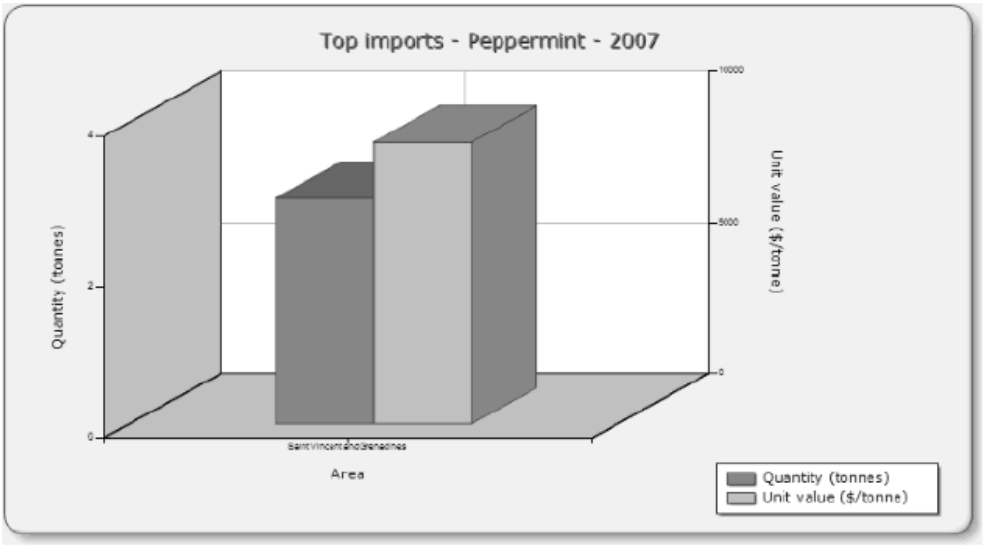
C. Consumption information by country/region

i. Per capita consumption

- Per capita consumption data for peppermint are currently not available through the U.S. Department of Agriculture (USDA) Economic Research Service Food Availability (Per Capita) Data System, the Food and Agriculture Organization of the United Nations Agricultural Trade Domain (FAOSTAT), the International Trade Centre (UNCTAD, WTO), or the USDA Foreign Agricultural Service.

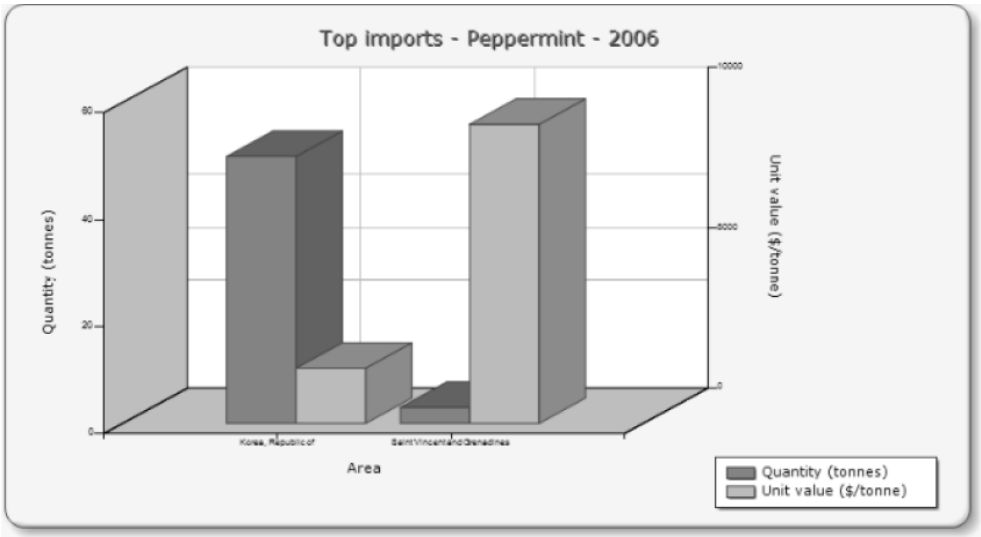
ii. Consumption trends by time

- Consumption trend statistics for peppermint are currently not available through the U.S. Department of Agriculture (USDA) Economic Research Service Food Availability (Per Capita) Data System, the International Trade Centre (UNCTAD, WTO), or the USDA Foreign Agricultural Service.



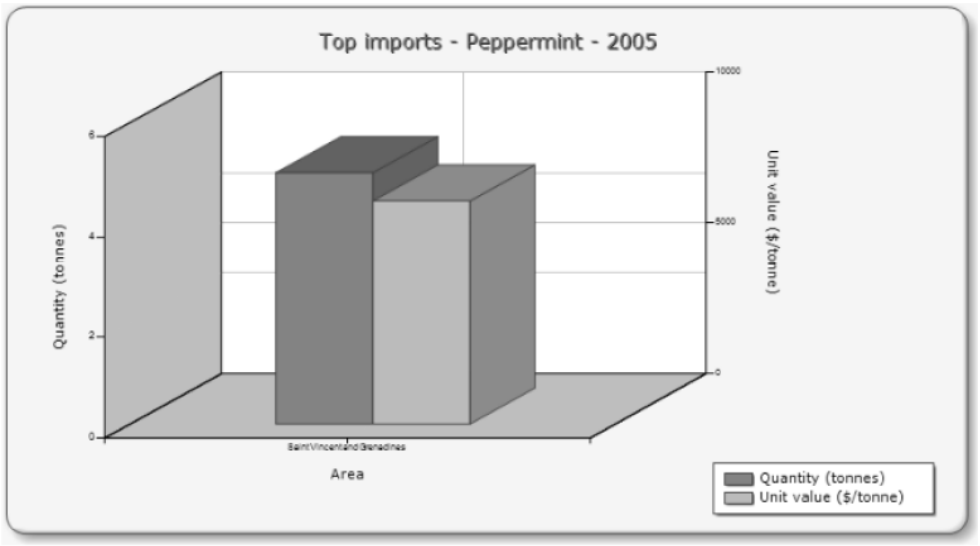
Rank	Area	Quantity (tonnes)	Flag	Value (1000 $)	Flag	Unit value ($/tonne)
1	Saint Vincent and Grenadines	3	F	28	F	9333

Source: Food and Agriculture Organization of the United Nations



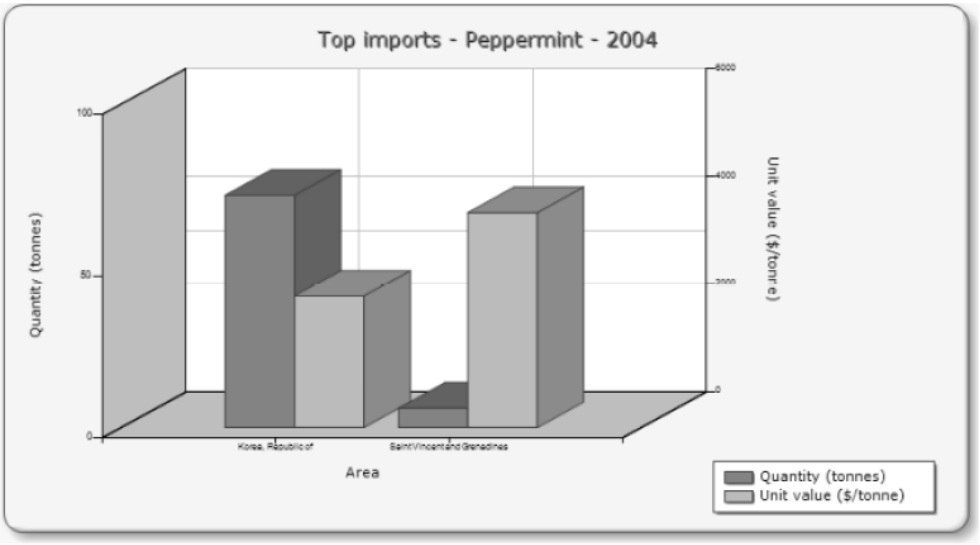
Rank	Area	Quantity (tonnes)	Flag	Value (1000 $)	Flag	Unit value ($/tonne)
1	Korea, Republic of	50		86		1720
2	Saint Vincent and Grenadines	3		28		9333

Source: Food and Agriculture Organization of the United Nations



Rank	Area	Quantity (tonnes)	Flag	Value (1000 $)	Flag	Unit value ($/tonne)
1	Saint Vincent and Grenadines	5		37		7400

Source: Food and Agriculture Organization of the United Nations



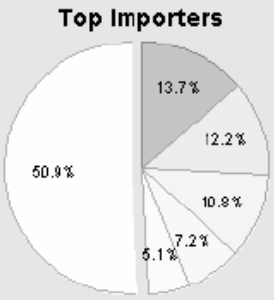
Rank	Area	Quantity (tonnes)	Flag	Value (1000 $)	Flag	Unit value ($/tonne)
1	Korea, Republic of	72		176		2444
2	Saint Vincent and Grenadines	6	*	24		4000

Source: Food and Agriculture Organization of the United Nations

Top Importers in the selection (View Map)

Reporter Title	Trade Value
United Kingdom	$90,803,122
Singapore	$81,174,089
USA	$71,574,065
Germany	$47,580,000
Mexico	$34,128,244
Other reporters	$337,533,361

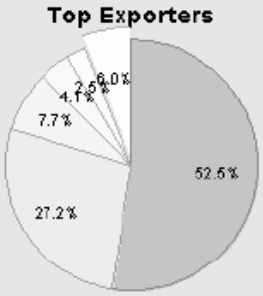
Total Import: $662,792,881



Top Exporters in the selection (View Map)

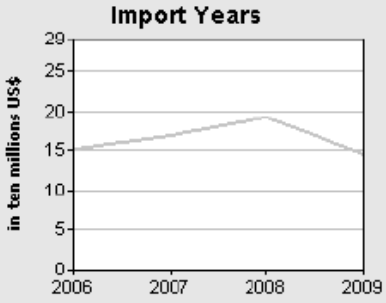
Reporter Title	Trade Value
USA	$415,685,195
India	$215,171,404
Singapore	$61,382,149
United Kingdom	$32,157,893
France	$19,977,318
Other reporters	$47,732,767

Total Export: $792,106,726



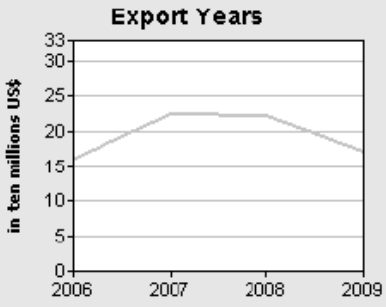
Recent Import Years in the selection

Period	Trade Value
2009	$146,648,953
2008	$192,901,491
2007	$170,442,670
2006	$152,799,767



Recent Exports Years in the selection

Period	Trade Value
2009	$173,853,650
2008	$225,509,107
2007	$226,902,895
2006	$165,841,074



Source: United Nations Commodity Trade Statistics Division

D. Harvest and storage information

- Peppermint is harvested just before the plant flowers, which, according to local conditions, is usually in middle to late summer. A first-year crop is cut with a sickle to prevent injury to the plants. Older crops may be harvested using scythes when the plants are sturdier. The herb is then raked into loose heaps for transportation. After harvesting, peppermint is distilled with water and low heat to produce an oil. Peppermint intended for drying is cut shortly above the stalk ends, taking care to avoid dry, shriveled leaves. The herb is then tied in bunches and dried.
- Optimal storage of fresh peppermint leaves is being wrapped in a damp paper towel in a plastic bag in the refrigerator. Dried peppermint should be stored in a tightly sealed container in a cool, dark, dry location. Fresh peppermint should keep in the refrigerator for several days, while dried peppermint should retain freshness for 9-12 months.

3. TRADITIONAL/ETHNIC MEDICINE

A. Medicinal uses by tradition/culture

i. Formula preparations

- Peppermint leaf may be used fresh, dried, or preserved in alcohol. Formulations include capsules, tablets, fresh extracts, infusions, teas, and tinctures. The essential oil of peppermint may be used in aromatherapy. It is also used in combination

formulas with other herbs. Poultices and other external preparations, such as footbaths, have also been employed. According to the German Commission E, an average daily dose of peppermint oil is 6-12 drops internally, acute administration of 0.2mL or 0.6mL enterically coated for irritable colon, 3-4 drops in hot water for inhalation, or, externally, a few drops rubbed into the affected area. Preparations include 5-20% semi-solid and oil preparations, 5-10% aqueous-ethanol preparations, and 1-5% essential oil nasal ointments. According to the German Commission E, an average daily dose of peppermint leaf is 3-6g of leaf or 5-15g of tincture.

i. Medicinal uses

- There has been clinical study on peppermint-containing products that were used as an antispasmodic and to treat irritable bowel syndrome (IBS), breast tenderness, dyspepsia, headache (topical), abdominal distention, abdominal pain, bad breath, cognitive improvement (in brain injury), common cold, dental plaque, hot flashes, mental performance and alertness, postherpetic neuralgia, postoperative nausea (inhalation), pruritus, stress, stroke recovery, tuberculosis, and urinary tract infection. According to the German Commission E monographs, peppermint oil (as well as peppermint leaf) has been used internally as an antispasmodic (upper gastrointestinal tract and bile ducts) and to treat irritable bowel syndrome, catarrh of the respiratory tract, and inflammation of the oral mucosa. Externally, peppermint oil has been used for myalgia and neuralgia. According to the German Commission E, peppermint oil may act as a carminative, cholagogue, antibacterial, and secretolytic, and it has a cooling action.

ii. Traditional uses by culture

- **General**: Peppermint is often used to treat congestion, the common cold, and headaches, and is employed as a treatment for gastrointestinal disorders across many cultures around the world. Preliminary studies have also tested the effects of peppermint for cancer (21), fever (22), respiratory disorders (23; 24), and nausea gravidarum (25).
- **American medicine**: In southern Appalachian folk medicine, peppermint teas were used as a carminative and to treat dyspepsia. An herbalist by the name of Clarence Gray (1917–1991) hypothesized that herbs could cure all diseases, including cancer; this had an influence throughout the southern Appalachian region. Peppermint is purportedly used in African-American traditional medicine as an ingredient in hot drinks to treat colds and congestion. The progenitors of naturopathic physicians (i.e., "eclectic physicians") used peppermint for coughs, headache, gastrointestinal disorders, and bronchitis, as an adjuvant to laxatives and an antispasmodic, and for flavoring.
- **Mohammedan medicine**: According to American herbalist Dr. James A. Duke, peppermint, bitter almond, vinegar, and starch were all combined to make a plaster for coughs.
- **Ayurveda**: Peppermint has many uses in Ayurvedic medicine, including the treatment of fainting, sunburn, sore throat, the common cold and flu, headaches, and hay fever. Peppermint is purportedly recommended for *pitta* constitutions and is said to clear the mind and promote emotional harmony. It is a purported stimulant, diaphoretic, analgesic (for conditions such as toothache), and carminative.
- **Chinese medicine**: In traditional Chinese medicine, peppermint is believed to rise to the head and exert a pungent, cooling effect, and it is used for the treatment of colds and cold-associated headaches. It is prepared as a boiled broth, which is then consumed hot or warm. Peppermint dabbed on the temples or under the nose, or consumed in tea, is also used for headaches. Peppermint is used as an herb to treat respiratory disorders.
- **European medicine**: In Europe, peppermint was first included in the London Pharmacopoeia in 1721 and since then has been used in England for medicinal purposes. The British Pharmacopoeia lists two preparations of peppermint, Peppermint Water and Spirit of Peppermint. According to the German Commission E monographs, peppermint oil (as well as peppermint leaf) has been used internally as an antispasmodic (upper gastrointestinal tract and bile ducts) and for irritable bowel syndrome, catarrh of the respiratory tract, and inflammation of the oral mucosa. Externally, peppermint oil has been used for myalgia and neuralgia. Peppermint oil may act as an antispasmodic, carminative, cholagogue, antibacterial, and secretolytic, and it has a cooling action.
- **Modern (Western) herbal medicine**: Contemporary herbalists use peppermint externally for pruritus and inflammation, and internally as a sleep aid and for colds, coughs, flu, headache, gastrointestinal disorders, fever, menstrual cramps, motion sickness, and nausea gravidarum.

iii. Properties

- Analgesic (21), anesthetic (21), anti-inflammatory (26), antimicrobial (21; 27-30), antioxidant (21), antispasmodic, carminative (31), catarrh, chemopreventive (21), cholagogue, immunomodulation (21), insecticide (32-36), odorant (20), pest repellent (37-39), radioprotectant, secretolytic, sleep aid (40), spermicide (41), and stimulant (42).

iv. Other uses

- Anorexia (22), anxiety, cardiovascular disease (43), dental procedures, detoxification (arsenic) (44), dysmenorrhea, fatigue, gallbladder disorders (45), hirsutism (46), hypertension (47), lice (*Pediculus humanus capitis*) (48-51), liver disorders (52), and mental disorders (53).

B. Select available consumer products

Product name	Manufacturer	Price	Manufacturer's suggested health benefits
Peppermint Oil	Solaray	$21.99	Intestinal support
PeppermintZ Intestinal Aid	Nature's Life	$14.95	Relieves gastrointestinal discomfort in the intestines
Peppermint Plus	Enzymatic Therapy	$17.50	Digestive health
Peppermint Gels with Ginger and Fennel Oils	NOW® Foods	$12.99	Digestive health

Product name	Manufacturer	Price	Manufacturer's suggested health benefits
Neutralizing Cordial - Peppermint	Eclectic Institute Inc.	$11.60	Digestive health
Peppermint Oil	Now® Foods	$11.99	Aromatherapeutic
Peppermint Leaves	Nature's Way	$5.49	Digestive health
Tummy Teas, Organic Peppermint Loose Tea	Heather's Tummy Care	$12.95	Dietary management of irritable bowel syndrome
Peppermint Leaf	Gaia Herbs	$11.59	Digestive health
Peppermint Spirits	Herb Pharm	$11.80	Digestive health
Tummy Tamers, Peppermint Oil	Heather's Tummy Care	$12.95	Dietary management of irritable bowel syndrome
Organic Peppermint Herbal Tea	Traditional Medicinals	$4.49	Digestive health

4. CLINICAL INFORMATION

A. Evidence based review of peppermint for specific health conditions

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Peppermint oil, fiber, or antispasmodics	Capsules, 450-748mg daily in 2-3 divided doses	Meta-analysis and systematic review	4 trials (54-57), 392 patients	Randomized, placebo controlled trials; the proportion of women in each trial ranged from 40% to 76%.	1-3 months	Global symptoms of irritable bowel syndrome; abdominal pain	NA	Only three trials scored 4 or more on the Jadad scale.	Ford AC, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, Moayyedi P. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ. 2008 Nov 13;337:a2313.	Yes	Large	NA	NA
Irritable bowel syndrome (IBS)	Pharmacologic agents for IBS, including Chinese herbal treatments and psychotropic drugs and enteric-coated peppermint oil (Colpermin®)	One 187mg capsule 3-4 times daily	Systematic review	1 trial (54)	Randomized, double-blind, placebo controlled, parallel, or crossover trials of adult patients with outcomes of improvement in global or irritable bowel-specific symptoms	One month	Severe symptoms of abdominal pain, abdominal distention, stool frequency, borborygmi, and flatulence	NA	Only one peppermint trial, in which randomization and blinding were not described clearly	Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med. 2000 Jul 18;133(2):136-47.	NA	NA	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Peppermint oil monopreparations (Colpermin® and Elanco LOK® enteric-coated capsules)	Capsules, 0.2-0.4mL three times daily	Meta-analysis and systematic review	Meta-analysis: 175 (5 trials) (55; 58-61) Review: 3 trials (62-64)	Studies using monotherapy preparations for treating IBS; five double-blind, randomized, controlled trials	2-6 weeks; six months for peppermint oil plus stress management program (64)	Global improvement of symptoms	NA	Most studies used crossover design without a washout period, although this may have decreased the measured benefits of peppermint. One reviewed trial (64) was not double-blinded or placebo controlled and also used a stress management program, so not discussed separately in this table for IBS.	Pittler, M. H. and Ernst, E. Peppermint oil for irritable bowel syndrome: a critical review and meta-analysis. Am J Gastroenterol 1998;93(7):1131-1135.	No	None	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil (Mintoil®)	Two 225mg capsules twice daily	Randomized controlled trial	57	IBS patients (confirmed by Rome II and investigations) without bacterial overgrowth in small intestine, lactose intolerance, or celiac disease	Four weeks	IBS symptoms, including abdominal bloating, abdominal pain or discomfort, diarrhea, constipation, a feeling of incomplete evacuation, pain at defecation, passage of gas or mucus, and urgency at defecation	5	Good study design with adequate description of randomization, blinding, and dropouts	Cappello, G., Spezzaferro, M., Grossi, L., Manzoli, L., and Marzio, L. Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. Dig Liver Dis 2007;39(6):530-536.	Yes	Medium	30% (week 4), 36% (week 8)	3 (week 4), 4 (week 8)
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil (Colpermin®)	One capsule three times daily	Randomized controlled trial	60	Outpatients with IBS	Eight weeks	Abdominal pain and discomfort	5	Good study design with adequate description of randomization, blinding, and dropouts	Merat S, Khalili S, Mostajabi P, Ghorbani A, Ansari R, Malekzadeh R. The Effect of Enteric-Coated, Delayed-Release Peppermint Oil on Irritable Bowel Syndrome. Dig Dis Sci. 2009 Jun 9.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Enteric coated peppermint oil (Colpermin®)	Patients weighing >45kg: two capsules (187mg per capsule) three times daily. Patients weighing 30-45kg: one capsule three times daily	Randomized controlled trial, double-blind	50	Children (eight years of age or older, >30kg of body weight) meeting Manning or Rome criteria for IBS with symptoms for the previous two weeks. Patients were not receiving other medications for IBS and were free of other chronic diseases.	Two weeks	Abdominal pain and other symptoms, such as heartburn, gas, urgency of stools, belching, or stool consistency	3	Unclear methods of randomization and blinding	Kline, R. M., Kline, J. J., Di Palma, J., and Barbero, G. J. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr. 2001;138(1):125-128.	Yes	Medium	56%	2
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil (Colpermin®)	One 187mg capsule 3-4 times daily, 15-30 minutes before meals	Randomized controlled trial	110	Patients with IBS confirmed by clinical diagnosis and investigations	One month	Severe symptoms of abdominal pain, abdominal distention, stool frequency, borborygmi (stomach growling), and flatulence	4	Unclear methods of randomization	Liu JH, Chen GH, Yeh HZ, Huang CK, Poon SK. Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol. 1997 Dec;32(6):765-8.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil (Colpermin®) with l-hyoscyamine (Egazil® tablets)	One or two 0.2-0.4mL capsules three times daily with hyoscyamine	Randomized controlled trial; cross over design	40	Patients with IBS who were not pregnant or lactating and did not have liver disease, active peptic ulcer disease, previous gastrectomy or vagotomy, concomitant need of anticholinergic treatment including tricyclic antidepressants, a contraindication to anticholinergic drugs	Two weeks	Symptom scores based on a five-point scale	3	Study limitations include the short duration, small sample size, and lack of use of a standardized assessment scale. Methods of randomization and double-blinding were not described.	Carling L, Svedberg L, and Hultsen S. Short term treatment of the irritable bowel syndrome: a placebo-controlled trial of peppermint oil against hyoscyamine. Opuscula Med 1989;34:55-57.	Yes	Small	NA	NA
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil	Three 0.2-0.4mL capsules daily	Randomized controlled trial, cross over design	25	Subjects with episodes of abdominal pain lasting for several days and recurring at least six times per year, abdominal distention, pain relief with defecation, and increased stool frequency; excluded patients with constipation as the primary symptom, coexisting disorders, or significant heartburn or reflux	Four weeks	IBS symptoms	4	Limitations include the small sample, unclear dose, and inadequate description of study design. Dropouts were not reported, but randomization, double-blinding, and methods were appropriate.	Lawson MJ, Knight RE, Tran K, and et al. Failure of enteric-coated peppermint oil in the irritable bowel syndrome: a randomized, double-blind crossover study. J.Gastroenterol Hepatol 1988;3(3):235-238.	No	None	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil	Three 0.2mL capsules daily (patients with severe symptoms received six capsules daily)	Randomized controlled trial, crossover design	18	Patients diagnosed with IBS	21 days	Abdominal discomfort, stool frequency, and distention	3	The small sample size, short study duration, inadequate description of randomization and blinding, and the lack of between-group comparisons were the main limitations of this study.	Rhodes J, Evans BK, and Rees WD. Peppermint oil in enteric coated capsules for the treatment of irritable bowel syndrome: a double blind controlled trial. Hepato-Gastroenterology 1980;27(Suppl):25.	Yes	Medium	NA	NA
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil (Colpermin®)	Dose not specified	Randomized controlled trial	60	IBS patients (80% female)	Six-week treatment phases preceded by two-week washout phases	Self-scored pain, bowel movements, transit time, accompanying symptoms, and general well-being	2	Blinding status, methods, and dropouts were not clearly described. Abstract.	Schneider MM and Otten MH. Efficacy of Colpermin in the treatment of patients with irritable bowel syndrome (abstract). Gastroenterology 1990;98(5):A389.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Enteric-coated peppermint oil (Colpermin®)	Two 0.2mL capsules three times daily	Randomized controlled trial	41	IBS patients diagnosed by standard methods	Two weeks	Symptoms recorded on a diary card; pain recorded on a visual analogue scale; and abdominal distention, flatus, and stool frequency recorded on a five-point scale	3	Not randomized	Nash, P., Gould, S. R., and Bernardo, D. E. Peppermint oil does not relieve the pain of irritable bowel syndrome. Br.J Clin Pract. 1986;40(7):292-293.	Yes	None	NA	NA
Irritable bowel syndrome (IBS)	Gelatin capsules containing peppermint oil (Elanco Lokcaps®)	One 0.2-0.4mL capsule 2-3 times daily, depending on symptoms	Randomized controlled trial, cross over design	29	IBS patients	Two weeks	IBS symptoms	3	Methods of randomization and dropouts were not discussed.	Dew, M. J., Evans, B. K., and Rhodes, J. Peppermint oil for the irritable bowel syndrome: a multicentre trial. Br J Clin Pract. 1984;38(11-12):394-398.	Yes	None	NA	NA
Irritable bowel syndrome (IBS)	Peppermint oil capsules	3-6 capsules daily	Randomized controlled trial, cross over design	20	IBS patients	Two weeks	IBS symptoms	P*	P*	Evans BK, Levine DF, Mayberry JF, and et al. Multicentre trial of peppermint oil capsules in irritable bowel syndrome. Scand J Gastroenterol 1982;17:503.	Yes	Small	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Irritable bowel syndrome (IBS)	Peppermint oil capsules (Elanco LOK®)	1-2 0.2mL capsules three times daily	Controlled clinical trial, cross over design	18	IBS patients	Three weeks	Severity of abdominal symptoms on a 0-3 scale	3	Randomization status and methods were not clearly described.	Rees, W. D., Evans, B. K., and Rhodes, J. Treating irritable bowel syndrome with peppermint oil. Br Med J 10-6-1979;2(6194):835-836.	Yes	Medium	NA	NA
Irritable bowel syndrome (IBS)	Peppermint oil	Enteric-coated capsules, 200mg three times daily, 30 minutes before meals	Randomized controlled trial, parallel groups	47	Patients with IBS determined by clinical diagnosis and investigations	Four weeks	Improvement in global symptoms	3	Methods of randomization were unclear; double-blinding may have been inadequate, as peppermint taste was a reported side effect	Lech, Y., Olesen, K. M., Hey, H., Rask-Pedersen, E., Vilien, M., and Ostergaard, O. [Treatment of irritable bowel syndrome with peppermint oil. A double- blind study with a placebo]. Ugeskr.Laeger 10-3-1988;150(40):2388-2389.	Yes	Medium	42%	2
Irritable bowel syndrome (IBS)	Peppermint oil	Two Mintoil capsules (dose unclear) three times daily	Randomized controlled equivalence trial, double-blind	35	Patients with IBS determined by Rome II diagnostic criteria; 22 men, 69 women, 18-72 years of age (mean: 44 years)	Three months	Improvement in global symptoms assessed by validated questionnaire	5 (reviewed by (65))	Good study design with adequate description of randomization, blinding, and dropouts (reviewed by (65))	Capanni M, Surrenti E, Biagini M, Milani S, Surrenti C, Galli A. Efficacy of peppermint oil in the treatment of irritable bowel syndrome: a randomized, controlled trial. Gazz Med Ital 2005; 164:119-26.	Yes	Medium	45%	2

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Antispasmodic	Peppermint oil and sorbitan mixture dissolved in water	20mL of peppermint oil solution or the placebo solution sprayed around the pyloric ring via the accessory channel of the endoscope	Randomized controlled trial	100	Consenting patients undergoing upper endoscopy, without prior surgery involving upper GI surgery; major comorbid condition contraindicating endoscopy; duodenal ulcer; gastric ulcer, ulcer scar, or gastric mass >2cm in size; bleeding; or penetrating gastric ulcer	Acute treatment	Percent change in diameter of the pyloric ring and the time until the disappearance of the contraction ring(s) using EGG (electrogastrography) monitoring	4	Appropriate randomization and blinding (double-dummy); dropouts not mentioned; administration of hyoscyamine by intramuscular instead of intravenous injection may have affected the time needed for the drug to inhibit peristalsis.	Hiki, N., Kurosaka, H., Tatsutomi, Y., Shimoyama, S., Tsuji, E., Kojima, J., Shimizu, N., Ono, H., Hirooka, T., Noguchi, C., Mafune, K., and Kaminishi, M. Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. Gastrointest.Endosc. 2003;57(4):475-482.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Antispasmodic	Peppermint oil	10mL of 1.6% peppermint oil solution administered orally with 8mL of barium suspension (220% W/V) and 2mL of gum syrup at the start of double-contrast barium meal examination (DCBM)	Randomized controlled trial, single-blind	215	Consenting patients undergoing DCBM during medical check-ups at Health Planning Center from March to August 2003 without history of gastrointestinal surgery	Acute treatment given at the beginning of DCBM; symptoms observed up to two days after treatment.	Ratings of spasm and overlapping with barium-filled duodenal loops	2	Randomization unclear; single-blind	Mizuno, S., Kato, K., Ono, Y., Yano, K., Kurosaka, H., Takahashi, A., Abeta, H., Kushiro, T., Miyamoto, S., Kurihara, R., Hiki, N., Kaminishi, M., Iwasaki, A., and Arakawa, Y. Oral peppermint oil is a useful antispasmodic for double-contrast barium meal examination. J Gastroenterol.Hepatol. 2006;21(8):1297-1301.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Antispasmodic	Peppermint oil	Peppermint oil mixed with barium solution during double-contrast barium meal examination (DCBM)	Randomized controlled trial	141	Consenting patients undergoing DCBM; 26 males (34-77 years of age, mean: 58.3 years), 40 females (18-77 years of age, mean: 52.4 years)	Acute treatment	Residual spasm	4	Randomization methods were not described.	Sparks, M. J., O'Sullivan, P., Herrington, A. A., and Morcos, S. K. Does peppermint oil relieve spasm during barium enema? Br.J Radiol. 1995;68(812):841-843.	Yes	Medium	29%	4
Antispasmodic	Peppermint oil solution	20mL or 40mL of 1.6% or 3.2% peppermint oil solution, with additional delivery for up to 100mL total for each patient	Case-control series	40	Patients scheduled for either diagnostic or therapeutic endoscopic retrograde cholangiopancreatography; not pregnant or lactating; without acute pancreatitis, other severe diseases, or allergy to peppermint	Acute treatment	Duodenal motility (measured by the number of contractions and a subjective rating by the endoscopist) pre- and post-peppermint oil administration	0	Study was not randomized or blinded; dropouts were not explicitly discussed, though results were reported for 40 subjects.	Yamamoto, N., Nakai, Y., Sasahira, N., Hirano, K., Tsujino, T., Isayama, H., Komatsu, Y., Tada, M., Yoshida, H., Kawabe, T., Hiki, N., Kaminishi, M., Kurosaka, H., and Omata, M. Efficacy of peppermint oil as an antispasmodic during endoscopic retrograde cholangiopancreatography. J GASTROENTEROL HEPATOL 2006;21(9):1394-1398.	No	None	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Breast tenderness	Peppermint oil in gel preparation	Gel containing 0.2% v/w peppermint oil applied topically after breastfeeding and washed off before subsequent feedings	Randomized controlled trial	216	Postpartum women over age 18 with full-term single births, not on medications, otherwise healthy, literate, and with telephones.	14 days	Rate of nipple and areola crack and pain	4	Appropriate randomization; blinding, and dropouts; adequacy of placebo unclear	Melli, M. S., Rashidi, M. R., Nokhoodchi, A., Tagavi, S., Farzadi, L., Sadaghat, K., Tahmasebi, Z., and Sheshvan, M. K. A randomized trial of peppermint gel, lanolin ointment, and placebo gel to prevent nipple crack in primiparous breastfeeding women. Med Sci Monit. 2007;13(9):CR406-CR411.	Yes	Medium	NA	NA
Breast tenderness	Peppermint water vs. expressed breast milk	Cotton soaked with peppermint water, applied to nipples and areola (after washing the nipples with water) after breastfeeding and washed off before subsequent feedings	Randomized equivalence trial	196	Postpartum women over age 18 with full-term single births, not on medications, otherwise healthy, literate, and with telephones. Children were exclusively breastfed (no bottles or pacifiers).	14 days	Rate of nipple and areola crack and pain	3	Appropriate description of randomization and dropouts; study was not blinded.	Sayyah Melli M, Rashidi MR, Delazar A, Madarek E, Kargar Maher MH, Ghasemzadeh A, Sadaghat K, Tahmasebi Z. Effect of peppermint water on prevention of nipple cracks in lactating primiparous women: a randomized controlled trial. Int Breastfeed J. 2007 Apr 19;2:7.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Dyspepsia	Herbal medicinal products for nonulcer dyspepsia, including peppermint oil in combination with caraway or ginger oils, and Iberogast® (peppermint leaves with caraway, bitter candy tuft, licorice, lemon balm, angelica, celandine, milk thistle, and chamomile)	Capsules (including enteric-coated or enteric-soluble) containing 108-270mg of peppermint oil daily. Dosing information not available for all reviewed studies.	Systematic review	9 trials (peppermint and caraway)	Randomized clinical trials examining herbal medicinal products for the relief of nonulcer dyspepsia	2-8 weeks (most commonly four weeks)	Dyspepsia symptoms, including cramps, stomach pains, bilious complaints, flatulence, nausea and sensation of fullness	NA	None of the studies used peppermint as a monotherapy. Methodological flaws included lack of double-blinding, unclear methods of randomization, and lack of discussion on subject withdrawals. Various (some unvalidated) methods of scoring symptoms. Large placebo response.	Thompson Coon J, Ernst E. Systematic review: herbal medicinal products for non-ulcer dyspepsia. Aliment Pharmacol Ther. 2002 Oct;16(10):1689-99.	NA	NA	NA	NA
Dyspepsia	Fixed combination of peppermint and caraway oils vs. placebo	Capsules containing 90mg of peppermint oil and 50mg of caraway oil twice daily	Randomized controlled trial	96	Outpatients with a current episode of dyspepsia lasting for at least 14 days	28 days	Intensity of pain, sensation of pressure, heaviness and fullness, and global improvement	5	Appropriate description of randomization, blinding methods and dropouts; combination product used	May, B., Kohler, S., and Schneider, B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. Aliment.Pharmacol Ther 2000;14(12):1671-1677.	Yes	Medium	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Dyspepsia	Fixed combination of peppermint and caraway oils vs. cisapride	Capsules containing 90mg of peppermint oil and 50mg of caraway oil twice daily	Equivalence trial, randomized, double-blind	120	Outpatients diagnosed with functional dyspepsia	Four weeks	Mean reductions in pain score	4	Appropriate description of randomization, blinding methods and dropouts. However, placebo was not used. Combination product used.	Madisch, A., Heydenreich, C. J., Wieland, V., Hufnagel, R., and Hotz, J. Treatment of functional dyspepsia with a fixed peppermint oil and caraway oil combination preparation as compared to cisapride. A multicenter, reference-controlled double-blind equivalence study. Arzneimittelforschung. 1999;49(11):925-932.	Yes	None	NA	NA
Dyspepsia	Fixed combination of peppermint oil and caraway oil	90mg of peppermint + 45mg of caraway oil vs. 36mg of peppermint oil + 20mg of caraway oil daily	Equivalence trial, randomized	223	Patients diagnosed with dysmotility-type, essential or idiopathic dyspepsia with irritable bowel syndrome (IBS)	28 days	Pain intensity	2	Unclear methods of randomization and blinding; no placebo group; combination product used	Freise J, Köhler S. [Peppermint oil-caraway oil fixed combination in non-ulcer dyspepsia--comparison of the effects of enteric preparations]. Pharmazie. 1999 Mar;54(3):210-5.	Yes	None	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Dyspepsia	Fixed combination of peppermint and caraway oils vs. placebo	Capsules containing 90mg of peppermint and 50mg of caraway oil three times daily	Randomized controlled trial	45	Outpatients diagnosed with nonulcer dyspepsia	Four weeks	Pain and clinical global impressions	3	Unclear methods of randomization; combination product used	May, B., Kuntz, H. D., Kieser, M., and Kohler, S. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. Arzneimittelforschung. 1996;46(12):1149-1153.	Yes	Medium	NA	NA
Dyspepsia	Enteric-coated peppermint oil (Colpermin®)	Two capsules three times daily	Randomized controlled trial	69	Women undergoing routine gynecological intraperitoneal surgery for benign pathology; treatment given postoperatively	Five days	Severity of symptoms daily, using a visual analogue scale. Measured symptoms included abdominal distention, flatulence, and pain.	4	Unclear methods of randomization; short study duration	Barnick CG and Cardozo LD. The treatment of abdominal distension and dyspepsia with enteric coated peppermint oil following routine gynaecological intraperitoneal surgery. J Obstet.Gynecol 1990;10(5):423-424.	No	None	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Headache (topical)	Peppermint oil (10%) in ethanol vs. placebo oil containing trace peppermint oil, with acetaminophen or placebo	Oil applied cutaneously over forehead and temples, and repeated after 15 and 30 minutes. Acetaminophen (two 500mg capsules) or placebo was taken orally.	Randomized controlled trial, crossover design, equivalence trial	41	Male and female patients (18-65 years of age) with tension-type headache according to IHS classification	One application repeated 15 and 30 minutes later	Headache parameters measured at 15-minute intervals over 60 minutes	3	Unclear methods of randomization; blinding may not have been adequate.	Gobel, H., Fresenius, J., Heinze, A., Dworschak, M., and Soyka, D. [Effectiveness of Oleum menthae piperitae and paracetamol in therapy of headache of the tension type]. Nervenarzt 1996;67(8):672-681.	Yes	None	NA	NA
Headache (topical)	Peppermint oil (10%) in ethanol with trace eucalyptus oil vs. placebo	Oil applied cutaneously over forehead and temples, and repeated after 15 and 30 minutes	Randomized controlled trial, crossover design, equivalence trial	32	Healthy male subjects	One application repeated 15 and 30 minutes later	Headache parameters	3	Unclear methods of randomization; blinding may not have been adequate.	Gobel, H., Schmidt, G., and Soyka, D. Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algesimetric headache parameters. Cephalalgia 1994;14(3):228-234.	Yes	None	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Abdominal distention	Peppermint oil (topical) hot compress on the abdomen three times daily vs. no treatment.	Peppermint oil (topical) 0.5-1.0mL with 2L hot water soaked into a towel (which was replaced every 2-3 minutes) and placed on the abdomen for 20-30 minutes three times daily beginning on postoperative day 1.	Randomized controlled trial	46	Postoperative gynecological patients	Unclear	Abdominal distention, pain, and duration to first gas passage	3	Unclear methods of randomization; no placebo group	Feng, X. Z. [Effect of peppermint oil hot compresses in preventing abdominal distension in postoperative gynecological patients]. Zhonghua Hu Li Za Zhi. 1997;32(10):577-578.	Yes	Medium	47.8	2.1

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Abdominal pain	Treatments used for recurrent abdominal pain in children, including famotidine, pizotifen, cognitive-behavioral therapy, biofeedback, and peppermint oil enteric-coated capsules (Colpermin®)	Patients weighing >45kg: two capsules (187mg per capsule) three times daily. Patients weighing 30-45kg: one capsule three times daily	Systematic review	1 trial for irritable bowel syndrome (IBS) (66)	Randomized controlled trials found in online bibliographic databases using the search terms "recurrent abdominal pain," "functional abdominal pain," "children," or "alternative therapies"	Two weeks	Abdominal pain and other symptoms, such as heartburn, gas, urgency of stools, belching, or stool consistency	NA	One trial evaluating the use of peppermint oil for the treatment of abdominal pain associated with IBS	Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. Pediatrics. 2003 Jan;111(1):e1-11.	NA	NA	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Abdominal pain	Peppermint oil (Colpermin®) vs. placebo	Two capsules (dose not specified) three times daily	Randomized controlled trial	40	Male and female postsurgical emergency appendicectomy patients, 10-35 years of age	Five days	Operative diagnosis, first passage of flatus and feces, girth measurements, analgesic requirements, suppository use, and assessment of patient symptomaticity (whether the patient was distended or colicky)	4	Unclear methods of randomization	Meyrick Thomas, J., Payne-James J., Carr, N., Glick, L. Peppermint oil following appendectomy: A (deliberately) small clinical trial. Surg Res Comm 2:285-287, 1988.	No	None	NA	NA
Bad breath	1:2:1 tea tree oil, peppermint, and lemon essential oil mixture (final concentration: 0.125%)	Day 1: three minute oral cleaning using oral essential oil solution Day 2: tantum	Before-and-after comparison	32	Volunteers in intensive care unit in South Korean hospital (mean age: 53 ± 19 years)	Two days	Oral malodor test (VAS) and volatile sulphur compounds (ppb).	0	Study was not randomized or blinded; dropouts not discussed. A combination product used, therefore it is difficult to deduce effects of peppermint monotherapy.	Hur, M. H., Park, J., Maddock-Jennings, W., Kim, D. O., and Lee, M. S. Reduction of mouth malodour and volatile sulphur compounds in intensive care patients using an essential oil mouthwash. Phytother Res 2007;21(7):641-643.	Yes	Small	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Cognitive improvement (in brain injury)	Peppermint oil scent vs. no scent	Peppermint fragrance delivered at approximately 0.05 parts per million (ppm)	Randomized trial	40	Normal volunteers (N=20) and patients with brain injury (N=20)	Acute treatment	30-minute vigilance assessment	2	Unclear methods of randomization; study not blinded.	Sullivan TE, Warm JS, Schefft BK, Dember WN, O'Dell MW, Peterson SJ. Effects of olfactory stimulation on the vigilance performance of individuals with brain injury. J Clin Exp Neuropsychol. 1998 Apr;20(2):227-36.	Yes	Medium	NA	NA
Common cold	Olbas® drops (Oleum Basileum, plant oils, and menthol)	Drops administered locally and by inhalation	Clinical trial	40	P*	Seven days	Cold symptoms	P*	A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Hansen B, Babiak G, Schilling M, and et al. A mixture of volatile oils in treatment of common cold. Therapiewoche 1984;34(13):2015-2019.	P*	P*	P*	P*

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Common cold	Mixture of aromatic vapors (eucalyptus, menthol, camphor)	Inhalation of a mixture of aromatic vapors	Clinical trial	24	Nonsmoking healthy adults with common colds	Acute administration	Lung and forced expiratory volumes, nasal, lower and total airway resistances, closing volume data, and phase III slope and MEFV derivatives on air and helium/oxygen breathing were recorded.	P*	A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Cohen, B. M. and Dressler, W. E. Acute aromatics inhalation modifies the airways. Effects of the common cold. Respiration 1982;43(4):285-293.	Yes	Small	NA	NA
Dental plaque	Fixed combination of thymol, menthol, methyl salicylate, and eucalyptol	Unclear	Randomized controlled trial	66	Healthy volunteers (males and females, aged 18-58) with plaque or gingivitis	Six months	Microbial flora	2	Methods of randomization, blinding, and dropouts not discussed. A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Charles, C. H., Vincent, J. W., Borycheski, L., Amatnieks, Y., Sarina, M., Qaqish, J., and Proskin, H. M. Effect of an essential oil-containing dentifrice on dental plaque microbial composition. Am J Dent. 2000;13(Spec No):26C-30C.	No	NA	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Hot flashes	Peppermint and neroli hydrolat spray	Spray whenever a hot flash was experienced	Randomized controlled trial, crossover, single-blind design	44	Women (aged 33-70 years) suffering from hot flashes due to breast cancer treatment	Two months	Number and severity (VAS) of hot flashes	3	Single-blind study. A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Dyer, J., Ashley, S., and Shaw, C. A study to look at the effects of a hydrolat spray on hot flushes in women being treated for breast cancer. Complement Ther Clin Pract. 2008;14(4):273-279.	NA	Small	NA	NA
Mental performance/alertness	Peppermint or lavender essential oils (Tisserand Aromatherapy) vs. control (no odor)	Diffuser pad containing four drops of essential oil	Controlled clinical trial, equivalence trial	144	Healthy volunteers (undergraduates and members of the general public)	Acute treatment (five minutes prior to test)	Cognitive performance (assessed using the Cognitive Drug Research computerized assessment battery) and mood scales (completed before and after cognitive testing)	2	Unclear methods of randomization; unblinded.	Moss M, Hewitt S, Moss L, Wesnes K. Modulation of cognitive performance and mood by aromas of peppermint and ylang-ylang. Int J Neurosci. 2008 Jan;118(1):59-77.	No	NA	NA	NA
Mental performance/alertness	Peppermint oil odor vs. control (no odor)	Peppermint oil (50ml) heated to 53°C to odorize the testing room	Controlled clinical trial	26	Healthy students (Five men, 21 women, mean age: 19.0 years, SD 5.6 years)	Acute treatment	Speed and accuracy on a typing task, in addition to ordering, and memorization tasks	0	No blinding, randomization, or description of withdrawals	Barker S, Grayhem P, Koon J, Perkins J, Whalen A, Raudenbush B. Improved performance on clerical tasks associated with administration of peppermint odor. Percept Mot Skills. 2003 Dec;97(3 Pt 1):1007-10.	Varied	Small	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Mental performance/alertness	Peppermint oil, jasmine, ylang-ylang, 1,8-cineole, or menthol vs. control	50mcL peppermint oil (44% menthol w/v) applied to a surgical mask	Controlled clinical trial, equivalence trial	140	Healthy subjects, 16-67 years of age	Acute treatment	Subjective ratings of pleasantness, intensity, effect, and degree of relaxation prior to a simple reaction task 25 minutes in duration	0	No blinding, randomization, or description of withdrawals	Ilmberger J, Heuberger E, Mahrhofer C, Dessovic H, Kowarik D, Buchbauer G. The influence of essential oils on human attention. I: alertness. Chem Senses. 2001 Mar;26(3):239-45.	No	NA	NA	NA
Postherpetic neuralgia	Peppermint oil (10% menthol)	2-3 drops of peppermint oil (10% menthol) were massaged in the skin at the site of pain 3-4 times daily.	Case report	1	76 year-old woman with postherpetic neuralgia	Four weeks	Pain relief	NA	Case series design, difficult to draw an inference for larger populations	Davies, S. J., Harding, L. M., and Baranowski, A. P. A novel treatment of postherpetic neuralgia using peppermint oil. Clin J Pain 2002;18(3):200-202.	NA	NA	NA	NA
Post-operative nausea (inhalation)	Peppermint oil vs. peppermint essence (inactive control) or no treatment	5mL of oil in a bottle as aromatherapy	Controlled clinical trial	18	Patients undergoing major gynecological surgery	Acute treatment	Subjective ratings of nausea using the Nausea Scale Score	0	Inadequate between-group comparisons; lack of absence of randomization or blinding	Tate S. Peppermint oil: a treatment for postoperative nausea. J Adv Nurs.1997 Sep;26(3):543-9.	Yes	Small	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Post-operative nausea (inhalation)	Peppermint oil vs. isopropyl alcohol vs. saline	Treatment placed on gauze and inhaled	Randomized controlled trial, equivalence trial, before-and-after comparison	33	Consenting patients (18 years of age or older) reporting nausea postoperatively	Acute treatment	Nausea ratings using a visual analog scale after aromatherapy as compared to pretreatment.	3	Methods of double-blinding were inadequate	Anderson LA, Gross JB. Aromatherapy with peppermint, isopropyl alcohol, or placebo is equally effective in relieving postoperative nausea. J Perianesth Nurs. 2004 Feb;19(1):29-35.	No	None	NA	NA
Pruritus	Sama lotion (containing 0.5% each of menthol, camphor, and phenol)	Lotion rubbed into skin	Randomized, controlled trial, crossover design, equivalence trial	31	Patients with uremic pruritus	21 days	Pruritus was assessed using a four-point verbal rating scale and a visual analogue scale.	P*	A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Tan, C. C., Wong, K. S., Thirumoorthy, T., Lee, E., and Woo, K-T. A randomized, crossover trial of Sarna and Eurax lotions in treatment of haemodialysis patients with uraemic pruritus. J Dermatol Treat 1990;1(5):235-238.	No	None	NA	NA
Pruritus	9.0% coal tar solution with 1.5% menthol	Topical application of shampoo	Randomized, double-blind, parallel design	P*	Patients with dandruff and associated scalp itch	Acute treatment	Relief of itching symptoms using visual analog and categorical scale	P*	A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Klausner, M. A., Whitmore, C., Henry, E. V., Baybutt, R. I., and Schachtel, B. P. Additional antipruritic activity of menthol when added to coal tar in dandruff-associated pruritus. Clin Pharmacol Ther 1988;43(2):173.	Yes	Small	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Stress	Lavender, peppermint, rosemary, and clary sage scents administered via an aroma lamp	P*	Quasi-experimental clinical trial	77	Junior nursing students	P*	Relief of stress symptoms	P*	A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Park, M. K. and Lee, E. S. [The effect of aroma inhalation method on stress responses of nursing students]. Taehan Kanho.Hakhoe.Chi 2004;34(2):344-351.	P*	P*	NA	NA
Stroke recovery	Lavender, rosemary, and peppermint aromatherapy	Acupressure session with or without aromatherapy lasting 20 minutes, performed twice daily	Randomized controlled trial	30	Stroke patients with hemiplegic shoulder pain	Two weeks	Shoulder pain and motor power	P*	A combination product was used, therefore it is difficult to deduce effects of peppermint monotherapy.	Shin, B. C. and Lee, M. S. Effects of aromatherapy acupressure on hemiplegic shoulder pain and motor power in stroke patients: a pilot study. J Altern.Complement Med 2007;13(2):247-251.	No	NA	NA	NA

Condition	Constituents	Dosing	Study Type	N	Population	Duration	End points	Study Quality	Limitations	Citation	Statistically significant?	MOB*	ARR*	NNT*
Tuberculosis	Peppermint essential oil	Inhalation (upon 20-minute vapor into the ambient room air), 0.01 and 0.005 mL/m^3 in conjunction with multidrug therapy	Clinical trial	P*	Patients with tuberculosis	Two months	Positive X-ray changes in the lung and attenuation of intoxication syndrome	P*	P*	Shkurupii, V. A., Kazarinova, N. V., Ogirenko, A. P., Nikonov, S. D., Tkachev, A. V., and Tkachenko, K. G. [Efficiency of the use of peppermint (Mentha piperita L) essential oil inhalations in the combined multi-drug therapy for pulmonary tuberculosis]. Probl.Tuberk. 2002;(4):36-39.	P*	Medium	P*	P*
Urinary tract infection	Peppermint tea	TMS forte (160mg of trimethoprim and 800mg of sulfamethoxazole twice daily) and five cups of Harntee 400 or peppermint tea.	Randomized controlled trial, equivalence trial	72	Patients with urinary tract infections	P*	Clinical and bacterial symptoms	P*	Peppermint tea was supposedly used as the placebo control. It is difficult to deduce effects of peppermint monotherapy.	Ebbinghaus K D. A 'tea' containing various plant products as adjuvant to chemotherapy of urinary tract infections. Therapiewoche 1985;35:2041-2051.	NA	NA	NA	NA

B. Population/epidemiological studies

- Not applicable.

C. Summary of evidence

Conditions/Indications	Scientific Evidence for Common/Studied Uses	Grade
Irritable bowel syndrome (IBS) A functional bowel disorder (conditions in which the bowel appears normal but does not function normally), characterized by chronic abdominal pain or discomfort, or change in bowel functioning without any known cause. Referred to as spastic colon, mucous colitis, spastic colitis, nervous stomach, or irritable colon.	Multiple randomized controlled trials, meta-analyses, and systematic reviews of peppermint suggest significant improvements in irritable bowel syndrome (IBS) symptoms (54-56; 58-75). Although the mechanism of action is not clear, preclinical study suggests that smooth muscle-relaxing properties (76-78), possibly due to calcium antagonism (79; 80), may play a role. Currently, clinical evidence appears to support the use of peppermint in the treatment of symptoms of IBS.	**A**
Antispasmodic An agent that prevents or relieves involuntary (smooth) muscle spasms or cramps.	Based on purported smooth muscle-relaxing properties, peppermint oil has been proposed as a potential antispasmodic (21; 81-87). Additional research remains necessary for a definitive assessment.	**B**
Breast tenderness Pain and soreness around the nipple or areola during breastfeeding. Nipples may be cracked or bleeding.	Peppermint is popularly used externally as a topical anesthetic for burns, wounds, itching, and inflammation. Preliminary evidence suggests daily peppermint use can prevent nipple cracking, reduce pain, and increase duration and number of feeds (88; 89). However, additional research is needed to confirm these early findings.	**B**
Dyspepsia Indigestion, characterized by discomfort, heartburn, or nausea.	There is preliminary evidence from a small number of controlled trials that a combination of peppermint oil and caraway oil may be beneficial for the alleviation of dyspepsia (heartburn) symptoms. However, most studies have been methodologically weak, with small sample sizes, inadequate use of control or placebo groups, unclear descriptions of blinding and randomization, and a lack of use of standardized scales for identifying subjects or assessing endpoints. It is not clear which constituent(s) may be beneficial. Nonetheless, the existing evidence does suggest the efficacy of this combination. At this time, further research is warranted before a definitive assessment can be made. It should be noted that dyspepsia can actually be a side effect of taking oral peppermint oil; this has been reported by patients in several controlled trials of peppermint oil (54; 55; 61; 62; 68). This may be due to the relaxation of the lower esophageal sphincter by peppermint oil. Therefore, patients with underlying gastroesophageal reflux disease (GERD) should use peppermint oil cautiously. Patients with chronic heartburn should be evaluated by a qualified healthcare provider and may be advised to undergo a diagnostic endoscopy prior to initiating any treatment for heartburn.	**B**

Conditions/Indications	Scientific Evidence for Common/Studied Uses	Grade
Headache (topical) Pain in the head, ranging from mild to debilitating, resulting from any number of physiological causes.	A small body of evidence indicates that peppermint oil applied topically may be an effective treatment for headache (90; 91). However, additional research is required before a definitive assessment conclusion can be drawn.	**B**
Abdominal distention The state of the abdomen being stretched beyond normal dimensions, usually from swallowed air or intestinal gas from fermentation. Also known as bloat.	There is currently a lack of sufficient evidence to draw a firm conclusion regarding the use of a peppermint oil for abdominal distention (92).	**C**
Abdominal pain Pain of the abdomen, usually from distention, ulcer, or spasm.	Peppermint oil has been found to reduce the pain children experience during acute phases of irritable bowel syndrome (IBS) as well as recurrent abdominal pain (66), and in colicky abdominal pain and distension following appendectomy in other populations (93). It has been suggested that the mechanism for this effect is due to the menthol component of peppermint, which causes inhibition of smooth muscle contractions by blocking calcium channels (79; 80). Peppermint may also reduce pain locally and coat the lower intestine (66).	**C**
Bad breath Bad-smelling breath, often caused by tooth decay, gum disease, digestive problems, smoking, or some systemic diseases. Also known as halitosis.	Limited early research suggests that cleaning the mouth with an essential oil mixture of diluted tea tree oil, peppermint, and lemon may improve bad breath in intensive care unit patients (94). However, high-quality study that investigates peppermint as a monotherapy is needed. The use of peppermint oil-flavored mouthwash, candy, and gum to improve breath is supported extensively by anecdotal and traditional use.	**C**
Cognitive improvement (in brain injury) Enhancement of mental function after brain damage.	Although early evidence is promising, there is a lack of sufficient evidence regarding the use of peppermint oil to affect vigilance following brain injuries (95).	**C**
Common cold A viral infection of the upper respiratory tract (nose and throat). Also referred to as viral rhinitis.	There are insufficient data concerning the use of peppermint in the treatment or prevention of the common cold (96; 97). Additional research using peppermint monotherapy is needed.	**C**

Conditions/Indications	Scientific Evidence for Common/Studied Uses	Grade
Dental plaque The noncalcified accumulation mainly of oral microorganisms and their products that adheres tenaciously to the teeth and is not readily dislodged.	There is currently insufficient evidence regarding the use of peppermint for dental plaque and gingivitis (98). Additional research using peppermint monotherapy is needed.	**C**
Hot flashes A brief flushing and feeling of heat that occurs after the end of menstruation in women ages 48-50.	There is insufficient evidence regarding the use of peppermint for hot flashes (99). Additional research using peppermint monotherapy is needed.	**C**
Mental performance/alertness A combination of factors, including reaction time, concentration, and memory.	In preliminary study, peppermint aroma has shown mixed effects on cognition, attention, and alertness (100-102). Additional research is required before a definitive assessment can be made.	**C**
Postherpetic neuralgia Neuralgia occurring as a consequence of infection by herpes virus.	There is insufficient research to determine if peppermint oil is of benefit in the treatment of postherpetic neuralgia (103). Further research is warranted.	**C**
Post-operative nausea (inhalation) A feeling of sickness in the stomach characterized vomiting or an urge to vomit. Commonly occurs as an adverse effect of anesthesia used in surgery.	There is insufficient evidence to evaluate the potential benefit of peppermint oil in the treatment of postoperative nausea (104; 105). Further research is warranted.	**C**
Pruritus A condition characterized by intensely itchy skin; it can be a symptom of a disease process, or result from emotional factors.	There is insufficient evidence regarding the use of peppermint for pruritus (106; 107). Additional research using peppermint monotherapy is needed.	**C**

Conditions/Indications	Scientific Evidence for Common/Studied Uses	Grade
Stress A mentally or emotionally disruptive or upsetting condition occurring in response to adverse external influences and capable of affecting physical health, usually characterized by increased heart rate, a rise in blood pressure, muscular tension, irritability, and depression.	There is currently insufficient evidence regarding the use of peppermint for stress (108). Additional research using peppermint monotherapy is needed.	**C**
Stroke recovery The process whereby patients undergo methodical rehabilitation in order to regain movement from paralysis that involves one side of the body in a lateral fashion.	Preliminary study has indicated that aromatherapy with acupressure may reduce hemiplegic shoulder pain in stroke patients (109). However, the effect of peppermint oil alone cannot be ascertained from these findings due to the concurrent use of acupressure and additional essential oils. Additional research is required before a definitive assessment can be made.	**C**
Tuberculosis A highly contagious infection caused by the bacterium *Mycobacterium tuberculosis*, characterized by the formation of tubercles in the lungs.	Peppermint oil has been traditionally inhaled to relieve nasal and pulmonary congestion. While some preliminary evidence has suggested that inhalation of peppermint oil may have therapeutic benefit in the treatment of tuberculosis, additional, methodologically rigorous research is required before a definitive conclusions can be made (110).	**C**
Urinary tract infection Bacterial infiltration of the urinary tract.	Peppermint tea has been used in combination with other therapies for the treatment of urinary tract infections; however, evidence remains inconclusive (111). Additional research is required using peppermint monotherapy.	**C**

Natural Standard evidence-based validated grading rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each monograph.
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (Strong Scientific Evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant

Level of Evidence Grade	Criteria
B (Good Scientific Evidence)	Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from ≥1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory. *This grade applies to situations in which a well designed randomized controlled trial reports negative results but stands in contrast to the positive efficacy results of multiple other less well designed trials or a well designed meta-analysis, while awaiting confirmatory evidence from an additional well designed randomized controlled trial*
C (Unclear or conflicting scientific evidence)	Evidence of benefit from ≥1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥1 cohort/case-control/non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory
D (Fair Negative Scientific Evidence	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.*This grade also applies to situations in which >1 well designed randomized controlled trial reports negative results, notwithstanding the existence of positive efficacy results reported from other less well designed trials or a meta-analysis. (Note: if there is ≥1 negative randomized controlled trials that are well designed and highly compelling, this will result in a grade of "F" notwithstanding positive results from other less well designed studies*
F (Strong Negative Scientific Evidence	Statistically significant negative evidence (i.e. lack of evidence of benefit) from ≥1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of Evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

* Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17[1]:1-12).
† Listed separately in monographs in the "Traditional Uses by culture" section and Appendix A.
*MOB=Magnitude of benefit
*ARR=Absolute risk reduction
*NNT=Number needed to treat
*P=Pending full article analysis

5. DOSAGE / TOXICITY INFORMATION

A. Clinical Doses

General:

- Doses may be based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparations of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization:

- The U.S. Pharmacopeia XVI, dating to the 1960s, defines peppermint oil as containing not less than 5% of the oil as esters, calculated as menthyl acetate, and not less than 50% of the total menthol content to be free menthol and menthol esters (112).
- Menthone and menthol are the predominant active compounds in peppermint. Gas chromatography (GC) has been found to be a suitable technique in determining the amount of menthone and menthol in peppermint (113; 114). A number of commercial peppermint oil samples analyzed with GC were found to have varying ratios in the content of its main ingredient (113).

Adult Dosing (age ≥18):

Oral:

- **Antispasmodic**: A single dose of five drops of peppermint oil in 10mL of water (87).

- **Bad breath**: Three minutes of oral cleaning (one day) with an essential oil solution (made of peppermint, tea tree, and lemon) (94).
- **Digestive disorders**: Peppermint oil (0.2-0.4mL) three times daily in dilute preparations or suspension (duration not indicated) (115).
- **Dyspepsia**: One to three enteric-coated capsules containing a fixed combination of 90mg of peppermint oil and 45-50mg of caraway oil used for up to 28 days (116-119). Two capsules of peppermint oil given three times daily orally for five days postoperatively (120). A single dose or peppermint oil (0.2mL) in water (25mL) prior to a meal (121).
- **Irritable bowel syndrome (IBS)**: 0.2mL capsules taken three times daily before or with meals for 2-3 weeks (58-61; 70; 71; 73). Patients with severe symptoms received six capsules daily (70). One to two enteric-coated capsules of Colpermin® (Tillotts Pharma, Ziefen, Switzerland) containing 187mg or 0.2mL of peppermint oil, three times daily, 15-30 minutes before meals for up to eight weeks (54; 64; 69). Enteric-coated peppermint oil 180-200mg taken half an hour before each meal (duration not indicated) (75). Two enteric-coated capsules of Mintoil® (Cadigroup, Rome, Italy), containing 225mg of peppermint oil and 45mg of Natrasorb (starch), twice daily for four weeks, had evidence of benefit (56). Peppermint oil 0.64mL following a test meal (200kcal per 200mL) after fasting overnight (72).
- **Sore throat**: Lozenges that contain 2-10mg of peppermint oil, as needed, according to secondary sources.
- **Vomiting**: Leaf (3-6g) and tincture (5-15g) as an antiemetic (duration not indicated), according to secondary sources.
- **Other traditional dosing**: For various indications of gastrointestinal tract, gall bladder, and bile duct: *Dried extract*: 2-4g of dried herb extract three times daily. *Infusion*: 1.5-3g of peppermint oil in 150mL of water three times daily. *Spirits*: (10% oil and 1% leaf extract) 1mL (20 drops) with water. *Tea*: 3-4 cups daily between meals of 3g of dried peppermint leaves in 250mL of boiling water. *Tincture*: (1:5 preparation 45% ethanol) 2-3mL three times daily.

Topical:

- **Abdominal distention**: Peppermint oil (0.5-1.0mL) with 2L of hot water soaked into a towel on the abdomen for 20-30 minutes three times daily (92).
- **Breast tenderness (preventing cracked nipples)**: Peppermint gel applied onto both nipples of lactating women for 14 days showed evidence of benefit; peppermint gel was prepared by dispersing various concentrations of carbopol 934 in water containing 0.2% propyl paraben and 0.1% methyl paraben as preservatives and 15mL of glycerin (as a humectant) for a period of 2 hours. Peppermint oil (0.2mL) was added gently to the carbopol dispersion under continuous stirring (200rpm) to produce a concentration of 0.2% v/w (88). Soaked cotton with peppermint water on the nipples and areola after washing the nipples with water following every breastfeed from day 1 to day 14 (89).
- **Headache**: A combination of eucalyptus and peppermint oil (19% in ethanol solution) applied to the temples and forehead at the onset of the symptoms, repeated every 15-30 minutes (90).
- **Postherpetic neuralgia**: Peppermint oil (2-4 drops; standardized to 10% menthol) massaged into skin 3-4 times daily (103).
- **Stroke recovery (hemiplegic shoulder pain)**: Peppermint aromatherapy acupressure sessions lasting for 20 minutes performed twice-daily for two weeks (109).
- **Note**: Avoid topical use of peppermint oil around the facial or chest areas of infants and young children, especially around the nose, as menthol can induce apnea, laryngeal and bronchial spasm, acute respiratory distress with cyanosis, or respiratory arrest if applied directly to these areas (122).

Inhalation:

- **Cough**: Inhalation of 3mL of 1% l-menthol-solution has been evaluated for efficacy in preventing coughing in patients undergoing fiberoptic bronchoscopy (123). Inhalation of menthol 75% in eucalyptus oil at one, two, three, four, and five hours (124).
- **Nasal congestion**: Traditionally, 3-4 drops of oil added to hot water and inhaled, as needed. Menthol 62.5mg in 1mL of petrolatum applied and inhaled (duration not indicated) (125).
- **Performance enhancement (cognitive and attentional function)**: Four drops of essential oil applied to a diffuser pad and placed inside work cubicle to enhance memory and alertness (101).

Enteral (excluding oral):

- **Antispasmodic**: A solution of peppermint oil 8mL (86) or 16mL (81) to treat colonic spasm. Peppermint (16mL) oil dissolved in hot water and infused intraluminally during upper endoscopy (81). Peppermint oil administered intraluminally at differing concentrations (20mL or 40mL of 1.6% or 3.2% peppermint oil solution, with additional delivery for up to 100mL total for each patient) (84).

Pediatric Dosing (age <18):

Oral:

- **Irritable bowel syndrome (IBS)**: Colpermin® 0.1-0.2mL ingested orally three times daily for two weeks, in children 8-10 years old (66).

B. Toxicology Information

- **LD_{50}**: The oral LD_{50} in Wistar male rats was found to be 4.4g/kg after 24 hours and 2.4g/kg after 48 hours (112). The intraperitoneal LD_{50} of peppermint oil USP was determined to be 819mg/kg after 24 hours (112).
- ***In vitro* study**: Peppermint was observed to induce mutations in a dose-dependent manner in human lymphocytes (sister chromatid exchange was dose-independent) (126).
- **Animal study**: In animal study, rats administered peppermint oil and pulegone (a constituent of peppermint oil) up to 100-160mg/kg of body weight daily were shown to develop brain lesions and encephalopathy after 28 days (127). Pulegone, a constituent of peppermint, is recognized as a hepatotoxin (128; 129). In other animal work, pulegone, at doses of 80-

160mg for 28 days, induced atonia and weight loss, decreased blood creatinine, and caused histopathological changes in the liver (130). Ataxia and convulsions have been observed following single doses of 3, 4, and 5g/kg of peppermint oil (131). Cyst-like spaces in the white matter of the cerebellum were observed after 90 days of peppermint oil administration at doses of 10, 40, and 100mg/kg of body weight daily in an animal study (130; 132). A decrease in creatinine and increases in alkaline phosphatase, bilirubin, and liver and spleen size occurred in rats given oral menthone (133). The no-effect level was <200mg of menthone per kilogram of body weight daily. In another study, rats exposed to peppermint-scented shavings reportedly had unusually high mortality rates compared to controls (134).

- In animal study, rats administered peppermint tea (20g/L of *Mentha spicata* tea and 40g/L of *Mentha spicata* tea) for 30 days experienced increased levels of plasma urea and creatinine and TBARS levels (22). A similar study by the same group investigated *M. piperita* tea (20g/L) in addition to *M. spicata* tea (20g/L and 40g/L), both of which were shown to cause dose-dependent hepatic damage and lipid peroxidation in male Wistar albino rats (135). A comparison of *Mentha spicata* and *Mentha piperita* indicated that *M. spicata* induced more nephrotoxic changes than *M. piperita* (22). 2u-globulin-binding to pulegone, a minor constituent of peppermint oil, was found to be the cause of previously observed retention of pulegone and metabolites in the kidneys of rodents (129). High doses of peppermint, at doses 2-3 orders of magnitude greater than recommended for human use, increased bile flow in acute administration and increased alkaline phosphatase after chronic administration in rats (136). Peppermint was found to stop segmental maturation in the seminiferous tubules of testicular tissue of rats (137).
- **Human study**: In a case study, injection of peppermint oil resulted in pulmonary edema and acute lung injury, presumably due to direct toxicity and a resultant increase in pulmonary vascular permeability (138).

C. Precautions & Contraindications

Allergy:

- Peppermint oil should be avoided in those with known allergy/hypersensitivity to peppermint oil, its constituents, or members of the Lamiaceae family.
- Allergic/hypersensitivity reactions may occur from using peppermint or menthol by mouth or on the skin; this may induce such symptoms as throat closing (laryngeal spasm), breathing problems (bronchial constriction/asthma-like reactions), or skin rash, hives, or contact dermatitis. Hypersensitivity reactions, contact dermatitis, and exacerbations of asthma may occur.
- Contact sensitivity to menthol has been reported and confirmed with positive patch tests, and shown to induce such conditions as burning mouth syndrome, recurrent oral ulceration, lichenoid reaction, or urticaria (12; 139-145). Skin rashes have also been described (54), including contact dermatitis during dental operations and with the use of mentholated cigarettes (146; 147), toothpaste (148; 149); (150; 151), fragrances (152), and foot spray (153), and in food handlers (154). Additionally, oral mucosal lesions due to mouthwashes containing peppermint oil (155) and vulval allergic contact dermatitis due to peppermint oil in herbal tea (156) have been noted.
- Cross-sensitivity to the Labiatae family or turpentine may be observed (157).
- Cheilitis was observed in a 74 year-old patient after use of a new toothpaste, occurring after several weeks despite withdrawal of the paste (158). The cheilitis was attributed to carvone, a flavor additive found in peppermint oil.

Adverse Effects/Post Market Surveillance:

- **General**: Reports of adverse reactions are rare but may include hypersensitivity reactions, contact dermatitis, heartburn, perianal burning, bradycardia, and muscle tremor when taken orally (21; 60; 61; 141).
- **Cardiovascular**: In a case-control study assessing peppermint oil as an antispasmodic, one patient (N=40) experienced bradycardia and one experienced a sympathovagal response, which was on par with the adverse effect rate seen in historical controls using glucagons (84). Atrial fibrillation has also been noted in a case report (159). A small cardioaccelerating effect has been observed following menthol administration in human study (160).
- **Dermatologic**: Contact sensitivity to menthol has been reported and confirmed with positive patch tests, and shown to induce such conditions as burning mouth syndrome, recurrent oral ulceration, lichenoid reaction, or urticaria (12; 139-145). Skin rashes and irritation from the topical use of peppermint oil and its derivatives have been noted (37; 54; 103), including contact dermatitis during dental operations and with the use of mentholated cigarettes (146; 147), toothpaste (148), fragrances (152), and foot spray (153), and from handling food (154). Breast infection leading to study withdrawal occurred in one (N=216) breastfeeding woman applying peppermint oil to the nipple (5/216 reported infection in the placebo group; results non-significant), although causality was unclear (88). Oral mucosal lesions due to mouthwashes containing peppermint oil have been noted (155). Case reports of chemical burns resulting from contact with peppermint oil have been reported (161), including one of a chemical burn to the oral mucosa of a woman who was ingesting drops of peppermint oil during an upper respiratory tract infection (162). In *in vitro* study using static diffusion cells mounted with human breast or abdominal skin, peppermint oil dose-dependently decreased the skin integrity (163). Cheilitis was observed in a 74 year-old patient after use of a new toothpaste; it occurred after several weeks despite withdrawal of the paste (158). The cheilitis was attributed to carvone, a flavor additive found in peppermint oil.
- **Gastrointestinal**: The most common complaint in trials of oral peppermint oil has been heartburn (54-56; 61; 62; 68; 69). It has been suggested that this may occur due to the relaxation of the lower esophageal sphincter and that caution is warranted in patients with underlying gastroesophageal reflux disease (62). Other symptoms occasionally reported with oral administration of peppermint oil include anal and perianal burning (62; 164), nausea and vomiting (68), abdominal pain (54), belching (69), dry mouth (69), and increased appetite (69). Abdominal distention and increased flatulence were reported by one patient in a trial of peppermint oil during upper endoscopy (81). One patient dropped out of a clinical trial due to a minty taste in the mouth from enteric-coated capsules, though it was noted that this may have been due to the chewing of the capsules (56). In a case-control study assessing peppermint oil as an antispasmodic, three of 40 subjects

experienced mild pancreatitis, which was on par with the adverse effect rate in the 16 historical controls using glucagons (84).

- **Genitourinary**: Vulval allergic contact dermatitis due to peppermint oil in herbal tea has been reported (156). Decreased libido has also been reported with peppermint use (46).
- **Hematological**: Non-thrombocytopenic purpura has been attributed to menthol-containing cigarettes (141).
- **Hepatic**: Based on animal study, peppermint may cause hepatic damage and lipid peroxidation in a dose-dependent manner (135). Pulegone, a constituent of peppermint, is recognized known hepatotoxin (128).
- **Neurologic/CNS**: In an animal study, brain lesions and neurotoxicity occurred at daily doses of 100mg/kg for 28 days (127).
- **Ocular/optic**: Blurry vision was reported in a trial of oral peppermint (68).
- **Pulmonary/respiratory**: In one case study, the injection of peppermint oil resulted in pulmonary edema and acute lung injury; these effects were presumably due to direct toxicity and a resultant increase in pulmonary vascular permeability (138). One case report in a 21 year-old female noted exacerbation of asthma symptoms following the use of a mint-flavored toothpaste (149). The patient was re-challenged with her toothpaste, resulting in a decrease in FEV1 by 36%. The patient was further challenged with hypersensitivity responses observed with spearmint, peppermint, and menthol, though not eucalyptol and anethole. Menthol fumes caused transient respiratory arrest or a drop in respiratory rate, as well as tachycardia in 44 premature infants (165).
- **Renal**: High doses of peppermint oil have been associated with interstitial nephritis and acute renal failure, according to secondary sources. Necrosis and interstitial nephritis have been observed with the topical application of methyl salicylate and menthol in combination with a heating pad (166).
- **Other**: Dental caries (167), gingivitis (168), and denture softening (169) have been reported with peppermint use. Excess consumption of mint-flavored candy has caused stomatitis and glossitis associated with extremely prominent circumvallate papillae (170).

Precautions/Warnings/Contraindications:

- Avoid in patients with known allergy/hypersensitivity to peppermint, its constituents, or other members of the Lamiaceae (Labiatae) family.
- Avoid excessive consumption of peppermint, as it has been associated with dental caries (167), gingivitis (168), and denture softening (169).
- Avoid topical use of peppermint oil around the facial or chest areas of infants and young children, especially around the nose, because the menthol constituent can induce apnea, laryngeal and bronchial spasm, acute respiratory distress with cyanosis, or respiratory arrest if applied directly to these areas (122).
- Use cautiously in patients with gastrointestinal disorders such as gastroesophageal reflux disease, achlorhydria, and hiatal hernia, due to lower esophageal sphincter-relaxing effects and reports of dyspepsia (21; 54; 61; 62; 68; 69; 171).
- Use peppermint cautiously, particularly in men, as peppermint tea has been shown to reduce free testosterone levels (without affecting the levels of total testosterone and DHEA in human study) (46; 172).
- Use cautiously in patients with underlying heart conditions, due to the observation of a small cardioaccelerating effect following menthol administration (160), atrial fibrillation (159), and bradycardia (84).
- Use cautiously when applied topically in combination with a heating pad, due to the possibility of excessive percutaneous absorption leading to necrosis and interstitial nephritis (observed with the topical application of methyl salicylate and menthol in combination with a heating pad) (166).
- Use cautiously in patients with sexual dysfunction, as decreased libido and reduced testosterone levels have been reported in human study (46).
- Use cautiously in patients with kidney dysfunction or those who are using nephrotoxic agents, as peppermint tea has been observed to cause nephrotoxicity in animal and human study (22; 166). Caution is also warranted in patients with or who have had kidney stones, based on a review (21).
- Use cautiously in patients with hepatic dysfunction or those who are using hepatotoxic agents, as spearmint tea has reportedly caused hepatic damage in animal study (135). Pulegone, a constituent of peppermint, is also a known hepatotoxin (128).
- Use cautiously in patients who are iron deficient, as peppermint inhibited iron absorption in animal research (173).
- Use cautiously with aminophylline, as concurrent use has been found to reduce peak concentrations of aminophylline *in vivo* (174).
- Use cautiously with cyclosporine, as, based on animal study, peppermint oil may increase the oral bioavailability of cyclosporine via the inhibition of the liver enzyme cytochrome P450 3A4 (175; 175).
- Use cautiously with cytochrome P450-metabolized agents as peppermint may (moderately) inhibit cytochromes P450 1A2, 2E, and 3A4, which may lead to increased blood levels of drugs metabolized by these isoenzymes (175; 175; 176; 176; 177).
- Use cautiously with salicylates, as peppermint has been found to contain salicylates, and menthol reportedly enhances absorption of salicylic acid (178; 179).
- Use cautiously in conjunction with other topical therapies, as peppermint and menthol have been found to enhance the transdermal delivery of various drugs (179-186).

Pregnancy & Lactation:

- Peppermint preparations are commonly used during pregnancy for conditions like pregnancy-induced nausea; however, data are limited regarding safety and efficacy (187-189).

- Peppermint oil has been used on the nipple to prevent cracks in breastfeeding women with some evidence of benefit (88). Breast infection leading to study withdrawal occurred in one breastfeeding woman (N=216) applying peppermint oil to the nipple (five of 216 reported infection in the placebo group; results nonsignificant), although causality was unclear (88).
- Information on peppermint's effects on lactation is currently lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

D. Spice / Herb / Food Interactions

Peppermint/Drug Interactions:

- **General**: Menthol has been found to enhance the percutaneous transfer and transdermal delivery of various drugs.
- **5-fluorouracil (5-FU)**: Peppermint oil may enhance skin absorption of topical 5-fluorouracil, based on animal research (186).
- **Acyclovir**: Peppermint has been found to enhance topical delivery of acyclovir *in vitro* and in animal experimentation (184).
- **Aminophylline**: Peppermint has been found to enhance permeation of aminophylline *in vivo* in human skin (174).
- **Analgesics**: Based on a variety of studies (human, animal, and *in vitro*), menthol has been shown to exert a direct antinociceptive effect (91; 182; 190-196). Menthol has also been observed to improve the analgesic efficacy of tetracaine topical gel, partially through enhanced percutaneous permeation, in animal study (181).
- **Antibiotics**: Based on *in vitro* study, peppermint oil and menthol may have synergistic effects with some antibiotics like ciprofloxacin (27; 197-200). These effects may be dependent on concentration, food pH, composition, storage temperature, and the nature of the microorganism (199).
- **Antidiabetic agents**: According to *in vitro* study, the phenolic compounds and antioxidant activities found in peppermint tea may have hypoglycemic effects (201).
- **Antifungals**: Synergistic effects against *Candida albicans* have been noted *in vitro* when peppermint essential oil was used with amphotericin B (200). Similarly, in laboratory study, menthol was found to enhance the efficacy of topical ketoconazole (180). In other laboratory work, peppermint displayed fungistatic and fungicidal activity against various fungi (202; 203). Based on animal study, peppermint oil and menthol may be effective against *Candida albicans*, *Fusarium oxysporum*, *Fusarium verticillioides*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Penicillium chrysogenum*, *Aspergillus niger*, *A. flavus*, *A. fumigatus*, *A. sulphureus*, *Mucor fragilis*, and *Rhizopus stolonifer* (204-210); (211-214).
- **Anti-inflammatory agents**: Peppermint has been reported as exhibiting dose-dependent anti-inflammatory activity in animal study (215).
- **Antiprotozoals**: In laboratory study, several peppermint extracts inhibited the growth and adherence of *Giardia lamblia*, the parasite that causes giardiasis (28).
- **Antispasmodic agents**: Scientific review indicates that peppermint's principal action is a dose-dependent antispasmodic effect on the gastrointestinal tract (216).
- **Antiulcer agents**: The commercial combination product STW-5 (Iberogast®), which contains extracts of peppermint leaf, as well as other herbal components, has been demonstrated to exert a dose-dependent antiulcerogenic effect associated with reduced acid output, increased mucin secretion, increased prostaglandin E2 release, and a decrease in leukotrienes (217).
- **Antitussives**: Based on animal study and widespread anecdotal evidence, menthol may have antitussive effects (218).
- **Benzoic acid**: Based on *in vitro* study, dermal application of low concentrations of peppermint oil may reduce the absorption of benzoic acid via the skin (163).
- **Caffeine**: Menthol (100 mg) has been shown to delay caffeine absorption but not affect caffeine metabolism in human study (219).
- **Calcium channel blockers**: *In vitro* experimentation with animal tissue has indicated that peppermint oil may possess channel-blocking activity (220).
- **Cardiovascular agents**: A small cardioaccelerating effect has been observed following menthol administration in human study (160). In a case-control study assessing peppermint oil as an antispasmodic, one patient (N=40) experienced bradycardia and one experienced a sympathovagal response, which was on par with the adverse effect rate seen in historical controls using glucagons (84). Atrial fibrillation has also been noted in a case report (159).
- **Corticosteroids**: Menthol, a constituent of peppermint, has been found to enhance the absorption of corticosteroids in animal study (179).
- **Cyclosporine**: Based on animal study (rats), peppermint oil may significantly increase the oral bioavailability of cyclosporine via the inhibition of liver enzyme cytochrome P450 3A4 (175).
- **Cytochrome P450-metabolized agents**: Based on preclinical data, peppermint oil may (moderately) inhibit cytochromes P450 1A2, 2E, and 3A4, which may lead to increased blood levels of drugs metabolized by these isoenzymes (175; 175; 176; 176; 177).
- **Diclofenac**: Menthol has been found to enhance the effects of transdermal diclofenac in animal experimentation (183; 221).
- **Hepatotoxic agents**: Peppermint has been shown to cause dose-dependent hepatic damage and lipid peroxidation in animals (135).
- **Hormonal agents**: Peppermint has been shown to have antiandrogenic effects in rats and may be associated with diminished libido (46). In human study, peppermint tea was observed to reduce the level of free testosterone in the blood, without affecting the levels of total testosterone and DHEA (46; 172). Based on animal study, the mechanism may involve

spearmint-induced oxidative stress in the hypothalamus as well as testicular antiandrogenicity (altered levels of gene expression, enzymes, and hormones) resulting in decreased synthesis of LH and FSH, which in turn downregulate the production of testicular testosterone through the disruption of a number of intermediate cascades (222).

- **Interleukins**: Based on lab study, the peppermint constituent alpha-humulene may increase interleukin-8 (IL-8) secretion (223).
- **Iron salts**: Polyphenol-containing peppermint beverages have been found to dose-dependently inhibit iron absorption in both animal and human study (173; 224).
- **Neostigmine**: Menthol has been shown to potentiate neostigmine stimulated colon activity in human study (76).
- **Ondansetron**: Menthol has been found to enhance the effects of transdermal ondansetron in animal study (183).
- **Oxytetracycline**: Based on *in vitro* experimentation, peppermint oil and menthol may react synergistically with oxytetracycline (27).
- **Propranolol**: In animal study, menthol has been found to enhance the absorption of topical propranolol, possibly through preferential distribution into intercellular spaces of the stratum corneum and reversible disruption of the intercellular lipid domain (225; 226).
- **Salicylates**: Menthol has been found to enhance the absorption of salicylic acid in animal study (179). Peppermint has also been shown to contain salicylates (178)
- **Tetracaine**: In animal study, menthol was shown to improve the analgesic efficacy of tetracaine topical gel, partially through enhanced percutaneous permeation (181; 182).
- **Venlafaxine**: Peppermint has been found to enhance the transdermal delivery of venlafaxine *in vitro* (185).
- **Zidovudine**: Menthol has been found to enhance transdermal permeation of zidovudine (AZT) *in vitro* (227).

Peppermint/Herb/Supplement Interactions:

- **Analgesics**: Based on a variety of studies (human, animal, and *in vitro*), menthol has been shown to exert a direct antinociceptive effect (91; 182; 190-196). Menthol has also been observed to improve the analgesic efficacy of tetracaine topical gel, partially through enhanced percutaneous permeation, in animal study (181).
- **Antibacterials**: Based on *in vitro* study, peppermint oil and menthol may have synergistic effects with some antibiotics like ciprofloxacin (27; 197-200). These effects may be dependent on concentration, food pH, composition, storage temperature, and the nature of the microorganism (199).
- **Antifungals**: Synergistic effects against *Candida albicans* have been noted *in vitro* when peppermint essential oil was used with amphotericin B (200). Similarly, in laboratory study, menthol was found to enhance the efficacy of topical ketoconazole (180). In other laboratory work, peppermint displayed fungistatic and fungicidal activity against various fungi (202; 203). Based on animal study, peppermint oil and menthol may be effective against *Candida albicans*, *Fusarium oxysporum*, *Fusarium verticillioides*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Penicillium chrysogenum*, *Aspergillus niger*, *A. flavus*, *A. fumigatus*, *A. sulphureus*, *Mucor fragilis*, and *Rhizopus stolonifer* (204-214). Concomitant use of peppermint and basil oil has been found to have synergistic antifungal effects (228).
- **Anti-inflammatory herbs**: Peppermint has been reported as exhibiting dose-dependent anti-inflammatory activity in animal study (215).
- **Antiparasitics**: In *in vitro* study, several peppermint extracts inhibited the growth and adherence of *Giardia lamblia*, the parasite that causes giardiasis (28). Theoretically, concurrent use of peppermint with antiparasitic agents may have additive effects.
- **Antispasmodics**: Scientific review indicates that peppermint's principal action is a dose-dependent antispasmodic effect on the gastrointestinal tract (216).
- **Antitussives**: Based on animal study and widespread anecdotal evidence, menthol may have antitussive effects (218).
- **Antiulcer herbs and supplements**: The commercial combination product STW-5 (Iberogast®), which contains extracts of peppermint leaf, as well as other herbal components, has been demonstrated to exert a dose-dependent antiulcerogenic effect, associated with reduced acid output, increased mucin secretion, increased prostaglandin E2 release, and a decrease in leukotrienes (217).
- **Basil**: Concomitant use of peppermint and basil oil has been found to have synergistic antifungal effects *in vitro* (228).
- **Caffeine-containing herbs**: Menthol (100 mg) has been shown to delay caffeine absorption but not affect caffeine metabolism in human study (219).
- **Cardiovascular herbs and supplements**: A small cardioaccelerating effect has been observed following menthol administration in human study (160). In a case-control study assessing peppermint oil as an antispasmodic, one patient (N=40) experienced bradycardia and one experienced a sympathovagal response, which was on par with the adverse effect rate seen in historical controls using glucagons (84). Atrial fibrillation has also been noted in a case report (159).
- **Cytochrome P450-metabolized herbs and supplements**: Based on preclinical data, peppermint oil may (moderately) inhibit cytochromes P450 1A2, 2E, and 3A4, which may lead to increased blood levels of drugs metabolized by these isoenzymes (175; 175; 176; 176; 177).
- **Hepatotoxic herbs and supplements**: Peppermint has been shown to cause dose-dependent hepatic damage and lipid peroxidation in animals (135).
- **Hormonal herbs and supplements**: Peppermint has been shown to have antiandrogenic effects in rats and may be associated with diminished libido (46). In human study, peppermint tea was observed to reduce the level of free testosterone in the blood, without affecting the levels of total testosterone and DHEA (46; 172). Based on animal study, the mechanism may involve spearmint-induced oxidative stress in the hypothalamus as well as testicular antiandrogenicity (altered levels of gene expression, enzymes and hormones) resulting in decreased synthesis of LH and

FSH, which in turn downregulate the production of testicular testosterone through the disruption of a number of intermediate cascades (222).

- **Hypoglycemics**: According to *in vitro* study, the phenolic compounds and antioxidant activities found in peppermint tea may have hypoglycemic effects (201).
- **Hypotensives**: Calcium channel-blocking activity of peppermint oil has been observed in animal models (220) and, in theory, peppermint oil may add to the effects of agents that may also theoretically drop blood pressure.
- **Immunosuppressants**: Based on lab study, the peppermint constituent alpha-humulene may increase interleukin-8 (IL-8) secretion (223).
- **Iron**: Polyphenol-containing peppermint beverages have been found to dose-dependently inhibit iron absorption in both animal and human study (173; 224).
- **Quercetin**: Based on animal study, menthol may enhance the absorption of topical quercetin (229).
- **Salicylate-containing herbs**: Menthol has been found to enhance the absorption of salicylic acid in animal study (179). Peppermint also contains salicylates, and concurrent use with other salicylates may have additive effects and increase salicylate levels (178).
- **Vitamin D**: Menthol has been found to enhance the antiproliferative activity of 1alpha,25-dihydroxyvitamin D(3) [1alpha,25(OH)(2)D(3)], an active form of vitamin D(3), *in vitro* (230).

Peppermint/Food Interactions:

- Insufficient available evidence.

Peppermint/Lab Interactions:

- **Blood glucose**: According to *in vitro* study, the phenolic compounds and antioxidant activities found in peppermint tea may have hypoglycemic effects (201).
- **Heart rate**: A small cardioaccelerating effect has been observed following menthol administration in human study (160). In a case-control study assessing peppermint oil as an antispasmodic, one patient (N=40) experienced bradycardia and one experienced a sympathovagal response, which was on par with the adverse effect rate seen in historical controls using glucagons (84). Atrial fibrillation has also been noted in a case report (159).
- **Hormone panel (LH, FSH, and estradiol levels)**: Peppermint has been shown to have antiandrogenic effects in rats and may be associated with diminished libido (46). In human study, peppermint tea was observed to reduce the level of free testosterone in the blood, without affecting the levels of total testosterone and DHEA (46; 172). Based on animal study, the mechanism may involve spearmint-induced oxidative stress in the hypothalamus as well as testicular antiandrogenicity (altered levels of gene expression, enzymes and hormones) resulting in decreased synthesis of LH and FSH, which in turn downregulate the production of testicular testosterone through the disruption of a number of intermediate cascades (222).
- **Liver function tests**: In animal study, peppermint was found to increase alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (135).

Peppemint/Nutrient Depletion:

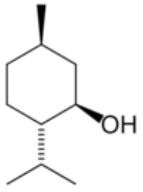
- **Iron**: Polyphenol-containing peppermint beverages have been found to dose-dependently inhibit iron absorption in both animal and human study (173; 224).

6. ACTIVE CONSTITUENTS/COMPOUNDS

A. Main bioactive constituents (listed in order of compounds with the most supporting evidence for potential health benefits)

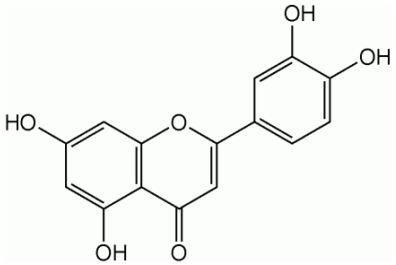
1) Menthol

- **Broad health benefits**: Menthol has demonstrated analgesic (191; 193; 231-233), anticancer (200; 204-214; 230; 234-239), antitussive (218), bone (240), cardiovascular (160), cognitive (100), dermatological (241-243), gastrointestinal (79; 80; 115), intracellular calcium (20), neurologic (244-249), pruritus (107), and respiratory (244-248; 250; 251) effects in preliminary study.
- **Molecular structure**:



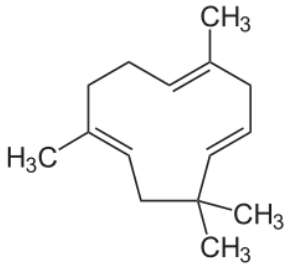
- **Molecular formula**: $C_{10}H_{20}O$
- **Physical properties**: white or colorless crystalline solid; molecular mass: 156.27g/M; melting point: 36-38°C; boiling point: 212°C; slightly soluble in water.
- **Similar constituents in other plants**: Menthol has been detected and quantified in numerous other plants. These plants include sunflower, corn, other mint species in the genera *Mentha* and *Pycnanthemum*, rose geranium, tarragon, savory, basil, pennyroyal, tea hyssop, and juniper.

2) **Luteolin**
   - **Broad health benefits**: Luteolin has demonstrated anticancer (252) effects in preliminary study.
   - **Molecular structure**:



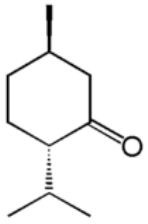
   - **Molecular formula**: $C_{15}H_{10}O_6$
   - **Physical properties**: yellow powder; molecular weight: 286.24g/M, melting point: ~330°C; soluble in methanol and alkaline solutions, slightly soluble in water.
   - **Similar constituents in other plants**: Luteolin may be present in celery, chamomile, green peppers, and thyme.

3) **Alpha-humulene**
   - **Broad health benefits**: Alpha-humulene has demonstrated anticancer (223) effects in preliminary study.
   - **Molecular structure**:



   - **Molecular formula**: $C_{15}H_{24}$
   - **Physical properties**: colorless to slightly yellow oily liquid; molecular weight: 204.35g/M; boiling point: 166-168°C; density: 0.889g/mL at 20°C, soluble in ethanol, oils, and ether, insoluble in water.
   - **Similar constituents in other plants**: Alpha-humulene has been detected in *Ageratum conyzoides* L. (Mexican ageratum), cinnamon, clove oil, bay leaf oil, and a host of other botanicals.

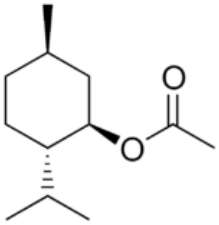
4) **Menthone**
   - **Broad health benefits**: The exact health benefits of menthone are unclear.
   - **Molecular structure**:



   - **Molecular formula**: $C_{10}H_{18}O$
   - **Physical properties**: colorless liquid; molecular mass: 154.25g/M; melting point: -6°C; boiling point: 207°C; slightly soluble in water, soluble in organic solvents.
   - **Similar constituents in other plants**: In addition to peppermint, menthone has been detected and quantified in other mint species in the genera *Pycnanthemum* and *Mentha* and also in European pennyroyal, savory, hyssop, marsh skullcap, and rose geranium.

5) **Menthyl acetate**
   - **Broad health benefits**: The exact health benefits of menthyl acetate are unclear.

- **Molecular structure**:



- **Molecular formula**: $C_{12}H_{22}O_2$
- **Physical properties**: colorless liquid; molecular mass: 198.30g/M; melting point: 23-24°C; boiling point: 229-230°C; soluble in alcohol.
- **Similar constituents in other plants**: Menthyl acetate has been detected and quantified in other mint species including water mint, Biblical mint, slenderleaf mountain mint, and also Balkan *Sideritis* and *Minthostachys mollis*.

B. Constituents

- **Phenolic compounds**:
  - **Flavonoids and flavonoid glycosides**: 5,7-dihydroxycromone-7-O-rutinoside (253), eriocitrin (21; 253-256), flavonoid compounds (255), flavonoids (21; 252), hesperidin (21; 253), hesperidoside (255), isorhoifolin (253), luteolin (21; 252), luteolin-7-rutinoside (255), luteolin-7-O-rutinoside (253), and narirutin (253).
  - **Hydroxycinnamic acids and cinnamates**: caffeic acid (254; 256), hydroxycinnamic compounds (255), and rosmarinic acid (21; 253-257).
  - **Polyphenolics**: polymerized polyphenols (258) and polyphenolic compounds (255; 256).
- **Alcohols**:
  - **Amino alcohols**: diosmin (253).
- **Amines**: betaine, choline.
- **Carboxylic acids**:
  - **Benzoic acids**: anisic acid (259).
- **Elements**: calcium (260), cobalt, iron (261), and trace elements (260-262).
- **Essential oil** (255).
- **Esters**: isopentyl isovalerate (259).
- **Heterocyclic compounds**:
  - **Benzopyrans**: coumarin (263).
- **Lactones**: methofurolactone (259).
- **Terpenes**:
  - **Monoterpenes and derivatives**: 1,8-cineole (264; 265), alpha-pinene, beta-myrcene (264), beta-pinene (264; 265), carvone, isomenthone (264), limonene (264; 265), linalool (264), menthol, (-)-menthol (21; 76; 255; 264-266), menthone, (-)-menthone (21; 264-266), menthyl acetate, (-)-menthyl acetate (264; 265), perillyl alcohol (258), piperitone (264), and pulegone (266).
  - **Monoterpenoids**: (+)-menthofuran and menthofuran (266-269).
  - **Sesquiterpenes**: alpha-humulene (223), a-bourbonene (259), and beta-caryophyllene (265).
- **Vitamins**: vitamin A (as provitamin A (beta-carotene)) (270) and tocopherols.

7. PHARMACOLOGY

- **Acetylcholinesterase effects**: Peppermint has been found to have high inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in laboratory study (271).
- **Analgesic effects**: In animal and laboratory study, peppermint has displayed analgesic effects that are likely dose-dependent (192; 195; 196; 215; 272; 273). Menthol has a complex sensory effect on thermal-sensitive nerves, which, it has been suggested, is a function of many variables, such as menthol concentration (193). Menthol has been shown to inhibit voltage-dependent sodium channels, which may contribute to the antinociceptive and local anesthetic effects of menthol (231).
- It was found that, in human study, topically applied peppermint oil stimulated the cold sensitive receptors located in the dermis by blocking the type-L-voltage gated channels, causing depolarization of the cold sensitive receptors and local modification of pain receptor sensitivity (91; 190). Menthol has also been found to sensitize cold-sensitive peripheral vasoactive C nociceptors and activate cold-specific A delta fibers (232). Application of menthol to the vermillion border of the lower lip of adults for several minutes inhibited the perception of heating over a range of temperatures, from the warmth threshold to heat pain, probably by desensitizing low-threshold warm receptors (191). The cooling effect of menthol has been attributed to activation of the TRPM8 receptor (233).
- **Antiallergy effects**: In animal study, 50% EtOH extract of peppermint has been shown to inhibit histamine release at a concentration of 1mcg/mL (274).

- **Antiandrogenic effects**: Peppermint has been shown to have antiandrogenic effects in rats and may be associated with diminished libido (46). In human study, peppermint tea was observed to reduce the level of free testosterone in the blood, without affecting the levels of total testosterone and DHEA (46; 172). Based on animal study, the mechanism may involve spearmint-induced oxidative stress in the hypothalamus as well as testicular antiandrogenicity (altered levels of gene expression, enzymes and hormones) resulting in decreased synthesis of LH and FSH, which in turn downregulate the production of testicular testosterone through the disruption of a number of intermediate cascades (222).
- **Antibacterial effects**: Peppermint oil has been reported as inhibitory toward all laboratory strains tested of obligate and facultative anaerobes relevant to dental disease (275). In addition, *in vitro* studies have demonstrated antibacterial effects against *Pseudomonas aeruginosa*, *Streptococcus mutans*, *Streptococcus pyogenes* , *Staphylococcus epidermidis*, *Enterobacter aerogenes*, *Escherichia coli*, *Helicobacter pylori*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Salmonella enteritidis*, *Shigella sonnei*, *Micrococcus flavus* ATTC 10,240, methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Saccharomyces cerevisiae* 0425 delta/1 and 0425 52C strains, with synergistic antimicrobial effects when simultaneously applied with oxytetracycline (27; 198; 203; 210; 276-285). Peppermint has also been found to exhibit bacteriostatic and bactericidal activity against the pathogenic bacteria *Streptococcus mutans*, *Streptococcus pyogenes*, and *E. coli* 015:H7 (29; 277). It has been suggested that these effects may be dependent on its concentration, as well as other factors such as the pH, composition, and storage temperature of the substrate, and the nature of the microorganism (29; 199).
- **Anticancer effects**: One *in vitro* study demonstrated that peppermint oil can revert tumor cells back to a differentiated state (258). Based on animal study, oral administration of *Mentha* extract may have chemopreventive and antimutagenic effects, possibly due to its antioxidative and radical-scavenging properties (286; 287). In an experiment employing peppermint leaf extract, strong free radical-scavenging activity was found against both DPPH* and ABTS*+ radicals in mice (287). Of the active compounds identified in the extract, monoterpene ketones were identified as exhibiting the strongest scavenging effect.
- Menthol has been shown to increase the antiproliferative activity of 1alpha,25-dihydroxy vitamin D(3) (230).
- In laboratory study, peppermint exhibited strong inhibitory effects on E2 sulfation within human colon carcinoma Caco-2 cells; IC_{50} values ranged from 1.9 to 4.4% (v/v) (288). A strong inhibition of the cytosolic estrogen SULT activity of Caco-2 cells was also noted *in vitro* (IC_{50} values ranged from 0.18 to 0.3% (v/v)). These inhibitory activities were found to be moderately lipophilic.
- Luteolin, a constituent of peppermint, has been found to reduce tumor growth *in vivo*, inhibit topoisomerases I and II, and sensitize tumor cells to the cytotoxic effects of anticancer drugs (252).
- **Antifungal activity**: Peppermint water displayed fungistatic and fungicidal activity against various fungi in the lab (202; 203). Based on findings from a variety of laboratory studies, peppermint oil and menthol have been found to posses action against a number of fungi including *Candida albicans*, *Fusarium oxysporum*, *Fusarium verticillioides*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *M. longifolia*, *P. lanceolata*, *A. austriaca*, *Candida tropicalis*, *Penicillium chrysogenum*, *Aspergillus niger*, *A. flavus*, *A. fumigatus*, *A. sulphureus*, *Mucor fragilis*, and *Rhizopus stolonifer* (200; 204-214; 234-239).
- **Anti-inflammatory effects**: Peppermint has been found to have a dose-dependent anti-inflammatory effect in xylene-induced ear edema experiments in mice, which suggested as attributable to its volatile oil, flavanoid, and resin content (215).
- **Antioxidant effects**: Peppermint has been shown to exhibit antioxidant activity (52; 203; 254; 256; 265; 289-293). It has been shown to act as a radical scavenger and inhibit lipid peroxidation (256). In other experiments, peppermint essential oil demonstrated antioxidant activity in a linoleic acid emulsion system by inhibiting conjugated dienes formation by 52.4% and linoleic acid secondary oxidized product generation by 76.9% (at 0.1% concentration) (265).
- **Antiparasitic effects**: Peppermint extract has been shown to exert antiparasitic activity in animal and laboratory study (28; 294). In a laboratory experiment, several peppermint extracts inhibited the growth and adherence of *Giardia lamblia*, the parasite that causes giardiasis (28). A dichloromethane fraction showed the best antigiardial activity, with an IC_{50} of 0.75mcg/mL after 48 hours of incubation.
- **Antitussive effects**: Menthol has been shown to exert antitussive effects in guinea-pigs (218).
- **Antiviral effects**: An antiviral substance was detected in peppermint oil with activity against the Newcastle disease virus (NDV), herpes simplex, vaccinia, Semliki forest, influenza A virus, and West Nile virus (295). In laboratory study, peppermint exhibited high virucidal activity against herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) (296; 297). Additionally, it has been found to have activity against the acyclovir-resistant strain of HSV-1 (297). Peppermint appears to affect HSV before adsorption, with no effect on the intracellular virus replication (296). It has been suggested that the lipophilic nature of the oil possibly contributes to these beneficial effects (297).
- The water-soluble polar substances of peppermint aqueous extract have displayed potent anti-HIV-1 activity (with an ED of 16mcg/mL) as well as inhibitory activity against HIV-1 reverse transcriptase *in vitro* (298; 299). It has been suggested that this effect may be due to increasing the virion density (298).
- **Bone effects**: Metabolites of (-)-menthol inhibited bone resorption *in vitro* (240).
- **Dermatologic effects**: An *in vitro* study on human skin showed that low-dose, topically applied peppermint oil protected the skin from the absorption of benzoic acid, though a higher dose of topical peppermint oil compromised the skin's integrity (163). Other experimentation has indicated that topically applied menthol may decrease histamine-induced itch intensity without changing skin temperature (241), though other research has not supported this finding (242). L-menthol has been noted as increasing cold perception, attenuating warmth perception, and possibly stimulating high-threshold cold fibers or cold-sensitive nociceptors in humans (243).

- **Cardiovascular effects**: A small cardioaccelerating effect has been observed following menthol administration in human study (160).
- **Gastrointestinal effects**: The principal effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature due to a mechanism that may involve antagonism of calcium channels (76-78). Peppermint oil has been reported to improve rhythmic peristaltic contractions of the intestinal tract and relieve intestinal spasm (300) and may similarly be related to reduction of calcium influx (79; 80). Peppermint oil relaxed animal (79) and human colon smooth muscle cells *in vitro* (79). Peppermint has also exhibited effects on the histaminic, 5-hydroxytriptaminic, and cholinergic systems of the gut (105; 301). Intravenous peppermint oil released morphine-induced contraction of Oddi's sphincter in guinea pigs (302). Peppermint's use in esophageal spasms has been reviewed (303; 304).
- It has been suggested that the choleretic and antifoaming effects of peppermint oil may play an additional role in medicinal use (216). The carminative properties of peppermint are believed to be due to menthol causing relaxation of the esophageal sphincter (115). Based on findings from animal experimentation, peppermint oil appears to inhibit enterocyte glucose uptake by directly acting on the brush border membrane of the intestine (220). Increased bile secretion, attributable to the flavonoid, terpene, and menthol content of peppermint oil, as well as improvements in the solubility of bile, have been noted in animal study (96; 305). In 12 healthy volunteers, 90mg of peppermint oil in a non-enteric-coated gelatin capsule inhibited gall bladder contraction as demonstrated by ultrasound and slowed intestinal transit time as determined by a lactulose H_2 breath test (306). When combined with caraway oil, peppermint oil reduced the visceral hyperalgesia in rats exposed to colonic inflammatory agents (307).
- It has been posited that the antiulcerogenic activity of peppermint may be due to its free radical-scavenging properties (291).
- **Hepatic effects**: Peppermint has exhibited liver protective effects in animal and laboratory study, likely mediated by antioxidant mechanisms (44; 52; 308). However, peppermint has also been shown to induced dose-dependent hepatic damage and lipid peroxidation in rats (135).
- **Immune effects**: The peppermint constituent, alpha-humulene, has been reported to increase interleukin-8 (IL-8) secretion in human intestinal epithelial Caco-2 cells, though it had no significant effect on the secretion of such other soluble factors as TNF-alpha, IL-1beta, IL-6, or NGF, suggesting that the effect of alpha-humulene was specific to IL-8 secretion (223). The expression level of IL-8 mRNA was also significantly increased by treating with alpha-humulene. It has been suggested that these results indicate that the secretion of IL-8 by alpha-humulene is regulated at the transcriptional level.
- **Intracellular calcium effects**: Menthol has been found to bind and activate transient receptor potential melastatin 8 (TRPM8), a Ca^{2+}-permeable nonselective cation channel (20).
- **Muscle effects**: Olfactory stimulation with peppermint was found to encourage muscle activity, particularly in the upper trapezius, in human study (309).
- **Neurologic effects**: L-menthol has been observed to increase the subjective sense of nasal air flow and induce a sensation of coolness in the nasal cavity following inhalation, likely via stimulation of the major palatine nerve (244-248). Orally, menthol caused warmth enhancement and cold attenuation, although pretreatment with menthol caused warmth attenuation (249).
- Peppermint oil inhibited the heat shock-induced DNA fragmentation and condensation of nuclear chromatin and modulated the apoptosis of astrocytes via the activation of the caspase-3 *in vitro* (310).
- **Olfactory effects**: Peppermint has been found to induce strong olfactory stimulation in human study (311-315). Other experimentation has indicated that peppermint-like odorants can initiate sufficiently differential responses in the oral cavity to permit identification as well as cause trigeminal stimulation (312; 316; 317). In animal study, exposure to peppermint increased carbon-14-labeled 2-deoxy-D-glucose uptake and [14C]2-deoxyglucose (2-DG) uptake in a focal glomerular area (311; 318). Exposure to peppermint resulted in a decrease in the magnitude of beta-waves and a decrease in the fingertip skin temperature in humans, both based on Welch's method, implying a decreasing propensity of the aroused state and of the arousal response (319).
- **Performance-enhancing effects**: Based on human study, peppermint aroma may have beneficial effects on cognition, attention, and alertness and improve tactile performance (100-102; 320). In animal research, peppermint essential oil increased ambulatory activity, possibly via inhibition of dopamine uptake (53; 321-323).
- **Radioprotective effects**: Peppermint has been shown to have protective effects against irradiation in animal study (324-332). This effect may be related to the amount of phenolic compounds and their antioxidant and radical-scavenging activities (324; 326).
- **Respiratory effects**: L-menthol inhalation has been shown to decrease the sensation of respiratory discomfort during loaded breathing, possibly due to stimulation of cold receptors in the upper airway (250). In addition, inhaled peppermint oil induced rapid positive changes in patients with infiltrative pulmonary tuberculosis, including regression of tuberculous inflammation (110).
- L-menthol has been observed to increase the subjective sense of nasal air flow and induce a sensation of coolness in the nasal cavity following inhalation, likely via stimulation of the major palatine nerve (244-248).
- In human study, menthol caused a direct stimulation of cold receptors modulating the cool sensation, involving the subjective feeling of a clear and wide nose (251).
- **Stimulatory effects**: In animal study, peppermint has been shown to reduce sleepiness, although the mechanism of action is not clear (333; 334).

Pharmacodynamics/Kinetics:

- **Concentration levels**: In human study, the mean maximum plasma concentration was found to be 1,196ng/mL after the administration of enteric-coated Enteroplant®, a combination of caraway and peppermint, and 1,492ng/mL following ingestion of the immediate release preparation in 16 healthy males (335). In other experimentation, the plasma area under the plasma concentration-time curve ratios for menthol capsule to mint candy/mint tea treatment averaged 9.2 (95% CI: 8.2-10.1) (160). Recovery of menthol from urine (as the associated glucuronide) averaged 45.6 and 56.6% for the menthol capsule and mint candy/tea, respectively (difference not significant).
- **Excretion**: Peppermint is primarily eliminated via the bile. The major biliary metabolite is menthol glucuronide (336; 337), which undergoes enterohepatic circulation. According to a review, the urinary metabolites resulted from hydroxylation at the C-7 methyl group at C-8 and C-9 of the isopropyl moiety, forming a series of mono- and dihydroxymenthols and carboxylic acids, some of which were excreted in part as glucuronic acid conjugates (216). The review also cites studies with tritiated L-menthol in rats, which indicate about equal excretion in feces and urine (the main metabolite identified was menthol-glucuronide). Additional metabolites included mono- or di-hydroxylated menthol derivatives.
- **Elimination half-life**: In human study, the elimination half-life of menthol glucuronide averaged 56.2 minutes in plasma (160).
- In human experimentation, enteric-coated Colpermin® peppermint oil capsules significantly delayed the menthol metabolite appearance in the urine, suggesting that it is released in the colon (338). In 13 humans, two different enteric-coated peppermint oil capsules led to peak urinary menthol concentrations at three hours and nine hours after oral administration (339).
- **Metabolism**: According to human research, menthol, the active constituent of peppermint, is rapidly metabolized (160). Per other findings, another constituent, pulegone, is biotransformed to menthofuran and menthones (diastereomeric menthone and isomenthone) in rodents (129).
- Isolated metabolites of peppermint include piperitone from pulegone or menthones; 8-hydroxymenthones from pulegone; mintlactones (diastereomeric mintlactone and isomintlactone) and 7a-hydroxymintlactone from menthofuran treatment (129). In animal study, metabolites isolated from l-menthol include: p-menthane-3, 8-diol; p-menthane-3,9-diol; and 3,8 dihydroxy-p-menthane-7-carboxylic acid (340). With repeated administration of 800mg/kg of l-menthol, cytochrome P450 content and NADPH-cytochrome C reductase activity increased by nearly 80% in rats. Rat liver microsomes readily converted l-menthol to p-menthane-3,8-diol in the presence of NADPH and O2.
- **Time to clinical effects**: The relief of headache has been reported to occur in 15 minutes with topical application of peppermint oil, with an increased response when applied every 15 minutes up to an hour (90). Peak response for the relief of colonic spasm occurred within 30 seconds once introduced into the colon (341).

8. NON-TECHNICAL SUMMARY

- Peppermint (*Mentha* x *piperita* L.) is a sterile hybrid or cross of spearmint (*Mentha spicata*) and water mint (*Mentha aquatica*), which was first documented as sprouting in a field of spearmint growing in England in 1696. Since then, it has been intensively cultivated for its fragrant oil. It is a perennial herb growing to the size of 1m along stream banks and wastelands throughout much of Europe and North America. Peppermint oil is obtained by steam distillation from the fresh aboveground parts of the flowering plant of *Mentha* x *piperita* L.
- The name peppermint comes from the Latin *piper*, meaning “pepper,” and *Minthē*, the name of a nymph in Greek or Roman mythology, who was metamorphosed into a plant. Records from ancient Egypt, Greece, and Rome show that other members of the family, especially spearmint, have been used medicinally for centuries (1). Peppermint has been used traditionally for gastrointestinal disorders, including irritable bowel syndrome, indigestion, nausea, colds, headache, and cramps (2). Peppermint is also a popular culinary ingredient, figuring prominently in a number of dishes around the world, many of which are desserts and confectionaries.
- Peppermint is used extensively as a flavoring agent (3-17). The largest consumers of peppermint oil are manufacturers of chewing gum, toothpaste, mouthwash, and pharmaceuticals. In dental procedures, peppermint may also be used as a debonding agent (18; 19). Menthol, a secondary alcohol of peppermint, is widely employed in the food and pharmaceutical industries as a cooling or soothing compound and as an odorant (20).
- There has been clinical study on peppermint-containing products that were used as an antispasmodic and to treat irritable bowel syndrome (IBS), breast tenderness, dyspepsia, headache (topical), abdominal distention, abdominal pain, bad breath, cognitive improvement (in brain injury), common cold, dental plaque, hot flashes, mental performance and alertness, postherpetic neuralgia, postoperative nausea (inhalation), pruritus, stress, stroke recovery, tuberculosis, and urinary tract infection. According to the German Commission E monographs, peppermint oil (as well as peppermint leaf) has been used internally as an antispasmodic (upper gastrointestinal tract and bile ducts) and to treat irritable bowel syndrome, catarrh of the respiratory tract, and inflammation of the oral mucosa. Externally, peppermint oil has been used for myalgia and neuralgia. According to the German Commission E, peppermint oil may act as a carminative, cholagogue, antibacterial, and secretolytic, and it has a cooling action.
- Some people may be allergic or sensitive to peppermint, its constituents, or other plants in the Lamiaceae (mint) family. Peppermint may have cardiovascular, dental, gastrointestinal, hepatotoxic, neurotoxic, ocular, pulmonary/respiratory, and renal effects. Potential interactions with peppermint include: 5-fluorouracil, acyclovir, aminophylline, analgesics, antibiotics, antidiabetic agents, antifungals, anti-inflammatory agents, antiprotozoals, antispasmodic agents, antiulcer agents, antitussives, benzoic acid, caffeine, calcium channel blockers, cardiovascular agents, corticosteroids, cyclosporine, cytochrome P450-metabolized agents, diclofenac, hepatotoxic agents, hormonal agents, interleukins, iron

salts, neostigmine, ondansetron, oxytetracycline, propranolol, salicylates, tetracaine, venlafaxine, zidovudine, and herbs and supplements with similar effects, as well as basil, quercetin, and vitamin D.

9. Appendix A - Summary of Clinical and Traditional Health Benefits

Condition/indication	Definition	Grade
Irritable bowel syndrome (IBS)	A functional bowel disorder (conditions in which the bowel appears normal but does not function normally), characterized by chronic abdominal pain or discomfort, or change in bowel functioning without any known cause. Referred to as spastic colon, mucous colitis, spastic colitis, nervous stomach, or irritable colon.	A
Antispasmodic	An agent that prevents or relieves involuntary (smooth) muscle spasms or cramps.	B
Breast tenderness	Pain and soreness around the nipple or areola during breastfeeding. Nipples may be cracked or bleeding.	B
Dyspepsia	Indigestion, characterized by discomfort, heartburn, or nausea.	B
Headache (topical)	Pain in the head, ranging from mild to debilitating, resulting from any number of physiological causes.	B
Abdominal distention	The state of the abdomen being stretched beyond normal dimensions, usually from swallowed air or intestinal gas from fermentation. Also known as bloating.	C
Abdominal pain	Pain of the abdomen, usually from distention, ulcer, or spasm.	C
Bad breath	Bad-smelling breath, often caused by tooth decay, gum disease, digestive problems, smoking, or some systemic diseases. Also known as halitosis.	C
Cognitive improvement (in brain injury)	Enhancement of mental function after brain damage.	C
Common cold	A viral infection of the upper respiratory tract (nose and throat). Also referred to as viral rhinitis.	C
Dental plaque	The noncalcified accumulation mainly of oral microorganisms and their products that adheres tenaciously to the teeth and is not readily dislodged.	C
Hot flashes	A brief flushing and feeling of heat that occurs after the end of menstruation in women ages 48-50.	C
Mental performance/alertness	A combination of factors, including reaction time, concentration, and memory.	C
Postherpetic neuralgia	Neuralgia occurring as a consequence of infection by herpes virus.	C
Post-operative nausea (inhalation)	A feeling of sickness in the stomach characterized vomiting or an urge to vomit. Commonly occurs as an adverse effect of anesthesia used in surgery.	C
Pruritus	A condition characterized by intensely itchy skin; it can be a symptom of a disease process, or result from emotional factors.	C
Stress	A mentally or emotionally disruptive or upsetting condition occurring in response to adverse external influences and capable of affecting physical health, usually characterized by increased heart rate, a rise in blood pressure, muscular tension, irritability, and depression.	C
Stroke recovery	The process whereby patients undergo methodical rehabilitation in order to regain movement from paralysis that involves one side of the body in a lateral fashion.	C
Tuberculosis	A highly contagious infection caused by the bacterium *Mycobacterium tuberculosis*, characterized by the formation of tubercles in the lungs.	C
Urinary tract infection	Bacterial infiltration of the urinary tract.	C
Analgesic	A substance that reduces or eliminates pain.	NA
Anesthetic	An agent that deadens sensation and produces insensitivity to pain.	NA
Anorexia	1. Loss of appetite. 2. A psychological illness that is characterized by an extremely low body weight and an obsessive fear of gaining weight.	NA
Anti-inflammatory	An agent that reduces inflammation.	NA

Condition/indication	Definition	Grade
Antimicrobial	An agent used to prevent or inhibit the growth of microorganisms, such as bacteria. Includes antibiotics, antifungals, antiprotozoals, and antivirals.	NA
Antioxidant	A chemical compound or substance, such as vitamin E, vitamin C, or beta-carotene, thought to protect the body's cells from the damaging effects of oxidation that occur during metabolic processes.	NA
Anxiety	Apprehension of danger, or dread, accompanied by nervous restlessness, tension, increased heart rate, and shortness of breath unrelated to a clearly identifiable stimulus.	NA
Cancer	A malignant growth or tumor caused by abnormal and uncontrolled cell division.	NA
Cardiovascular disease	A disease that affects the heart and blood vessels.	NA
Carminative	An agent that relieves abdominal pain or distension by expelling gas from the stomach and intestines.	NA
Catarrh	1. Inflammation of mucous membranes, especially of the nasal air passages or respiratory system. 2. A condition of the mucous membranes, particularly those of the upper respiratory tract, including the sinuses and throat, characterized by inflammation and conspicuous, mainly mucinous discharge.	NA
Chemopreventive	The ability of a natural or laboratory-made substance to help prevent cancer.	NA
Cholagogue	An agent that stimulates the flow of bile from the liver.	NA
Dental procedures	Medical operations or interventions involving the teeth.	NA
Detoxification (arsenic)	A process in which poisonous substances are reduced or eliminated by the body.	NA
Dysmenorrhea	A condition characterized by painful menstruation.	NA
Fainting	Temporary loss of consciousness.	NA
Fatigue	Loss of energy.	NA
Fever	An elevated body temperature over 100°F (37.8°C) that can be caused by many different disease processes, such as infection with a microorganism.	NA
Flavoring	An agent, such as an extract or spice, used to impart flavor to the substance it is added to.	NA
Gallbladder disorders	Disorders of the gallbladder or along the bile tract.	NA
Hey fever	An allergic response to pollen or mold that negatively affects the mucous membranes of the eyes, nose, and air passages.	NA
Hirsutism	Presence of excessive bodily and facial hair, usually in a male pattern, especially in women; may be present in normal adults as an expression of an ethnic characteristic or may develop in children or adults as the result of androgen excess due to tumors, or nonandrogenetic or other drugs.	NA
Hypertension	Elevated blood pressure.	NA
Immunomodulation	Immunomodulation, also called immunoregulation; refers to the adjustment of the immune response to a desired level, as in immunopotentiation, immunosuppression, or induction of immunologic tolerance.	NA
Insecticide	An agent used to kill or control the growth of insects.	NA
Lice (*Pediculus humanus capitis*)	Plural form of louse, any of the small, wingless, usually flattened insects that are parasitic on warm-blooded animals and constitute the orders Anoplura and Mallophaga.	NA
Liver disorders	Disorders affecting the liver.	NA
Menstrual cramps	Lower abdominal aching or pain resulting from menstruation.	NA
Mental disorders	Illnesses of the brain that cause disruptions in a patient's thinking, feeling, moods, and ability to relate to others.	NA
Motion sickness	A feeling of discomfort characterized by nausea, vomiting, and dizziness, resulting from a mismatch between internal and external perception of motion, often occurring during travel in a moving vehicle.	NA
Myalgia	Muscular pain or tenderness.	NA
Nausea gravidarum	The nausea and vomiting of early pregnancy. Also called “morning sickness.”	NA
Odorant	A substance designed to emit an aroma.	NA

Condition/indication	Definition	Grade
Pest repellent	An agent used to repel pests, such as insects or rodents.	NA
Radioprotectant	Substance that prevents or lessens the effects of radiation.	NA
Respiratory disorders	Any disorder affecting organs or structures of the respiratory tract, including the nose, throat, trachea, bronchi, or lungs.	NA
Sleep aid	An agent that promotes sleep.	NA
Sore throat	A condition characterized by pain or discomfort on swallowing that may be due to any of a variety of inflammations of the tonsils, pharynx, or larynx, usually caused by a viral or bacterial infection.	NA
Spermicide	An agent that kills spermatozoa or sperm.	NA
Stimulant	An agent that increases physiological activity in the body.	NA
Sunburn (prevention)	Prevention of inflammation, blistering, and damage of the skin caused by overexposure to direct sunlight.	NA

10. BIBLIOGRAPHY

1. Briggs C. Peppermint: medicinal herb and flavouring agent. Can Pharm J 1993;126(2):89-92.
2. Spirling, L. I. and Daniels, I. R. Botanical perspectives on health peppermint: more than just an after-dinner mint. J R.Soc.Promot.Health 2001;121(1):62-63.
3. Ameen, V. Z., Pobiner, B. F., Giguere, G. C., and Carter, E. G. Ranitidine (Zantac) syrup versus Ranitidine effervescent tablets (Zantac) EFFERdose) in children: a single-center taste preference study. Paediatr.Drugs 2006;8(4):265-270.
4. Berman, T. M. Peppermint-flavored lidocaine. N.Engl.J Med 8-23-1979;301(8):437.
5. Cohen, M., Wolfe, R., Mai, T., and Lewis, D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheumatol. 2003;30(3):523-528.
6. Gregory, D. F., Koestner, J. A., and Tobias, J. D. Stability of midazolam prepared for oral administration. South.Med J 1993;86(7):771-2, 776.
7. HARRIS, Z. Peppermint flavored topical anesthetics. Anesthesiology 1948;9(1):88.
8. Huffington, A. Peppermint prozac. US News World Rep. 8-18-1997;123(7):28.
9. Jaffe, G. and Grimshaw, J. J. A comparison between Gastrils and Aludrox in the treatment of gastric hyperacidity in general practice. J Int Med Res 1982;10(6):437-442.
10. Jahnsen, T. and Thorn, P. An acceptability study of two pivampicillin mixtures in children in general practice. Scand.J Prim.Health Care 1987;5(4):241-243.
11. Muramoto, M. L., Ranger-Moore, J., and Leischow, S. J. Efficacy of oral transmucosal nicotine lozenge for suppression of withdrawal symptoms in smoking abstinence. Nicotine.Tob.Res 2003;5(2):223-230.
12. Pape, L. A. Problems of peppermint-flavored lidocaine. N.Engl.J Med 1-10-1980;302(2):121-122.
13. Ralston, S. L. Feeding behavior. Vet.Clin North Am Equine Pract. 1986;2(3):609-621.
14. Scott, R. C., Besag, F. M., Boyd, S. G., Berry, D., and Neville, B. G. Buccal absorption of midazolam: pharmacokinetics and EEG pharmacodynamics. Epilepsia 1998;39(3):290-294.
15. Tolia, V., Johnston, G., Stolle, J., and Lee, C. Flavor and taste of lansoprazole strawberry-flavored delayed-release oral suspension preferred over ranitidine peppermint-flavored oral syrup: in children aged between 5-11 years. Paediatr.Drugs 2004;6(2):127-131.
16. Tolia, V., Han, C., North, J. D., and Amer, F. Taste Comparisons for Lansoprazole Strawberry-Flavoured Delayed-Release Orally Disintegrating Tablet and Ranitidine Peppermint-Flavoured Syrup in Children. Clin Drug Investig. 2005;25(5):285-292.
17. Tolksdorf, W., Bremerich, D., and Nordmeyer, U. [Midazolam for premedication of infants. A comparison of the effect between oral and rectal administration]. Anasth.Intensivther.Notfallmed. 1989;24(6):355-361.
18. Larmour, C. J. and Chadwick, R. G. Effects of a commercial orthodontic debonding agent upon the surface microhardness of two orthodontic bonding resins. J Dent. 1995;23(1):37-40.
19. Larmour, C. J., McCabe, J. F., and Gordon, P. H. An ex vivo investigation into the effects of chemical solvents on the debond behaviour of ceramic orthodontic brackets. Br.J Orthod. 1998;25(1):35-39.
20. Mahieu, F., Owsianik, G., Verbert, L., Janssens, A., De Smedt, H., Nilius, B., and Voets, T. TRPM8-independent menthol-induced Ca2+ release from endoplasmic reticulum and Golgi. J Biol.Chem 2-2-2007;282(5):3325-3336.
21. McKay, D. L. and Blumberg, J. B. A review of the bioactivity and potential health benefits of peppermint tea (Mentha piperita L.). Phytother.Res 2006;20(8):619-633.
22. Akdogan, M., Kilinc, I., Oncu, M., Karaoz, E., and Delibas, N. Investigation of biochemical and histopathological effects of Mentha piperita L. and Mentha spicata L. on kidney tissue in rats. Hum.Exp Toxicol. 2003;22(4):213-219.
23. Rakover, Y., Ben Arye, E., and Goldstein, L. H. [The treatment of respiratory ailments with essential oils of some aromatic medicinal plants]. Harefuah 2008;147(10):783-8, 838.
24. Alvarado-Guzman, J. A., Gavillan-Suarez, J., and Germosen-Robineau, L. TRAMIL ethnopharmacological survey: knowledge distribution of medicinal plant use in the southeast region of Puerto Rico. P.R.Health Sci.J 2009;28(4):329-339.
25. Wilkinson, J. M. What do we know about herbal morning sickness treatments? A literature survey. Midwifery 2000;16(3):224-228.

26. Neves, A., Rosa, S., Goncalves, J., Rufino, A., Judas, F., Salgueiro, L., Lopes, M. C., Cavaleiro, C., and Mendes, A. F. Screening of five essential oils for identification of potential inhibitors of IL-1-induced Nf-kappaB activation and NO production in human chondrocytes: characterization of the inhibitory activity of alpha-pinene. Planta Med 2010;76(3):303-308.
27. Schelz, Z., Molnar, J., and Hohmann, J. Antimicrobial and antiplasmid activities of essential oils. Fitoterapia 2006;77(4):279-285.
28. Vidal, F., Vidal, J. C., Gadelha, A. P., Lopes, C. S., Coelho, M. G., and Monteiro-Leal, L. H. Giardia lamblia: the effects of extracts and fractions from Mentha x piperita Lin. (Lamiaceae) on trophozoites. Exp Parasitol. 2007;115(1):25-31.
29. Imai, H., Osawa, K., Yasuda, H., Hamashima, H., Arai, T., and Sasatsu, M. Inhibition by the essential oils of peppermint and spearmint of the growth of pathogenic bacteria. Microbios 2001;106 Suppl 1:31-39.
30. Hawrelak, J. A., Cattley, T., and Myers, S. P. Essential oils in the treatment of intestinal dysbiosis: A preliminary in vitro study. Altern.Med Rev. 2009;14(4):380-384.
31. Robson, N. J. Carminative property of peppermint in magnesium trisilicate mixture, BP. Anaesthesia 1987;42(7):776-777.
32. Choi, W. I., Lee, E. H., Choi, B. R., Park, H. M., and Ahn, Y. J. Toxicity of plant essential oils to Trialeurodes vaporariorum (Homoptera: Aleyrodidae). J Econ.Entomol. 2003;96(5):1479-1484.
33. Erler, F., Ulug, I., and Yalcinkaya, B. Repellent activity of five essential oils against Culex pipiens. Fitoterapia 2006;77(7-8):491-494.
34. Youssef, N. N., Oliver, J. B., Ranger, C. M., Reding, M. E., Moyseenko, J. J., Klein, M. G., and Pappas, R. S. Field evaluation of essential oils for reducing attraction by the Japanese beetle (Coleoptera: Scarabaeidae). J Econ.Entomol. 2009;102(4):1551-1558.
35. Thorsell, W., Mikiver, A., and Tunon, H. Repelling properties of some plant materials on the tick Ixodes ricinus L. Phytomedicine. 2006;13(1-2):132-134.
36. Yadav, S., Mittal, P. K., Saxena, P. N., and Singh, R. K. Effect of synergist piperonyl butoxide (PBO) on the toxicity of some essential oils against mosquito larvae. J Commun.Dis. 2008;40(4):263-268.
37. Barnard, D. R. Repellency of essential oils to mosquitoes (Diptera: Culicidae). J Med Entomol. 1999;36(5):625-629.
38. Girgenti, P. and Suss, L. [Repellent activity against Aedes aegypti (L.) of formulas based on natural vegetable extracts or synthetic active agents]. Ann.Ig 2002;14(3):205-210.
39. Samarasekera, R., Weerasinghe, I. S., and Hemalal, K. P. Insecticidal activity of menthol derivatives against mosquitoes. Pest.Manag.Sci. 2008;64(3):290-295.
40. Guney, M., Oral, B., Karahanli, N., Mungan, T., and Akdogan, M. The effect of Mentha spicata Labiatae on uterine tissue in rats. Toxicol.Ind.Health 2006;22(8):343-348.
41. Buch, J. G., Dikshit, R. K., and Mansuri, S. M. Effect of certain volatile oils on ejaculated human spermatozoa. Indian J Med Res 1988;87:361-363.
42. Goel, N. and Lao, R. P. Sleep changes vary by odor perception in young adults. Biol.Psychol. 2006;71(3):341-349.
43. Conti, A. A., Dilaghi, B., Modesti, P. A., and Nozzoli, C. New evidence in general practice, internal medicine and cardiovascular medicine. Intern.Emerg.Med 2009;4(2):157-159.
44. Sharma, A., Sharma, M. K., and Kumar, M. Protective effect of Mentha piperita against arsenic-induced toxicity in liver of Swiss albino mice. Basic Clin Pharmacol Toxicol. 2007;100(4):249-257.
45. SCHENK, H. [Clinical experiences with cholagutt in gallbladder diseases.]. Med Klin.(Munich) 12-28-1956;51(52):2218-2220.
46. Akdogan, M., Tamer, M. N., Cure, E., Cure, M. C., Koroglu, B. K., and Delibas, N. Effect of spearmint (Mentha spicata Labiatae) teas on androgen levels in women with hirsutism. Phytother.Res 2007;21(5):444-447.
47. KROGH, L. The anti-hypertensive action of folia Menthae piperitae. S.Afr.Med J 2-2-1957;31(5):104-105.
48. Veal, L. The potential effectiveness of essential oils as a treatment for headlice, Pediculus humanus capitis. Complement Ther Nurs.Midwifery 1996;2(4):97-101.
49. Canyon, D. V. and Speare, R. A comparison of botanical and synthetic substances commonly used to prevent head lice (Pediculus humanus var. capitis) infestation. Int J Dermatol. 2007;46(4):422-426.
50. Gonzalez, Audino P., Vassena, C., Zerba, E., and Picollo, M. Effectiveness of lotions based on essential oils from aromatic plants against permethrin resistant Pediculus humanus capitis. Arch.Dermatol.Res 2007;299(8):389-392.
51. Khater, H. F., Ramadan, M. Y., and El Madawy, R. S. Lousicidal, ovicidal and repellent efficacy of some essential oils against lice and flies infesting water buffaloes in Egypt. Vet.Parasitol. 10-14-2009;164(2-4):257-266.
52. Katikova, O. I., Kostin, IaV, Iagudina, R. I., and Tishkin, V. S. [Effect of plant preparations on lipid peroxidation parameters in acute toxic hepatitis]. Vopr.Med Khim. 2001;47(6):593-598.
53. Umezu, T., Sakata, A., and Ito, H. Ambulation-promoting effect of peppermint oil and identification of its active constituents. Pharmacol Biochem.Behav. 2001;69(3-4):383-390.
54. Liu, J. H., Chen, G. H., Yeh, H. Z., Huang, C. K., and Poon, S. K. Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol. 1997;32(6):765-768.
55. Lech, Y., Olesen, K. M., Hey, H., Rask-Pedersen, E., Vilien, M., and Ostergaard, O. [Treatment of irritable bowel syndrome with peppermint oil. A double- blind study with a placebo]. Ugeskr.Laeger 10-3-1988;150(40):2388-2389.
56. Cappello, G., Spezzaferro, M., Grossi, L., Manzoli, L., and Marzio, L. Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. Dig Liver Dis 2007;39(6):530-536.
57. Capanni M, Surrenti E, Biagini M, and et al. Efficacy of peppermint oil in the treatment of irritable bowel syndrome: a randomized, controlled trial. Gazz Med Ital 2005;164:119-126.
58. Carling L, Svedberg L, and Hultsen S. Short term treatment of the irritable bowel syndrome: a placebo-controlled trial of peppermint oil against hyoscyamine. Opuscula Med 1989;34:55-57.
59. Dew, M. J., Evans, B. K., and Rhodes, J. Peppermint oil for the irritable bowel syndrome: a multicentre trial. Br J Clin Pract. 1984;38(11-12):394-398.

60. Nash, P., Gould, S. R., and Bernardo, D. E. Peppermint oil does not relieve the pain of irritable bowel syndrome. Br.J Clin Pract. 1986;40(7):292-293.
61. Rees, W. D., Evans, B. K., and Rhodes, J. Treating irritable bowel syndrome with peppermint oil. Br Med J 10-6-1979;2(6194):835-836.
62. Lawson MJ, Knight RE, Tran K, and et al. Failure of enteric-coated peppermint oil in the irritable bowel syndrome: a randomized, double-blind crossover study. J.Gastroenterol Hepatol 1988;3(3):235-238.
63. Schneider MM and Otten MH. Efficacy of colpermin in the treatment of patients with irritable bowel syndrome (abstract). Gastroenterology 1990;98(5):A389.
64. Shaw, G., Srivastava, E. D., Sadlier, M., Swann, P., James, J. Y., and Rhodes, J. Stress management for irritable bowel syndrome: a controlled trial. Digestion 1991;50(1):36-42.
65. Ford, A. C., Talley, N. J., Spiegel, B. M., Foxx-Orenstein, A. E., Schiller, L., Quigley, E. M., and Moayyedi, P. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008;337:a2313.
66. Kline, R. M., Kline, J. J., Di Palma, J., and Barbero, G. J. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr. 2001;138(1):125-128.
67. Jailwala, J., Imperiale, T. F., and Kroenke, K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med 7-18-2000;133(2):136-147.
68. Pittler, M. H. and Ernst, E. Peppermint oil for irritable bowel syndrome: a critical review and meta-analysis. Am J Gastroenterol 1998;93(7):1131-1135.
69. Merat, S., Khalili, S., Mostajabi, P., Ghorbani, A., Ansari, R., and Malekzadeh, R. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. Dig.Dis.Sci. 2010;55(5):1385-1390.
70. Rhodes J, Evans BK, and Rees WD. Peppermint oil in enteric coated capsules for the treatment of irritable bowel syndrome: a double blind controlled trial. Hepato-Gastroenterology 1980;27(Suppl):252.
71. Evans BK, Levine DF, Mayberry JF, and et al. Multicentre trial of peppermint oil capsules in irritable bowel syndrome. Scand J Gastroenterol 1982;17:503.
72. Inamori, M., Akiyama, T., Akimoto, K., Fujita, K., Takahashi, H., Yoneda, M., Abe, Y., Kubota, K., Saito, S., Ueno, N., and Nakajima, A. Early effects of peppermint oil on gastric emptying: a crossover study using a continuous real-time 13C breath test (BreathID system). J Gastroenterol 2007;42(7):539-542.
73. Logan, A. C. and Beaulne, T. M. The treatment of small intestinal bacterial overgrowth with enteric- coated peppermint oil: A case report. Altern Med Rev 2002;7(5):410-417.
74. Czalbert, J, Neder, M., and Feher, K. Experiences with Colpermin therapy (Tillots-England) in patients with irritable bowel syndrome. Gyogyszereszet 1990;34(251):253.
75. Grigoleit, H. G. and Grigoleit, P. Peppermint oil in irritable bowel syndrome. Phytomedicine. 2005;12(8):601-606.
76. Grigoleit, H. G. and Grigoleit, P. Gastrointestinal clinical pharmacology of peppermint oil. Phytomedicine. 2005;12(8):607-611.
77. Micklefield, G., Jung, O., Greving, I., and May, B. Effects of intraduodenal application of peppermint oil (WS(R) 1340) and caraway oil (WS(R) 1520) on gastroduodenal motility in healthy volunteers. Phytother.Res 2003;17(2):135-140.
78. Micklefield, G. H., Greving, I., and May, B. Effects of peppermint oil and caraway oil on gastroduodenal motility. Phytother.Res 2000;14(1):20-23.
79. Taylor B, Luscombe D, and Duthie H. Inhibitory effect of peppermint oil on gastrointestinal smooth muscle. Gut 1983;24:A992.
80. Hawthorne M, Ferrante J, and et al. The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. J Aliment Pharmacol Therap 1988;2:101-118.
81. Hiki, N., Kurosaka, H., Tatsutomi, Y., Shimoyama, S., Tsuji, E., Kojima, J., Shimizu, N., Ono, H., Hirooka, T., Noguchi, C., Mafune, K., and Kaminishi, M. Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. Gastrointest.Endosc. 2003;57(4):475-482.
82. Sparks, M. J., O'Sullivan, P., Herrington, A. A., and Morcos, S. K. Does peppermint oil relieve spasm during barium enema? Br.J Radiol. 1995;68(812):841-843.
83. Mizuno, S., Kato, K., Ono, Y., Yano, K., Kurosaka, H., Takahashi, A., Abeta, H., Kushiro, T., Miyamoto, S., Kurihara, R., Hiki, N., Kaminishi, M., Iwasaki, A., and Arakawa, Y. Oral peppermint oil is a useful antispasmodic for double-contrast barium meal examination. J Gastroenterol.Hepatol. 2006;21(8):1297-1301.
84. Yamamoto, N., Nakai, Y., Sasahira, N., Hirano, K., Tsujino, T., Isayama, H., Komatsu, Y., Tada, M., Yoshida, H., Kawabe, T., Hiki, N., Kaminishi, M., Kurosaka, H., and Omata, M. Efficacy of peppermint oil as an antispasmodic during endoscopic retrograde cholangiopancreatography. J GASTROENTEROL HEPATOL 2006;21(9):1394-1398.
85. Asao, T., Kuwano, H., Ide, M., Hirayama, I., Nakamura, J. I., Fujita, K. I., and Horiuti, R. Spasmolytic effect of peppermint oil in barium during double-contrast barium enema compared with Buscopan. Clin Radiol. 2003;58(4):301-305.
86. Asao, T., Mochiki, E., Suzuki, H., Nakamura, J., Hirayama, I., Morinaga, N., Shoji, H., Shitara, Y., and Kuwano, H. An easy method for the intraluminal administration of peppermint oil before colonoscopy and its effectiveness in reducing colonic spasm. Gastrointest.Endosc. 2001;53(2):172-177.
87. Pimentel, M., Bonorris, G. G., Chow, E. J., and Lin, H. C. Peppermint oil improves the manometric findings in diffuse esophageal spasm. J Clin Gastroenterol 2001;33(1):27-31.
88. Melli, M. S., Rashidi, M. R., Nokhoodchi, A., Tagavi, S., Farzadi, L., Sadaghat, K., Tahmasebi, Z., and Sheshvan, M. K. A randomized trial of peppermint gel, lanolin ointment, and placebo gel to prevent nipple crack in primiparous breastfeeding women. Med Sci Monit. 2007;13(9):CR406-CR411.
89. Sayyah, Melli M., Rashidi, M. R., Delazar, A., Madarek, E., Kargar Maher, M. H., Ghasemzadeh, A., Sadaghat, K., and Tahmasebi, Z. Effect of peppermint water on prevention of nipple cracks in lactating primiparous women: a randomized controlled trial. Int Breastfeed.J 2007;2:7.

90. Gobel, H., Fresenius, J., Heinze, A., Dworschak, M., and Soyka, D. [Effectiveness of Oleum menthae piperitae and paracetamol in therapy of headache of the tension type]. Nervenarzt 1996;67(8):672-681.
91. Gobel, H., Schmidt, G., and Soyka, D. Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algesimetric headache parameters. Cephalalgia 1994;14(3):228-234.
92. Feng, X. Z. [Effect of peppermint oil hot compresses in preventing abdominal distension in postoperative gynecological patients]. Zhonghua Hu Li Za Zhi. 1997;32(10):577-578.
93. Thomas JM, Payne-James J, Carr N, and et al. Peppermint oil following appendicectomy. A (deliberately) small clinical trial. Surg.Res Commun 1988;2(4):285-287.
94. Hur, M. H., Park, J., Maddock-Jennings, W., Kim, D. O., and Lee, M. S. Reduction of mouth malodour and volatile sulphur compounds in intensive care patients using an essential oil mouthwash. Phytother Res 2007;21(7):641-643.
95. Sullivan, T. E., Warm, J. S., Schefft, B. K., Dember, W. N., O'Dell, M. W., and Peterson, S. J. Effects of olfactory stimulation on the vigilance performance of individuals with brain injury. J Clin Exp Neuropsychol. 1998;20(2):227-236.
96. Hansen B, Babiak G, Schilling M, and et al. A mixture of volatile oils in treatment of common cold. Therapiewoche 1984;34(13):2015-2019.
97. Cohen, B. M. and Dressler, W. E. Acute aromatics inhalation modifies the airways. Effects of the common cold. Respiration 1982;43(4):285-293.
98. Charles, C. H., Vincent, J. W., Borycheski, L., Amatnieks, Y., Sarina, M., Qaqish, J., and Proskin, H. M. Effect of an essential oil-containing dentifrice on dental plaque microbial composition. Am J Dent. 2000;13(Spec No):26C-30C.
99. Dyer, J., Ashley, S., and Shaw, C. A study to look at the effects of a hydrolat spray on hot flushes in women being treated for breast cancer. Complement Ther Clin Pract. 2008;14(4):273-279.
100. Ilmberger, J., Heuberger, E., Mahrhofer, C., Dessovic, H., Kowarik, D., and Buchbauer, G. The influence of essential oils on human attention. I: alertness. Chem Senses 2001;26(3):239-245.
101. Moss, M., Hewitt, S., Moss, L., and Wesnes, K. Modulation of cognitive performance and mood by aromas of peppermint and ylang-ylang. Int J Neurosci. 2008;118(1):59-77.
102. Barker, S., Grayhem, P., Koon, J., Perkins, J., Whalen, A., and Raudenbush, B. Improved performance on clerical tasks associated with administration of peppermint odor. Percept.Mot.Skills 2003;97(3 Pt 1):1007-1010.
103. Davies, S. J., Harding, L. M., and Baranowski, A. P. A novel treatment of postherpetic neuralgia using peppermint oil. Clin J Pain 2002;18(3):200-202.
104. Anderson, L. A. and Gross, J. B. Aromatherapy with peppermint, isopropyl alcohol, or placebo is equally effective in relieving postoperative nausea. J Perianesth.Nurs. 2004;19(1):29-35.
105. Tate, S. Peppermint oil: a treatment for postoperative nausea. J Adv.Nurs. 1997;26(3):543-549.
106. Tan, C. C., Wong, K. S., Thirumoorthy, T., Lee, E., and Woo, K-T. A randomized, crossover trial of Sarna and Eurax lotions in treatment of haemodialysis patients with uraemic pruritus. J Dermatol Treat 1990;1(5):235-238.
107. Klausner, M. A., Whitmore, C., Henry, E. V., Baybutt, R. I., and Schachtel, B. P. Additional antipruritic activity of methol when added to coal tar in dandruff-associated pruritus. Clin Pharmacol Ther 1988;43(2):173.
108. Park, M. K. and Lee, E. S. [The effect of aroma inhalation method on stress responses of nursing students]. Taehan Kanho.Hakhoe.Chi 2004;34(2):344-351.
109. Shin, B. C. and Lee, M. S. Effects of aromatherapy acupressure on hemiplegic shoulder pain and motor power in stroke patients: a pilot study. J Altern.Complement Med 2007;13(2):247-251.
110. Shkurupii, V. A., Kazarinova, N. V., Ogirenko, A. P., Nikonov, S. D., Tkachev, A. V., and Tkachenko, K. G. [Efficiency of the use of peppermint (Mentha piperita L) essential oil inhalations in the combined multi-drug therapy for pulmonary tuberculosis]. Probl.Tuberk. 2002;(4):36-39.
111. Ebbinghaus K D. A 'tea' containing various plant products as adjuvant to chemotherapy of urinary tract infections. Therapiewoche 1985;35:2041-2051.
112. Eickholt, T. H. and Box, R. H. Toxicities of peppermint and Pycnanthemun albescens oils, fam. Labiateae. J Pharm Sci 1965;54(7):1071-1072.
113. Mori, M., Ikeda, N., Kato, Y., Minamino, M., and Watabe, K. [Quality evaluation of essential oils]. Yakugaku Zasshi 2002;122(3):253-261.
114. Yeung, D. Y., Lee, T., Grant, G., Ma, M., and Kwong, E. A SPME-GC procedure for monitoring peppermint flavor in tablets. J Pharm Biomed.Anal. 1-1-2003;30(5):1469-1477.
115. Giachetti D, Taddei E, and Taddei T. Pharmacological activity of Mentha piperita, Salvia officinalis and Rosmarinus officinalis essences on Oddi?s sphincter. Planta Med 1986;52:543-544.
116. Freise, J. and Kohler, S. [Peppermint oil-caraway oil fixed combination in non-ulcer dyspepsia-- comparison of the effects of enteric preparations]. Pharmazie 1999;54(3):210-215.
117. May, B., Kohler, S., and Schneider, B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. Aliment.Pharmacol Ther 2000;14(12):1671-1677.
118. Madisch, A., Heydenreich, C. J., Wieland, V., Hufnagel, R., and Hotz, J. Treatment of functional dyspepsia with a fixed peppermint oil and caraway oil combination preparation as compared to cisapride. A multicenter, reference-controlled double-blind equivalence study. Arzneimittelforschung. 1999;49(11):925-932.
119. May, B., Kuntz, H. D., Kieser, M., and Kohler, S. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. Arzneimittelforschung. 1996;46(12):1149-1153.
120. Barnick CG and Cardozo LD. The treatment of abdominal distension and dyspepsia with enteric coated peppermint oil following routine gynaecological intraperitoneal surgery. J Obstet.Gynecol 1990;10(5):423-424.
121. Dalvi, S. S., Nadkarni, P. M., Pardesi, R., and Gupta, K. C. Effect of peppermint oil on gastric emptying in man: a preliminary study using a radiolabelled solid test meal. Indian J Physiol Pharmacol 1991;35(3):212-214.
122. Wyllie, J. P. and Alexander, F. W. Nasal instillation of 'Olbas Oil' in an infant. Arch Dis Child 1994;70(4):357-358.

123. Haidl, P., Kemper, P., Butnarasu, S. J., Klauke, M., Wehde, H., and Kohler, D. [Does the inhalation of a 1% L-menthol solution in the premedication of fiberoptic bronchoscopy affect coughing and the sensation of dyspnea?]. Pneumologie 2001;55(3):115-119.
124. Morice, A. H., Marshall, A. E., Higgins, K. S., and Grattan, T. J. Effect of inhaled menthol on citric acid induced cough in normal subjects. Thorax 1994;49(10):1024-1026.
125. Eccles, R., Jawad, M. S., and Morris, S. The effects of oral administration of (-)-menthol on nasal resistance to airflow and nasal sensation of airflow in subjects suffering from nasal congestion associated with the common cold. J Pharm Pharmacol 1990;42(9):652-654.
126. Lazutka, J. R., Mierauskiene, J., Slapsyte, G., and Dedonyte, V. Genotoxicity of dill (Anethum graveolens L.), peppermint (Menthaxpiperita L.) and pine (Pinus sylvestris L.) essential oils in human lymphocytes and Drosophila melanogaster. Food Chem Toxicol. 2001;39(5):485-492.
127. Olsen P and Thorup I. Neurotoxicity in rats dosed with peppermint oil and pulegone. Disease, Metabolism and Reproduction in the Toxic Response to Drugs ad other Chemicals 1984;Suppl 7:408-409.
128. 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.
129. Ferguson, L. J., Lebetkin, E. H., Lih, F. B., Tomer, K. B., Parkinson, H. D., Borghoff, S. J., and Burka, L. T. 14C-labeled pulegone and metabolites binding to alpha2u-globulin in kidneys of male F-344 rats. J Toxicol.Environ.Health A 2007;70(17):1416-1423.
130. Thorup, I., Wurtzen, G., Carstensen, J., and Olsen, P. Short term toxicity study in rats dosed with peppermint oil. Toxicol Lett. 1983;19(3):211-215.
131. Mengs U and Stotzem CD. Toxicological evaluation of peppermint oil in rodents and dogs. Medical Science Research 1989;17(11):499-500.
132. Spindler, P. and Madsen, C. Subchronic toxicity study of peppermint oil in rats. Toxicol.Lett. 1992;62(2-3):215-220.
133. Madsen, C., Wurtzen, G., and Carstensen, J. Short-term toxicity study in rats dosed with menthone. Toxicol.Lett. 1986;32(1-2):147-152.
134. Pappas, B. A., Vickers, G., Buxton, M., and Pusztay, W. Infant rat hyperactivity elicited by home cage bedding is unaffected by neonatal telencephalic dopamine or norepinephrine depletion. Pharmacol Biochem.Behav. 1982;16(1):151-154.
135. Akdogan, M., Ozguner, M., Aydin, G., and Gokalp, O. Investigation of biochemical and histopathological effects of Mentha piperita Labiatae and Mentha spicata Labiatae on liver tissue in rats. Hum.Exp Toxicol. 2004;23(1):21-28.
136. Vo, L. T., Chan, D., and King, R. G. Investigation of the effects of peppermint oil and valerian on rat liver and cultured human liver cells. Clin Exp Pharmacol Physiol 2003;30(10):799-804.
137. Akdogan, M., Ozguner, M., Kocak, A., Oncu, M., and Cicek, E. Effects of peppermint teas on plasma testosterone, follicle-stimulating hormone, and luteinizing hormone levels and testicular tissue in rats. Urology 2004;64(2):394-398.
138. Behrends, M., Beiderlinden, M., and Peters, J. Acute lung injury after peppermint oil injection. Anesth.Analg. 2005;101(4):1160-1162.
139. McGowan EM. Menthol urticaria. Arch Dermatol 1966;94:62-63.
140. Morton, C. A., Garioch, J., Todd, P., Lamey, P. J., and Forsyth, A. Contact sensitivity to menthol and peppermint in patients with intra- oral symptoms. Contact Dermatitis 1995;32(5):281-284.
141. Wilkinson, S. M. and Beck, M. H. Allergic contact dermatitis from menthol in peppermint. Contact Dermatitis 1994;30(1):42-43.
142. Foti, C., Conserva, A., Antelmi, A., Lospalluti, L., and Angelini, G. Contact dermatitis from peppermint and menthol in a local action transcutaneous patch. Contact Dermatitis 2003;49(6):312-313.
143. Dooms-Goossens, A., Degreef, H., Holvoet, C., and Maertens, M. Turpentine-induced hypersensitivity to peppermint oil. Contact Dermatitis 1977;3(6):304-308.
144. Lewis, F. M., Shah, M., and Gawkrodger, D. J. Contact sensitivity to food additives can cause oral and perioral symptoms. Contact Dermatitis 1995;33(6):429-430.
145. Schempp, C. M., Schopf, E., and Simon, J. C. [Plant-induced toxic and allergic dermatitis (phytodermatitis)]. Hautarzt 2002;53(2):93-97.
146. Camarasa G and Alomar A. Menthol dermatitis from cigarettes. Contact Dermatitis 1978;4:169-170.
147. Papa CM and Shelly WB. Menthol hypersensitivity. JAMA 1964;189:546-548.
148. Anderson, F. E. Chronic bullous eruptions of the skin. Aust.Fam.Physician 1978;7(12):1516-4.
149. Subiza, J., Subiza, J. L., Valdivieso, R., Escribano, P. M., Garcia, R., Jerez, M., and Subiza, E. Toothpaste flavor-induced asthma. J Allergy Clin Immunol 1992;90(6 Pt 1):1004-1006.
150. Andersen, K. E. Contact allergy to toothpaste flavors. Contact Dermatitis 1978;4(4):195-198.
151. Sainio, E. L. and Kanerva, L. Contact allergens in toothpastes and a review of their hypersensitivity. Contact Dermatitis 1995;33(2):100-105.
152. Calnan, C. D., Bandmann, H. J., Cronin, E., Fregert, S., Hjorth, N., Magnusson, B., Malten, K., Meneghini, C. L., Pirila, V., and Wilkinson, D. S. Hand dermatitis in housewives. Br J Dermatol. 1970;82(6):543-548.
153. Kalavala, M., Hughes, T. M., Goodwin, R. G., Anstey, A. V., and Stone, N. M. Allergic contact dermatitis to peppermint foot spray. Contact Dermatitis 2007;57(1):57-58.
154. Peltonen, L., Wickstrom, G., and Vaahtoranta, M. Occupational dermatoses in the food industry. Derm.Beruf.Umwelt. 1985;33(5):166-169.
155. Moghadam, B. K., Gier, R., and Thurlow, T. Extensive oral mucosal ulcerations caused by misuse of a commercial mouthwash. Cutis 1999;64(2):131-134.
156. Vermaat, H., van Meurs, T., Rustemeyer, T., Bruynzeel, D. P., and Kirtschig, G. Vulval allergic contact dermatitis due to peppermint oil in herbal tea. Contact Dermatitis 2008;58(6):364-365.

157. Gijzen, M., Lewinsohn, E., and Croteau, R. Antigenic cross-reactivity among monoterpene cyclases from grand fir and induction of these enzymes upon stem wounding. Arch.Biochem.Biophys. 5-1-1992;294(2):670-674.
158. Hausen, B. M. [Toothpaste allergy]. Dtsch.Med Wochenschr. 2-24-1984;109(8):300-302.
159. NURICK, S. Atrial fibrillation and peppermint eating. Report of a case. Guys.Hosp.Rep. 1963;112:171-174.
160. Gelal, A., Jacob, P., III, Yu, L., and Benowitz, N. L. Disposition kinetics and effects of menthol. Clin Pharmacol Ther 1999;66(2):128-135.
161. Parys, B. T. Chemical burns resulting from contact with peppermint oil mar: a case report. Burns Incl.Therm.Inj. 1983;9(5):374-375.
162. Tamir, S., Davidovich, Z., Attal, P., and Eliashar, R. Peppermint oil chemical burn. Otolaryngol.Head Neck Surg. 2005;133(5):801-802.
163. Nielsen, J. B. Natural oils affect the human skin integrity and the percutaneous penetration of benzoic acid dose-dependently. Basic Clin Pharmacol Toxicol. 2006;98(6):575-581.
164. Weston, C. F. Anal burning and peppermint oil. Postgrad Med J 1987;63(742):717.
165. Javorka, K., Tomori, Z., and Zavarska, L. Protective and defensive airway reflexes in premature infants. Physiol Bohemoslov. 1980;29(1):29-35.
166. Heng, M. C. Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. Cutis 1987;39(5):442-444.
167. Wandelt, S. [Abuse of peppermint and caries. 1. Clinical observations and experimental studies]. Dtsch Zahnarztl.Z 2-1-1966;21(2):281-289.
168. Bhatavadekar, N., Khandelwal, N., and Bouquot, J. E. Oral and maxillofacial pathology case of the month. Plasma cell gingivitis. Tex.Dent.J 2008;125(4):372-373.
169. Shahdad, S. A., McCabe, J. F., and Wassell, R. W. Developments in denture teeth to prevent softening by food solvents. J Mater.Sci.Mater.Med 2007;18(8):1599-1603.
170. Rogers, S. N. and Pahor, A. L. A form of stomatitis induced by excessive peppermint consumption. Dent.Update. 1995;22(1):36-37.
171. Friedman, G. Nutritional therapy of irritable bowel syndrome. Gastroenterol.Clin North Am 1989;18(3):513-524.
172. Grant, P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. Phytother.Res 2010;24(2):186-188.
173. Akdogan, M., Gultekin, F., and Yontem, M. Effect of Mentha piperita (Labiatae) and Mentha spicata (Labiatae) on iron absorption in rats. Toxicol.Ind.Health 2004;20(6-10):119-122.
174. Wang, L. H., Wang, C. C., and Kuo, S. C. Vehicle and enhancer effects on human skin penetration of aminophylline from cream formulations: evaluation in vivo. J Cosmet.Sci. 2007;58(3):245-254.
175. Wacher, V. J., Wong, S., and Wong, H. T. Peppermint oil enhances cyclosporine oral bioavailability in rats: comparison with D-alpha-tocopheryl poly(ethylene glycol 1000) succinate (TPGS) and ketoconazole. J Pharm Sci. 2002;91(1):77-90.
176. Dresser, G. K., Wacher, V., Wong, S., Wong, H. T., and Bailey, D. G. Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. Clin Pharmacol Ther 2002;72(3):247-255.
177. Maliakal, P. P. and Wanwimolruk, S. Effect of herbal teas on hepatic drug metabolizing enzymes in rats. J Pharm Pharmacol 2001;53(10):1323-1329.
178. Swain, A. R., Dutton, S. P., and Truswell, A. S. Salicylates in foods. J Am Diet.Assoc. 1985;85(8):950-960.
179. Wu, S. X., Wang, Z. R., and Chen, X. H. Enhanced percutaneous penetration with menthol. Chinese Journal of Hospital Pharmacy 1994;14:366-368.
180. Abd-ElGawad, A. E., Sakr, F. M., Borg, T. M., Elhanbly, S., and Abu, Hashim, II. Comparison of different perrmeation enhancers on topical ketoconazole formulations. Arzneimittelforschung. 2007;57(1):47-50.
181. Liu, Y., Ye, X., Feng, X., Zhou, G., Rong, Z., Fang, C., and Chen, H. Menthol facilitates the skin analgesic effect of tetracaine gel. Int J Pharm 11-23-2005;305(1-2):31-36.
182. Fang, C., Liu, Y., Ye, X., Rong, Z. X., Feng, X. M., Jiang, C. B., and Chen, H. Z. Synergistically enhanced transdermal permeation and topical analgesia of tetracaine gel containing menthol and ethanol in experimental and clinical studies. Eur J Pharm Biopharm 2008;68(3):735-740.
183. Krishnaiah, Y. S., Kumar, M. S., Raju, V., Lakshmi, M., and Rama, B. Penetration-enhancing effect of ethanolic solution of menthol on transdermal permeation of ondansetron hydrochloride across rat epidermis. Drug Deliv. 2008;15(4):227-234.
184. Shishu, Rajan, S., and Kamalpreet. Development of novel microemulsion-based topical formulations of acyclovir for the treatment of cutaneous herpetic infections. AAPS.PharmSciTech. 2009;10(2):559-565.
185. Singh, G., Ghosh, B., Kaushalkumar, D., and Somsekhar, V. Screening of venlafaxine hydrochloride for transdermal delivery: passive diffusion and iontophoresis. AAPS.PharmSciTech. 2008;9(3):791-797.
186. Abdullah, D., Ping, Q. N., and Liu, G. J. Enhancing effect of essential oils on the penetration of 5-fluorouracil through rat skin. Yao Xue.Xue.Bao.(Acta Pharmaceutica Sinica) 1996;31(3):214-221.
187. Holst, L., Wright, D., Haavik, S., and Nordeng, H. Safety and efficacy of herbal remedies in obstetrics-review and clinical implications. Midwifery 9-24-2009;
188. Moussally, K., Oraichi, D., and Berard, A. Herbal products use during pregnancy: prevalence and predictors. Pharmacoepidemiol.Drug Saf 2009;18(6):454-461.
189. Westfall, R. E. Use of anti-emetic herbs in pregnancy: women's choices, and the question of safety and efficacy. Complement Ther Nurs.Midwifery 2004;10(1):30-36.
190. Eccles, R., Griffiths, D. H., Newton, C. G., and Tolley, N. S. The effects of menthol isomers on nasal sensation of airflow. Clin Otolaryngol. 1988;13(1):25-29.
191. Green, B. G. Menthol inhibits the perception of warmth. Physiol Behav 1986;38(6):833-838.
192. Green, B. G. and McAuliffe, B. L. Menthol desensitization of capsaicin irritation. Evidence of a short-term anti-nociceptive effect. Physiol Behav. 2000;68(5):631-639.

193. Lundy, R. F., Jr. and Contreras, R. J. Neural responses of thermal-sensitive lingual fibers to brief menthol stimulation. Brain Res 4-4-1994;641(2):208-216.
194. Gu, S., Gao, J., Hou, X., Ding, B., Zhang, W., Gao, S., and Ding, X. Effects of penetration enhancers on Shuangwu traumatic formula: In vitro percutaneous absorption and in vivo pharmacodynamic evaluation of an herb medicine. Eur J Pharm Biopharm 2009;73(3):385-390.
195. Kavaliers, M. and Innes, D. G. Population differences in benzodiazepine sensitive male scent-induced analgesia in the deer mouse, Peromyscus maniculatus. Pharmacol Biochem.Behav. 1989;32(3):613-619.
196. Kavaliers, M. and Innes, D. G. Male scent-induced analgesia in the deer mouse, Peromyscus maniculatus: involvement of benzodiazepine systems. Physiol Behav. 1988;42(2):131-135.
197. Betoni, J. E., Mantovani, R. P., Barbosa, L. N., Di Stasi, L. C., and Fernandes, Junior A. Synergism between plant extract and antimicrobial drugs used on Staphylococcus aureus diseases. Mem.Inst.Oswaldo Cruz 2006;101(4):387-390.
198. Lis-Balchin, M., Steyrl, H., and Krenn, E. The comparative effect of novel Pelargonium essential oils and their corresponding hydrosols as antimicrobial agents in a model food system. Phytother.Res 2003;17(1):60-65.
199. Tassou, C. C., Drosinos, E. H., and Nychas, G. J. Effects of essential oil from mint (Mentha piperita) on Salmonella enteritidis and Listeria monocytogenes in model food systems at 4 degrees and 10 degrees C. J Appl.Bacteriol. 1995;78(6):593-600.
200. van Vuuren, S. F., Suliman, S., and Viljoen, A. M. The antimicrobial activity of four commercial essential oils in combination with conventional antimicrobials. Lett.Appl.Microbiol. 2009;48(4):440-446.
201. Buyukbalci, A. and El, S. N. Determination of in vitro antidiabetic effects, antioxidant activities and phenol contents of some herbal teas. Plant Foods Hum.Nutr 2008;63(1):27-33.
202. el Naghy, M. A., Maghazy, S. N., Fadl-Allah, E. M., and el Gendy, Z. K. Fungistatic action of natural oils and fatty acids on dermatophytic and saprophytic fungi. Zentralbl.Mikrobiol. 1992;147(3-4):214-220.
203. Mimica-Dukic, N., Bozin, B., Sokovic, M., Mihajlovic, B., and Matavulj, M. Antimicrobial and antioxidant activities of three Mentha species essential oils. Planta Med 2003;69(5):413-419.
204. Duarte, M. C., Figueira, G. M., Sartoratto, A., Rehder, V. L., and Delarmelina, C. Anti-Candida activity of Brazilian medicinal plants. J Ethnopharmacol 2-28-2005;97(2):305-311.
205. Lopez, A. G., Theumer, M. G., Zygadlo, J. A., and Rubinstein, H. R. Aromatic plants essential oils activity on Fusarium verticillioides Fumonisin B(1) production in corn grain. Mycopathologia 2004;158(3):343-349.
206. Mabrouk, S. S. and El Shayeb, N. M. Inhibition of aflatoxin formation by some spices. Z Lebensm.Unters.Forsch. 1980;171(5):344-347.
207. Pattnaik, S., Subramanyam, V. R., and Kole, C. Antibacterial and antifungal activity of ten essential oils in vitro. Microbios 1996;86(349):237-246.
208. Rai, M. K. and Upadhyay, S. Laboratory evaluation of essential oil of Mentha piperita Linn. against Trichophyton mentagrophytes. Hindustan Antibiot.Bull. 1988;30(3-4):82-84.
209. Sarbhoy, A. K., Varshney, J. L., Maheshwari, M. L., and Saxena, D. B. Efficacy of some essential oils and their constituents on few ubiquitous molds. Zentralbl.Bakteriol.Naturwiss. 1978;133(7-8):723-725.
210. Yadegarinia, D., Gachkar, L., Rezaei, M. B., Taghizadeh, M., Astaneh, S. A., and Rasooli, I. Biochemical activities of Iranian Mentha piperita L. and Myrtus communis L. essential oils. Phytochemistry 2006;67(12):1249-1255.
211. Sokovic, M. D., Glamoclija, J., Marin, P. D., Brkic, D. D., Vukojevic, J., Jovanovic, D., Bulajic, N., and Kataranovski, D. Antifungal activity of the essential oil of mentha x piperita. Pharm Biol 2006;44(7):511-515.
212. Hugbo, P. G. Evaluation of antifungal properties of peppermint water. Int J Pharm 1982;10:193-198.
213. Pandey, A. K. Composition and in-vitro antifungal activity of the essential oil of menthol mint (Mentha arvensis L.) growing in central India. Ind Drugs 2003;40:126-128.
214. Inouye, S., Uchida, K., Nishiyama, Y., Hasumi, Y., Yamaguchi, H., and Abe, S. Combined effect of heat, essential oils and salt on fungicidal activity against Trichophyton mentagrophytes in a foot bath. Nippon Ishinkin.Gakkai Zasshi 2007;48(1):27-36.
215. Atta, A. H. and Alkofahi, A. Anti-nociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts. J Ethnopharmacol 1998;60(2):117-124.
216. Grigoleit, H. G. and Grigoleit, P. Pharmacology and preclinical pharmacokinetics of peppermint oil. Phytomedicine. 2005;12(8):612-616.
217. Khayyal, M. T., Seif-El-Nasr, M., El Ghazaly, M. A., Okpanyi, S. N., Kelber, O., and Weiser, D. Mechanisms involved in the gastro-protective effect of STW 5 (Iberogast) and its components against ulcers and rebound acidity. Phytomedicine 2006;13 Suppl 5:56-66.
218. Laude, E. A., Morice, A. H., and Grattan, T. J. The antitussive effects of menthol, camphor and cineole in conscious guinea-pigs. Pulm.Pharmacol 1994;7(3):179-184.
219. Gelal, A., Guven, H., Balkan, D., Artok, L., and Benowitz, N. L. Influence of menthol on caffeine disposition and pharmacodynamics in healthy female volunteers. Eur J Clin Pharmacol 2003;59(5-6):417-422.
220. Beesley, A., Hardcastle, J., Hardcastle, P. T., and Taylor, C. J. Influence of peppermint oil on absorptive and secretory processes in rat small intestine. Gut 1996;39(2):214-219.
221. Wang, H, Xu, W. M., and Wang, Z. R. Effect of l-menthol and synthetic bomeol on enhanced percutaneous penetration. Chinese Traditional and Herbal Drugs 1997;28:93-95.
222. Kumar, V., Kural, M. R., Pereira, B. M., and Roy, P. Spearmint induced hypothalamic oxidative stress and testicular anti-androgenicity in male rats - altered levels of gene expression, enzymes and hormones. Food Chem Toxicol. 2008;46(12):3563-3570.
223. Satsu, H., Matsuda, T., Toshimitsu, T., Mori, A., Mae, T., Tsukagawa, M., Kitahara, M., and Shimizu, M. Regulation of interleukin-8 secretion in human intestinal epithelial Caco-2 cells by alpha-humulene. Biofactors 2004;21(1-4):137-139.
224. Hurrell, R. F., Reddy, M., and Cook, J. D. Inhibition of non-haem iron absorption in man by polyphenolic-containing beverages. Br.J Nutr 1999;81(4):289-295.

225. Kunta, J. R., Goskonda, V. R., Brotherton, H. O., Khan, M. A., and Reddy, I. K. Effect of menthol and related terpenes on the percutaneous absorption of propranolol across excised hairless mouse skin. J Pharm Sci. 1997;86(12):1369-1373.
226. Zahir, A., Kunta, J. R., Khan, M. A., and Reddy, I. K. Effect of menthol on permeability of an optically active and racemic propranolol across guinea pig skin. Drug Dev.Ind.Pharm 1998;24(9):875-878.
227. Narishetty, S. T. and Panchagnula, R. Effect of L-menthol and 1,8-cineole on phase behavior and molecular organization of SC lipids and skin permeation of zidovudine. J Control Release 1-20-2005;102(1):59-70.
228. Edris, A. E. and Farrag, E. S. Antifungal activity of peppermint and sweet basil essential oils and their major aroma constituents on some plant pathogenic fungi from the vapor phase. Nahrung 2003;47(2):117-121.
229. Olivella, M. S., Lhez, L., Pappano, N. B., and Debattista, N. B. Effects of dimethylformamide and L-menthol permeation enhancers on transdermal delivery of quercetin. Pharm Dev.Technol. 2007;12(5):481-484.
230. Park, E. J., Kim, S. H., Kim, B. J., Kim, S. Y., So, I., and Jeon, J. H. Menthol Enhances an Antiproliferative Activity of 1alpha,25-Dihydroxyvitamin D(3) in LNCaP Cells. J Clin Biochem.Nutr 2009;44(2):125-130.
231. Haeseler, G., Maue, D., Grosskreutz, J., Bufler, J., Nentwig, B., Piepenbrock, S., Dengler, R., and Leuwer, M. Voltage-dependent block of neuronal and skeletal muscle sodium channels by thymol and menthol. Eur J Anaesthesiol. 2002;19(8):571-579.
232. Wasner, G., Schattschneider, J., Binder, A., and Baron, R. Topical menthol--a human model for cold pain by activation and sensitization of C nociceptors. Brain 2004;127(Pt 5):1159-1171.
233. McKemy, D. D., Neuhausser, W. M., and Julius, D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 3-7-2002;416(6876):52-58.
234. Agarwal, V., Lal, P., and Pruthi, V. Prevention of Candida albicans biofilm by plant oils. Mycopathologia 2008;165(1):13-19.
235. Bluma, R., Amaiden, M. R., Daghero, J., and Etcheverry, M. Control of Aspergillus section Flavi growth and aflatoxin accumulation by plant essential oils. J Appl.Microbiol. 2008;105(1):203-214.
236. Magro, A., Carolino, M., Bastos, M., and Mexia, A. Efficacy of plant extracts against stored-products fungi. Rev.Iberoam.Micol. 2006;23(3):176-178.
237. Sokovic, M. D., Vukojevic, J., Marin, P. D., Brkic, D. D., Vajs, V., and van Griensven, L. J. Chemical composition of essential oils of Thymus and Mentha species and their antifungal activities. Molecules. 2009;14(1):238-249.
238. Tampieri, M. P., Galuppi, R., Macchioni, F., Carelle, M. S., Falcioni, L., Cioni, P. L., and Morelli, I. The inhibition of Candida albicans by selected essential oils and their major components. Mycopathologia 2005;159(3):339-345.
239. Yigit, D., Yigit, N., and Ozgen, U. An investigation on the anticandidal activity of some traditional medicinal plants in Turkey. Mycoses 2009;52(2):135-140.
240. Spichiger, M., Brenneisen, R., Felix, R., and Muhlbauer, R. C. The inhibition of bone resorption in rats treated with (-)-menthol is due to its metabolites. Planta Med 2006;72(14):1290-1295.
241. Bromm, B., Scharein, E., Darsow, U., and Ring, J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. Neurosci Lett 3-10-1995;187(3):157-160.
242. Yosipovitch, G., Szolar, C., Hui, X. Y., and Maibach, H. Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. Arch Dermatol Res 1996;288(5-6):245-248.
243. Green, B. G. The sensory effects of l-menthol on human skin. Somatosens.Mot.Res 1992;9(3):235-244.
244. Burrow, A., Eccles, R., and Jones, A. S. The effects of camphor, eucalyptus and menthol vapour on nasal resistance to airflow and nasal sensation. Acta Otolaryngol. 1983;96(1-2):157-161.
245. Eccles, R. and Jones, A. S. The effect of menthol on nasal resistance to air flow. J Laryngol Otol 1983;97(8):705-709.
246. Eccles, R., Griffiths, D. H., Newton, C. G., and Tolley, N. S. The effects of D and L isomers of menthol upon nasal sensation of airflow. J Laryngol Otol 1988;102(6):506-508.
247. Naito, K., Ohoka, E., Kato, R., Kondo, Y., and Iwata, S. The effect of L-menthol stimulation of the major palatine nerve on nasal patency. Auris Nasus Larynx 1991;18(3):221-226.
248. Naito, K., Komori, M., Kondo, Y., Takeuchi, M., and Iwata, S. The effect of L-menthol stimulation of the major palatine nerve on subjective and objective nasal patency. Auris Nasus Larynx 1997;24(2):159-162.
249. Green, B. G. Menthol modulates oral sensations of warmth and cold. Physiol Behav 1985;35(3):427-434.
250. Nishino, T., Tagaito, Y., and Sakurai, Y. Nasal inhalation of l-menthol reduces respiratory discomfort associated with loaded breathing. Am J Respir Crit Care Med 1997;156(1):309-313.
251. Lindemann, J., Tsakiropoulou, E., Scheithauer, M. O., Konstantinidis, I., and Wiesmiller, K. M. Impact of menthol inhalation on nasal mucosal temperature and nasal patency. Am J Rhinol. 2008;22(4):402-405.
252. Lopez-Lazaro, M. Distribution and biological activities of the flavonoid luteolin. Mini.Rev.Med Chem 2009;9(1):31-59.
253. Inoue, T., Sugimoto, Y., Masuda, H., and Kamei, C. Antiallergic effect of flavonoid glycosides obtained from Mentha piperita L. Biol.Pharm Bull. 2002;25(2):256-259.
254. Dorman, H. J., Kosar, M., Baser, K. H., and Hiltunen, R. Phenolic profile and antioxidant evaluation of Mentha x piperita L. (peppermint) extracts. Nat Prod Commun. 2009;4(4):535-542.
255. Duband, F., Carnat, A. P., Carnat, A., Petitjean-Freytet, C., Clair, G., and Lamaison, J. L. [Aromatic and polyphenolic composition of infused peppermint, Mentha x piperita L.]. Ann.Pharm Fr. 1992;50(3):146-155.
256. Sroka, Z., Fecka, I., and Cisowski, W. Antiradical and anti-H2O2 properties of polyphenolic compounds from an aqueous peppermint extract. Z Naturforsch.C. 2005;60(11-12):826-832.
257. Ellis, B. E. and Towers, G. H. Biogenesis of rosmarinic acid in Mentha. Biochem.J 1970;118(2):291-297.
258. Belanger, J. T. Perillyl alcohol: applications in oncology. Altern Med Rev 1998;3(6):448-457.
259. Sakata, I. and Hashizume, T. Constituents of Japanese peppermint oil. Part III. Isolation and identification of two new constituents from Shubi. Agr Biol Chem 1971;35:128-131.
260. Fijalek, Z., Soltyk, K., Lozak, A., Kominek, A., and Ostapczuk, P. Determination of some micro- and macroelements in preparations made from peppermint and nettle leaves. Pharmazie 2003;58(7):480-482.

261. Lozak, A., Soltyk, K., Ostapczuk, P., and Fijalek, Z. Determination of selected trace elements in herbs and their infusions. Sci.Total Environ. 4-22-2002;289(1-3):33-40.
262. Raczuk, J., Biardzka, E., and Daruk, J. [The content of Ca, Mg, Fe and Cu in selected species of herbs and herb infusions]. Rocz.Panstw.Zakl.Hig. 2008;59(1):33-40.
263. Rychlik, M. Quantification of free coumarin and its liberation from glucosylated precursors by stable isotope dilution assays based on liquid chromatography-tandem mass spectrometric detection. J Agric.Food Chem 2-13-2008;56(3):796-801.
264. Gherman, C., Culea, M., and Cozar, O. Comparative analysis of some active principles of herb plants by GC/MS. Talanta 10-2-2000;53(1):253-262.
265. Schmidt, E., Bail, S., Buchbauer, G., Stoilova, I., Atanasova, T., Stoyanova, A., Krastanov, A., and Jirovetz, L. Chemical composition, olfactory evaluation and antioxidant effects of essential oil from Mentha x piperita. Nat Prod Commun. 2009;4(8):1107-1112.
266. Mahmoud, S. S. and Croteau, R. B. Menthofuran regulates essential oil biosynthesis in peppermint by controlling a downstream monoterpene reductase. Proc.Natl.Acad.Sci.U.S.A 11-25-2003;100(24):14481-14486.
267. BEDOUKIAN, P. Z. Occurrence of menthofuran in oil of peppermint (Mentha piperita vulgaris S.). J Am Chem Soc. 1948;70(2):621.
268. LEMLI, J. A. The occurrence of menthofuran in oil of peppermint. J Pharm Pharmacol 1957;9(2):113-117.
269. Rohloff, J. Monoterpene composition of essential oil from peppermint (Mentha x piperita L.) with regard to leaf position using solid-phase microextraction and gas chromatography/mass spectrometry analysis. J Agric.Food Chem 1999;47(9):3782-3786.
270. Almeida-Muradian, L. B., Rios, M. D., and Sasaki, R. Determination of provitamin A of green leafy vegetables by high performance liquid chromatography and open column chromatography. Boll.Chim.Farm 1998;137(7):290-294.
271. Orhan, I., Kartal, M., Kan, Y., and Sener, B. Activity of essential oils and individual components against acetyl- and butyrylcholinesterase. Z Naturforsch.C. 2008;63(7-8):547-553.
272. Kavaliers, M. and Tepperman, F. S. Exposure to novel odors induces opioid-mediated analgesia in the land snail, Cepaea nemoralis. Behav.Neural Biol. 1988;50(3):285-299.
273. Kim, M. J., Nam, E. S., and Paik, S. I. [The effects of aromatherapy on pain, depression, and life satisfaction of arthritis patients]. Taehan Kanho.Hakhoe.Chi 2005;35(1):186-194.
274. Inoue, T., Sugimoto, Y., Masuda, H., and Kamei, C. Effects of peppermint (Mentha piperita L.) extracts on experimental allergic rhinitis in rats. Biol.Pharm Bull. 2001;24(1):92-95.
275. Shapiro, S., Meier, A., and Guggenheim, B. The antimicrobial activity of essential oils and essential oil components towards oral bacteria. Oral Microbiol.Immunol. 1994;9(4):202-208.
276. Castillo-Juarez, I., Gonzalez, V., Jaime-Aguilar, H., Martinez, G., Linares, E., Bye, R., and Romero, I. Anti-Helicobacter pylori activity of plants used in Mexican traditional medicine for gastrointestinal disorders. J Ethnopharmacol 3-18-2009;122(2):402-405.
277. Fazlara, A., Najafzadeh, H., and Lak, E. The potential application of plant essential oils as natural preservatives against Escherichia coli O157:H7. Pak.J Biol.Sci. 9-1-2008;11(17):2054-2061.
278. Ibrahim, Y. K. and Ogunmodede, M. S. Growth and survival of Pseudomonas aeruginosa in some aromatic waters. Pharm Acta Helv. 1991;66(9-10):286-288.
279. Iscan, G., Kirimer, N., Kurkcuoglu, M., Baser, K. H., and Demirci, F. Antimicrobial screening of Mentha piperita essential oils. J Agric.Food Chem 7-3-2002;50(14):3943-3946.
280. Khan, M. S., Zahin, M., Hasan, S., Husain, F. M., and Ahmad, I. Inhibition of quorum sensing regulated bacterial functions by plant essential oils with special reference to clove oil. Lett.Appl.Microbiol. 2009;49(3):354-360.
281. Mohsenzadeh, M. Evaluation of antibacterial activity of selected Iranian essential oils against Staphylococcus aureus and Escherichia coli in nutrient broth medium. Pak.J Biol.Sci. 10-15-2007;10(20):3693-3697.
282. Pattnaik, S., Rath, C., and Subramanyam, V. R. Characterization of resistance to essential oils in a strain of Pseudomonas aeruginosa (VR-6). Microbios 1995;81(326):29-31.
283. Rafii, F. and Shahverdi, A. R. Comparison of essential oils from three plants for enhancement of antimicrobial activity of nitrofurantoin against enterobacteria. Chemotherapy 2007;53(1):21-25.
284. Sandasi, M., Leonard, C. M., and Viljoen, A. M. The in vitro antibiofilm activity of selected culinary herbs and medicinal plants against Listeria monocytogenes. Lett.Appl.Microbiol. 2010;50(1):30-35.
285. Shayegh, S., Rasooli, I., Taghizadeh, M., and Astaneh, S. D. Phytotherapeutic inhibition of supragingival dental plaque. Nat Prod Res 3-20-2008;22(5):428-439.
286. Samarth, R. M., Panwar, M., and Kumar, A. Modulatory effects of Mentha piperita on lung tumor incidence, genotoxicity, and oxidative stress in benzo[a]pyrene-treated Swiss albino mice. Environ.Mol.Mutagen. 2006;47(3):192-198.
287. Samarth, R. M., Panwar, M., Kumar, M., and Kumar, A. Protective effects of Mentha piperita Linn on benzo[a]pyrene-induced lung carcinogenicity and mutagenicity in Swiss albino mice. Mutagenesis 2006;21(1):61-66.
288. Saruwatari, A., Isshiki, M., and Tamura, H. Inhibitory effects of various beverages on the sulfoconjugation of 17beta-estradiol in human colon carcinoma Caco-2 cells. Biol.Pharm Bull. 2008;31(11):2131-2136.
289. Blomhoff, R. [Antioxidants and oxidative stress]. Tidsskr.Nor Laegeforen. 6-17-2004;124(12):1643-1645.
290. Dragland, S., Senoo, H., Wake, K., Holte, K., and Blomhoff, R. Several culinary and medicinal herbs are important sources of dietary antioxidants. J Nutr 2003;133(5):1286-1290.
291. Khayyal, M. T., El Ghazaly, M. A., Kenawy, S. A., Seif-El-Nasr, M., Mahran, L. G., Kafafi, Y. A., and Okpanyi, S. N. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung. 2001;51(7):545-553.
292. Lopez, V., Martin, S., Gomez-Serranillos, M. P., Carretero, M. E., Jager, A. K., and Calvo, M. I. Neuroprotective and neurochemical properties of mint extracts. Phytother.Res 2010;24(6):869-874.

293. Montes-Belmont, R. and Carvajal, M. Control of Aspergillus flavus in maize with plant essential oils and their components. J Food Prot. 1998;61(5):616-619.
294. De Almeida, M. A., Domingues, L. F., Almeida, G. N., Simas, M. M., Botura, M. B., Da Cruz, A. C., Da Silva, A. V., Menezes, T. P., and Batatinha, M. J. [Effects of aqueous extracts of Mentha piperita L. and Chenopodium ambrosioides L. leaves in infective larvae cultures of gastrointestinal nematodes of goats]. Rev.Bras.Parasitol.Vet. 2007;16(1):57-59.
295. Herrmann, E. C., Jr. and Kucera, L. S. Antiviral substances in plants of the mint family (labiatae). 3. Peppermint (Mentha piperita) and other mint plants. Proc Soc Exp Biol Med 1967;124(3):874-878.
296. Nolkemper, S., Reichling, J., Stintzing, F. C., Carle, R., and Schnitzler, P. Antiviral effect of aqueous extracts from species of the Lamiaceae family against Herpes simplex virus type 1 and type 2 in vitro. Planta Med 2006;72(15):1378-1382.
297. Schuhmacher, A., Reichling, J., and 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):504-510.
298. Geuenich, S., Goffinet, C., Venzke, S., Nolkemper, S., Baumann, I., Plinkert, P., Reichling, J., and Keppler, O. T. Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density. Retrovirology. 2008;5:27.
299. Yamasaki, K., Nakano, M., Kawahata, T., Mori, H., Otake, T., Ueba, N., Oishi, I., Inami, R., Yamane, M., Nakamura, M., Murata, H., and Nakanishi, T. Anti-HIV-1 activity of herbs in Labiatae. Biol Pharm Bull 1998;21(8):829-833.
300. Hills, J. M. and Aaronson, P. I. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. Gastroenterology 1991;101(1):55-65.
301. Duthie HL. The effect of peppermint oil on colonic motility in man. Br J Surg 1981;68:820.
302. Giachetti, D., Taddei, E., and Taddei, I. Pharmacological activity of essential oils on Oddi's sphincter. Planta Med 1988;54(5):389-392.
303. Massey, B. T. Diffuse esophageal spasm: a case for carminatives? J Clin Gastroenterol. 2001;33(1):8-10.
304. Tutuian, R. and Castell, D. O. Review article: oesophageal spasm - diagnosis and management. Aliment.Pharmacol Ther 5-15-2006;23(10):1393-1402.
305. Pasechnik, I. K. [Study of choleretic properties of flavonoid compounds isolated from Folia Menthae piperitae]. Farmakol.Toksikol. 1966;29(6):735-737.
306. Goerg, K. J. and Spilker, T. Effect of peppermint oil and caraway oil on gastrointestinal motility in healthy volunteers: a pharmacodynamic study using simultaneous determination of gastric and gall-bladder emptying and orocaecal transit time. Aliment.Pharmacol Ther 2003;17(3):445-451.
307. Adam, B., Liebregts, T., Best, J., Bechmann, L., Lackner, C., Neumann, J., Koehler, S., and Holtmann, G. A combination of peppermint oil and caraway oil attenuates the post-inflammatory visceral hyperalgesia in a rat model. Scand.J Gastroenterol. 2006;41(2):155-160.
308. Katikova, O. I., Kostin, IaV, and Tishkin, V. S. [Hepatoprotective effect of plant preparations]. Eksp.Klin.Farmakol. 2002;65(1):41-43.
309. Schwartz, R. K. Olfaction and muscle activity: an EMG pilot study. Am J Occup.Ther 1979;33(3):185-192.
310. Koo, H. N., Jeong, H. J., Kim, C. H., Park, S. T., Lee, S. J., Seong, K. K., Lee, S. K., Lyu, Y. S., and Kim, H. M. Inhibition of heat shock-induced apoptosis by peppermint oil in astrocytes. J Mol.Neurosci. 2001;17(3):391-396.
311. Coopersmith, R. and Leon, M. Enhanced neural response to familiar olfactory cues. Science 8-24-1984;225(4664):849-851.
312. Dragich, A. M. and Halpern, B. P. An oral-cavity component in retronasal smelling of natural extracts. Physiol Behav. 2-27-2008;93(3):521-528.
313. Ganz, H. [Assessing olfaction in general practice. A study of suitable odors]. HNO 1987;35(12):511-514.
314. Krone, D., Mannel, M., Pauli, E., and Hummel, T. Qualitative and quantitative olfactometric evaluation of different concentrations of ethanol peppermint oil solutions. Phytother.Res 2001;15(2):135-138.
315. Sarnat, H. B. Olfactory reflexes in the newborn infant. J Pediatr. 1978;92(4):624-626.
316. Pinching, A. J. Clinical testing of olfaction reassessed. Brain 1977;100(2):377-388.
317. Stephenson, D. and Halpern, B. P. No oral-cavity-only discrimination of purely olfactory odorants. Chem Senses 2009;34(2):121-126.
318. Coopersmith, R., Henderson, S. R., and Leon, M. Odor specificity of the enhanced neural response following early odor experience in rats. Brain Res 1986;392(1-2):191-197.
319. Satoh, T. and Sugawara, Y. Effects on humans elicited by inhaling the fragrance of essential oils: sensory test, multi-channel thermometric study and forehead surface potential wave measurement on basil and peppermint. Anal.Sci. 2003;19(1):139-146.
320. Ho, C. and Spence, C. Olfactory facilitation of dual-task performance. Neurosci.Lett. 11-25-2005;389(1):35-40.
321. Umezu, T. and Morita, M. Evidence for the involvement of dopamine in ambulation promoted by menthol in mice. J Pharmacol Sci. 2003;91(2):125-135.
322. Umezu, T. Evidence for dopamine involvement in ambulation promoted by menthone in mice. Pharmacol Biochem.Behav. 2009;91(3):315-320.
323. Umezu, T. Evidence for dopamine involvement in ambulation promoted by pulegone in mice. Pharmacol Biochem.Behav. 2010;94(4):497-502.
324. Samarth, R. M. and Samarth, M. Protection against radiation-induced testicular damage in Swiss albino mice by Mentha piperita (Linn.). Basic Clin Pharmacol Toxicol. 2009;104(4):329-334.
325. Samarth, R. M. Protection against radiation induced hematopoietic damage in bone marrow of Swiss albino mice by Mentha piperita (Linn). J Radiat.Res (Tokyo) 2007;48(6):523-528.
326. Samarth, R. M., Panwar, M., Kumar, M., and Kumar, A. Radioprotective influence of Mentha piperita (Linn) against gamma irradiation in mice: Antioxidant and radical scavenging activity. Int J Radiat.Biol. 2006;82(5):331-337.

327. Samarth, R. M., Goyal, P. K., and Kumar, A. Protection of swiss albino mice against whole-body gamma irradiation by Mentha piperita (Linn.). Phytother.Res 2004;18(7):546-550.
328. Samarth, R. M. and Kumar, A. Mentha piperita (Linn.) leaf extract provides protection against radiation induced chromosomal damage in bone marrow of mice. Indian J Exp Biol. 2003;41(3):229-237.
329. Samarth, R. M. and Kumar, A. Radioprotection of Swiss albino mice by plant extract Mentha piperita (Linn.). J Radiat.Res (Tokyo) 2003;44(2):101-109.
330. Samarth, R. M., Goyal, P. K., and Kumar, A. Modulation of serum phosphatases activity in Swiss albino mice against gamma irradiation by Mentha piperita Linn. Phytother.Res 2002;16(6):586-589.
331. Samarth, R. M., Saini, M. R., Maharwal, J., Dhaka, A., and Kumar, A. Mentha piperita (Linn) leaf extract provides protection against radiation induced alterations in intestinal mucosa of Swiss albino mice. Indian J Exp Biol. 2002;40(11):1245-1249.
332. Samarth, R. M., Goyal, P. K., and Kumar, A. Modulatory effect of Mentha piperita (Linn.) on serum phosphatases activity in Swiss albino mice against gamma irradiation. Indian J Exp Biol. 2001;39(5):479-482.
333. Lim, W. C., Seo, J. M., Lee, C. I., Pyo, H. B., and Lee, B. C. Stimulative and sedative effects of essential oils upon inhalation in mice. Arch.Pharm Res 2005;28(7):770-774.
334. Norrish, M. I. and Dwyer, K. L. Preliminary investigation of the effect of peppermint oil on an objective measure of daytime sleepiness. Int J Psychophysiol. 2005;55(3):291-298.
335. Mascher, H., Kikuta, C., and Schiel, H. Pharmacokinetics of menthol and carvone after administration of an enteric coated formulation containing peppermint oil and caraway oil. Arzneimittelforschung 2001;51(6):465-469.
336. Kaffenberger, R. M. and Doyle, M. J. Determination of menthol and menthol glucuronide in human urine by gas chromatography using an enzyme-sensitive internal standard and flame ionization detection. J Chromatogr. 4-27-1990;527(1):59-66.
337. Nolen, H. W., III and Friend, D. R. Menthol-beta-D-glucuronide: a potential prodrug for treatment of the irritable bowel syndrome. Pharm Res 1994;11(12):1707-1711.
338. Somerville, K. W., Richmond, C. R., and Bell, G. D. Delayed release peppermint oil capsules (Colpermin) for the spastic colon syndrome: a pharmacokinetic study. Br.J Clin Pharmacol 1984;18(4):638-640.
339. White DA, Thompson SP, Wilson CG, and et al. A pharmacokinetic comparison of two delayed-release peppermint oil preparations, Colpermin and Mintec, for treatment of irritable bowel syndrome. Int J Pharm 1987;40:151-155.
340. Madyastha, K. M. and Srivatsan, V. Studies on the metabolism of l-menthol in rats. Drug Metab Dispos. 1988;16(5):765-772.
341. Leicester, R. J. and Hunt, R. H. Peppermint oil to reduce colonic spasm during endoscopy. Lancet 10-30-1982;2(8305):989.

