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Evaluation of Medicines for Human Use

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**ASSESSMENT REPORT ON
MENTHA X PIPERITA L., FOLIUM**

ASSESSMENT REPORT

**FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS
THEREOF WITH TRADITIONAL USE**

***Mentha x piperita* L., folium**

**BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS
AMENDED**

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole or cut dried leaf of <i>Mentha x piperita</i> L.
Herbal preparation(s)	Infusion Tinctures
Pharmaceutical forms	Solid and liquid dosage forms
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1 INTRODUCTION

Peppermint is a perennial plant native to Europe, highly aromatic that may grow as tall as three feet. The ancient Egyptians, Greeks and Romans knew it as flavouring for food and as medicine. It was first cultivated in England commercially around 1750 while its aerial parts have been widely used for their medicinal effects.

Peppermint is widely known to relieve digestive ailments, being a popular remedy for at least two centuries. *Mentha x piperita* L. is believed to be a hybrid of spearmint (*Mentha spicata* L.) and water mint (*Mentha aquatica* L.) (Murray et al, 1972), belonging to Labiatae family. The essential oil is obtained from the fresh leaves of *Mentha piperita* L. by steam distillation and it is widely used all over the world for flavouring, cosmetic and medicinal purposes.

At the herbarium of the English botanist John Ray (1628-1705) it can be found one of the oldest specimens of peppermint. In 1721, *Mentha piperita* became the official item of Materia Medica in the London Pharmacopoeia as *Mentha piperitis sapore* (Fluckiger 1879, Herbalgram, American Botanical Council, 1996).

The data researched is able to demonstrate the traditional basis of the plant and its products, as it effective use in several clinical situations.

1.1 Description of the traditional herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)¹²

Whole or cut dried leaf of *Mentha piperita* L.

- Herbal preparation(s)¹²

Comminuted herbal substance for tea preparation

Tincture (1:5; ethanol 45% (V/V))

2. TRADITIONAL MEDICINAL USE

- It should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

2.1 Information on period of medicinal use in the Community regarding the specified indication

Ellingwood, in 1902, in the book “Materia medica and Therapeutics – Chicago Medical Press: recommends peppermint water (distillate) for “flatulent colic, gastrodynia, nausea, vomiting, intestine spasmodic pain, hiccough, palpitation from indigestion, griping, cholera morbus, cholera infantum, irritability of the stomach, diarrhoea with abdominal pain, nervous headache, painful gonorrhoea”.

In the Indian Materia Medica, leaves of *Mentha piperita* L. , in infusion, are used in cases of vomiting, gastric colic, cholera, diarrhoea, flatulence, weak digestion, hiccup and palpitation of the heart (Nadkarni’s – reprint of third edition – 1982)

¹ According to “Note for guidance on Quality of herbal medicinal products” (CPMP/QWP/2819/00)

² According to “Note for guidance on Specifications: Test procedures and acceptance criteria for herbal drugs, herbal preparations and herbal medicinal products” (CHMP/QWP/2820/00)

2.2 Type of tradition, where relevant

European phytotherapy

Ayurvedic medicine

2.3 Bibliographic/expert evidence on the medicinal use

Peppermint leaves are traditionally used (Forster 1996) as *carminative herbal medicinal product* with therapeutic indications for the symptomatic treatment of digestive disorders such as dyspepsia (e.g. spastic complaints of the upper gastrointestinal tract), flatulence, gastritis, enteritis and also as cholagogue.

On the British Herbal Compendium its action is carminative, spasmolytic and choleric (Bradley 1992).

Described as having carminative, digestive and stimulant properties (Costa Aloísio, 1986), and used as an infusion for indigestion, gastric colic and diarrhoea.

Used for dyspeptic ailments and respiratory infections, hepatobiliary dysfunction (Proença da Cunha, 2003).

As a *general digestive aid* a tea of dried peppermint leaves is employed for internal oral use, such as intestinal spasms (Bradley 1992, Schilcher 1997).

In folk medicine is used as an emmenagogue, vermifuge, lactation enhancer and sedative. Also used to treat bronchitis, bacillary dysentery, diabetes, diarrhoea, dysmenorrhoea, fevers, hypertension, jaundice, nausea, pain, and respiratory and urinary tract infections (WHO monographs)

2.3.1 Evidence regarding the indication/traditional use

According to **ESCOP**, 2nd edition:

- Used in the symptomatic treatment of digestive disorders such as dyspepsia, flatulence and gastritis

According to **British Herbal Compendium**:

- Dyspepsia, flatulence, intestinal colic, biliary disorders (Bradley 1992).

Belgium (*Circulaire No. 367 of July 1991: Mentha piperitae* L. herbe):

- Traditionally used in the symptomatic treatment of digestive disorders, although its activity has not been proved in accordance with the current evaluation criteria for medicines.

(*Circulaire No. 450 of 1994: Mentha piperitae* L. herbe):

- Traditionally used in the symptomatic treatment of digestive disorders, after any serious pathological condition has been excluded.

France (*Bulletin officielle No. 90/22 bis: Menthe; feuille, sommité fleurie*) :

Information for medical profession

- 030. Traditionally used topically as a soothing and antipruriginous application for dermatological ailments, as a protective treatment for cracks, grazes, chapped skin and against insect bites

- 041. Traditionally used in the symptomatic treatment of digestive disorders such as: epigastric distension; sluggishness of the digestion; belching; flatulence.
- 043. Traditionally used as adjuvant treatment for the painful component of spasmodic colitis.
- 045. Traditionally used to promote renal and digestive elimination functions.
- 122. Traditionally used in cases of nasal congestion and of common cold.
- 142. Traditionally used topically (mouth and throat washes, pastilles) as an anodyne for affections of the buccal cavity and/or orofaringe.
- 144. Traditionally used topically in mouth washes, for oral hygiene.

Germany (*Commission E monograph published 30.11.85, amended 13.3.90 and 1.9.90*):

- Spastic complaints of the gastrointestinal tract as well as gallbladder and bile ducts.
Standardzulassung N°. 1499.99.99 published 3.12.82 for a standard medicinal tea: Pfefferminzblätter.
- Gastro-intestinal and gall-bladder ailments.

2.3.2 Evidence regarding the specified strength

Tincture – (1:5 preparations, 45% ethanol) - (Bradley, 1992)

Tincture – (1:5 preparations, 70% ethanol) – (Erg.B.6, 1953, Commission E monographs, 1985)

1,5-9g of leaf – (ESCOP, Commission E)

2.3.3 Evidence regarding the specified posology

General use:

Infusion – usually prepared with one or two teaspoons (1, 5 to 3, 0 grams) of the dried leaves per 8 ounces of water (Bradley, 1992; Wichtl, 1989)

Tincture – (1:5 preparation, 45% ethanol) – 2 to 3 ml, three times daily (Bradley, 1992)

(*Kommission E monograph published 30.11.85, amended 13.3.90 and 1.9.90*):

- 5 – 15 g tincture/daily (1:5 preparations, 70% ethanol)
- 3 - 6 g of leaf

ESCOP 2nd Edition:

- Adults
 - o As an infusion, 1.5 – 3 g of the drug to 150 ml of water, three times daily
 - o Tincture (1:5, 45% ethanol), 2-3 ml, three times daily
- Elderly – the same as adults
- Children from 4 years of age, daily dose as infusions only:
 - o 4-10 years, 3-5 g
 - o 10-16 years, 3-6 g

2.3.4 Evidence regarding the route of administration

See point 2.3.2

2.3.5 Evidence regarding the duration of use

No restriction. If symptoms persist or worsen after 2 weeks, a doctor or a qualified health practitioner should be consulted.

2.3.6 Assessor's overall conclusion on the traditional medicinal use

Peppermint leaves are a very well known herbal medicinal product, widely used since a long time, being a popular remedy inside and outside European countries, for its antispasmodic, choleric and carminative properties, as we can confirm in a large number of publications.

On the literature we can find references to several preparations such as tinctures, liquid extracts and infusions, on single or combination products. The data about the 30 years of use for the tincture (1:5, 45% of ethanol) was not found, just the publication from Bradley from 1992, 16 years to now in Europe. Being the one with the best explanation about the posology and accepted by the interested parties, I propose to include it on the monograph.

2.4 Bibliographic review of safety data of the traditional herbal medicinal substances

2.4.1 Patient exposure

Peppermint leaves and extract can be used in cosmetic formulations as fragrance ingredients. Peppermint water can be used as a flavouring agent or, also, as a fragrance component.

Menthol

In 1976, FAO/WHO Joint Expert Committee on Foods Additives established an ADI of 0, 2 mg/kg body weight/day for menthol. In 2000, an ADI of 0-4mg/kg of body weight/day was allocated.

Pulegone and menthofuran

Maximum levels for pulegone in foodstuff and beverages to which flavourings or other food ingredients with flavouring properties have been added: 25 mg/kg in foodstuff, 100 mg/kg in beverages, with the exception of 250 mg/kg in peppermint or mint flavoured beverages and 350 mg/kg in mint confectionery (Annex II of Directive 88/388/EEC). Pulegone may not be added as such to foodstuff. Committee of Experts on Flavouring Substances (CEFS) of the Council of Europe (1997): Menthofuran is the proximate hepatotoxin of pulegone. Tolerated daily intake (TDI) of menthofuran and pulegone was set to 0.1 mg/kg bw, based on a no effect level (NOEL) of 20 mg/kg bw/d in the 28 days oral toxicity study in rats (Thorup et al. 1983 a,b) with a safety factor of 200. Menthofuran is listed in the register of chemically defined flavouring substances laid down in Commission Decision (1999/217/EC, 2002/113/EC).

USA: Pulegone and menthofuran have FEMA GRAS status and are listed among the authorized synthetic flavouring substances. JECFA (Joint FAO/WHO Expert Committee on Food Additives, 2000): "No safety concern" was applied to (R)-(+)-pulegone and structurally related flavouring agents including (R)-(+)-menthofuran.

Because of the toxicity of pulegone, the CIR expert Panel limited it to $\leq 1\%$ in cosmetic grade. Recent data reported that peppermint leaves are used in $<0, 2\%$ on formulations.

2.4.2 Adverse events

Peppermint teas contain only a low amount of menthol and menthone. In adults, the adverse reactions are, in general, related with a high intake of menthol by other products, as confectionary or pharmaceuticals.

The normal and prolonged use of peppermint tea, rarely leads to adverse effects (ESCOP, 2nd ed), but the gastro-oesophageal reflux may be worsened by taking it, as peppermint relaxes the lower oesophageal sphincter. Due to this effect, it is not recommended to people with and gastroesophageal reflux.

Peppermint may stimulate the production of bile. In case of cholangitis, gallstones and other biliary disorders, this product should be used with caution and under the supervision of a medical doctor.

2.4.3 Serious events and deaths

Not known

2.4.3.1 Intrinsic (including elderly and children)/extrinsic factors

The oil of peppermint should be used with caution in infants and young children, as the nasal mucosa is an autonomic reflexogen organ, which has a distance action to the heart, lungs and circulation and may lead to sudden apnoea and glottal constriction. The children less than 2 years old present particularly this reflex, so all the substances with a strong odour must be avoided. Peppermint oil must be avoided at this range of age.

A cup of tea contains ca. 2.5 mg of menthol, which is as exciting as 5 drops (0.5 ml) of a 20 % alcoholic solution of *Mentha* essential oil (Duband et al, 1992).

2.4.3.2 Drug-drug interactions and other interactions

Not reported.

2.4.3.3 Use in pregnancy and lactation

Data on the use during pregnancy and lactation is not available. Some references appoint that peppermint may dry up milk secretions (Mills, 2005).

As a general precaution, the use is not recommended, unless medical advice proposed benefit is higher than the potential risk.

2.4.3.4 Overdose

An intoxication of a 9 years boy with a menthe (carvone) infusion prepared with 30 leaves is reported. The symptoms were tachycardia and agitation, relieved after 24 hours (Augiseau et al, 1987).

This is not the case of *Mentha piperitae folium*.

2.4.3.5 Drug abuse

Not applicable

2.4.3.6 Withdrawal and rebound

Not applicable

2.4.3.7 Effects on ability to drive or operate machinery

Not applicable

Contra indications (hypersensitivity and allergic potential to be both covered)

People with hypersensitivity to peppermint preparations should not take this medicinal product.

Non-clinical safety data

Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

(e.g. single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, local tolerance, other special studies)

Toxicity

A dry peppermint leaf extract was given to 12 mice as a single dose at 4000mg/kg body weight. None of the animals died or showed macroscopic signs of toxicity over a 7-day period (Della Loggia et al, 1990).

20g/L of *M. piperitae* tea were given to 48 rats during 30 days; serum iron and ferritin levels were reduced ($p < 0.05$), and increased unsaturated iron-binding capacity ($p < 0.01$), on a study of Akdogan et al. (2004a).

On another study, the biochemical and histopathological effects of *Mentha piperitae* L. and *Mentha spicata* L on liver tissue of rats was investigated. Ast and Alt activities were increased, but not statistically significant on the group with 20g/L of *M. piperita* tea, daily, during 30 days, In this group, the histopathological evaluation there was minimal hepatocyte degeneration. The damage seems to be dose dependent, according to the author (Akdogan et al., 2004b).

A similar study on the kidney of Wistar albino rats found no evidence of nephrotoxicity on the group drinking 20g/L of *M. piperitae* tea, daily, during 30 days. The histopathological changes were observed, slight on the group of *M. piperitae* compared with the group of *M. spicata*. They consist of hydropic degeneration of tubular epithelial cells, epithelial cells with picnotic nuclei and eosinophilic cytoplasm, enlargement of bowman capsules (Akdogan et al., 2003).

Peppermint oil, pulegone and menthofurane

Short-term toxicity studies demonstrated that peppermint oil (40 and 100 mg/kg b.w. day) and pulegone (80 and 160mg/kg b.w.day) induced brain lesions in rats at oral doses.

The oral LD₅₀ of peppermint oil U.S.P. in fasted Wistar male rats after 24 h was found to be 4441±653 mg/kg. After 48h was 2426 mg/kg.

The interest in toxicity of pulegone, menthofuran and peppermint oil appears to have been provoked by three reports in the literature. It was reported that pulegone, when given to rats for 28 days, caused histopathological changes in the liver (vacuolisation) and the brain (“cystlike spaces”) (Thorup et al. 1983a,b; Olsen and Thorup, 1984). The histopathological changes were seen in rats receiving 80 and 160 mg/kg/day of pulegone. However, all haematological and clinical chemical parameters were found to be within the normal range in all groups. There were neither obvious signs of clinical symptoms due to encephalopathy. Based on these studies the NOEL (no effect level) of pulegone was considered to be 20mg/kg bw/day. Later “confirmatory” studies by the same group, however, reported that there were no significant histopathological changes in the liver or the brain. The “cyst-like spaces” reported in the brain in the earlier studies were thus not confirmed and may have arisen from inadequate tissue fixation procedures (Molck et al. 1998). In this study the clinical biochemical examinations revealed increased plasma glucose, alkaline phosphatase and ALAT and a decreased creatinine in the dosed group. In later studies the liver toxicity of pulegone has been confirmed and a mechanism of action has been proposed based on its metabolism to menthofuran and other reactive metabolites, which are the ultimate hepatotoxins (see SCF report on Public statement on the use of HMP containing pulegone and menthofurane – EMEA/HMPC/138386/2005).

Menthone

The oral toxicity of menthone was evaluated in an animal model. The decrease in plasma creatinine and the increase in phosphatase alkaline and bilirubin were dose dependent, after levels of 0, 200, 400

and 800 mg/kg b. w. /day. The NOEL for menthone in this study was lower than 200 mg/kg b.w. /day. A NOEL of 400 mg/kg b. w. /day was reported in a 28 day toxicity study in rats (FAO/WHO Expert Committee on Food Additives, 2000).

Teratogenicity

Menthol

For maximum oral doses of 190, 220, 400, and 430 mg/kg/day, respectively, were not observed teratogenic effects in mice, rats and hamsters (FAO/WHO expert on Food Additives, 2000).

Reproductive toxicity

The effects of *Mentha piperita* and *Mentha spicata* herbal teas on plasma total testosterone, luteinizing hormone and follicle-stimulating hormone levels and testicular histologic features were evaluated. The rats (200-250g) were randomized in four groups of 12 each. The experimental group was given 20g/L *M. piperita* tea, or 20g/L *M. spicata* tea or 40g/L *M. spicata* tea. The group control had commercial drinking water. The follicle-stimulating hormone and luteinizing hormone had increased and total levels of testosterone had decreased, comparing with the control group, being statistically significant. The Johnsen testicular biopsy scores were different but not statistically significant (Akdogan et al., 2003).

Genotoxicity

A chemopreventive action and a antigenotoxic effect was observed on an evaluation of aqueous extracts of *Mentha piperitae* leaves, when is giving after an initiating dose of benzo[a]pyrene (0,5mg) in newborn Swiss albino mice (Akdogan et al. 2004a, Samarth et al. 2006).

Six herbal infusions (*Matricaria chamomilla*, *Tilia cordata*, *Mentha piperitae*, *Mentha pulegium*, *Uncaria tomentosa* and *valeriana officinalis*) were tested for antigenotoxicity, using the SMART test in *Drasophila melanogaster*. Hydrogen peroxidase was used as an oxidative genotoxic agent.

The infusion of *M. pulegium* is desmutagenic in the SMART when assayed with hydrogen peroxide in combined treatments. Both *M. perita* and *M. pulegium* infusions showed similar levels of anti-genotoxicity (141 and 134%, respectively).

The authors conclude that the results of inhibition obtained for *M. chamomilla*, *T. cordata*, *M. piperita*, *M. pulegium* and *V. officinalis* surpassing 100% (ranging from 125 to 141%), can only be explained by a synergism between their phenolic contents and the hydrogen peroxide due to the known ability of phenols to scavenge reactive oxygen species such as those generated by hydrogen peroxide (Romero-Jimenez 2005).

The oil of *Mentha piperitae* is the worst scenario. Peppermint oil was negative in two validated tests of genotoxicity, the Ames test and the mouse lymphoma assay. Weak and inconsistent genotoxic responses in other non-validated tests are probably toxicologically inconsequential. There is more evidence for genotoxicity potential of menthol and there seems to be a discrepancy between peppermint oil and its most important constituent menthol. However, the present evidence points to a very weak or totally absent genotoxicity of peppermint oil.

Carcinogenicity

Chemopreventive action

In studies where some agents induced the carcinogenicity, peppermint showed a preventive and a reduction effect.

A study was performed comparing a powdered tobacco mixture (15g) with and without 15g of peppermint leaves, on the induction of morphological changes and tumors. These mixtures were painted onto the cheek pouches of Syrian golden hamsters 3 times/week for 20 weeks. The non-mint

tobacco mixture increased mucosal thickening (n=20/22 in non mint groups vs 9/15 in mint containing group), leukoplasia (20/22 vs 3/15) and frank tumors (19/22 vs 0/15) in the oral cavity. 86.3% of the animals on the group without peppermint present tumor bearing at week 30, while the group with peppermint had 0% of tumors (Samman et al, 1998).

The results of the study performed by Sameena and Ashoc, on the papilloma-genesis of the skin induced by 7,12-dimethylbenz (a) anthracene (DMBA) in mice, suggest that there is a chemopreventive effect of peppermint on the development of skin papillomas, being most effective during the promotional stage of carcinogenesis (Sameena et al., 2001).

An aqueous extract of *Mentha piperitae* leaves were evaluated by using 9-week medium term model of benzo[a]pyrene-induced lung tumors in new born Swiss albino mice. The number of lung tumors was reduced, after oral administration of *Mentha* extract, in an inhibition rate of 61, 26% in the *Mentha* treated group with respect to the reference group. *Mentha* extract reduced the frequency of BP induced chromosomal aberrations and micronuclei in bone marrow cells and decreased the levels of lipoperoxides and increased sulphhydryl groups in liver and lung (Samarth et al, 2006).

The effects of peppermint extracts against sub-lethal and lethal doses of gamma radiation in Swiss albino mice were tested in several studies. Pretreatment with an aqueous extract of peppermint prior to the radiation (whole body), 1g/kg administered 3 days before the irradiation with 8 Gy, increased the hematological parameters. The survival rate was also better on the pretreatment group compared with the irradiated control, 10 days post-irradiation (Samarth et al., 2004).

The serum alkaline phosphatase was increased and the acid phosphatase decreased, using the same protocol, compared with the control, after irradiation, returning to normal after 5 days (Samarth et al., 2002).

The intestinal mucosa of mice suffered increased villus height, total number of mitotic cells, and decreased the number of goblet and dead cells after taking 1g/Kg peppermint extract, within 20 days post-irradiation at 8 Gy (Mckay, 2006).

2.4.4 Assessor's overall conclusions on safe use

On the studies performed were observed antimutagenic, anti-genotoxic and chemopreventive effects, after the induction of several agents.

Toxicity tests in animals have not given cause for concern, with the recommended dosage range.

3 PHARMACOLOGICAL PROPERTIES³

3.1 Overview of pharmacological effects of herbal substance(s), herbal preparation(s) and relevant constituents thereof on the basis of long-standing use and experience

Composition

The chemical components of peppermint leaves vary with plant maturity, variety, geographical region and processing conditions. The fatty acid composition of the non-polar lipid fraction of peppermint leaves is dominated by palmitic (16:0), linoleic (18:2) and linolenic (18:3) acids (Mackay, 2006).

The main active component is the essential oil. Its major constituents are menthol (30-55%) and menthone (14-32%). Other monoterpenes present are limonene (1-5%), cineole (3, 5-14%), menthofuran (1-9%), isomenthone (1,5-10%), menthyl acetate (2,8-10%), pulegone (until 4%), carvone (until 1%) with a ratio of cineole content to limonene content greater than 2.

³ Not required as per Article 16c(1)(a)(ii) of Directive 2001/83/EC as amended

Various flavonoids are present including luteolin and its 7-glycoside, rutin, hesperidin, eriocitrin and highly oxygenated flavones. Other constituents include phenolic acids and small amounts of triterpenes (ESCOP 2003, Julien et al 1984, Litvinenko et al 1975, Croteau, Loomis 1973).

Eriocitrin, with a concentration range of 6.6-15.0%, is the dominant flavonoid glycoside, accompanied by luteolin 7-*O*-rutinoside, hesperidin and rosmarinic acid, on a study of 40 clones of *Mentha piperita* (Nair B., 2001).

About 75% of the polyphenolic compounds present in the leaves are extracted in an infusion (Mackay, Blumberg 2006).

The leaves contain 1.2 – 3.9% (v/w) essential oil (Blumenthal *et al.*). The cut drug contains not less than 9 mg/kg of essential oil (ESCOP).

An infusion of dried leaves is reported to contain 21% of the original oil (25mg/L) (Duband et al, 1992).

a. *In vitro* studies

Antioxidant

The antioxidant capacity of peppermint has been determined using of different assay methods. Among some medicinal herbs, *Mentha piperitae* leaves showed a high oxygen radical absorbance capacity (ESCOP).

Antimicrobial

A significant antiviral activity was reported in aqueous extracts of peppermint leaves towards Influenza A, Newcastle disease virus, Herpes simplex virus and Vaccinia virus, in egg and cell culture systems (Herrmann, Kucera, 1967). The antibacterial and fungicidal activity was demonstrated in several studies, especially with peppermint oil.

The inhibition of the growth of *Salmonella typhimurium*, *Staphylococcus aureus* and *Vibrio parahaemolyticus* were achieved with addition of ground leaves to the agar medium at concentrations of 0,1-2,0% (w/v) (Aktug, Karapinar, 1986)

On another study was observed the reduction of the number of plaques of the rinderpest virus with aqueous and ethanol extracts of the leaves of *Mentha piperita*, at concentrations of 4-8mg/ml (Alwan AH et al, 1988).

Antispasmodic

Among other studies, alcoholic extracts of Peppermint leaf have antispasmodic effects on the isolated guinea pig ileum. 2.5 and 10.0 ml/litre of a Peppermint leaf extract (1:3.5, ethanol 31% w/w) were tested using acetylcholine and histamine as spasmodic agents. Both doses produced a significant increase of the ED₅₀, for acetylcholine and histamine-induced contractions and a significant decrease of the maximum possible contractility. The effect obtained with 10.0 ml/litre corresponded to that of 0.13 mg atropine (effective dose of atropine in the treatment of abdominal spasms: 0.5 - 1.0 mg) (Forster et al, 1980, 1983).

Flavonoids isolated from Peppermint leaf and dissolved in water, so that 1 ml corresponded to approximately 0.5 g of dried leaf, inhibited muscular contraction of the guinea pig ileum induced by barium chloride (Lallement-Guilbert et al, 1970).

Aqueous extracts of *Mentha piperitae* showed a significant, dose dependent relaxation effect on isolated rabbit duodenum (Mahmood et al, 2003), being the dried leaf extract more effective than the fresh one.

The mode of action on gastric motility of a combination (Iberogast ®) and its individual components (hydroethanolic herbal extracts from *Iberis amara totalis*, *Menthae piperitae folium* – 1:2.5-3.5, *Matricariae flos*, *Liquorice root*, *Angelica radix*, *Carvi fructus*, *Cardus marianus fructus*, *Melissae folium* and *Chelidonium herba*) was studied. Peppermint leaf extract did not show consistent responses in the proximal stomach, inducing relaxation and contraction (Schemann et al, 2006).

On another study in vitro model, was used the same product and some of its isolated compounds. The study was performed to test their activity on histamine-induced contractions and spontaneous motility, of intestinal samples from guinea pig. *Mentha piperita* leaves, as *Iberis amara*, *Melissa folium* had significant effects on decreasing the contraction amplitude (Heinle et al, 2006).

b. In vivo studies

Gastrointestinal action

In experiments with cannulated dogs Peppermint tea (0.4 g/kg body weight) increased the secretion of bile. Flavonoids, as well as the essential oil, seemed to contribute to this action (Steinegger et al 1992, Pasechnik 1967).

Mixed flavonoids from Peppermint leaf (optimum dose 2 mg/kg.), showed choleric activity in dogs. Flavomentin, a flavonoid preparation from Peppermint leaf, stimulated bile secretion and the synthesis of bile acids in dogs at doses of 0.5-6 mg/kg (optimum 2 mg/kg) (Pasechnik 1967).

In experiments with cannulated rats, intravenous injection of 0.5 ml of a Peppermint tea (1:5) per rat or a flavonoid preparation (dosage corresponding to 3.3 g of Peppermint leaf per kg) proved effective in increasing the amount of bile acids (Lallement-Guilbert et al, 1970).

The carminative action is due to a reduction in tonus of the oesophageal sphincter by Peppermint leaf extracts, enabling release of entrapped air (ESCOP).

In the large intestine of pigs, peppermint extract and L-methionine reduced the production of volatile sulphur compounds by the metabolism of intestinal bacteria (ESCOP). In another study (Ando et al, 2003), Holstein steers fed with peppermint, there were lower concentrations in the rumen of ammonia nitrogen and reduction of the numbers of protozoa.

On the article (Mckay and Blumberg, 2006) where the bioactivity of peppermint was reported, a study of female Wistar rats demonstrated modulatory effects of peppermint tea on selected hepatic phase I metabolising enzymes. The pre-treatment with a 2% solution for 4 weeks ($n = 5$), the activities of cytochrome P450 isoforms CYP1A2 (24%) and CYP2E (48%) were significantly reduced, compared with a control group.

The potential antiulcerogenic, antisecretory and cytoprotective activity of the combination (Iberogast®) and its individual components (hydroethanolic herbal extracts from *Iberis amara* totalis, *Menthae piperitae* folium [containing 0,44 menthol and menthone] *Matricariae* flos, Liquorice root, Angelica radix, Carvi fructus, Cardus marianus fructus, *Melissae* folium and *Chelidonium* herba) were tested in male Wistar rats. A modified formulation of the combination was also tested, taking out three components. Gastric ulcers were induced acutely by indometacin and cimetidine was used as a reference anti-ulcerogenic. The parameters used were the free acidity, mucin and pepsin concentrations in the gastric juice, and the prostaglandin and leukotriene levels in the gastric mucosa. The stomach was histologically examined. Both preparations and their individual components protect the stomach from the ulcerative damage caused by indomethacin, inhibiting the release of aggressive factors like acid and leukotrienes, promoting the production of mucin and prostaglandins. This effect could be attributed, according to the authors, to the presence of flavonoids (Khayal et al, 2001).

Antiallergic action

A study was performed to clarify the effects of extracts of the leaves and stems of *Mentha piperita* L. on experimental allergic rhinitis. The extraction process includes the removal of essential oil, fat, followed by fractionation. This 50% ethanol extract had an effect, which was dose-dependent, on the inhibition of histamine release from rat peritoneal mast cells. The compound 48/80 induced this reaction and the inhibition was observed at a concentration of 3µg/ml. The water, 50% ethanol eluate, separated by column Chromatography also shows a similar effect at a dose of 1µg/ml. The oral administration of 50% EtOH inhibited sneezing and nasal rubbing induced by antigen-antibody reaction. The repeated administration was more effective than a single administration (Inoue et al, 2001).

Following these results, the same authors studied the antiallergic effect of the flavonoid glycosides obtained from *Mentha piperita* L. Among the flavonoids isolated from the aerial part of *M. piperita* L., luteolin-7-O-rutinoside showed a dose-related inhibitory effect of an antigen induced nasal response at doses of 100 and 300 mg/kg

NCS action

An aqueous extract of Peppermint leaf (50 g of dried leaf infused for 10 min in 500 ml hot water, then spray-dried) administered orally in 2 single doses of 300 mg/kg and 1000 mg/kg in 16 mice showed a weak sedative action in several tests: hexobarbital-induced sleep, exploratory behaviour, spontaneous motility and motor coordination.

The peppermint extract, at a dose of 1000 mg/kg causes in rats, in the behavioural tests, a biphasic effect with initial stimulation, followed by depression. It seems that the effect observed is due to the oil contained in the extract. At a lower dose, 300mg/kg, the excitatory response is too weak and transient, and only the depressive effect is recorded

The same Peppermint leaf extract, administered in the same two doses, showed a weak diuretic effect in mice (Della Logia et al, 1990).

Diuretic action

The effect of peppermint on diuresis is weak. The effective dose is about 30 times higher than that of aminophylline. At 1000 mg/kg oliguria was observed (Della logia et al, 1990).

c. Clinical studies (in combinations)

Controlled studies

The efficacy and safety of the STW 5-II for the treatment of functional dyspepsia was assessed on a double blind, randomized, placebo controlled, multicentre trial, for 4 week treatment blocks. STW 5-II is a herbal combination of fresh plant extract (1:2, 50% v/v ethanol)of *Iberis amara totalis* and extracts (1:3, 30% v/v ethanol) of matricaria flower (*Matricariae flos*, 30ml), peppermint leaves (*Menthae piperitae folium*, 30ml), caraway (*Carvi fructus*, 20 ml), licorice root (*Liquiritiae radix*, 10ml) and lemon balm (*Melissa folium*, 15 ml). 120 patients with recurrent and persistent dyspepsia for 6 months (Rome I criteria) were recruited in hospitals and private practice by gastroenterologists. The primary outcome measure was the improvement of a standardized gastrointestinal score (GIS), which decreased in patients on the active treatment compared to placebo (p<0,001). Symptoms improved on the next 4 weeks, also for the patients who switched to the active treatment, and got worse on those who switched to placebo (Madisch et al, 2004).

Meta-analysis

Six randomized-controlled trials of STW 5(Iberogast) were identified for functional dyspepsia. Three of them were placebo-controlled studies, met the inclusion criteria, and were included for this study. One reference –controlled study supported the safety analysis. According to the authors, STW 5 demonstrated to be a valid therapeutic option for functional dyspepsia, considering efficacy and safety (Melzer et al, 2004).

3.2 ASSESSOR'S OVERALL CONCLUSIONS

Mentha piperita leaves is a well known and a traditional herbal medicinal product used for centuries in the European countries.

There is enough literature to demonstrate its use for medicinal purposes, for the symptomatic treatment of digestive disorders.

The pharmacological studies in vitro and in vivo showed antispasmodic effects of the smooth muscle of the digestive tract, choleric activity, and reduction in tonus of the oesophageal sphincter enabling

the release of the entrapped air. Other studies indicate that there is a dose dependent analgesic and anti-inflammatory action.

There are no clinical studies on the efficacy of *Menthae piperitae folium* alone, but just in combination with other plants, given no reason for the inclusion on the well-established use.

The clinical studies of the essential oil, have demonstrated efficacy for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain,

These results support the therapeutic indication for the long-standing use of *Menthae piperitae folium* in digestive disorders, on the doses and preparations recommended and used traditionally:

- Symptomatic relief of digestive disorders such as dyspepsia and flatulence.

ANNEXES

COMMUNITY HERBAL MONOGRAPH ON *MENTHA X PIPERITA* L., FOLIUM

LITERATURE REFERENCES