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KARMEN KAPP

Polyphenolic and Essential Oil Composition of *Mentha* and Their Antimicrobial Effect

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ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Pharmacy of the University of Helsinki, for public examination in Auditorium 1041 at Biocenter 2 (Viikinkaari 5E) on December 22nd 2015 at 12 o`clock.

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II Kapp, K., Hakala, E., Orav, A., Pohjala, L., Vuorela, P., Püssa, T., Vuorela, H. and Raal, A. (2013). Commercial peppermint (*Mentha × piperita* L.) teas: antichlamydial effect and polyphenolic composition. *Food Research International,* 53(2): 758-766.

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The publications are referred to in the text by their roman numerals.
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CONTRIBUTION OF KARMEN KAPP TO ORIGINAL PUBLICATIONS (I–V)

I Participation in planning the experiments; collection and distillation of plant material; participation in writing the publication.

II Planning the experiments in collaboration; collection, distillation and extraction of plant material; participation in performing the HPLC-UV-MS/MS experiments; performing the HPLC-UV-MS/MS data analysis; writing the publication.

III Participation in planning the experiments; collection and distillation of sample material; improving the distillation method; participation in performing the GC-MS experiments and data analysis; participation in writing the publication.

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V Planning the experiments in collaboration; collection, distillation and extraction of sample material; participation in performing the GC-MS analyses; analysing the GC-MS data; participation in performing the HPLC-UV-MS/MS experiments; analysing the HPLC-UV-MS/MS data; performing the antimicrobial activity experiments; writing the publication.

ABBREVIATIONS

AB	abbreviate body
ATCC	American Type Culture Collection
BGA	Bacillus subtilis producing thermostable ε-galactosidase
C.	*Chlamydia*
CAP	community-acquired pneumonia
cf.	*confer* (Latin); compare with
CFU	colony forming unit
CLSI	Clinical and Laboratory Standards Institute
CN	*Bacillus pumilus* Meyer and Gottheil 1901, strain CN607
cv.	cultivar
Da	dalton
DAD	diode array detector
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DST	diagnostic sensitivity test
EB	elementary body
E.	*Escherichia*
ESBL	extended-spectrum *β*-lactamase
ESI	electrospray ionization
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FBS	fetal bovine serum
GC	gas-chromatography
HL	Human Line
HPLC	high-performance liquid chromatography
HSV-1	Herpes simplex virus type-1
IC_{90}	concentration giving 90% inhibition
K7	*C. pneumoniae* strain Kajaani-7
LPS	lipopolysaccharide
M.	*Mentha*
MBC	minimal bactericidal concentration
$M\text{-}H^-$	negative ion mode
MHA	Mueller Hinton Agar II
MHB	Mueller Hinton Broth II
m/z	mass-to-charge ratio
NCM	National Collection of Industrial Microorganisms
MOI	multiplicity of infection
MS	mass-spectrometry
MS/MS	Tandem mass-spectrometry
PBS	phosphate buffered saline
RB	reticulate body
RPMI	Roswell Park Memorial Institute
RI	retention index
rpm	revolutions per minute
RNA	ribonucleic acid
spp.	species
S.	*Staphylococcus*
t_R	retention time
UV	ultraviolet

ABSTRACT

Mentha plants are used in pharmaceutical and food industries and characterized by high morphological variation and natural interspecies hybridization. Thus, the systematics of genus *Mentha* has been a matter of speculation for decades. Based on morphological, cytological and genetic characteristics, the genus *Mentha* has recently been classified into 18 species, 11 hybrids and hundreds of subspecies, varieties and cultivars.

The medicinal and culinary properties of *Mentha* plants are chiefly bounded to the composition of polyphenolic compounds and essential oils. In recent years, an increasing number of studies have been focused on studying the phenolic composition of the *Mentha* plants. Nevertheless, detailed description of such compounds is needed. Essential oil content and composition of *Mentha* plants varies and is related to the environmental conditions.

In the present study, the polyphenolic and essential oil composition of 47 *Mentha* plants cultivated or growing wild in Estonia were studied. Similar profiling was conducted for 27 commercial peppermint tea samples originating from nine countries. In addition, this was the first more detailed study to present the composition of mint flavourings isolated from 45 candies and food supplements.

For the first time, the effects of peppermint teas water extracts, mint flavouring hydrodistilled extracts and terpenoidic reference substances against respiratory tract pathogen *Chlamydia pneumoniae* were investigated *in vitro*. *Mentha* plants water extracts and essential oils, mint flavouring hydrodistilled extracts and terpenoidic reference substances were also tested *in vitro* for their antimicrobial properties against the potential pathogens *Escherichia coli* and *Staphylococcus aureus*. Furthermore, the antimicrobial effects of *M*. × *villosa* Huds., *M*. *suaveolens* Ehrh., *M*. × *gracilis* Sole, *M. arvensis* L. water extracts and mint flavouring hydrodistilled extracts were studied for the first time on *E. coli* and *S. aureus*.

The polyphenolic profile of *Mentha* plants and peppermint teas water extracts was rather similar. The most abundant polyphenols found in the *Mentha* plants water extracts were rosmarinic acid, eriocitrin, salvianolic acid B and salvianolic acid E. In the peppermint teas water extracts major compounds were eriocitrin, rosmarinic acid, 12-hydroxyjasmonate sulphate and luteolin-*O*-rutinoside. In addition, nine compounds were detected for the first time in the *Mentha* plants. Compounds found were 12-hydroxyjasmonate sulphate, medioresinol, medioresinol sulphate, prolithospermic acid, salvianolic acid H, salvianolic acid I, rosmarinic acid sulphate, salvianolic acid E, isosalvianolic acid A. In addition, danshensu was for the first time reported in *M*. × *piperita* L.

The total content of the essential oils varied in the range of 0.1-3.0% (w/w) among the 47 *Mentha* samples. Less than a half (n = 12) of the commercial peppermint teas samples exceeded the Ph. Eur. 7th Ed. total content limit of 0.9%. The main compounds found in the *Mentha* plants essential oils were 3-octanone, limonene, linalool, menthofuran, menthol, carvone, *cis*-piperitone oxide, linalool acetate, *α*-terpinyl acetate and piperitenone oxide. The essential oil composition analyses of peppermint teas showed that three tea samples may contain *M. spicata* L., different from that claimed on the package.

The total content of the isolated mint flavouring hydrodistilled extracts ranged 0.01-0.9% (w/w). The isolated extract content was higher in mint flavoured sugar candies, pastilles and tablets than in chocolates. The three most abundant flavouring compounds were limonene, menthol and menthone.

All seven peppermint teas water extracts were active against *C. pneumoniae*, the growth inhibition ranging from 20.7% to 69.5%. In most cases, the antichlamydial activity was related to high content of luteolin and apigenin glycosides. Results obtained by treating *C. pneumoniae* elementary bodies (EBs) with the mint flavouring hydrodistilled extracts or terpenoidic reference substances showed that a significant decrease in EB infectivity was achieved with most of the extracts and reference substances. This antichlamydial activity could be related to the relatively high menthol content of the extracts.

Six *Mentha* plants water extracts showed antibacterial activity against *S. aureus*, whereas the extract of *M*. *× piperita* L. was found to be bactericidal. Five of the tested essential oils inhibited the growth of *E. coli,* while all the tested nine oils were antibacterial to *S. aureus*. The MIC_{90} values for *S. aureus* were lower than for *E. coli*. Three of the tested mint flavouring hydrodistilled extracts were antimicrobial to *E. coli* and eight extracts on *S. aureus*. Linalool acetate and (-)-carvone were the most active reference substances against both bacteria. Suprisingly, the antimicrobial activity was not always in accordance with the composition or the activities of respective reference substances.

During the years, the everyday diet has developed to contain regularly *Mentha* plants and its ingredients. This study showed, what could be the basis for this trend by confirming that the consumption of *Mentha* plants may be beneficial for human health.

1. INTRODUCTION

The economic importance of mints, *Mentha*, is evident as their essential oils, dried and fresh plant material are in daily use as a part of confectionary, beverages, bakery, cosmetics, pharmaceuticals and pesticides (Shaikh *et al*., 2014). Solely in North-America, 3318 tonns of *Mentha × piperita* L., 478 of *M. × gracilis* Sole and 346 tonns of *M. spicata* L. were produced in year 2004 (Sheldon, 2006). Many of the *Mentha* plants are cultivated worldwide and described as official drugs in several pharmacopoeias (Mimica-Dukić and Bozin, 2008). As an example, the European Pharmacopoeia gives the botanical identification parameters and essential oil content limits of *M. × piperita* L. and *M. canadensis* L. essential oil (European Pharmacopoeia, 2010). *Mentha* plants are perennial, fast growing and generally tolerate a wide range of agroclimatic conditions with the distribution across Europe, Africa, Asia, Australia, and North America (Brickell and Zuk, 1997).

The taxonomy of the genus *Mentha* has been in a fluctuating state, with more than 3000 names from species to *formae* published since the starting date of the modern plant nomenclature (Linnaeus, 1753; Tucker and Naczi, 2006). The systematics of *Mentha* plants is complicated and often questionable due to the natural interspecies hybridization, occurring with high frequency in wild populations and in cultivation (Gobert *et al*., 2002; Harley, 1972). The species *M. arvensis* L., *M. aquatica* L., *M. spicata* L., *M. longifolia* (L.) L. *and M. suaveolens* Ehrh. have produced eleven naturally occurring hybrids. Because of the heterozygosity and cytomixis of these nominally accepted species, many hybrids can be generated by self-pollination. Most hybrids are infertile, but vegetative propagation due to their highly invasive rhizome system enables them to persist (Spencer *et al*., 1993). Thus, complex hybrid populations may arise, not necessarily correlated with any geographical or ecological distribution. This has prompted some taxonomists to publish paroxysms of species and subspecific taxa (Tucker and Naczi, 2006; Gobert *et al*., 2002).

Mentha plants are mainly used for treatment of disorders of gastrointestinal tract. They have also been reported to have antioxidant, anti-inflammatory, antimicrobial, analgesic and anticarcinogenic effects (Shaikh *et al*., 2014; Rita and Animesh, 2011; McKay and Blumberg, 2006). The pharmacological effects of *Mentha* plants are chiefly bound to the presence of two main compound groups: phenolic and essential oil compounds. The main phenolics in reported *Mentha* plants include derivatives of caffeic acid and glycosidic forms of the flavonoids luteolin, apigenin, eriodictyol and naringenin. However, previous studies on the chemical composition and biological activity of *Mentha* have mainly focused on the essential oils. *Mentha* plants essential oils are mainly composed of monoterpenes and sesquiterpenes, which content and composition varies (Kumar *et al*., 2011; Maffei *et al*., 2006).

The present thesis aims to broaden the knowledge of the chemical composition of *Mentha* plants. Widely consumed mint flavouring and peppermint teas are studied for their potential effect to prevent respiratiory tract infections by testing their antimicrobial effect against *Chlamydia pneumoniae*. Also, the antimicrobial activity of *Mentha* plants essential oils, water extracts and mint flavouring extracts were evaluated. The present study supports the use of *Mentha* plants and their constituents as health promoting agents.

2. REVIEW OF THE LITERATURE

2.1. Genus *Mentha* L.

2.1.1. Taxonomy and *Mentha* plants

Mentha plants are herbaceous and perennial aromatic herbs that are cultivated for health care and culinary purposes. *Mentha* plants belong to the family *Lamiaceae*, tribe *Mentheae*, genus *Mentha* L. and occure in all five continents. The taxonomy of genus *Mentha* is complicated and within the genus, more than 3000 names have been published from species to *formae* since 1753 which is the starting date of modern nomenclature (Linnaeus, 1753). About 95% of these names are synonyms or illegitimate and presently, only the names of about 1800 have been adequately studied (Tucker and Naczi, 2006). Studies have attempted to describe the genetic relationships in genus *Mentha* using morphological (Šarić-Kundalić *et al*., 2009), cytological (Gobert *et al*., 2002; Sharma and Bhanttacharyya, 1959) and genetic characteristics (Wang *et al*., 2013a; Attiya *et al*., 2012; Shasany *et al*., 2005). According to the latest taxonomic classification, plants in the genus *Mentha* are divided into four sections (*Tubulosae*, *Eriodontes*, *Pulegium*, *Mentha*) and 18 species on the basis of the number of chromosomes and morphological features (Table 1; Tucker and Naczi, 2006).

Table 1. Infrageneric classification of the *Mentha* plants into the sections *Tubulosae*, *Eriodontes*, *Pulegium*, *Mentha* (Tucker and Naczi, 2006).

Species	Section
M. aquatica L.	*Mentha*
M. arvensis L.	*Mentha*
M. australis R.Br.	*Eriodontes*
M. canadensis L.	*Mentha*
M. cervina L.	*Eriodontes*
M. dahurica Fisch. ex Benth.	*Mentha*
M. diemenica Spreng.	*Tubulosae*
M. gattefossei Maire	*Eriodontes*
M. grandiflora Benth.	*Pulegium*
M. japonica (Miq.) Makino	*Mentha*
M. laxiflora Benth.	*Eriodontes*
M. longifolia (L.) L.	*Mentha*
M. pulegium L.	*Pulegium*
M. repens (Hook. f.) Briq.	*Tubulosae*
M. requienii Benth.	*Pulegium*
M. satureoides R.Br.	*Eriodontes*
M. spicata L.	*Mentha*
M. suaveolens Ehrh.	*Mentha*

The plants in the section *Pulegium* are characterized by uniformly prostrate to upright habit while flowering. The presence of stolons is not described. The leaves are petiolate, ovate to suborbicular, obtuse to cuneate and entire to serrate (Appendix 1). Inflorescence shape is verticillate with four to many flowers. Chromosome number varies, being x = 9, 10 (Tucker and Naczi, 2006).

The section *Tubulosae* plants are described by upright habit while flowering. Stolons are absent. The leaves are petiolate, ovate to lanceolate, obtuse to cuneate, entire and revolute. Inflorescence is verticillate with two to eight flowers. Chromosome number x = 60 (Tucker and Naczi, 2006).

The plants in the section Eriodontes have upright habit while flowering. Stolons are reported to be subterranean or aerial. The leaves are sessile to petiolate, oblong-lanceolate to linearoblanceolate, cordate to attenuate and entire to serrate. Inflorescence is verticillate with four to many flowers. Chromosome number varies, being x = 12, 13 (Tucker and Naczi, 2006).

In the section *Mentha,* the plants are uniformly upright in habit. Stolons are subterranean or aerial. The leaves are sessile or petiolate, ovate to lanceolate, cordate to cuneate, entire to serrate or crenate. Inflorescence is various (verticillate, spicate or capitate) with four to many flowers. Chromosome number is x = 12 (Tucker and Naczi, 2006).

Interspecies hybridization exists in the section *Mentha* that includes eight species: *M. suaveolens* Ehrh., *M. longifolia* (L.) L., *M. spicata* L., *M. arvensis* L., *M. canadensis* L., *M. aquatica* L., *M. dahurica* Fisch. ex Benth. and *M. japonica* (Miq.) Makino (Tucker and Naczi, 2006). The systematics of the latter species is especially difficult because of the ease of hybridization, which is further favoured by polymorphism, polyploidy and vegetative propagation. The five species *M. arvensis* L., *M. aquatica* L., *M. spicata* L., *M. longifolia* (L.) L. and *M. suaveolens* Ehrh. have produced 11 naturally occurring hybrids (Table 2; Tucker and Naczi, 2006). Most hybrids are sterile or subfertile, but vegetative propagation enables them to persist (Gobert *et al*., 2002).

Morphologically, *M. × carinthiaca* Host and *M. × dalmatica* Tausch resemble *M. arvensis* L. Also, *M. × dalmatica* Tausch has been confused with pubescent collections of *M. × gracilis* Sole. Whereas *M. × dumetorum* Schultes has been confused with pubescent collections of *M. × piperita* L. (Tucker and Naczi, 2006). *M. × villoso-nervata* Opiz usually appears almost morphologically indistinguishable from *M. spicata* L., but some forms are recognizable (Harley, 1975). Also, the inflorescence of *M. × gracilis* Sole and *M. × verticillata* L. has been reported to vary from subverticillate to subspicate (Tucker and Naczi, 2006).

Table 2. Hybrids of the genus *Mentha* (Tucker and Naczi, 2006).

Hybrid	Species of originated
M. × carinthiaca Host	*M. arvensis* L. *× M. suaveolens* Ehrh.
M. × dalmatica Tausch	*M. arvensis* L. *× M. longifolia* (L.) L.
M. × dumetorum Schultes	*M. aquatica* L. *× M. longifolia* (L.) L.
M. × gracilis Sole	*M. arvensis* L. *× M. spicata* L.
M. × maximilianea F. W. Schults	*M. aquatica* L. *× M. suaveolens* Ehrh.
M. × piperita L.	*M. aquatica* L. *× M. spicata* L.
M. × rotundifolia (L.) Huds.	*M. longifolia* (L.) L. *× M. suaveolens* Ehrh.
M. × smithiana R. Graham	*M. aquatica* L. *× M. arvensis* L. *× M. spicata*
M. × verticillata L.	*M. aquatica* L. *× M. arvensis* L.
M. × villosa Huds.	*M. spicata* L. *× M. suaveolens* Ehrh.
M. × villoso-nervata Opiz	*M. longifolia* (L.) L. *× M. spicata* L.

The *Mentha* species distributed in Europe are *M. aquatica* L., *M. arvensis* L., *M. cervina* L., *M. pulegium* L. and *M. requienii* Benth. Also, *M. spicata* L. is described in Europe but its distribution is

highly associated with cultivation. In Australia and Tasmania can be found *M. australis* R.Br., *M. diemenica* Spreng., *M. grandiflora* Benth., *M. laxiflora* Benth., *M. repens* (Hook. f.) Briq. and *M. satureoides* R.Br. In Asia have been described *M. dahurica* Fisch. ex Benth. and *M. japonica* (Miq.) Makino. In addition, *M. canadensis* L. that is also found in North America. *M. suaveolens* Ehrh. is found in two continents, respectively in Europe and Africa. *M. longifolia* (L.) L. has the most extensive geographical range, found in Europe, Asia and Africa (Tucker and Naczi, 2006).

Most of the *Mentha* plants prefer moist habitat. In the shores of ponds, lakes, canals and waterfalls can be found *M. cervina* L., *M. gattefossei* Maire, *M. japonica* (Miq.) Makino, *M. aquatica* L., *M. australis* R.Br. and *M. canadensis* L. Besides, *M. cervina* L. is also growing in water up to 60 cm deep. In damp fields, roadsides and meadows are growing *M. arvensis* L., *M. canadensis* L., *M. dahurica* Fisch. ex Benth., *M. pulegium* L. and *M. repens* (Hook. f.) Briq. Close to waterbodies or in fields and meadows are found also *M. spicata* L., *M. longifolia* (L.) L. and *M. suaveolens* Ehrh. In forests and gullies is growing *M. laxiflora* Benth. Sandy or loamy soil is preferred by *M. grandiflora* Benth. and *M. satureoides* R.Br (Tucker and Naczi, 2006).

2.1.2. Polyphenolic composition of *Mentha* plants

Several studies have demonstrated that *Mentha* plants are rich in phenolic compounds, particularly in phenolic acids and flavonoids (Appendix 2). From all phenolic acids, genus *Mentha* is particularly enriched in caffeic acid and its derivatives, the latter reported to represent 60-80% of their total phenolic compounds (Pereira and Cardoso, 2013; Misan *et al*., 2011; Dorman *et al*., 2009; Fecka and Turek, 2007; Shan *et al*., 2005; Kosar *et al*., 2004; Zgorka *et al*., 2001). Caffeic acid is frequently detected as a minor phenolic component (Dorman *et al*., 2003). Besides the free form of the acid, the glucuronide isomer has been found in *M. pulegium* L. (Taamalli *et al*., 2015). The presence of chlorogenic acid has been described in several *Mentha* plants such as *M. × piperita* L. (Misan *et al*., 2011), *M. spicata* L. (Igoumenidis *et al*., 2016; Fatiha *et al*., 2015) and *M. longifolia* (L.) L. (Benedec *et al*., 2013). Rosmarinic acid is the most abundant phenolic in *Mentha* plants (Pereira and Cardoso, 2013). Its content in *M. × piperita* L. has been reported being about 30% of the total phenolics (Misan *et al*., 2011; Dorman *et al*., 2009; Fecka and Turek, 2007; Kosar *et al*., 2004; Zgorka *et al*., 2001). Also, it has been detected in wide variety of *Mentha* plants (Tang *et al*., 2016; Fatiha *et al*., 2015; Taamalli *et al*., 2015; Shen *et al*., 2011; Dorman *et al*., 2009, 2003; Kosar *et al*., 2004). In addition, seven salvianolic acids have been described in *Mentha* plants (Taamalli *et al*., 2015; Krzyzanowska *et al*., 2011; She *et al*., 2010).

Besides caffeic acid and its derivatives, other organic acids have been reported**.** For example caftaric acid (Benedec *et al*., 2013), cinnamic acid (Igoumenidis *et al*., 2016; Rita and Animesh *et al*., 2011), *p*-coumaric acid (Fatiha *et al*., 2015; Benedec *et al*., 2013; Kivilompo and Hyotylainen, 2007), ferulic acid (Igoumenidis *et al*., 2016; Benedec *et al*., 2013; Papageorgiou *et al*., 2008a; Proestos *et al*., 2005), oleanolic acid (Igoumenidis *et al*., 2016; Shen *et al*., 2011) and vanillic acid (Igoumenidis *et al*., 2016; Taamalli *et al*., 2015; Papageorgiou *et al*., 2008a) have been found in *Mentha* plants.

Mentha plants are rich in flavonoids, particularly in flavones and flavanones, the latter being 10-70% of their total phenolics (Pereira and Cardoso, 2013). Luteolin and its derivatives are the main flavones described in *Mentha* plants (Benedec *et al*., 2013; Misan *et al*., 2011; Hossain *et al*., 2010; Fecka and Turek, 2007; Kosar *et al*., 2004). Moreover, glycosidic derivatives like luteoline-*O*-glucoside and luteoline-*O*-rutinoside are often described as major phenolic compounds (Krzyzanowska *et al*., 2011; Fecka and Turek, 2007; Kosar *et al*., 2004; Dorman *et al*., 2003). Apigenin (Taamalli *et al*., 2015;

Bimakr *et al*., 2011; Misan *et al*., 2011) and its derivatives like glucosides (Stanisavljević *et al*., 2012) and rutinosides (Aksit *et al*., 2014; Reichling *et al*., 2008; Kosar *et al*., 2004; Dorman *et al*., 2003) can also be found in *Mentha.* Other flavones described in mints include for example acacetin and its glycosides (Taamalli *et al*., 2015; Salin *et al*., 2011), diosmin (Taamalli *et al*., 2015; Fatiha *et al*., 2015), salvigenin (Voirin *et al*., 1999; Zaidi *et al*., 1998) and thymonin (Voirin *et al*., 1999; Zaidi *et al*., 1998).

Mentha plants are rich in flavanones and compounds of this class include mainly derivatives of eriodictyol, naringenin and hesperitin. Frequently these compounds appear as glucoside derivatives (Pereira and Cardoso, 2013). For example, hesperidin (hesperetin-7-*O*-rutinoside), eriodictyol-*O*-glucoside and naringenin-7-*O*-glucoside have been reported in *M. × piperita* L. (Misan *et al*., 2011; Dolzhenko *et al*., 2010; Fecka and Turek, 2007). On the other hand, eriocitrin (eriodictyol-7-*O*-rutinoside) is the most abundant flavanone in *Mentha* plants according to Krzyzanowska *et al*. (2011), Fecka and Turek (2007), Dorman *et al*. (2009, 2003) and Areias *et al*. (2001). Also, narirutin (naringenin-7-*O*-rutinoside) has been detected as a major compound in *M. × piperita* L. (Dolzhenko *et al*., 2010; Fecka and Turek, 2007; Inoue *et al*., 2002; Guedon and Pasquier, 1994).

Flavonols and dihydroflavonols have been less reported in *Mentha* plants. However, the flavonol kaempferol has been found in several *Mentha* plants (Igoumenidis *et al*., 2016; Zaidi *et al*., 1998) and its glucosides, rhamnosides, rutinosides and sophoroside in *M. × piperita* L. or *M. longifolia* (L.) L. (Stanisavljević *et al*., 2012; Dolzhenko *et al*., 2010). Also the presence of rutin has been described by several authors (Fatiha *et al*., 2015; Benedec *et al*., 2013; Bimakr *et a*l., 2011). Other flavonols or dihydroflavonols detected include for example quercetin (Igoumenidis *et al*., 2016; Misan *et al*., 2011) and myricetin (Bimakr *et al*., 2011).

Flavanols reported in *Mentha* plants are for example catechin (Igoumenidids *et al*., 2016; Taamalli et al., 2015) and epicatechin (Igoumenidis *et al*., 2016; Bimakr *et al*., 2011). Coumarins reported are esculetin (Dobias *et al*., 2010) and scopoletin (Adam *et al*., 2009). In *M. × rotundifolia* (L.) Huds. have been described the anthocyanidins cyaniding, delphinidin, luteolinidin, pelargonidin and petunidin (Marin Pares, 1983). Also, stilbenoid resveratrol and phenylethanoid tyrosol have been found in *M. spicata* L. (Igoumenidis *et al*., 2016).

2.1.3. Essential oil composition of *Mentha* plants

Essential oils are complex mixtures of volatile compounds produced by living organisms and isolated by physical means only (pressing and distillation) from a whole plant or plant part of known taxonomic origin (Franz and Novak, 2010). Essential oils are produced by specialized secreting tissues called glandular trichomes (Maffei *et al*., 2006).

Two types of glandular trichomes occur on *Mentha* plants leaf surface: small, capitate trichomes, with a single secretory head cell and peltate glandular trichomes, with an eight-celled head and a huge subcuticular oil storage cavity (Fialova *et al*., 2015). The main oils of the *Mentha* plants that have achieved high economic importance are *M. canadensis* L., *M. × piperita* L., *M. spicata* L. and *M. gracilis* Sole. In addition, to a lesser extend the oils of *M. citrata* and *M. pulegium* L. are of commercial importance (Tucker and Naczi, 2006).

The essential oils of *Mentha* plants are colourless, pale yellow or greenish-yellow liquids consisting mainly of hydrocarbons, alcohols, esters, ketones, ethers and oxides (Appendix 3). Major hydrocarbons found include limonene in *M. arvensis* L. (Lawrence, 2006a,b; Malingre´, 1971),

germacrene D (Lawrence, 2006a,b; Umemoto, 1994) and *β*-caryophyllene. The latter has also been reported in many *Mentha* plants essential oils like *M. × verticillata* L., *M. × smithiana* R. Graham and *M. × dumetorum* Schultes (Lawrence 2006b; Umemoto, 1994; Lawrence, 1978).

Alcohols as main components are more diversified than hydrocarbons in *Mentha* plants. Most well known of them is probably menthol, frequently reported as most abundant in *M. × piperita* L. essential oils (Grulova *et al*., 2015; Moghaddam *et al*., 2013; Işcan *et al*., 2002). Also, it has been found in the oils isolated from *M. canadensis* L. (Ikeda *et al*., 1971), *M. × maximilianea* F.W. Schults (Lawrence, 1978) and *M. × verticillata* L. (Maffei, 1990). On the other hand, menthol isomer neomenthol has been found as a major compound in the oil of *M. × gracilis* Sole (Umemoto and Nagasawa, 1978). Sweet odored linalool has been detected in several *Mentha* plants essential oils like *M. longifolia* (L.) L. (Baser *et al*., 1999) and *M. spicata* L. (Gora and Kalemba, 1979). Other alcohols determined include for example 3-octanol, terpinen-4-ol and geraniol (Lawrence, 2006b).

Most widely detected ester as a main compound is menthyl acetate, found in essential oils of *Mentha* plants such as *M. × rotundifolia* (L.) Huds. (Kokkini, 1983), *M. × dumetorum* Schultes (Lawrence, 1978) and *M. cervina* L. (Velasco-Negueruela *et al*., 1987). Also, neomenthyl acetate has been characterized as a major compound in the oil of *M. diemenica* Spreng. (Brophy *et al*., 1996). Decyl acetate, dihydrocarvyl acetate, 1,2-epoxyneomenthyl acetate and *α*-terpinyl acetate are other major esters described in the essential oils (Lawrence, 2006b).

Several most abundant essential oils compounds of *Mentha* plants are ketones. Carvone, often reported as a main component of *M. spicata* L. oil (Hussain *et al*., 2010; Soković *et al*., 2009; Sticher and Flück, 1968), has also been reported for plants like *M. longifolia* (L.) L. (Baser *et al*., 1999), *M. suaveolens* Ehrh. (De la Torre and Torres, 1977), *M. × villosa* Huds. and *M. × smithiana* R. Graham (Lawrence, 1978). In addition, the *cis*- and *trans*- isomers of dihydrocarvone have been described as major compounds of the previously mentioned *Mentha* plants (Lawrence, 2006b). Other more prevalent ketones are menthone, isomenthone and pulegone. In addition, 3-octanone, piperitenone and piperitone have been characterized as main components (Lawrence, 2006b).

The two dominating ethers found in higher concentration are 1,8-cineole and menthofuran, both found in a variety of *Mentha* plants. Also, oxides like caryophyllene oxide, piperitenone oxide and piperitone oxide have been reported to be abundant in the essential oils of *Mentha* plants (Lawrence, 2006b).

Chemotypes are defined as individual plants producing distinctive dominant secondary compounds (Keefover-Ring *et al*., 2009; Santesson, 1968). These are usually qualitative designations, making the concept of chemotype somewhat arbitrary, due to large amounts of variation in the chemistry of any particular plant species (Keefover-Ring *et al*., 2009). According to the essential oil composition, existence of nine chemotypes has been reported for the *Mentha* plants (Table 3, Mimica-Dukić and Bozin, 2008; Kokkini, 1991). The highest number of chemotypes, namely five, has been described for *M. longifolia* (L.) L., followed by *M. arvensis* L. and *M. spicata* L., both with four chemotypes. For *M. aquatica* L., chemotypes rich in menthofuran or linalool and linalool acetate have been detected.

Table 3. Chemotypes described in the genus *Mentha* (Mimica-Dukić and Bozin, 2008; Kokkini, 1991).

	Main components of chemotype	*Mentha* plants
I	Geraniol and/or Geranyl acetate	*M. arvensis* L.
II	Linalool and/or Linalool acetate	*M. aquatica* L., *M. longifolia* (L.) L., *M. spicata* L.
III	Carvone/Dihydrocarvone	*M. longifolia* (L.) L, *M. spicata L., M. suaveolens* Ehrh., *M. × villosa* Huds.
IV	Piperitone/Piperitone oxide	*M. longifolia (*L.) L.
V	Piperitenone oxide/Piperitone oxide	*M. longifolia* (L.) L., *M. spicata* L., *M. suaveolens* Ehrh., *M. × villosa* Huds.
VI	Menthofuran	*M. aquatica* L.
VII	Pulegone/Isopulegone	*M. arvensis* L.
VIII	Pulegone/Menthone/Isomenthone	*M. arvensis* L., *M.* spicata L., *M. suaveolens Ehrh.*
IX	Menthone/Isomenthone/Menthol isomers	*M. arvensis* L., *M. longifolia* (L.) L., *M. × piperita L.*

2.1.4. Variation of the chemical composition of *Mentha* plants

The variation in the chemical composition of *Mentha* plants has been attributed to several factors. According to Hussain *et al*. (2010) the essential oil content of *M. × piperita* L., *M. arvensis* L., *M. spicata* L. and *M. longifolia* (L.) L. was higher when harvested in summer. Also, the content of most of the compounds was higher in the oil isolated in summer. Plant growth stage was found not to have influence on the oil content of *M. × piperita* L. However, the content of menthol, menthone and menthyl acetate showed increasing levels from early to late bloom, whereas the ketones menthone and isomenthone decreased (Rohloff *et al*., 2005; Rohloff, 1999). On the contrary, according to Aflatuni *et al*. (2006), the oil content was higher in *Mentha* plants cut late August due to higher herb yield and plant height. Similarly to Rohloff *et al*. (2005), menthol content in *M. × piperita* L. was higher in full bloom than during the onset of flowering. The effect of UV-B radiation on *M. spicata* L. oil has been studied by Karousou *et al*. (1998). No particular influence on the total oil content was found. However, the increase of piperitenone oxide was observed. Also, plant morphology may have effect on the essential oli composition. According to Rohloff (1999), *M. × piperita* L. flowers contain higher content of menthofuran than the leaves. The effect of water stress was studied by Kolodziej (2008). The obtained results indicated that *M. × piperita* L. requires irrigation in order to achieve higher yield of plant material and essential oil. Furthermore, nitrogen was shown to increase the biomass and oil yield (Zheljazkov *et al*., 2010a).

The processing method may also alter the essential oil content and composition. Higher oil content has been obtained from the dry plant material than from the fresh biomass (Zheljazkov *et al*., 2010b). Besides, drying in the room temperature or 30m 40 °C resulted in the higher oil content than in the oven or drying chamber at the temperature of 50 °C and 70 °C (Wang *et al*., 2013b; Rohloff *et al*., 2005). Drying was also found to increase the content of 1,8m cineole and menthol (Zheljazkov *et al*., 2010b).

Also the polyphenolic composition may vary due to the environmental factors. The accumulation of rosmarinic acid in *M. × piperita* L. and *M. spicata* L. has been studied by Fletcher *et al*. (2009) and Papageorgiou *et al*. (2008a,b). Exposure to short photoperiod of 12 h in comparison to

16 h reduced rosmarinic acid accumulation (Fletcher *et al*., 2009). Besides, the content of rosmarinic acid was higher before flowering (Fletcher *et al*., 2009; Papageorgiou *et al*., 2008a,b). Cold stress of 4 °C during 6 weeks time period had no effect on the rosmarinic acid content (Fletcher *et al*., 2009).

2.1.5. *Mentha* plants used in food industry

Essential oils isolated from the *Mentha* plants have a long history of use as improving the flavour of foods like confectionaries and beverages. Mint flavour, which includes spearmint, peppermint and cornmint, is probably the third most important flavour used after vanilla and citrus (Maftei, 1992). As a result, *Mentha* plants are among the most important commercial herbs cultivated for dry leaf production in Germany, Spain, Poland, Bulgaria, Egypt, Morocco, Greece, Israel, United Kingdom, Turkey, Nigeria and China (Hayes *et al*., 2006).

The peppermint flavour is primarily based on menthol, menthone and their isomers, menthyl esters and piperitone (Tucker, 2006; Arctander, 1969). (-)-Menthol not only provides the classic minty note, but also activates the cold-sensitive receptors in the oral cavity to produce a cooling effect (Salles, 2006; Eccles, 1994). It is also an interesting molecule with a sensation of bitterness. Thus, it stimulates both aroma and taste receptors (Salles, 2006). Menthofuran adds a distinctive mustiness, described as sweet, haylikeminty odor, sometimes referred to as lactone-odor (Tucker, 2006; Arctander, 1969). Spearmint flavour is primarily based on R-(-)-carvone, dihydrocarvone, carveol, dihydrocarveol, carvyl- and dihydrocarvyl esters and to a lesser extent limonene. Carvone is of particular interest because it exists in two enantiomeric forms with different aroma properties. R-(-)-carvone smells of spearmint and is extracted from *Mentha spicata* L. The S-(+)- enantiomer resembles caraway, accounting for 50% of the essential oil in caraway seeds (Parker *et al*., 2015). The concept of a pennyroyal flavour is based on pulegone and its isomers and alcohols. Bergamot or orange mint flavour is based on linalool and linalool acetate (Tucker, 2006; Arctander, 1969).

Although mint oils are often associated with chewing gums and toothpastes, they have also other flavouring uses. The oils and mint flavouring which generally contain some mint oils or mint isolates are used to flavour confections such as hard and soft candy, breath mints including the popular extra strong mint tablets, after-dinner mints, chocolates and chewing gum. Other than confections, mint oils and their corresponding isolates are used in both nonalcoholic and alcoholic beverages. They can also be found as flavourings in frozen dairy products such as ice cream and ice lollies, baked goods, icings, toppings, cake frostings, puddings, sauces and chutneys. Spearmint oil is used in the preparation of mint jelly (Hayes *et al*., 2006). *Mentha* plants have also shown to be efficient food preservatives in improving the shelf life and safety of meat and other flesh foods (Najeeb *et al*., 2015; Kanatt *et al*., 2008). The interest in using mint in food industry is also reflected by the fact that there are about 1000 patents on the use of mint flavourings.

2.1.6. Health benefits of *Mentha* plants

Mentha plants are one of the most popular herbs that have been used for their medicinal and aromotherapeutic properties since ancient times. Mint is mentioned in the Icelandic Pharmacopoeias of the 13th century. Their cultivation is also reported in China during Ming Dynasty (1368-1644) (Dai, 1981). In 1721, *M. × piperita* L. became the official item of Materia Medica in the London Pharmacopoeia as *Mentha piperitis sapore* (Flückiger and Hanbury, 1879). In Europe, it came into general use as a medicine during the middle of the 18th century (Kumar *et al*., 2011; Grieve, 1931).

Various health benefits reported for *Mentha* plants are listed in Table 4. *In vivo* experiments with mice have shown essential oils and alcoholic extracts of *Mentha* plants to possess analgesic activity. For example, the extracts of *M. arvensis L.* and *M. spicata* L. reduced the writhing (Biswas *et al*., 2014; Yousuf *et al*., 2013) and *M. × villosa* Huds. the paw licking time (Sousa *et al*., 2009). Also, the *in vitro* studies showed *M. suaveolens* Ehrh. to possess a significant diminution in the contractile effects induced by histamine, serotonin and acetylcholine (Moreno *et al*., 2002).

Arumugam *et al*. (2008) evaluated the anti-inflammatory effects *in vivo* of aqueos, chloroform, ethyl acetate and hexane extracts of *M. spicata* L. Ethyl acetate and aqueous fractions were both effective in reducing the chronic and acute inflammation of mice. In addition, *M. × piperita* L. essential oil exhibited potent anti-inflammatory activities in a croton oil induced mouse ear edema model (Sun *et al*., 2014). Edema reduction was also observed by topic use of *M. aquatica* L. alcohol extract (Conforti *et al*., 2008).

Several studies have indicated that *Mentha* plants contain constituents with cytotoxic properties that may find use in developing anticancer agents. For example, M. *arvensis* L., *M. longifolia* (L.) L., *M. spicata* L. and *M. viridis* extracts showed anti-proliferative effect against various cancer cell-lines *in vitro* (Sharma *et al*., 2014). *M. longifolia* (L.) L. and *M. × piperita* L. were also respectively found to possess cyctotoxic activity against human breast cancer (Al-Ali *et al*., 2013) and human laryngeal epidermoid carcinoma (Abirami and Nirmala, 2014). Moreover, *M. × piperita* L. extract was found to be radioprotective against gamma radiation (Kaushik *et al*., 2012; Samarth *et al*., 2003).

Free radical species such as hydroxyl radicals and superoxide anion radicals as well as non-free radical species such as hydrogen peroxide cause oxidative harm to organic molecules like proteins, lipids, nucleic acids and carbohydrates. The cellular damage or oxidative injury seems to be a major predisposing factor behind a range of ailments (Shaikh *et al*., 2014). Various *Mentha* plants and their extracts or essential oils have been shown to possess antioxidative activity (Biswas *et al*., 2014; Teixeira *et al*., 2012; Conforti *et al*., 2008; Dorman *et al*., 2003).

The antiallergic effect of flavonoid glycosides isolated from the aerial part of *M. × piperita* L. was shown by Inoue *et al*. (2002). The compounds, such as eriocitrin, narirutin and disomin, showed a potent inhibitory effect on histamine release. On the other hand, *M. longifolia* (L.) L. and M. *arvensis* L. were shown to be possess hepatoprotective effect (Patil and Mall, 2012; Mimica-Dukić *et al*., 1999). Furthermore, *M. arvensis* L. alcohol extract showed the potentiation of pentobarbitone induced sleeping time (Verma *et al*., 2003).

Mentha plants are frequently used in the treatment of gastrointestinal tract disorders. For example, the essential oils of *M. × piperita* L. and *M. spicata* L. were shown to reduce the chemotherapy-induced vomiting and nausea (Tayarani-Najaran *et al*., 2013). In addition, extracts of *M. pulegium* L. caused concentration-dependent antispasmodic effect in rat isolated ileum test (Estrada-Soto *et al*., 2010). Similar effect was observed by Naseri *et al.* (2008) for *M. longifolia* (L.) L.

Antiviral properties have been shown for several *Mentha* plants. *M. × piperita* L. and *M. spicata* L. essential oils were screened for their antiviral activity against Herpes simplex type-1 (HSV-1) and parainfluenza type-3. Both oils displayed antiviral activity, yet the effect against HSV-1 was stronger (Orhan *et al*., 2012).

The antibacterial and antifungal activities of *Mentha* plants have been studied on various bacteria or fungi (Shaikh *et al*., 2014; Peixoto *et al*., 2009; Mimica-Dukić and Bozin, 2008; McKay and Blumberg, 2006). The essential oils have been proven to possess antibacterial activity against plant, human pathogenic and food-borne bacteria (Tyagi and Malik, 2011; Hussain *et al*., 2010;

Nedorostova *et al*., 2009; Soković *et al*., 2008; İşcan *et al*., 2002; Adam *et al*., 1998). The antibacterial or antifungal activity of *Mentha* plants extracts have been studied to much lesser extend. Nevertheless, the extracts have shown to posses antibacterial (Biswas *et al*., 2014; Verma *et al*., 2013; Gulluce *et al*., 2007; Sofia *et al*., 2007) and antifungal activity (Hussain *et al*., 2010; Gulluce *et al*., 2007).

Table 4*. Health benefits of various *Mentha* plants.

Health benefit	*Mentha* plants	Preparation used	Reference
		***In vitro* studies**	
Analgesic	*M. suaveolens* Ehrh.	alcohol extract	Moreno *et al*., 2002
Antiallergic	*M. × piperita* L. *M. spicata* L.	alcohol extract	Yamamura *et al*., 1998
Antibacterial Antifungal	M. *arvensis* L. *M. longifolia* (L.) L. *M. × piperita* L. *M. pulegium* L. *M. × rotundifolia* (L.) Huds. *M. spicata* L.	alcohol extract essential oil water extract	Biswas *et al*., 2014 Verma *et al*., 2013 Ait-Ouazzou *et al*., 2012 Teixeira *et al*., 2012 Derwich *et al*., 2010 Hussain *et al*., 2010 Mimica-Dukić *et al*., 2003
Anti-inflammatory	*M. × piperita* L.	alcohol extract	Belemkar *et al*., 2013
Antioxidant	*M. arvensis* L. *M. aqutica* L. *M. × dalmatica* L. *M. haplocalyx* Briq. *M. pulegium* L. *M. spicata* L. *M. × verticillata* L.	alcohol extract essential oil water extract	Biswas *et al*., 2014 Teixeira *et al*., 2012 Conforti *et al*., 2008 Dorman *et al*., 2003
Antiviral	*M. × piperita* L. *M. spicata* L. *M. suaveolens* Ehrh.	essential oil	Civitelly *et al*., 2014 Orhan *et al*., 2012
Antitumor Cytotoxic Radioprotective	*M. arvensis* L. *M. longifolia* (L.) L. *M. × piperita* L. *M. spicata* L. *M. × villosa* Huds.	water extract alcohol extract essential oil petroleum extract water extract	Amaral *et al*., 2015 Sharma *et al*., 2014 Al-Ali *et al*., 2013 Abirami and Nirmala, 2014 Hajighasemi *et al*., 2011 Jain *et al*., 2011
Spasmolytic	*M. longifolia* (L.) L.	alcohol extract	Shah *et al*., 2015
		***In vivo* studies**	
Analgesic	*M. arvensis* L. M. longifolia (L.) L. *M. × piperita* L. *M. spicata* L. *M. suaveolens* Ehrh. *M. × villosa* Huds.	alcohol extract essential oil	Biswas *et al*., 2014 Belemkar *et al*., 2013 Yousuf *et al*., 2013 Sousa *et al*., 2009 Moreno *et al*., 2002

Antiallergic	*M. × piperita* L.	alcohol extract	Inoue *et al*., 2002
Antiemetic	*M. × piperita L.* *M. spicata L.*	essential oil	Tayarani-Najaran *et al*., 2013
Anti-inflammatory	*M. aquatica* L. *M. arvensis* L. *M. × piperita* L. *M. spicata* L.	alcoholic extract chloroform extract essential oil hexane extract water extract	Sun *et al*., 2014 Arumugam *et al*., 2008 Conforti *et al*., 2008 Verma *et al*., 2003
Antitumor Cytotoxic Radioprotective	*M. arvensis* L. *M. × piperita* L. *M. × villosa* Huds.	alcohol extract essential oil	Amaral *et al*., 2015 Sun *et al*., 2014 Kaushik *et al*., 2012 Samarth *et al*., 2003
Hepatoprotective	*M. longifolia* (L.) L. *M. arvensis* L.	alcohol extract chloroform extract water extract	Patil and Mall, 2012 Mimica-Dukić *et al*., 1999
Sedative	*M. arvensis* L.	alcohol extract	Verma *et al*., 2003
Spasmolytic	*M. longifolia* (L.) L. *M. × piperita* L. *M. pulegium* L.	hexane extract dichloromethane extract essential oil	Estrada-Soto *et al*., 2010 Naseri *et al*., 2008 Mizuno *et al*., 2006 Melzer *et al*., 2004

* References given refer to several *Mentha* plants and preparation types indicated for their specific health benefit.

2.2. *Chlamydia pneumoniae*

Chlamydia pneumoniae is a Gram-negative bacterium and an oblicate intracellular parasite of eukaryotic cells (Moulder *et al.,* 1984). *C. pneumoniae* was initially isolated in 1965 from the eye of a child participating in a trachoma vaccine study in Taiwan (Grayston, 2000) and was first associated with respiratory disease as *C. psittaci* (TWAR) in 1985 when it was identified as the cause of a mild pneumonia epidemic in two geographically separated regions in Finland (Saikku *et al*., 1985) and subsequently reclassified as *C. pneumoniae* in 1989 (Roulis *et al*., 2013; Grayston *et al*., 1989).

The multiplication of the bacterium can only occur inside eukaryotic cells, in a membranous organelle detached from the host cell's endocytic vesicle system upon the bacterium's entry into the cell (Hanski and Vuorela P., 2014). After host cell infection by receptor-mediated endocytosis, the elementary body differentiates into reticulate bodies (RB). These reticulate bodies are the larger, metabolically active noninfectious form of the organism. Inside the host cell, the reticulate bodies divide by binary fission, forming microcolonies referred to as intracytoplasmic inclusions. During this process, chlamydial antigens are released onto the host cell surface, inducing a host immune response. After 48 to 72 h, the reticulate bodies reorganize themselves and condense to form new elementary bodies (EB). After host cell lysis, the elementary bodies are released and initiate a new infectious cycle (Burillo and Bouza, 2010; Essig, 2007). The persistant infection of *C. pneumoniae* is characterized with the presence of a specific intracellular form known as aberrant body (AB). In this viable but non-replicating form the bacteria residing in ABs continue to manipulate their host cell by secreting effector proteins, which interfere with host structures and signaling pathways (Hanski and Vuorela P., 2014; Kern *et al*., 2009).

C. pneumoniae spreads from person to person via respiratoy droplets. *C. pneumoniae* infection is ubiquitous, with an antibody prevalence of 50% by age 20 years and 70-80% at age 60-70 years (Blasi *et al*., 2009). Acute *C. pneumoniae* infection can cause mild respiratory tract infections, pharyngitis or sinusitis, and also lower respiratory tract infections, such as bronchitis and pneumonia (Grayston *et al*., 1990). It has been identified as a significant cause of community-acquired pneumonia (CAP), responsible for an estimated 10% of CAP cases and 5% of bronchitis cases (Hammerschlag, 2000). Moreover, in the past 20 years, a heterogeneous spectrum of extrapulmonary diseases has been linked to *C. pneumoniae*, including atherosclerotic cardiovascular disease (Andraws *et al*., 2005; Saikku *et al*., 1988), multiple sclerosis (Sriram *et al*., 2005; Moses and Sriram, 2001), asthma (Johnston *et al*., 2006; Little, 2006), age-related macular degeneration (Baird *et al*., 2008), Alzheimer disease (Horvath and Vecsei, 2006), chronic fatigue syndrome (Chia and Chia, 1999) and chronic skin wounds (King *et al*., 2001).

As other Gram-negative bacteria, the outermost structure of *C. pneumoniae* itself is a lipopolysaccharide (LPS)-rich outer membrane, which poses significant challenges for drug penetration. In general, the outer membrane is the primary reason for inherent resistance of Gram-negative bacteria towards various antibacterial agents. In the case of *C. pneumoniae*, additional permeability barriers are formed by host cell plasma membrane and the inclusion membrane surrounding the bacterium in its replicating (RB) form. Any compound targeting proteins or other components within RBs must thus be able to penetrate all these membranes in order to reach its target site (Hanski and Vuorela P., 2014).

The best practice against defined *C. pneumoniae* infection is a long treatment with antibiotics that interfer with prokaryotic DNA, RNA or protein synthesis, such as quinolones, tetracyclines and macrolides (Hanski and Vuorela P., 2014; Hammerschlag and Kohloff, 2012; Senn *et al*., 2005). Erythromycin, tetracycline and doxycycline are used as first-line therapy for acute respiratory infections (Burillo and Bousa, 2010; Kuo and Grayston, 1988). Antibiotics of the rifampicin group are highly chlamydiacidic (Dreses-Werringloer *et al*., 2003) but due to rapid emergence of resistance not widely recommended (Kutlin *et al*., 2005; Dreses-Werringloer *et al*., 2003). The *β*-lactam target is the bacterial cell wall, a structure absent in *Chlamydiae*. However, penicillin and ampicillin, although showing no effect on *Chlamydia* viability, can limit binary fission and the transition between development forms (McCoy and Maurelli, 2006).

The effect of *M. arvensis* L. extract on acute *C. pneumoniae* infection *in vitro* and *in vivo* has been studied by Salin *et al*. (2011). The extract was found to inhibit the growth of *C. pneumoniae* in dose-dependent manner with the maximum inhibition of 90% at the concentration of 256 mg/ml. In addition, both of the main components of the extract, rosmarinic acid and linarin, showed >60% activity. In the mouse study, *M. arvensis* L. extract administered intraperitoneally was able to decrease *C. pneumoniae*-induced inflammatory responses. The inflammation detected in the lung tissue histopathology was milder. Also, several flavonoids found in the *Mentha* plants like luteolin and apigenin have shown to be highly active against *C. pneumoniae* (Alvesalo *et al*., 2006).

2.3. *Escherichia coli*

Escherichia coli is a Gram-negative, facultative anaerobe non-spore forming bacilli. *E. coli* is the most prevalent commensal inhabitant of the gastrointestinal tracts of humans and warm-blooded animals, as well as one of the most important pathogens (Allocati *et al*., 2013; Kaper *et al*., 2004). *E. coli* is commonly fimbriated and motile in liquid by peritrichous flagella (Einstein, 1987).

Among *E. coli* isolates, there is considerable variation and many combinations of somatic and flagellar antigens. Among pathogenic strains, there are few patterns of these antigens and few phylogenetic groupings (Whitfield and Valvano, 1993). Most *E. coli* strains are capable of growing over a wide range of temperature (15-48 °C) and within a pH range of approximately 5.5-8.0. Some diarrheagenic strains have even the ability to tolerate exposure to pH 2.0 (Sousa, 2006).

There are *E. coli* strains that are harmless commensals of the intestinal tract and other strains that are major pathogens of humans and animals (Sousa, 2006; Kaper *et al*., 2004). Although most *E. coli* strains are harmless, certain specific, highly-adapted *E. coli* strains are capable of causing a variety of different diseases. Infections due to pathogenic *E. coli* may be limited to colonization of a mucosal surface or can disseminate throughout the body (Nataro *et al*., 1987). Based on the type of virulence factor present and host clinical symptoms, *E. coli* strains are classified into seven enteric and three extraintestinal strains (Table 5, Allocati *et al*., 2013; Kaper *et al*., 2004). Intestinal pathogens spread through the faecal-oral route by ingestion of contaminated food or water.

Table 5. *E.coli* pathogenic types (Allocati *et al*., 2013; Kaper *et al*., 2004).

Pathotype	Symptoms/diseases caused	References
Enteric *E.coli*		
EnteroPathogenic *E.coli* (EPEC)	diarrhoea in children	Kaper *et al*., 2004
EnteroHaemorrhagic *E.coli* (EHEC)	haemorrhagic colitis	Bilinski *et al*., 2012
	haemolytic-uraemic syndrome	Kaper *et al*., 2004
EnteroToxigenic *E.coli* (ETEC)	traveller`s diarrhoea	Al-Abri *et al*., 2005
		Qadri *et al*., 2005
EnteroAggregative *E.coli* (EAEC)	diarrhoea in children	Weintraub, 2007
		Nataro *et al*., 1998
Diffusly Adherent *E.coli* (DAEC)	acute diarrhoea in children	Servin, 2005
EnteroInvasive E.*coli* (EIEC)	Shigellosis-like diarrhoea	Kaper *et al*., 2004
		Nataro *et al*., 1998
Adherent Invasive *E.coli* (AIEC)	persistent intestinal inflammation	Negroni *et al*., 2012
		Darfeuille-Michaud, 2002
Extraintestinal *E. coli*		
UroPathogenic *E.coli* (UPEC)	lower unrinary tract infections	Kaper *et al*., 2004
	and systemic infections	Johnson and Stell, 2000
Neonatal Meningitis *E.coli* (NMEC)	neonatal meningitis	Pouillot *et al*., 2012
		Gaschignard *et al*., 2011
Avian Pathogenic *E.coli* (APEC)	probable source of food-borne	Johnson *et al*., 2007
	disease	Rodriguez-Siek *et al*.,
		2005

Trimethoprim-sulfamethoxazole, quinolones/fluoroquinolones and extended-spectrum cephalosporins are used commonly for treatment of human *E. coli* infections (Johnson *et al*., 2007). However, antimicrobial resistance in *E. coli* has been reported worldwide and increasing rates of resistance among *E. coli* is a growing concern in both developed and developing countries (Allocati *et al*., 2013; El Koholy *et al*., 2003; Bell *et al*., 2002). *β*-lactamase production is the most important mediator of resistance of *E. coli* to broad spectrum of *β*-lactams. Extended spectrum *β*-lactamases

(ESBL) confer resistance to several antibiotics including third- and fourth-generation cephalosporins and monobactams (Poirel *et al*., 2012; Livermore *et al*., 2007). Carbapenems resistance in *E. coli* is primarily caused by plasmid-encoded carbapenemases. These enzymes are mainly found in nosocomial isolates of *E. coli*. In Europe, the prevalence of these strains appears to follow a north-south distribution (Glasner *et al*., 2013; Canton *et al*., 2012). *E. coli* also exhibits (fluoro)quinolone resistance which is frequently observed in conjunction with ESBL genes (Ruiz *et al*., 2012).

The antimicrobial effect of *Mentha* plants extracts and essential oils on *E. coli* has been studied with various activity results. In general, the extracts have found to possess less activity than the essential oils. For example, absence of antimicrobial activity has been reported for alcoholic extracts of *M. longifolia* (L.) L. (Akroum *et al*., 2009; Hajlaoui *et al*., 2009; Gulluce *et al*., 2007), *M. spicata* L. (Chan *et al*., 2012), *M. × piperita* L. (Albayrak *et al*., 2013) and water extracts of *M. × piperita* L. (Albayrak *et al*., 2013). However, Nascimento *et al*., (2009) showed *M. arvensis* L. alcoholic extract to inhibit the growth of *E. coli*. Widely consumed *M. × piperita* L. essential oil has been shown to possess activity on *E. coli* (Hussain *et al*., 2010; İşcan *et al*., 2002). Also, the oils of *M. longifolia* (L.)L., *M. spicata* L. (Hussain *et al*., 2010; Gulluce *et al*., 2007), *M. arvensis* L. (Zhou and Xie, 2011) and *M. aquatica* L. (Dhifi *et al*., 2011; Mimica-Dukić *et al*., 2008) have been reported to be antibacterial against *E. coli*.

2.4. *Staphylococcus aureus*

Staphylococcus aureus is a Gram-positive spherical bacterium. Staphyloccoci are facultative anaerobes capable of generating energy by aerobic respiration and by fermentation which yields mainly lactic acid (Plata *et al*., 2009). *S. aureus* is distinguished from other staphylococcal species on the basis of the gold pigmentation of colonies and positive results of coagulase, mannitol fermentation and deoxyribonuclease tests (Lowy 1998; Wilkinson 1997). Staphylococci produce numerous toxins that are grouped on the basis of their mechanisms of action. Cytolytic toxins cause pore formation and leakage of the cell`s content and lysis (Foster, 2005). The consequent cellular damage may contribute to manifestations of the sepsis syndrome (Lowy, 1998; Walev *et al*., 1995; Bhakdi and Tranum-Jensen, 1991).

S. aureus is a commensal and a pathogen. The anterior nares are the major site of colonization in humans. About 20-30% of individuals are persistent and 30% intermittent carriers of *S. aureus* (Wertheim *et al*., 2005). The virulence of *S. aureus* infection is remarkable, given that the organism is a commensal that colonizes the nares, axillae, vagina, pharynx or damaged skin surfaces (Noble *et al*., 1967). *S. aureus* is one of the main causes of hospital- and community-acquired infections which can result in serious consequences (Diekema *et al*., 2001). Nosocomial *S. aureus* infections affect the bloodstream, skin, soft tissues and lower respiratory tracts. *S. aureus* can be a cause of central venous catheter-associated bacteremia and ventilator-assisted pneumonia. It also causes serious deep-seated infections, such as endocarditis and osteomyelitis (Tong *et al*., 2015; Schito, 2006). In addition to the infections listed above, *S. aureus* is often responsible for toxin-mediated diseases, such as toxic shock syndrome, scalded skin syndrome and staphylococcal foodborne diseases. Hospitalized patients are particularly exposed to *S. aureus* infections due to their compromised immune system and frequent catheter insertions and injections (Tong *et al*., 2015; Plata *et al*., 2009; Lindsay and Holden, 2004).

The management of *S. aureus* infections varies according to strain and clinical manifestations. *β*-lactam antibiotics are used if the isolate is sensitive to it. A semisynthetic penicillin

(nafcillin or oxacillin) is indicated for *β*-lactamase producing strains. Vancomycin is the drug of choice for methicillin-resistant isolates. Patients unable to tolerate vancomycin have been treated with fluoroquinolones, trimethoprim–sulfamethoxazole, clindamycin, or minocycline. Quinolones with enhanced antistaphylococcal activity are available, but their use may also be limited by the development of resistance during therapy. Antimicrobial combinations have been used to increase bactericidal activity or to prevent the development of antimicrobial resistance. The combination of *β*-lactams and aminoglycosides increases bacterial killing *in vitro* and in animal models of endocarditis (Lowy, 1998).

The effects of certain *Mentha* plants extracts and essential oils have been studied on *S. aureus*. For example, Verma *et al*. (2013) and Sofia *et al*. (2007) reported antibacterial effects against *S. aureus* for *M. × piperita* L. extract. Similar activity against *S. aureus* was shown for essential oils of *M. × piperita* L. (Hussain *et al*., 2010; Mimica-Dukić *et al*., 2008; İşcan *et al*., 2002), *M. longifolia* (L.) L. (Mimica-Dukić *et al*., 2008; Gulluce et al., 2007), *M. × villosa* Huds. (Arruda *et al*., 2006), *M. aquatica* L. (Mimica-Dukić *et al*., 2008) and *M. arvensis* L. (Hussain *et al*., 2010).

3. AIMS OF THE STUDY

The aim of the thesis was to investigate the health-supporting basis in the use of *Mentha* as a common ingredient in food products. For that purpose, the analyses of the polyphenolic and essential oil composition were carried out. The composition was attempted to link with the antimicrobial activity. The focus of antimicrobial studies was on potentially harmful human pathogens such as obligate intracellular bacterium *Chlamydia pneumoniae*, Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*.

Specific aims of the thesis:

I Determination of phenolic composition in *Mentha* plants and commercial peppermint teas by HPLC-UV-MS/MS analyses.

II Determination of essential oil or hydrodistilled extract composition of *Mentha* plants, commercial peppermint teas and mint flavoured candies and food supplements by GC-MS analyses.

III Studying the antichlamydial activity of peppermint teas water extracts and mint flavouring hydrodistilled extracts.

IV Studying the antibacterial activity of hydrodistilled mint flavouring extracts, *Mentha* plants essential oils and water extracts against *Escherichia coli* and *Staphylococcus aureus*.

V Evaluation of the antimicrobial activity in relation to the polyphenolic and essential oil composition of the tested samples.

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. *Mentha* plants

The leaves of cultivated or wild grown *Mentha* plants studied (n=47) were collected in July or August 2011 and 2012 from different areas in Estonia (Table 6). Samples collected represented various and commonly consumed *Mentha* plants available in Estonia. The plant material was dried at room temperature (20 ± 2 °C) protected from direct sunlight. Each sample was labelled, packed in a paper-bag and stored for 2-6 months in room temperature until assayed.

Herbarium voucher specimens were prepared and identified by botanist Dr. Ülle Reier from the Department of Botany, University of Tartu and Intendant Arto Kurtto, Finnish Museum of Natural History, University of Helsinki. Voucher specimens were not prepared of *Mentha* plants collected from Tartu Botanical Garden (Nos 24-32). Also, for those that did not survive the winter (Nos 6, 8, 9, 13-15, 23) and plants Nos 46, 47 that were obtained from retail pharmacies in Estonia. *Mentha* plants without voucher specimens are marked with an asterisk in Table 6. The voucher specimens have been deposited at the Institute of Pharmacy, University of Tartu, Estonia. The *Mentha* plants without original taxonomic data and identification by voucher specimen are given with genus and cultivar name.

Table 6. *Mentha* plants studied.

No	*Mentha* plants	Growth place	Origin	Collection time
1	*M. × piperita* L. „Swiss“	Võnnu borough, Tartu county, Estonia	Open market of Tartu city, Tartu county, Estonia	August 2012
2	*M. × piperita* L. „Chocolate“	Võnnu borough, Tartu county, Estonia	PUUR Aroma, Margraten, The Netherlands	August 2012
3	*M. × piperita* L. „Cinderella“	Võnnu borough, Tartu county, Estonia	PUUR Aroma, Margraten, The Netherlands	August 2012
4	*M. × piperita* cv. „Grenada“	Võnnu borough, Tartu county, Estonia	Open market of Tartu city, Tartu county, Estonia	August 2012
5	*M. × piperita* L. „Mitcham“	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
6	*M.* „Blue Palsam“ *	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
7	*M. spicata* L. „Lime“	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
8	*M.* „Black Beauty“ *	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
9	*M.* „Chocomint“ *	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
10	*M. × villosa* Huds.	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012

11	*M. longifolia* (L.) L. "Asian"	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
12	*M. cf. × gracilis* Sole „Aureus"	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
13	*M.* „Golden Mint" *	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
14	*M. suaveolens* Ehrh. „Apfel" *	Võnnu borough, Tartu county, Estonia	PUUR Aroma, Margraten, The Netherlands	August 2012
15	*M. × gracilis* Sole „Ginger" *	Võnnu borough, Tartu county, Estonia	PUUR Aroma, Margraten, The Netherlands	August 2012
16	*M. spicata* L. „Taškent"	Võnnu borough, Tartu county, Estonia	Rebase Talu arboretum, Meegaste village, Valga county, Estonia	August 2012
17	*M. spicata* L. „Marrocan"	Võnnu borough, Tartu county, Estonia	PUUR Aroma, Margraten, The Netherlands	August 2012
18	*M. spicata* L. „Kentucky Colonel"	Võnnu borough, Tartu county, Estonia	Juhani arboretum, Lohkva village, Tartu county, Estonia	August 2012
19	*M. aquatica* L.	Emajõgi river shore, Ihaste, Tartu county, Estonia	unknown	August 2012
20	*M. × piperita* L.	Võnnu borough, Tartu county, Estonia	unknown	August 2012
21	*M. arvensis* L.	Võnnu, Tartu county, Estonia	Ala village, Valga county, Estonia	August 2012
22	*M. arvensis* L.	Võnnu, Tartu county, Estonia	unknown	August 2012
23	*M.* „Pineapple" *	Ülenurme borough, Tartu county, Estonia	unknown	August 2012
24	*M. longifolia* (L.) L. *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
25	*M. × gracilis* Sole „Variegata" *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
26	*M. × piperita* L. „Lime" *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
28	*M. × piperita* L. „Barnes & Cream" *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
28	*M. × piperita* L. „Chocolate" *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
29	*M. × piperita* L. „Black beauty" *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
30	*M. × piperita* L. „Morrocan" *	Tartu Botanical Garden, University of Tartu,	unknown	August 2012

		Estonia		
31	*M. × piperita* L. „Basil mint“ *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
32	*M. × piperita* L. „Lavender mint“ *	Tartu Botanical Garden, University of Tartu, Estonia	unknown	August 2012
33	*M. cf. × gracilis* „Orange“	Võnnu, Tartu county, Estonia	unknown	August 2012
34	*M. spicata* L.	Karepa, Lääne-Viru county, Estonia	unknown	July 2011
35	*M. spicata* L.	Võnnu, Tartu county, Estonia	unknown	July 2011
36	*M. spicata* L.	Puurmanni, Jõgeva county, Estonia	unknown	July 2011
37	*M. × piperita* L.	Pangodi, Tartu county, Estonia	unknown	July 2011
38	*M. longifolia* (L.) L.	Pudisoo, Harju county, Estonia	unknown	July 2011
39	*M. × piperita* L.	Võnnu, Tartu county, Estonia	unknown	July 2011
40	*M. arvensis* L.	Võnnu, Tartu county, Estonia	unknown	July 2011
41	*M. arvensis* L.	Võnnu, Tartu county, Estonia	unknown	July 2011
42	*M. spicata* L.	Võnnu, Tartu county, Estonia	unknown	July 2011
43	*M. longifolia* (L.) L.	Tartu Botanical Garden, University of Tartu, Estonia	unknown	July 2011
44	*M. longifolia* (L.) L.	Tartu Botanical Garden, University of Tartu, Estonia	unknown	July 2011
45	*M. longifolia* (L.) L.	Tartu Botanical Garden, University of Tartu, Estonia	unknown	July 2011
46	*M. × piperita* L.* [a]	Saaremaa, Saare county, Estonia	unknown	-
47	*M. × piperita* L. * [a]	Ronisoo, Tartu county, Estonia	unknown	July 2011

* - no voucher specimen

[a] - packages labelled as *Menthae piperitae folium*

4.1.2. Commercial peppermint tea samples

Commercially available peppermint teas (n = 27; Table 7) represented teas with various origin and form of marketing. The tea samples in the form of crude herb or tea bags were purchased from food markets, health shops or retail pharmacies. Sample Nos 1-9 and 12-14 were bought in Estonia (2009-2010), Nos 10-11 in Egypt (2011), No 15 from USA (2010), Nos 16-24 from Germany (2011) and

Nos 25-27 from Finland (2012). The tea samples were stored at room temperature away from humidity and direct sunlight.

Table 7. Commercial peppermint tea samples.

No	Country of origin	Amount (g) and number of teabags, package	Obtained from	Making of tea	Amount (g) used for 1 cup of tea
1	EU	1.0 x 20 teabags with strand	Food market	Boiling water (200 ml), 2-3 min	1.0
2	Germany	2.25 x 20 teabags with strand in paper packages	Food market	Boiling water, 5-8 min	2.25
3	Germany	1.5 x 20 teabags	Food market	Boiling water, 5-8 min	1.5
4	Latvia	1.5 x 20 teabags with strand	Food market	Boiling water (150 ml), 3-4 min	1.5
5	Poland	1.5 x 20 teabags	Food market	Boiling water, 5-8 min	1.5
6	Poland	1.5 x 30 teabags	Food market	Boiling water, 5-8 min	1.5
7	The Netherlands	1.5 x 20 teabags	Food market	Boiling water (150 ml), 3-4 min	1.5
8	Latvia	1.0 x 20 teabags	Food market	Boiling water (200 ml), 3-5 min	1.0
9	Poland	1.5 x 20 teabags	Food market	Boiling water, 5-7 min	1.5
10	Egypt	1.0 x 20 teabags	Food market	Boiling water, (1 cup), 5 min	1.0
11	Egypt	1.5 x 12 teabags	Food market	Boiling water (1 cup), 3 min	1.5
12	Estonia	Crude drug, 15.0	Pharmacy	2-3 g of herb and 1 cup of boiling water, 5-10 min	3.0
13	Estonia	Crude drug, 15.0	Pharmacy	1-2 teaspoons of herb and boiling water, 5-7 min	1.0
14	Estonia	Crude drug, 30.0	Pharmacy	Not described	1.0
15	USA	1.25 x 20 teabags	Pharmacy	Boiling water, 3-5 min	1.25
16	Germany	1.5 x 20 teabags with strand in paper packages	Pharmacy	Boiling water, 10-15 min	1.5
17	Germany	1.5 x 20 teabags with strand in paper packages	Pharmacy	Boiling water (150 ml), 10-15 min	1.5
18	Germany	Crude drug, 50.0	Pharmacy	Boiling water (150 ml) and 1,5 g of herb, 10-15 min	1.5
19	Germany	Crude drug, 50.0	Health shop	1-2 teaspoons of drug and 1 cup of boiling	1.0

				water, 5-10 min	
20	Germany	Crude drug, 50.0	Health shop	1 teaspoon of drug and 1 cup (150 ml) of boiling water, 5-10 min	0.8
21	Germany	1.5 x 12 teabags with strand in paper packages	Health shop	Boiling water (150 ml), 10-15 min	1.5
22	Germany	2.25 x 25 teabags with strand in paper packages	Food market	Boiling water, 5-6 min	2.25
23	Germany	2.25 x 25 teabags with strand in paper packages	Food market	1 liter of boiling water and 4 teabags, 5-6 min	2.25
24	Germany	1.75 x 20 teabags with strand in paper packages	Food market	Boiling water, 6 min	1.75
25	UK	1.6 x 20 teabags with strand in packages	Health shop	Boiling water, 2-5 min	1.6
26	Finland	Crude drug, 40.0	Health shop	1-2 teaspoons of drug and 1 cup of boiling water, 5-15 min	1.2
27	Finland	Crude drug, 30.0	Health shop	1 teaspoon of drug is infused 10-20 min in hot water	0.7

Sample No 27 contains *M. × piperita* L., *M. spicata* L. and *M. × dalmatica* Tausch.

4.1.3. Mint flavoured candies and food supplements

Mint flavoured candies bought represented the commonly consumed types of mint candies like sugar candies, pastilles and chocolates. The food supplements were those ordinarily flavoured with mint. The samples obtained presented as well products with various origin. The mint flavoured candies and food supplements were purchased from food markets, candy shops or retail pharmacies in Estonia and Finland (n=45; Table 8). The samples were purchased during October 2012 - April 2013 and originated from 16 different countries. The candies and food supplements were stored for 5 months at room temperature protected from humidity and direct sunlight until assayed.

Table 8. Mint flavoured candies and food supplements.

No	Country of origin	Product	Flavouring indicated on package	Marketing place
1	Finland	Pastille	Natural flavourers	Food market
2	Finland	Sugar candy	Flavouring	Food market
3	Sweden	Sugar candy	Natural peppermint oil	Food market
4	Italy	Sugar candy	Essential oil of Piedmontese peppermint, flavours	Candy shop
5	Italy	Pastille	Essential oil of Piedmontese peppermint, flavours	Candy shop
6	Finland	Pastille	-	Pharmacy
7	Finland	Pastille	Natural flavouring (peppermint oil)	Food market
8	Finland	Pastille	Natural flavouring (peppermint oil, menthol)	Food market
9	Belgium	Sugar candy	Natural mint oil	Food market
10	Finland	Pastille	Peppermint oil, menthol, anise oil	Food market
11	Finland	Tablet	Natural peppermint aroma	Pharmacy
12	Finland	Pastille	Flavourings	Food market
13	Finland	Pastille	Aroma (natural peppermint)	Candy shop
14	Finland	Sugar candy	Peppermint oil	Candy shop
15	Finland	Pastille	Aroma (menthol, mint)	Food market
16	Finland	Pastille	Aroma (peppermint oil)	Food market
17	Finland	Pastille	Peppermint oil	Food market
18	Denmark	Pastille	Aroma, peppermint oil	Food market
19	Finland	Pastille	Aroma	Food market
20	Russian Federation	Tablet	Peppermint oil	Pharmacy
21	Moldova	Sugar candy	Flavours (mint oil, barberry extract)	Food market
22	Lithuania	Sugar candy	Mint flavour, menthol	Food market
23	Ukraine	Sugar candy	Food aromatizing identical to natural mint	Food market
24	Lithuania	Sugar candy	Flavour and aroma “Mint”	Food market
25	England	Pastille	Flavour and aroma (peppermint oil)	Food market
26	Estonia	Sugar candy	Flavour	Food market
27	Lithuania	Sugar candy	Mint oil	Food market
28	Finland	Tablet	Peppermint oil, menthol	Pharmacy
29	Finland	Chocolate	Peppermint oil	Food market
30	Finland	Chocolate	Flavouring (mint oil, vanillin)	Food market
31	Switzerland	Chocolate	Peppermint sugar granules (incl. peppermint leave, flavourings)	Food market
32	Bolivia	Chocolate	Peppermint oil	Food market
33	Germany	Chocolate	Natural peppermint oil	Candy shop
34	Finland	Chocolate	Aroma (peppermint, vanillin)	Food market
35	Finland	Chocolate	Aroma (vanillin, peppermint oil)	Food market
36	Spain	Chocolate	Peppermint natural flavour	Food market

37	Finland	Chocolate	Aroma (peppermint oil)	Food market
38	Germany	Chocolate	Natural mint aroma	Food market
39	Finland	Chocolate	Aromas	Food market
40	Finland	Chocolate	Flavourings (peppermint oil, vanillin)	Food market
41	France	Chocolate	Aromas (peppermint oil, vanillin)	Food market
42	Germany	Chocolate	Peppermint oil, natural flavouring	Food market
43	Estonia	Chocolate	Flavourings (peppermint oil, vanillin)	Food market
44	Finland	Chocolate	Flavoutings (incl. peppermint oil)	Food market
45	Germany	Chocolate	Peppermint oil, flavourings	Candy shop

4.1.4. Reagents and instruments

Organic solvents and reagents used were of analytical grade. Methanol, xylene, dimethyl sulfoxide (DMSO), formic acid, diosmin, salvianolic acid B, gallic acid, menthol racemic, (1R,2S,5R)-(−)-menthol, (1S,2R,5S)-(+)-menthol, (−)-menthone, jasmonic acid, usnic acid and resazurin were from Sigma-Aldrich (Steinheim, Germany). (-)-Carvone, gentamicin and rifampicin were obtained from Fluka (Buchs, Switzerland). The reference standards of luteolin, apigenin, narirutin, eriodictyol-7-*O*-glucuronide and rosmarinic acid were supplied from Extrasynthese (Genay, France). 1,8-Cineole, menthone mixture of isomers, menthofuran, (1S)-(+)-menthyl acetate and (1R)-(-)-menthyl acetate were purchased from Alfa Aesar GmbH ja Co KG (Karlsruhe, Germany). Limonene, linalool and linalool acetate originated from Haarmann & Reimer GmbH (Holzminden, Germany). Acetonitrile for liquid chromatography-mass spectrometry (LC-MS) was of ultragradient grade obtained from Romil (Cambridge, UK). *N*-hexane LiChrosolv® was obtained from Merck Millipore (Darmstadt, Germany). Water used was prepared by an EASYpure RF compact system (Barnstead, U.S.A) and Milli-Q® Integral Water Purification System (Merck Millipore, Darmstadt, Germany). Roswell Park Memorial Institute medium (RPMI) 1640, L-glutamine and fetal bovine serum (FBS), phosphate buffered saline (PBS) were purchased from BioWhittaker, Lonza (Basel, Switzerland). Ethanol Etax A was obtained from Altia Oyj, Finland and Pathfinder Chlamydia culture confirmation system reagent from Bio-Rad Laboratories, France. Plate Count Agar, Mueller Hinton II agar (MHA) and Mueller Hinton II broth (MHB) were from Becton Dickinson and Company, New Jersey, USA. Iso-Sensitest Agar and DST-Agar were from Oxoid Ltd., Basingstroke, UK. Ciprofloxacin hydrochloride was purchased from ICN Biomedicals Inc., Ohio, USA. Cuplaton® anti-foam agent was produced by Orion Pharma, Espoo, Finland. Roswell Park Memorial Institute medium (RPMI) 1640, L-glutamine and fetal bovine serum (FBS) were all purchased from BioWhittaker, Lonza (Basel, Switzerland).

Multiskan GO microplate spectrophotometer was provided by Thermo Scientific, Hudson, NH, USA and VarioSkan™ Flash plate reader by Thermo Fischer Scientific, Vantaa, Finland. Rotary evaporator used was from Heidolph Instruments Model VV2000, Schwabach, Germany. Lyophilizer was produced by Heto LyoPro 3000, Alleroed, Denmark and fluorescent microscope Nikon Eclipse TE300 from Tokyo, Japan or Inverted Evos® FL by Advanced Microscopy Group, USA. NunclonTM Delta Surface 96-well microplates were obtained from Thermo Scientific, Roskilde, Denmark. Petri dishes were produced by Heger Plastics, Rjukan, Norway. 24-wellplates were from Corning Inc., USA and coverslips from Menzel-Gläser, Braunschweig, Germany. Cell culture flasks were obtained from Greiner, Bio-One, Frickenhausen, Germany. Pathfinder *Chlamydia* culture confirmation system reagent was purchased from Bio-Rad Laboratories, France.

4.2. Methods

4.2.1. Extraction of *Mentha* plants

In preliminary tests, the infusion time was tested with naturally grown *M. × piperita* L. plant material. Time periods tested were 1, 5, 15, 30 min and 1, 3, 12 h. The water temperature was 100 °C in the beginning of the preliminary tests. Infusion time already 5 min was exhaustive to polyphenols as longer infusion time did not increase the content. Therefore, the commercial peppermint tea infusions (n=1) were made with distilled water according to the manufacturer's instructions written on the packages. For that, the maximum recommended quantity of herb and extraction time were used. If the amount of water or plant material was not specified, 200 ml and two teaspoons (2 × 5 ml, 1.0 g) were taken, respectively. After extraction, the extracts were filtered and centrifuged. For the *C. pneumoniae* experiments, the infusions were concentrated, residues from a rotary evaporator were frozen at -20 °C and lyophilized for 7 days.

The sample material was limited of naturally grown or cultivated *Mentha* plants No 1-33 from Estonia. Thus, water extracts (n=1) were prepared from the plant material previously subjected to distillation (section 4.2.2.). The *Mentha* plants 2 h decoctant was further processed as the commercial peppermint tea extracts for *C. pneumoniae* experiments.

4.2.2. Isolation of *Mentha* plants essential oil

The essential oils were isolated from commercial peppermint teas and *Mentha* samples No 34-47 by the distillation method described in the Ph. Eur. 7th Ed. (European Pharmacopoeia, 2010). 20 g of the sample and 0.5 ml of xylene were used to separate the essential oils. Distillation time was 2 h at a rate of 3-4 ml/min.

The essential oils of *Mentha* samples No 1-33 were isolated by using a Marcusson's type micro-apparatus (Bicchi *et al.*, 1983) with 300 µl *n*-hexane as the trap. 0.85-5.0 g of the sample with 100 ml of distilled water were subjected to distillation for 2 h. The essential oil amount was determined gravimetrically by evaporating *n*-hexane in nitrogen flow. All the essential oils (n=1) were stored in sealed vials under refrigeration (-20 °C) prior to analysis.

4.2.3. Isolation of mint flavouring hydrodistilled extracts

Simultaneous hydrodistillation was used to isolate mint flavouring using the Marcusson's type micro-apparatus with *n*-hexane (300 µl). The isolated distillates were named as mint flavouring hydrodistilled extracts. For the isolation procedure, 50 g of mint flavoured candy or food supplement and respectively 100 or 120 ml (chocolates) distilled water was used. The isolation was carried out with the presence of 150 mg of anti-foam agent. Distillation time was 2 h. The isolated extract amount was determined gravimetrically by evaporating n-hexane in nitrogen flow. The extracts (n=1) were stored in sealed vials under refrigeration (-20 °C) prior to analysis.

4.2.4. Sample material preparations studied

The sample material preparations used in the present study are shown in Table 9.

Table 9. Sample material preparations used in the study.

Sample preparations	Sample origin
Peppermint teas water extracts	Peppermint tea infusions (HPLC-UV-MS/MS analyses) or lyophilized peppermint tea infusions dissolved in water (*C. pneumoniae* experiments)
Mentha plants water extracts	Lyophilized decoctum of *Mentha* plants dissolved in water
Peppermint teas essential oils	Essential oils isolated from commercial peppermint tea samples
Mentha plants essential oils	Essential oils isolated from *Mentha* plants
Mint flavouring hydrodistilled extract	Flavouring isolated from mint flavoured candies and food supplements by hydrodistillation

4.2.5. High performance liquid chromatography-mass spectrometry

Agilent Technologies LC–DAD-ESI-MS/MS described in the original publications (**II**; **V**) was used for the identification and quantitation of polyphenols (n=1).

Phenolic compounds were identified by comparing the retention times, UV spectra and MS/MS fragmentation spectra either with respective reference standards or with literature data. Quantification was done using calibration curves built up using eight different concentrations of the standard compounds (0.003-0.3 mg/ml). The milligrams per gram of herb were converted into percentage concentrations by summarizing all the polyphenols and considering the latter sum as a total.

4.2.6. Gas chromatography-mass spectrometry

The essential oils of peppermint commercial teas, *Mentha* plants and mint flavourings hydrodistilled extracts were analysed using gas-chromatograph described in the original publications (n=1; **I**-**V**). Identification of compounds was confirmed by retention indices (RI) of reference standards and literature data. The composition of the oils was calculated as the percentage from peak areas using normalization method without correction factors. The relative standard deviation of percentages of oil components in three repeated GC analyses of a single oil sample did not exceed 5%.

4.2.7. Antichlamydial high-throughput screening

4.2.7.1. Cell culture and *C. pneumoniae* stock

Human epithelial HL-cells of respiratory tract origin (Kuo and Grayston, 1990) were grown at 37 °C, 5% CO_2 and 95% humidity to confluence in cell culture flasks using a medium consisting of RPMI 1640, 2 mM L-glutamine and 7.5% FBS and with 20 µg gentamicin per ml. *C. pneumoniae* clinical isolate K7 (Ekman *et al*., 1993) was obtained from Professor Pekka Saikku, from the

Department of Medical Microbiology, Institute of Diagnostics, University of Oulu, Finland and propagated as described by Alvesalo *et al*. (2006).

4.2.7.2. Infections

All infections were preceded by seeding the Human Line HL-cells into 24-wellplates with coverslips at density 4×10^5 cells per well and incubated overnight at 37 °C. The bacteria were diluted in the cell growth medium followed by inoculation of HL-cell monolayers with the multiplicity of infection (MOI) 0.1 or 0.2. The infections were all done in the presence of 1.0 µg/ml of cycloheximide. After inoculating the cells, the plates were centrifuged at 4 °C and then incubated at 37 °C. Thereafter the infection medium was removed from the wells and fresh medium supplemented with 1.0 µg/ml cycloheximide containing the extracts or controls was added as three replicates. Nontreated infected or non-infected samples were used as controls, in addition to an infected control treated with 0.009 µg of antibiotic rifampicin in 1 ml of ethanol. In each well the concentration of DMSO was adjusted to 0.25%. Plates were incubated in the cell culture conditions described above. After 72 h post infection, the wells were washed with phosphate buffered saline (PBS) and fixed with methanol. The coverslips were removed and stained after drying. The staining of host cells and chlamydia inclusions was carried out using Pathfinder *Chlamydia* culture confirmation system reagent and the inclusion counts were determined under a fluorescent microscope with a 20x magnification. Inhibition percentage was calculated on the basis of the average number of inclusions per coverslip by comparing the number of inclusions in a treated sample to the number of inclusions in infected control samples.

4.2.7.3. Infectious progeny assay

Assaying the effect of the samples on the production of infectious progeny, the infection protocol was conducted as follows: two parallel replicates were used and after the 72 h infection period two of the coverslips were fixed and stained to count the inclusions and thus confirm the inhibitory effect of the sample. From the other two wells the medium was removed, 200 µl of fresh medium supplemented with 1.0 µg/ml cycloheximide was added, and cells were scraped off. This suspension was mixed in the presence of glass beads to release the chlamydia by breaking of the host cells. Then the suspension was used to infect fresh HL-cell monolayers. After a second round of 72 h infection, *i.e*., at 144 h, two wells corresponding to each sample were fixed and stained to determine the amount of infectious progeny in the second passage of infection.

4.2.7.4. Host cell viability assay

The host cell viability was determined by a resazurin assay in which the signals reflect the amount of viable cells that are able to reduce resazurin to a highly fluorescent derivate, resorufin. The HL-cells were seeded into a 96-wellplate at density of 6×10^4 cells per well and incubated overnight (37 °C) before adding the samples. Then the plate was incubated at 37 °C for 72 h. After the exposure period the medium was removed and resazurin, diluted in PBS to 20 µM, was added into the wells. The plate was incubated at 37 °C for 2 h and the fluorescence was measured with VarioSkan™ Flash plate reader at 570/590 nm (excitation/emission) and 22 °C. Wells containing no cells filled with medium were used as a blank. Concentration of DMSO in the sample wells was 0.25%. Usnic acid was used as a positive control at a concentration 50 µM.

4.2.8. Antimicrobial susceptibility testing

4.2.8.1. Agar diffusion method

Preliminary antimicrobial susceptibility testing was performed by a modified agar diffusion method (Raudsepp *et al*., 2013; Pikkemaat *et al*., 2008). Bacterial strains were obtained from the strain collections of the Estonian Veterinary and Food Laboratory. Gram-negative bacteria was represented by *Yersinia ruckeri* (NCIM 13282). Gram-positive bacteria were *Bacillus cereus* (ATCC 11778), *Bacillus subtilis* (BGA), *Bacillus pumilus* (CN607) and *Micrococcus luteus* (ATCC 9341). Cultures from the solid medium were subcultivated into liquid media. Incubated bacterial suspension was mixed with sterilized Iso-Sensitest Agar *(Bacillus cereus, Micrococcus luteus)*, Plate-count agar *(Bacillus subtilis, Yersinia ruckeri)* or Diagnostic Sensitivity Test Agar, DST-agar *(Bacillus pumilus)* to obtain the final density of 10^6 colony-forming units (CFU)/ml and then poured into Petri dishes for the solidification at the room temperature. Wells were made into agar gel (6 mm in diameter) and filled with 30 µl of essential oil, mint flavouring hydrodistilled extract or reference standard dissolved in *n*-hexane. *Mentha* plants water extracts dissolved in water were also tested. After 24 h incubation at 37 °C the radius of the inhibition zone was measured.

4.2.8.2. Broth dilution method

4.2.8.2.1. Microbial strains

Clinical control strains of *Staphylococcus aureus* (Gram-positive, ATCC 25923) and *Escherichia coli* (Gram-negative, ATCC 25922) were obtained from Microbiologics Inc. (St. Cloud, MN, USA) and used for the antimicrobial screening. Bacterial strains were grown on MHA. Media were prepared in water, according to the manufacturer's instructions, and autoclaved at 121 °C for 15 min. Prior to the assay, bacterial suspensions were prepared in MHB from fresh slant cultures and incubated at 37 °C for 16-20 h at 100 rpm.

4.2.8.2.2. Broth dilution assay

Bacterial suspensions were prepared as described above and diluted with MHB to obtain a final inoculum of 5×10^5 CFU/ml in the assay (determined on the basis of absorbance values at 620 nm previously calibrated against plate counts). Assays were carried out by tube dilution method combined with absorbance measurement at 620 nm in 96-well microtiter plates.

245 µl of MHB and 250 µl of bacteria suspension were added to the tube, followed by test samples dissolved in 5 µl of water (*Mentha* plants water extracts) or DMSO (reference substances, *Mentha* plants essential oils and mint flavouring extracts). Ciprofloxacin was used as a positive control. The tubes were incubated at 37 °C for 24 h at 100 rpm and observed for turbidity at 4, 8 and 24 h. Absorbance was measured at 620 nm with a Multiskan GO microplate spectrophotometer by transferring the incubated samples to 96-well microplates. The antimicrobial activity of the samples was calculated from the absorbance values by comparing to untreated controls and expressed as the percentage inhibition of growth. Compounds were assayed at the final concentrations of 8.0-0.0625 µg/ml (n = 1-5). The MIC_{90} was defined as the lowest concentrations that showed ≥90% inhibition of growth.

4.2.8.2.3. Determination of minimal bactericidal concentration

Samples with ≥90% inhibition of growth were further tested for minimal bactericidal concentration (MBC). 50 µl samples from the MIC assay were plated on fresh MHA plates and incubated for 24 h at 37 °C. Concentration at which 99.9% of the initial bacterial inoculum had been killed was considered as MBC.

4.2.9. Statistical analysis

Basic statistics and for comparison of groups t-test with independent samples were carried out by using IBM® SPSS® Statistics version 21.0. The figures were produced in MS Excel 2010.

5. RESULTS AND DISCUSSION

5.1. Polyphenolic composition of *Mentha* plants

The content of polyphenols identified in the water extracts of the *Mentha* plants 1-33 and commercial peppermint teas varied, but composition profile was rather similar (**II**, **V**). Likewise to earlier studies, the major polyphenols found were caffeic acid derivatives and flavonoids. In general, *M. × piperita* L. extracts were richer in diverse polyphenolic compounds than other *Mentha* plants analysed.

Nine compounds were detected for the first time in *Mentha* plants. Compounds found were 12-hydroxyjasmonate sulphate, medioresinol, prolithospermic acid, salvianolic acid H, salvianolic acid I, rosmarinic acid sulphate, salvianolic acid E and isosalvianolic acid A. A compound characterized by m/z 467 and a constant neutral loss of 80 Da indicating to sulphate moiety was found to be medioresinol sulfate. In addition, danshensu, one of the main compounds and previously detected in *Mentha haplocalyx* (She *et al.,* 2010), was recorded for the first time in *M. × piperita* L. According to Miersch and co-authors (2008), 12-hydroxyjasmonic acid and its derivatives are constituents of various organs of many plant species. Thus, it is surprising that 12-hydroxyjasmonate sulphate has earlier not been reported in *Mentha* plants. Salvianolic acids are the most abundant water-soluble compounds extracted from *Radix Salvia miltiorrhiza* (Hu *et al*., 2005). Salvianolic acids, especially salvianolic acid A and salvianolic acid B, have been found to possess potent anti-oxidative capabilities due to their polyphenolic structure (Sun *et al*., 2009; Zhao *et al*., 2008).

The most abundant polyphenols identified were eriocitrin and rosmarinic acid (Table 10, 11). As reported by Fecka and Turek (2007), eriocitrin was found as the most abundant compound in the commercial peppermint tea water extracts. Among the *Mentha* plants, rosmarinic acid was in the highest content, as shown by Fatiha *et al*. (2015). Remarkably high in content were also found 12-hydroxyjasmonate sulphate and salvianolic acid B. Flavone luteolin was present as luteolin-di-*O*-glucuronides, luteolin-*O*-glucuronide and luteolin-*O*-rutinoside, the latter found most abundant. Besides the rutinoside (eriocitrin), eriodictyol was also detected as an aglycone and eriodictyol glucoside. Apigenin was detected as a rutinoside and in the *Mentha* plants also in the form of a glucuronide. Naringenin was found only as a rutinoside (narirutin). Other flavonoids detected were diosmin and myricetin-*O*-glucoside.

Organic acids were found in the extracts in minor quantities. Acids present were malic acid, citric acid, chlorogenic acid, coutaric acid, fertaric acid, caffeic acid and caffeoylquinic acids. Also, a glucoside of protocatechuic acid and a derivative of elenolic acid were detected.

Five of the *Mentha* plants samples distinguished by their compositional profile. *M. × gracilis* Sole (Nos 12, 15, 25) and *M. arvensis* L. (Nos 21, 22) extracts highlighted due to the absence of main compounds medioresinol and eriocitrin. Also, the content of 12-hydroxyjasmonate sulphate was low in these extracts.

Based on the analyses of the polyphenols in the extracts, no species specific compounds could be proposed. Although certain *Mentha* plants water extracts indicated a trend based on the content of individual compounds, the use of quantitative composition of compounds for species identification is doubtful. Thus, more extensive studies are needed to evaluate the feasibility of using polyphenolic compounds as taxonomical parameters.

Table 10. The LC-DAD-MS/MS characteristics and relative percentage content of total phenols of major compounds identified in the water extracts of *Mentha* samples No 1-33 (**V**).

Retention time (t_R, min)	m/z of parent and fragment ions	Identification	Content (%)
5.0	197 $[M-H]^-$; MS^2: 179; 73	Danshensu	1.1-6.7
19.1	305 $[M-H]^-$; MS^2: 225; 97	12-hydroxyjasmonate sulphate	tr-12.2
19.6	467 $[M-H]^-$; MS^2: 387; 241; 207	Medioresinol sulphate	nd-5.5
21.9	387 $[M-H]^-$; MS^2: 207; 163; 369	Medioresinol	tr-5.1
23.1	357 $[M-H]^-$; MS^2: 313; 269; 159	Prolithospermic acid	nd-2.3
25.7	637 $[M-H]^-$; MS^2: 351; 285	Luteolin-di-*O*-glucuronide	nd-3.9
27.8	537 $[M-H]^-$; MS^2: 339; 229; 493; 295	Salvianolic acid I	nd-6.6
28.4	595 $[M-H]^-$; MS^2: 287	Eriocitrin	nd-15.0
27.8	537 $[M-H]^-$; MS^2: 295; 519; 493	Salvianolic acid H	nd-9.1
29.7	461 $[M-H]^-$; MS^2: 285	Luteolin-*O*-glucuronide 1	nd-4.8
30.1	593 $[M-H]^-$; MS^2: 285	Luteolin-*O*-rutinoside	nd-5.1
32.0	579 $[M-H]^-$; MS^2: 271	Narirutin	nd-7.4
33.0	439 $[M-H]^-$; MS^2: 259; 359; 215; 161	Rosmarinic acid sulphate	nd-5.6
33.8	577 $[M-H]^-$; MS^2: 269	Apigenin-*O*-rutinoside	nd-3.8
34.3	445 $[M-H]^-$; MS^2: 269; 175	Apigenin-*O*-glucuronide	nd-2.8
35.9	359 $[M-H]^-$; MS^2: 223; 197; 161	Rosmarinic acid	4.9-83.4
37.0	607 $[M-H]^-$; MS^2: 299; 284	Diosmin	nd-8.4
37.2	717 $[M-H]^-$; MS^2: 519; 537; 321; 339	Salvianolic acid E	nd-15.6
37.9	461 $[M-H]^-$; MS^2: 285	Luteolin-*O*-glucuronide 2	nd-3.4
38.2	493 $[M-H]^-$; MS^2: 295; 313; 159; 183	Isosalvianolic acid A	nd-7.4
44.0	717 $[M-H]^-$; MS^2: 519; 321; 339; 393	Salvianolic acid B	nd-20.8

tr - traces, <1.0%

nd - not detectable

Table 11. The LC-DAD-MS/MS characteristics and relative percentage content of total phenols of major compounds identified in the water extracts of commercial peppermint teas (**II**).

Retention time (t_R, min)	m/z of parent and fragment ions	Identification	Content (%)
19.6	305 $[M-H]^-$; MS^2: 225; 97	12-Hydroxyjasmonate sulphate	3.2-39.3
26.9	637 $[M-H]^-$; MS^2: 351; 285	Luteolin-di-*O*-glucuronide	nd-13.0
30.1	595 $[M-H]^-$; MS^2: 287	Eriocitrin	8.8-68.1
31.3	461 $[M-H]^-$; MS^2: 285	Luteolin-*O*-glucuronide 1	tr-5.1
31.7	593 $[M-H]^-$; MS^2: 285	Luteolin-*O*-rutinoside	3.2-28.9
33.3	579 $[M-H]^-$; MS^2: 271	Narirutin	nd-4.3
34.8	577 $[M-H]^-$; MS^2: 269	Apigenin-*O*-rutinoside	nd-5.1
36.0	359 $[M-H]^-$; MS^2: 223; 197; 161	Rosmarinic acid	2.1-54.2
37.0	607 $[M-H]^-$; MS^2: 299; 284	Diosmin	tr-11.7
37.2	461 $[M-H]^-$; MS^2: 285	Luteolin-*O*-glucuronide 2	nd-3.2
38.7	287 $[M-H]^-$; MS^2: 151; 135; 125; 107	Eriodictyol	nd-13.8
40.5	717 $[M-H]^-$; MS2: 519; 321; 339; 393	Salvianolic acid B	nd-9.7

tr - traces, <1.0%

nd - not detectable

5.2. Essential oil composition of *Mentha* plants

The total content of the essential oils of *Mentha* plants No 1-47 varied in the range of 0.1-3.0% (n=1; Table 12; **I**, **V**). The lowest and highest oil yield were found respectively in samples No 8 (0.1%) and Nos 37, 46 (3.0%). The essential oil content from different *M. spicata* L. samples was in the range of 0.2-2.3%, *M. arvensis* L. 0.2-1.4%; *M. × gracilis* Sole 0.4-0.8% and in *M. longifolia* (L.) L. 0.8-2.5%. The oil content in *M. × villosa* Huds. was 0.7%. *M. aquatica* L. and *M. suaveolens* Ehrh. stood out by rather low (≤0.4%) oil content.

The major compounds detected in the *Mentha* plants essential oils were terpenoid hydrocarbons, alcohols, esters, ketones, ethers, esters and oxides (Table 12). The essential oils were found to be rich in 3-octanone (max. 30.6%), limonene (max. 41.0%), linalool (max. 61.0%), menthofuran (max. 52.0%), menthol (max. 59.1%), *cis*-piperitone oxide (max. 81.4%), carvone (max. 72.2%), linalool acetate (max. 33.5%), *α*-terpinyl acetate (max. 47.8%) and piperitenone oxide (max. 47.8%). Other compounds found in ≥3.0% content were *i.e.* isomenthone, isomenthol, *β*-pinene, (E)-*β*-caryophyllene, germacrene D, *α*-terpineol, 3-octanone and myrcene.

Due to the rather unusual essential oil composition, several samples were highlighted. *M. × piperita* L. samples Nos 4, 26, 27, 30, 31 and 32 did not contain menthol and menthone as the major compounds commonly found in peppermint essential oil (Hussain *et al*., 2010; Mimicam Dukić *et al*., 2003; İşcan *et al*., 2002). Instead they were found to be rich in carvone, limonene, linalool acetate or linalool. The oils of *M. spicata* L. are usually found to contain carvone as the most prominent component (Hussain *et al*., 2010; Soković *et al*., 2009; Mohan Rao, 2000; Lawrence, 1993). However, *M. spicata* L. samples Nos 7, 36 and 42 were respectively found to contain menthofuran, piperitenone oxide and *α*-terpinyl acetate most abundant. The essential oil of *M. × gracilis* Sole No 33 contained carvone similarly to earlier studies as the most dominating component (Zheljazkov *et al*., 2010c; Bienvenu and Edwards, 1999; Tucker *et al*., 1991). On the other hand, in the oils of *M. × gracilis* Sole samples Nos 12, 15 and 25, linalool was found to be the major constituent. Essential oils of *M. longifolia* (L.) L. samples Nos 11 and 16 were rich in *cis*-piperitone oxide as decribed by Hussain *et al*. (2010), Kokkini and Papageorgiou (1988). In contrast, the oils of the *M. longifolia* (L.) L. samples Nos 43, 44 and 45 contained carvone as the major component as found by Mathela *et al*. (2005). Further, the *M. longifolia* (L.) L. No 24 essential oil was found to contain *α*-terpinyl acetate most abundant. The oils of *M. arvensis* L. were diverse in composition, found to contain 3-octanone, 1,8-cineole or (Z)-*β*-ocimene as the main components, whereas Verma *et al*. (2010) and Pandey *et al*. (2003) showed it to contain menthol. In the present study, an ocimene-rich chemotype for *M. arvensis* L. essential oil was found. In addition, sample No 8 (*M*. "Black beauty") was the only to contain an unknown compound with the RI 1143 in the content of 22.4%. Sample No 8 also highlighted by high content of menthofuran (21.0%) and pulegone (6.7%).

Among all the 27 commercial peppermint tea samples essential oils, less than a half (n = 12) exceeded the Ph. Eur. 7th Ed. limit of 0.9% for the total oil content (n=1; **II**-Supplementary data). From peppermint teas packed in teabags (n = 19), 8 fulfilled the pharmacopoeia requirement. From teas available as a crude drug (n = 8), 4 samples met the standard. The total content of essential oil ranged from 0.4 to 2.2%. The minimum content of 0.4% was found in teas No 20 and No 27, while the maximum 2.2% in sample No 15**.**

The highest content of menthol 57.6% was observed in peppermint tea sample No 20, remarkably lower in sample Nos 10 and 27, 11.0% and 15.0% respectively. In peppermint tea no. 14, menthol was not present. The content of carvone was very high in teas Nos 10, 12, 14 and 27. In the

sample No 14, the content of carvone was up to 71-fold higher than the Ph. Eur. 7th Ed. limit (max. 1%). As high content of carvone is a specific marker for *M. spicata* L. (Lawrence 2006a,b), it can be presumed that three peppermint teas (Nos 10, 12 and 14) consisted of *M. spicata* L.

The results of the essential oil composition analyses reflect the diversity among the *Mentha* plants. In addition, they raise the need for better quality control of *Mentha* products in food and pharmaceutical industry.

Table 12. Total essential oil content (%; w/w) and major essential oil components (%; ≥3.0%) isolated from the *Mentha* plants.

1. *M. × piperita* L. "Swiss" Total content 1.0		**2. *M. × piperita* L. "Chocolate" Total content 0.7**		**3. *M. × piperita* L. "Cinderella" Total content 0.8**		**4. *M. × piperita* cv. L. "Grenada" Total content 0.6**		**5. *M. × piperita* L. "Mitcham" Total content 0.8**		**6. *M.* "Blue palsam" Total content 0.9**	
Menthol	45.5	Menthol	55.6	Menthol	58.4	Linalool	45.6	Menthol	58.4	Menthol	59.1
Menthone	22.6	1,8-Cineole	8.2	1,8-Cineole	7.8	Linalool acetate	30.1	Menthyl acetate	7.8	Menthone	8.2
Limonene	6.8	Menthyl acetate	5.2	Menthone	4.3	1,8-Cineole	4.3	Menthone	7.3	1,8-Cineole	6.9
Menthyl acetate	3.9	Isomenthone	4.2	Isomenthone	4.1	*α*-Terpineol	4.0	1,8-Cineole	6.2	Menthyl acetate	4.6
Isomenthone	3.5	(E)-*β*-Ionone	3.9	(E)-*β*-Ionone	3.4			Isomenthone	4.4	Menthofuran	4.2
1,8-Cineole	3.4	Menthone	3.2	Menthyl acetate	3.1			Menthofuran	3.2	Isomenthone	3.9
										cis-Sabinene hydrate	3.2

7. *M.spicata* L. "Lime" Total content 0.2		**8. *M.* "Black beauty" Total content 0.1**		**9. *M.* "Chocomint" Total content 0.4**		**10. *M. × villosa* Huds. Total content 0.7**		**11. *M.longifolia* (L.) L. "Asian" Total content 0.8**		**12. *M.cf. × gracilis* Sole "Aureus" Total content 0.8**	
Menthofuran	33.0	m/z 79, 93, 107, 121, 43, 136	22.4	Carvone	55.9	Carvone	55.9	*cis*-Piperitone oxide	57.9	Linalool	48.2
m/z 79, 93, 107, 121, 43, 136	16.8	Menthofuran	21.0	Limonene	12.0	Dihydrocarveol	15.5	Piperitenone oxide	32.3	*γ*-Terpinene	8.4
1,8-Cineole	9.1	1,8-Cineole	9.3	Myrcene	4.6	Limonene	14.1			*β*-Pinene	7.3
Pulegone	4.0	m/z 79, 93, 107, 121, 136	7.1	(Z)-Dihydrocarvone	4.4					(Z)- *β*-Ocimene	5.9
		Pulegone	6.7	1,8-Cineole	3.6					(E)-*β*-Caryophyllene	3.9
		β-Pinene	3.2	Dihydrocarveol	3.1					1,8-Cineole	3.1
		Carvone	3.0							Thymol	3.1

13. *M.* "Golden mint" Total content 0.6		**14. *M. suaveolens* Ehrh. "Apfel" Total content 0.4**		**15. *M. × gracilis* Sole "Ginger" Total content 0.5**		**16. *M. longifolia* (L.) L. "Taškent" Total content 0.9**		**17. *M. spicata* L. "Marrocan" Total content 0.4**		**18. *M. spicata* L. "Kentucky colonel" Total content 0.6**	
cis-Piperitone oxide	81.4	Piperitenone oxide	47.8	Linalool	32.5	*cis*-Piperitone oxide	79.0	Carvone	51.2	Carvone	65.0
Piperitenone oxide	6.3	(E)-*β*-Ionone	7.7	(E)-*β*-Caryophyllene	9.9	m/z 43, 112, 87, 109, 127	4.6	Dihydrocarveol	13.8	Limonene	10.3
		(E)-*β*-Caryophyllene	6.9	(Z)-*β*-Ocimene	6.2	Piperitenone oxide	3.2	Neodihydro-carveol	13.8	Germacrene D	4.1
		Myrcene	6.4	*β*-Pinene	5.8			Limonene	11.3	Myrcene	3.3
		Carvone	5.2	Germacrene D	4.8			Dihydrocarveyl acetate, iso-	3.0		
		1-Octen-3-ol acetate	3.6	Thymol	4.5						
				Myrcene	3.0						

19. *M. aquatica* L. Total content 0.2		**20. *M. × piperita* L. Total content 0.8**		**21. *M. arvensis* L. Total content 0.8**		**22. *M. arvensis* L. Total content 0.2**		**23. *M.* "Pineapple" Total content 0.3**		**24. *M. longifolia* (L.) L. Total content 1.0**	
Menthofuran	52.0	Menthol	53.8	3-Octanone	30.6	1,8-Cineole	10.2	Carvone	65.5	*α*-Terpinyl acetate	47.8
m/z 105, 91, 93, 107, 161	9.5	Menthone	12.2	1,8-Cineole	14.2	(Z)-*β*-Ocimene	8.3	Limonene	15.6	(E)-*β*-Caryophyllene	6.9
1,8-Cineole	6.2	1,8-Cineole	6.0	(Z)-*β*-Ocimene	6.3	(E)-*β*-Ocimene	7.2	Germacrene D	3.3	Myrcene	6.4
Limonene	6.1	Neomenthol	3.9	(E)-*β*-Caryophyllene	5.2	*β*-Pinene	6.3			Carvone	5.2
(E)-*β*-Caryophyllene	6.0	Germacrene D	3.5	(E)-*β*-Ocimene	5.1	Borneol	6.2			1-Octen-3-ol acetate	3.6
		cis-Sabinene hydrate	3.1	*β*-Pinene	3.8	3-Decanone	3.6			m/z 82, 108, 43, 107, 150	4.2
				Germacrene D	3.4						
				α-Terpineol	3.0						

25. *M. × gracilis* Sole "Variegata" Total content 0.4		**26. *M. × piperita* L. "Lime" Total content 0.4**		**27. *M. × piperita* L. "Barnes & Cream" Total content 0.5**		**28. *M. × piperita* L. "Chocolate" Total content 1.2**		**29. *M. × piperita* L. "Black beauty" Total content 1.0**		**30. *M. × piperita* L. "Marrocan" Total content 1.9**	
Linalool	61.0	Limonene	41.0	Carvone	22.4	Menthol	52.0	Menthol	53.1	Carvone	72.2
(E)-*β*-Caryophyllene	5.2	Hedycaryol	10.7	1,8-Cineole	10.5	1,8-Cineole	7.5	Menthone	6.9	Limonene	14.7
(Z)-*β*-Ocimene	4.1	m/z 105, 107, 91, 93, 161	8.1	Hedycaryol	10.1	Menthone	7.2	1,8-Cineole	6.8		
β-Pinene	3.7	Epiglobulol	8.1	Myrcene	6.4	Neomenthol	6.2	Menthyl acetate	5.1		
Thymol	3.5	(Z)- *β*-Ocimene	7.1	Epiglobulol	4.5	*cis*-Sabinene hydrate	4.3	Neomenthol	4.4		
γ-Terpinene	3.1	1,8-Cineole	6.8	Dihydrocarveyl acetate, -iso	3.9	Menthyl acetate	3.7	Germacrene D	3.6		
Germacrene D	3.1	Germacrene D	5.9	Germacrene D	3.8						
		Myrcene	4.0	Limonene	3.0						

31. *M. × piperita* L. "Basil mint" Total content 0.5		**32. *M. × piperita* L. "Lavender" Total content 0.7**		**33. *M. cf. × gracilis* Sole "Orange" Total content 0.5**		**34. *M. spicata* L. Total content 2.1**		**35. *M. spicata* L. Total content 2.1**		**36. *M. spicata* L. Total content 0.9**	
Linalool acetate	33.5	Linalool	47.8	Carvone	44.1	Carvone	67.4	Carvone	62.1	Piperitenone oxide	61.9
Linalool	26.6	Linalool acetate	26.1	Limonene	19.8	Limonene	10.4	Limonene	11.8	1,8-Cineole	5.8
Limonene	10.7	Limonene	4.6	*β*-Pinene	4.9			*cis*-Dihydrocarvone	4.8	Myrcene	5.5
Hedycaryol	7.0			Dihydrocarveol	4.7					Germacrene D	3.3
α-Terpineol	3.7			Dihydrocarvyl acetate, iso-	3.0						

37. *M. × piperita* L.		**38. *M. longifolia* (L.) L.**		**39. *M. × piperita* L.**		**40. *M. arvensis* L.**		**41. *M. arvensis* L.**		**42. *M. spicata* L.**	
Total content 3.0		**Total content 1.4**		**Total content 2.4**		**Total content 0.9**		**Total content 1.4**		**Total content 1.1**	
Menthone	31.9	Carvone	57.6	Menthol	47.7	*cis*-β-Ocimene	16.2	(Z)-β-Ocimene	20.5	α-Terpinyl acetate	32.3
Menthol	26.4	Limonene	10.3	Menthone	13.6	*trans*-β-Ocimene	16.0	(E)-β-Ocimene	19.1	*trans*-β-Caryophyllene	11.4
Limonene	8.9	*trans*-β-Caryophyllene	4.3	Limonene	9.8	β-Pinene	9.1	β-Pinene	13.0	Acetic acid, 1-methyl-1-(4-methyl-5-oxo-cyclohex-3-enyl) ethyl ether	6.5
Isomenthone	7.0	*cis*-Dihydrocarvone	3.7	Menthofuran	3.9	α-Terpineol	8.2	1,8-Cineole	7.9	Myrcene	5.8
Germacrene D	3.3					1,8-Cineole	7.6	1-Octen-3-ol	4.7	1,8-Cineole	4.1
Menthofuran	3.3					n-Decyl acetate	5.0	α-Pinene	3.1	γ-Muurolene	3.2
						(E)-β-Caryophyllene	3.8	α-Terpineol	3.5		
						Germacrene D	3.4				

43. *M. longifolia* (L.) L.		**44. *M. longifolia* (L.) L.**		**45. *M. longifolia* (L.) L.**		**46. *M. × piperita* L.**		**47. *M. spicata* L.**	
Total content 2.2		**Total content 0.7**		**Total content 2.5**		**Total content 3.0**		**Total content 2.3**	
Carvone	56.8	Carvone	51.4	Carvone	56.4	Menthol	31.3	Carvone	66.5
γ-Muurolene	9.4	γ-Muurolene	12.0	Limonene	18.8	Menthone	30.1	Limonene	13.9
Limonene	8.2	*trans*-β-Caryophyllene	9.7	γ-Muurolene	4.2	1,8-Cineole	4.8	Myrcene	3.3
trans-β-Caryophyllene	7.7					Menthofuran	4.5		
						cis-Sabinene hydrate	3.2		

5.3. Mint flavouring hydrodistilled extract composition

The total yield of the mint flavouring hydrodistilled extracts isolated from candies and food supplements ranged 0.01 to 0.9% (w/w; Table 13; **IV**). The lowest extract amount was found in the chocolate No 40 and the highest in the pastille No 15.

In general, higher hydrodistilled extract content was isolated from mint flavoured sugar candies and pastilles than from chocolates. Extract content ≥0.1% was isolated from 15 mint flavoured sugar candies and pastilles samples out of the total of 25. Among the chocolates, content of ≥0.1% was isolated from only one sample (No 39).

The three food supplements did not highlight with low or high hydrodistilled extract content. The lowest content 0.02% was obtained from the tablet No 28 and the highest 0.3% from the tablet No 11.

The main compounds identified in the mint flavouring hydrodistilled extracts are shown in the Table 13 (**III, IV**). Extracts included mainly monoterpenoid and sesquiterpenoid hydrocarbons, terpenoic alcohols, ketones, aldehydes, ethers and esters. Two most abundant compounds were limonene (max. 57.4%) and menthol (max. 89.4%). Other major compounds were for example 1,8-cineole, menthone, menthofuran, isomenthone, neomenthol, (E-)-anethole and menthyl acetate. Orav and Kann (2001) analysed the flavouring content in one sugar candy and one chewing gum product originating from Estonia. Menthole, menthone and menthyl acetate were according to them, the main compounds found.

The greatest variation was found in the contents of limonene (0.1%-66.4%) and menthol (17.5-89.4%). The highest limonene content was found in extracts of the pastille No 12 (66.4%) and sugar candy No 2 (57.4%). Lowest limonene content 0.1% was in the tablet No 28. Highest menthol content 89.4% was detected in the pastille No 18 and lowest 17.5% in the pastille No 12. Menthone and menthol were dominating flavourings in most of the extracts. Highest menthone content (25.9%) was found in the extract of the chocolate No 45, lowest (1.25%) in the extract of the pastille No 19. The only extract to contain (E-)-anethole in the high content of 12.4% was the pastille No 10. Relatively high content of menthofuran (7.2%) was found in the extract isolated from the sugar candy No 9.

In general, the composition of the hydrodistilled extracts was rather similar and close to the essential oils of *Mentha* plants. Chocolate extracts were richer in menthone than extracts isolated from sugar candies and pastilles. Food supplements differed from each other only by the quantitative content of individual components. The research on the aspect of mint flavouring content is scarce.

Table 13. Total mint flavouring hydrodistilled extract content (%; w/w) and major extracts components (%, ≥3.0%) isolated from the mint flavoured candies and food supplements.

1. Pastille Total content 0.5		2. Sugar candy Total content 0.03		3. Sugar candy Total content 0.06		4. Sugar candy Total content 0.04		5. Pastille Total content 0.1		6. Pastille Total content 0.6	
Menthol	70.6	Limonene	57.4	Menthol	51.1	Menthol	61.4	Menthol	54.8	Menthol	68.6
Menthone	8.5	Menthol	20.4	Menthone	20.8	Menthone	16.0	Menthone	18.8	Menthone	11.3
Menthyl acetate	4.9	Menthone	8.5	Menthyl acetate	5.7	Menthyl acetate	3.6	Menthyl acetate	4.4	Menthofuran	5.5
Menthofuran	3.5			Menthofuran	5.0	Neomenthol	3.2	Limonene	3.5	Neomenthol	4.1
				Limonene	4.5			Menthofuran	3.6		
				Neomenthol	3.2			Neomenthol	3.2		

7. Pastille Total content 0.09		8. Pastille Total content 0.08		9. Sugar candy Total content 0.2		10. Pastille Total content 0.3		11. Tablet Total content 0.3		12. Pastille Total content 0.2	
Menthol	73.7	Menthol	73.6	Menthol	57.7	Menthol	54.8	Menthol	63.8	Limonene	66.4
Neomenthol	7.5	Menthone	5.9	Menthone	14.8	(E-)-Anethole	12.4	Neomenthol	6.4	Menthol	17.5
Menthyl acetate	5.4	Neomenthol	4.7	Menthofuran	7.2	Menthone	12.1	Menthone	4.3	*γ*-Terpinene	3.2
Menthone	4.4	Menthyl acetate	4.3	Menthyl acetate	3.6	Menthofuran	4.7				
		Isomenthone	3.8			Limonene	3.3				

13. Pastille Total content 0.5		14. Sugar candy Total content 0.02		15. Pastille Total content 0.9		16. Pastille Total content 0.1		17. Pastille Total content 0.5		18. Pastille Total content 0.8	
Menthol	68.8	Menthol	52.3	Menthol	79.7	Menthol	77.9	Menthol	76.0	Menthol	89.4
Menthone	12.5	Menthone	15.3	Limonene	7.2	Limonene	11.3	Menthone	9.5	Menthone	4.2
Menthyl acetate	3.7	Isomenthone	6.0	Menthone	5.9	Menthone	4.0	Isomenthone	4.5		
Isomenthone	3.6	Neomenthol	5.5								
Neomenthol	3.0	Menthyl acetate	5.4								
		1,8-Cineole	3.1								

19. Pastille Total content 0.05		20. Tablet Total content 0.09		21. Sugar candy Total content 0.04		22. Sugar candy Total content 0.1		23. Sugar candy Total content 0.03		24. Sugar candy Total content 0.09	
Menthol	47.8	Menthol	55.3	Menthol	45.0	Menthol	75.6	Menthol	75.6	Menthol	71.5
Isomenthol	5.7	Isomenthone	13.7	Menthone	17.5	Menthone	9.3	Menthone	6.9	Menthone	11.6
Limonene	4.9	Menthyl acetate	7.2	Isomenthone	9.9	Isomenthone	4.8	Isomenthone	4.1	Isomenthone	5.7
		Isomenthone	6.4	Menthyl acetate	4.6	Menthyl acetate	4.2				
		Neomenthol	4.2	Neomenthol	4.6						
				Terpinen-4-ol	3.0						

25. Pastille Total content 0.5		26. Sugar candy Total content 0.2		27. Sugar candy Total content 0.2		28. Tablet Total content 0.02		29. Chocolate Total content 0.04		30. Chocolate Total content 0.05	
Menthol	52.8	Menthol	53.4	Menthol	69.2	Menthol	83.0	Menthol	49.6	Menthol	47.7
Menthone	16.5	Menthone	18.2	Menthone	12.0	Menthone	3.5	Menthone	18.4	Menthone	19.5
Isomenthone	8.1	Isomenthone	8.7	Isomenthone	6.0			Menthofuran/iso-menthone	8.6	Limonene	8.2
Neomenthol	5.0	Menthyl acetate	4.8	Neomenthol	4.0			Limonene	6.9	Menthofuran/iso-menthone	7.5
Menthyl acetate	3.2	Neomenthol	4.6					Neomenthol	5.0	Neomenthol	5.3
								Menthyl acetate	4.1	Menthyl acetate	4.0

31. Chocolate Total content 0.1		32. Chocolate Total content 0.04		33. Chocolate Total content 0.03		34. Chocolate Total content 0.04		35. Chocolate Total content 0.02		36. Chocolate Total content 0.06	
Menthol	45.1	Menthol	52.8	Menthol	56.9	Menthol	49.2	Menthol	46.2	Menthol	56.1
Menthone	23.3	Menthone	23.8	Menthone	24.8	Menthone	22.3	Menthone	18.7	Menthone	14.8
Menthofuran	8.2	Limonene	4.6	Limonene	7.2	Menthofuran/iso-menthone	9.9	Menthofuran/iso-menthone	9.6	1,8-Cineole	5.2
Neomenthol	4.3	Menthofuran/iso-menthone	4.6	Isomenthone	4.7	Menthyl acetate	3.4	Limonene	8.1	Isomenthone	4.9
Menthyl acetate	4.0	Menthyl acetate	4.2	Menthyl acetate	3.4	Limonene	3.1	Neomenthol	4.9		
		Neomenthol	3.8					Menthyl acetate	4.0		

37. Chocolate Total content 0.02		38. Chocolate Total content 0.02		39. Chocolate Total content 0.1		40. Chocolate Total content 0.01		41. Chocolate Total content 0.02		42. Chocolate Total content 0.08	
Menthol	50.2	Menthol	48.8	Menthol	42.5	Menthol	57.2	Menthol	30.6	Menthol	59.3
Menthone	21.0	Menthone	22.4	Menthone	21.7	Menthone	19.6	Menthone	25.4	Menthone	16.8
Isomenthone	8.4	Isomenthone	6.7	Limonene	6.8	Limonene	3.9	Isomenthole	17.8	Isomenthone	7.9
Neomenthol	4.6	Menthyl acetate	5.1	Menthofuran/iso-menthone	5.7	Menthyl acetate	3.4	Menthofuran/iso-menthone	6.0	Neomenthol	4.0
Menthyl acetate	3.9	Neomenthol	4.0	1,8-Cineole	5.4	Menthofuran/iso-menthone	3.4	Menthyl acetate	4.2	Menthyl acetate	3.3
				Menthyl acetate	3.5			Limonene	3.5		
								Neomenthol	3.1		

43. Chocolate Total content 0.4		44. Chocolate Total content 0.04		45. Chocolate Total content 0.04	
Menthol	62.6	Menthol	49.5	Menthol	39.4
Menthone	12.8	Menthone	21.6	Menthone	25.9
Neomenthol	5.1	Limonene	9.3	Menthofuran/iso-menthone	7.3
Isomenthone	4.8	Menthofuran/iso-menthone	6.3	Menthyl acetate	6.2
Menthyl acetate	3.3	Menthyl acetate	3.3	Neomenthol	3.7
				1,8-Cineole	3.3

5.4. Antibacterial activity

5.4.1. Preliminary antimicrobial activity tests

The preliminary tests showed that the *Mentha* plants water extracts and essential oils, mint flavouring hydrodistilled extracts and reference substances showed clear bacteriostatic or bactericidic inhibition (**IV**; **V**). The bacteria represented the common strains used in the preliminary sensitivity tests. *Yersinia ruckeri* represented Gram-negative bacteria. *Bacillus cereus, Bacillus subtilis*, *Bacillus pumilus* and *Micrococcus luteus* represented Gram-positive bacteria. The experiments encouraged further studies with the potentially pathogenic bacteria *Chlamydia pneumoniae*, *Escherichia coli* and *Staphylococcus aureus*.

5.4.2. Antichlamydial activity

5.4.2.1. Commercial peppermint tea samples

The ability of the seven commercial peppermint tea water extracts to inhibit the growth of *C. pneumoniae* clinical respiratory isolate K7 was determined at 250.0 µl/mg (n=3; Table 14; **II**). The viability of host cells was determined upon exposure to each of the seven extracts at the concentration of 250 µg/ml. For the experiments, the peppermint teas were selected according to the relatively high and low total polyphenol contents, representative of crude herb and tea bags, as well as teas with a different origin.

The tea samples diminished the chlamydial growth in the range of 20.7-69.5%. Tea No 23 had the lowest 20.7% inhibition percentage and No 19 had the highest 69.5%. The host cell viability after the 72 h exposure to the peppermint herbal teas ranged from 82.4% to 99.4% (**II**).

The tea samples with antichlamydial activity were high in content of luteolin and apigenin glycosides. These two flavonoids as aglycones have been shown to possess high antichlamydial activity in the earlier study by Alvesalo *et al*. (2006). Also, rosmarinic acid, one of the major compounds of the water extracts, has been reported to have antichlamydial effect (Salin *et al*., 2011). The water extracts of commercial peppermint teas were shown to possess antichlamydial activity. This finding is in accordane with earlier findings with *M. arvensis* L. by Salin *et al*. (2011).

Table 14. The effect of peppermint tea water extracts or mint flavouring hydrodistilled extracts on *C. pneuomoniae* growth and infectivity.

Tea extract	Concentration (µg/ml)	Inhibition of growth 72 h (%)(SEM)	Mint flavouring extract	Concentration (mg/ml)	Inhibition of infectivity 2 h (%)(SEM)
No 18	250.0	30.0 (8.9)	No 7, pastille	2.0	64.0 (2.0)
No 19	250.0	69.5 (2.8)	No 9, sugar candy	2.0	69.0 (2.0)
No 22	250.0	29.2 (7.7)	No 12, pastille	2.0	100.0 (nd)
No 23	250.0	20.7 (2.7)	No 21, sugar candy	2.0	54.0 (4.8)
No 25	250.0	51.6 (9.0)	No 31, chocolate	2.0	29.0 (5.5)
No 26	250.0	51.2 (7.8)	No 42, chocolate	2.0	68.0 (3.0)

nd - not defined

5.4.2.2. Mint flavouring hydrodistilled extracts

The effect of six mint flavouring hydrodistilled extracts on inhibiting the infectivity of *C. pneumoniae* isolate K7 was evaluated by treating the EBs with the extracts at a concentration of 1.0

mg/ml (No 12) and 2.0 mg/ml (n≥4; Table 14; **III**). The chosen extracts were diverse in composition and represented various candy products with different origin.

Most extracts resulted in a significant yet moderate inhibition of *C. pneumoniae* infectivity. However, the extract No 12, rich in limonene, yielded in a full inhibition of *C. pneumoniae* EB infectivity at the concentration of 2.0 mg/ml (Table 14). The host cell viability after 2 h exposure of the extracts ranged from 83.0-102.0% with the exception of the extract No 12 that had a moderate effect on HL cells viability (**III**). Nevertheless, extract No 12 did not decrease the cells viability at the concentration of 1.0 mg/ml but did suppress *C. pneumoniae* infectivity by >90%.

To evaluate which components influenced the inhibitory effects of the flavouring extracts, a set of reference substances representing the main components of the extracts was assayed in the *C. pneumoniae* EB infectivity and cell viability assays (**III**). (+)-Menthol, (-)-menthone and (-)-menthone decreased *C. pneumoniae* infectivity respectively by 47.0%, 42.0% and 57.0% at the concentration of 1.0 mg/ml. Menthofuran inhibited the infectivity by 98.0% at the concentration of 0.25 mg/ml and limonene by 94.0% at the concentration of 1.0 mg/ml. The latter two compounds were also found to be toxic to the HL cells.

These results indicate that the harmful effects of menthofuran and limonene are less pronounced when they are present in the extracts as a mixture of numerous components than as pure substances alone. Another observation related to the relationship of the chemical composition and the inhibitory activity of the extracts was the difference between the antichlamydial activity of the two chocolate-derived flavouring extracts No 31 and 42. Despite rather similar chemical composition, these two samples resulted in inhibition values with a statistically significant difference. These findings illustrate the potential impact of the original matrix on the results.

5.4.3. Activity against *Escherichia coli* and *Staphylococcus aureus*

5.4.3.1. Water extracts of *Mentha* plants

Eight *Mentha* plants water extracts were tested for their antibacterial activity against *E.coli* and *S. aureus* at the concentration of 1.0-4.0 mg/ml (n=2; Table 15, 16; **V**). The water extracts selected represented different *Mentha* plants. Also, their composition was rather diverse. Furthermore, the antimicrobial effect of *M. × villosa* Huds., *M. suaveolens* Ehrh., *M. × gracilis* Sole and *M. arvensis* L. water extracts was studied for the first time on *E. coli* and *S. aureus*.

None of the water extracts was active against *E. coli*. Similar results have been reported for alcoholic extracts of *M. longifolia* (L.) L. (Akroum *et al*., 2009; Hajlaoui *et al*., 2009; Gulluce *et al*., 2007), *M. spicata* L. (Chan *et al*., 2012), *M. × piperita* L. (Albayrak *et al*., 2013) and water extracts of *M. × piperita* L. (Albayrak *et al*., 2013). On the contrary, Nascimento *et al*., (2009) showed *M. arvensis* L. alcoholic extract to inhibit the growth of *E. coli*.

The most dominating compound in the *Mentha* plant water extracts was rosmarinic acid, found to possess no antimicrobial activity on *E. coli* (Moreno *et al*., 2006). Eriodictyol and luteolin, the two other major compounds in the extracts, have reported to exhibit antimicrobial effect on *E. coli* (Mandalari *et al*., 2007; Cottiglia *et al*., 2001). Nevertheless, it can be assumed that the total content of active eriodictyol and luteolin glycosides in the *Mentha* plants extracts was too low to inhibit the growth of *E. coli* in the present study.

On the other hand, four of the *Mentha* plants water extracts inhibited *S. aureus* at the concentration of 2.0 mg/ml and two extracts at 3.0 mg/ml (Table 16). Similar antibacterial activity has been reported also by Verma *et al*. (2013) and Sofia *et al*. (2007) for *M. × piperita* L. Furthermore, the water extract of *M. × piperita* L. sample No 2 was found to be bactericidal against

S. aureus at the concentration of 2.0 mg/ml. *M. aquatica* L. (No 19) and *M. arvensis* L. (No 22) extracts showed no inhibition.

Eriodictyol (Mandalari *et al*., 2007), luteolin and apigenin (Cottiglia *et al*., 2001; Sato *et al*., 2000) have been found to possess antimicrobial activity against *S. aureus* strains. Thus, the unactivity of the water extract of *M. arvensis* L. No 22 could be due to low content of luteolin derivatives and absence of eriodictyol and apigenin glycosides.

5.4.3.2. Essential oils of *Mentha* plants

The antibacterial activity of nine *Mentha* plant essential oils was evaluated at the concentrations of 1.0-4.0 mg/ml (Table 15, 16; **V**; n=2-3). The chosen essential oils were diverse in composition. Also, they represented various *Mentha* plants.

Table 15 shows that five oils demonstrated antibacterial activity towards *E. coli* (**V**). The MIC_{90} values for four of the samples were 3.0 mg/ml and for the sample No. 6, 4.0 mg/ml. *M. × piperita* L. oil has been shown earlier to possess activity on *E. coli* (Hussain *et al*., 2010; İşcan *et al*., 2002). However, the higher MIC_{90} value of *M. × piperita* L. oil No 6 can be due to high menthol content in the oil, found to be not active as a pure compound in the present study (**IV**). The essential oils of *M. longifolia* (L.)L. and *M. spicata* L. have been shown earlier to be antibacterial against *E. coli* (Hussain *et al*., 2010; Gulluce *et al*., 2007). Nevertheless, the oil No 18 was rich in carvone, found to possess high antimicrobial activity in the present study (**IV**; table 15) and by Hussain *et al*. (2010) and Naigre *et al*. (1996). Suprisingly, the oil of *M. aquatica* L. was not found to be active, though it contained most abundant menthofuran that was found to inhibit *E. coli* (**IV**; Table 15). Furthermore, *M. aquatica* L. essential oil rich in pulegone and menthofuran has been shown to be antibacterial on *E. coli* by Dhifi *et al*. (2011) and Mimica-Dukić *et al*. (2008). Similarly to Arruda *et al*. (2006), the oil of *M. × villosa* Huds. possessed no activity.

All the studied essential oils showed inhibition of ≥90% of *S. aureus* at the concentration of 1.0 mg/ml, and sample No 32 at 2.0 mg/ml (Table 16; **V**). This antibacterial activity has been shown also in earlier studies for *M. × piperita* L. (Hussain *et al*., 2010; Mimica-Dukić *et al*., 2008; İşcan *et al*., 2002), *M. longifolia* (L.) L. (Mimica-Dukić *et al.,* 2008; Gulluce *et al.,* 2007), *M. × villosa* Huds. (Arruda *et al.,* 2006), *M. aquatica* L. (Mimica-Dukić *et al.,* 2008) and *M. arvensis* L. (Hussain *et al.,* 2010). The essential oil from *Mentha* plant No 32 contained linalool and linalool acetate as the major compounds. These two compounds were found to have MIC_{90} values 2.0 mg/ml and 1.0 mg/ml respectively (Table 16; **IV**). However, the higher MIC_{90} value of the essential oil of plant No 32 can be noted.

Table 15. MIC_{90} values (mg/ml) of *E. coli*.

***Mentha* plants essential oils**		**Reference substances**	
6. *M. × piperita* L. "Blue palsam"	4.0	Menthone, racemic	7.0 *
10. *M. × villosa* Huds.	3.0 *	1,8-Cineole	5.0 *
13. *M.* "Golden mint"	3.0	(-)-Menthone	4.0 *
16. *M. longifolia* (L.) L. "Taškentin"	3.0	Menthofuran	7.0 *
18. *M. spicata* L. "Kentucky colonel"	3.0	Linalool	1.0 *
Mint flavouring hydrodistilled extracts		Linalool acetate	1.0 *
No 10, pastille	2.0	(-)-Carvone	1.0
No 25, pastille	4.0		
No 31, chocolate	4.0		

* - Minimal bactericidal concentration

Table 16. MIC_{90} values (mg/ml) of *S. aureus*.

***Mentha* plants essential oils**		**Reference substances**	
2. *M. × piperita* L. „Chocolate"	1.0	Menthol racemic	1.5
6. *M. × piperita* L. "Blue palsam"	1.0	(+)-Menthol	1.0
10. *M. × villosa* Huds.	1.0	(-)-Menthol	1.0
13. *M.* "Golden mint"	1.0	Menthone, racemic	2.5
16. *M. longifolia* (L.) L. "Taškentin"	1.0	(-)-Menthone	2.5
18. *M. spicata* L. "Kentucky colonel"	1.0	Menthofuran	2.0
19. *M. aquatica* L.	1.0	Linalool	2.0
22. *M. arvensis* L.	1.0	Linalool acetate	1.0
32. *M. × piperita* L. "Lavender"	2.0	(-)-Carvone	1.0
Mint flavouring hydrodistilled extracts		***Mentha* plants water extracts**	
No 9, sugar candy	1.0	2. *M. × piperita* L. „Chocolate"	2.0 *
No 10, pastille	1.0	10. *M. × villosa* Huds.	3.0
No 18, pastille	1.0	14. *M.suaveolens* Ehrh. „Apfel"	2.0
No 25, pastille	1.0	15. *M. × gracilis* Sole „Ginger"	2.0
No 26, sugar candy	1.5	18. *M. spicata* L. „Kentucky Colonel"	2.0
No 27, sugar candy	1.0	24. *M. longifolia* (L.) L.	3.0
No 36, chocolate	4.0		
No 39, chocolate	1.0		

* - Minimal bactericidal concentration

5.4.3.3. Reference substances

The antimicrobial activity against *E. coli* and *S. aureus* was tested using terpenoidic reference substances found as main compounds in the *Mentha* plants essential oils and mint flavouring hydrodistilled extracts. The reference substances were tested in the concentration range of 0.0625-8.0 mg/ml (n=2-5; Table 15, 16; **IV**).

E. coli was inhibited by 1,8-cineole and menthofuran with MIC_{90} values of 5.0 mg/ml and 7.0 mg/ml, respectively. Racemic menthone and (-)-menthone demonstrated antibacterial activity against *E. coli* with MIC_{90} values of 7.0 mg/ml and 4.0 mg/ml, respectively. Linalool, linalool acetate and (-)-carvone showed higher antibacterial activity with equal MIC_{90} values of 1.0 mg/ml. Racemic menthol, (+)-menthol and (-)-menthol were found to be inactive against *E. coli*. For most of the reference substances MIC_{90} values against *E. coli* were also minimal bactericidal concentrations (MBC).

Racemic menthol and menthol enantiomers inhibited *S. aureus* by ≥90% at concentrations of 1.5 mg/ml and 1.0 mg/ml, respectively. MIC_{90} values for racemic menthone and (-)-menthone were 2.5 mg/ml. Menthofuran and linalool showed antibacterial activity on *S. aureus* at concentration of 2.0 mg/ml. For linalool acetate and (-)-carvone the MIC_{90} value was equally 1.0 mg/ml.

(+)-Menthyl acetate, (-)-menthyl acetate and limonene were found to be inactive towards both of the bacteria.

The results of the previous studies on the antimicrobial activity of menthol and menthone on *E. coli* and *S. aureus* are consistent with the present study. Menthol and menthone show higher antimicrobial activity on Gram-positive bacteria *S. aureus* than on Gram-negative *E. coli* (Hussain *et al.,* 2010; İşcan *et al*., 2002). However, the MIC values determined by Hussain *et al.* are much lower. Also, İşcan *et al*. reported (-)-menthol to inhibit the growth of *E. coli* at 1.25 mg/ml. The antibacterial activity of carvone has been studied by Hussain *et al.* (2010). Contrary to the results of the present study, the MIC values of Hussain *et al.* were reported to be higher for *E. coli*.

5.4.3.4. Mint flavouring hydrodistilled extracts

Among all the tested 10 mint flavouring hydrodistilled extracts at the concentration of 1.0-4.0 mg/ml, three inhibited the growth of *E. coli* (n= 1-3; Table 15; **V**). The MIC_{90} for the extract No 10 was obtained at 2.0 mg/ml and for extracts No 25 and No 31 at 4.0 mg/ml.

Suprisingly, the active extract No 10 contained high amount of menthol, which as a reference substance was found to be non-active on *E. coli*. Sample No 25 had higher content of menthone, found to be active as a reference substance (**IV**; Table 15). This stands also for flavouring extract No 31. The latter was also richer in antibacterially active 1,8-cineole.

Eight mint flavouring extracts were antibacterial against *S. aureus*. The MIC_{90} values for most of them were 1.0 mg/ml (n= 1-3; Table 16; **IV**), similarly to their main component menthol. The MIC_{90} concentration for extract No 26 was obtained at 1.5 mg/ml and for extract No 36 at 4.0 mg/ml. Mint flavouring extracts No 11 and No 31 showed no activity towards *S. aureus*.

Regarding extract No 11, its main compound was the antimicrobially active menthol. However, the hydrodistilled extract was less diverse in compounds. Also, it contained lower amount of menthone compared to other tested extracts. The other non-active extract (No 31) was rich in antimicrobially active compounds such menthol and menthone.

Thus, it can be concluded that the other ingredients apart from essential oil components may influence the activity. However, further studies are needed for each type of mint flavoured products regarding their antimicrobial potential.

6. CONCLUSIONS

Mentha plants are one of the common herbs used for their medicinal and aromotherapeutic properties since written history. However, the taxonomy of the genus *Mentha* L. has been a matter of speculation for decades. *Mentha* plants show a large phenotypic plasticity and most species are capable of hybridization with each other. According to the latest taxonomical classification, genus *Mentha* is consisting of 18 species, 11 hybrids and hundreds of subspecies, varieties and cultivars.

The problematic taxonomy was been faced as well in the present study. Many of the *Mentha* samples turned out to be difficult to classify or their identity remained unknown as the plants died off in freezing winter temperatures. Also, the composition of many mints was different or unique compared to previous reports. The present study also raised the need for a proper taxonomical quality control in industry. The analyses showed that three commercial peppermint tea samples may contain *M. spicata* L., different from that claimed on the package.

The composition of the essential oil is characteristic for each *Mentha* plant. Nevertheless, due to hybridization, the composition of *Mentha* plants may resemble each other. Additionally, the oil composition varies from year to year according to the environmental conditions. The polyphenolic compounds in *Mentha* have become of interest in recent years. Thus, detailed profiling of such compounds in *Mentha* plants is needed. In the present study, essential oil and polyphenolic composition of various wild growing or cultivated mints originating from Estonia were described. An ocimene-rich chemotype for *M. arvensis* L. essential oil was found. Also, nine new compounds were described for the polyphenolic profile of *Mentha* plants. However, the identity of some compounds remained unraveled, indicating the necessity for further studies with mints.

Mentha plants are not only consumed as herbal teas. They are commonly used to improve the flavour of food and medicinal products. This was the first more detailed study on the composition of mint flavouring isolated from widely consumed mint flavoured candies and food supplements produced in various countries.

The antibacterial properties and testing methodologies of *Mentha* essential oils have been reported in numerous studies for *Escherichia coli* and *Staphylococcus aureus*. Nevertheless, the microdilution methodology could not be effectively used with the mint hydrodistilled extracts of the present study. Various microtiter plate sealing films, incubation regimes, solvents and sample applying methods did not give the results described in the literature. Thus, an adapted broth dilution method was developed. An adjustment in the methodology was also needed in *Chlamydia pneumoniae* experiments. Sealing film and preparation of test samples prior the experiments were used to prevent the risk of sample evaporation.

The antichlamydial experiments indicated that the consumption of *Mentha* herbal tea or mint flavoured candies and food supplements may be beneficial to prevent respiratory infections and other ailments caused by *C. pneumoniae*. Also, the use of mint products may protect from the diseases caused by potential pathogens *E. coli* and *S. aureus*.

During the years, the everyday diet has developed to contain regularly *Mentha* plants and its ingredients. The presenr study showed, what could be the basis for this trend by confirming that the consumption of mints may be beneficial for health.

As highlighted can be shown the following main results:

- The present study demonstrates the complexity of the taxonomy of genus *Mentha* and gives rise for further research in the field.

- New compunds detected in the polyphenolic composition of genus *Mentha*.
- Commercial *Mentha* teas need quality control.
- New activity of peppermint teas found against *Chlamydia pneumoniae.*
- The antimicrobial effect of *M. × villosa* Huds., *M. suaveolens* Ehrh., *M. × gracilis* Sole and *M. arvensis* L. water extracts was studied for the first time on *Escherichia coli* and *Staphylococcus aureus*.
- The *Mentha* plants water extracts showed antimicrobial activity against *Staphylococcus aureus.*
- The composition of mint flavouring from candies and food supplements is similar to essential oils of *Mentha* plants.
- The mint flavouring hydrodistilled extracts were found to possess antimicrobial effect against *Chlamydia pneumoniae, Escherichia coli* and *Staphylococcus aureus*.
- Test method development for the essential oils and mint flavouring extracts against *Escherichia coli* and *Staphylococcus aureus.*
- *Mentha* seems to be a beneficial component of the diet.

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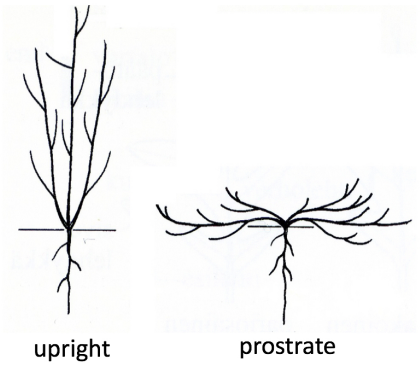
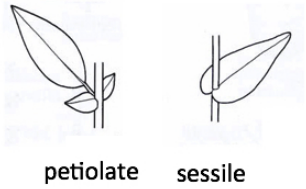
APPENDIX 1

Morphological characteristics of *Mentha* plants.



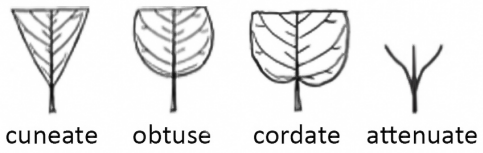
Upright and prostrate habit of growth

Illustration origin: Retkeilykasvio, Luonnontieteellinen keskusmuseo, Kasvimuseo, Helsinki 1998



Petiolate and sessile leaf attachment

Illustration origin: Retkeilykasvio, Luonnontieteellinen keskusmuseo, Kasvimuseo, Helsinki 1998



Leaf bases

entire serrate crenate revolute

Leaf margins

verticillate spicate capitate

Inflorescense types

ovate lanceolate oblong suborbicular

Leaf shapes

APPENDIX 2

Polyphenols identified in *Mentha* plants.

Compound	*Mentha* plants	Reference
	Caffeic acid derivatives	
Caffeic acid	*M. aquatica* L.	Kosar *et al.,* 2004
	M. arvensis L.	Kosar *et al.,* 2004
		Dorman *et al.,* 2003
	M. australis R. Br.	Tang *et al.,* 2016
	M. canadensis L.	Shan *et al.,* 2005
	M. × dalmatica Tausch	Dorman *et al.,* 2003
	M. "Morocco"	Kosar *et al.,* 2004
	M. "Native Wilmet"	Kosar *et al.,* 2004
	M. × piperita L.	Misan *et al.,* 2011
		Dorman *et al.,* 2009, 2003
		Reichling *et al.,* 2008
		Fecka and Turek, 2007
		Zgorka *et al.,* 2001
	M. pulegium L.	Fatiha *et al.,* 2015
		Proestos *et al.,* 2005
	M. rotundifolia Huds.	Fatiha et al., 2015
		Marin Pares, 1983
	M. spicata L.	Fatiha *et al.,* 2015
		Papageorgiou et al., 2008a
		Kivilompolo and Hyotylainen, 2007
		Wang *et al.,* 2004
		Dorman *et al.,* 2003
		Janicsak *et al.,* 1999
Caffeic acid glucuronide isomer	*M. pulegium* L.	Taamalli *et al.,* 2015
Chlorogenic acid	*M. longifolia* (L.) L.	Benedec *et al.,* 2013
	M. × piperita L.	Misan *et al.,* 2011
	M. pulegium L.	Fatiha *et al.,* 2015
		Taamalli *et al.,* 2015
		Kivilompolo and Hyotylainen, 2007
	*M. × rotundifolia (*L.) Huds.	Kivilompolo and Hyotylainen, 2007
	M. spicata L.	Igoumenidis *et al.,* 2016
		Fatiha *et al.,* 2015
	M. viridis var. crispa	Benedec *et al.,* 2013
Didehydro-salvianolic acid	*M. longifolia* (L.) L.	Krzyzanowska *et al.,* 2011
	M. × piperita L.	Krzyzanowska *et al.,* 2011
Isosalvianolic acid	*M. pulegium* L.	Taamalli *et al.,* 2015
Lithospermic acid	*M. haplocalyx* Briq.	She *et al.,* 2010
	M. × piperita L.	Fecka and Turek, 2007

	M. pulegium L.	Taamalli *et al.,* 2015
		She *et al.,* 2010
Lithospermic acid B	*M. haplocalyx* Briq.	She *et al.,* 2010
Magnesium lithospermate B	*M. haplocalyx* Briq.	She *et al.,* 2010
Nepetoidin A/B	*M. aquatica* L.	Grayer *et al.,* 2003
	M. longifolia (L.) L.	Grayer *et al.,* 2003
	M. × villosa Huds.	Grayer *et al.,* 2003
Rosmarinic acid	*M. aquatica* L.	Shen *et al.,* 2011
		Kosar *et al.,* 2004
	M. aquatica ×	Shen *et al.,* 2011
	M. suaveolens	
	M. arvensis L.	Salin *et al.,* 2011
		Kosar *et al.,* 2004
		Dorman *et al.,* 2003
	M. australis R. Br.	Tang *et al.,* 2016
	M. canadensis L.	Shen *et al.,* 2011
		Shan *et al.,* 2005
	M. × dalmatica Tausch	Dorman *et al.,* 2003
	M. dumetorum	Aksit *et al.,* 2014
	M. gracilis Sole	Shen *et al.,* 2011
	M. haplocalyx Briq.	She *et al.,* 2010
		Dorman *et al*., 2003
	M. longifolia (L.) L.	Shen *et al.,* 2011
	M. "Morocco"	Kosar *et al.,* 2004
	M. "Native Wilmet"	Kosar *et al.,* 2004
	M. × piperita L.	Krzyzanowska *et al.,* 2011
		Misan *et al.,* 2011
		Shen *et al.,* 2011
		Dorman *et al.,* 2009, 2003
		Fecka and Turek, 2007
		Kosar *et al.,* 2004
		Zgorka *et al.,* 2001
	M. pulegium L.	Fatiha *et al.,* 2015
		Taamalli *et al.,* 2015
	M. × rotundifolia (L.) Huds.	Fatiha *et al.,* 2015
	M. × smithiana R. Graham	Shen *et al.,* 2011
	M. spicata L.	Fatiha *et al.,* 2015
		Shen *et al.,* 2011
		Papageorgiou *et al.,* 2008a
		Kivilompolo and Hyotylainen, 2007
		Kosar *et al.,* 2004
		Wang *et al.,* 2004
		Dorman *et al.,* 2003
		Janicsak *et al.,* 1999
	M. × villosa Huds.	Shen *et al.,* 2011

Cis-Salvianolic acid J	*M. haplocalyx* Briq.	She *et al.,* 2010
Salvianolic acid B	*M. pulegium* L.	Taamalli *et al.,* 2015
Salvianolic acid C	*M. pulegium* L.	Taamalli *et al.,* 2015
Salvianolic acid E	*M. pulegium* L.	Taamalli *et al.,* 2015
Salvianolic acid H	*M. pulegium* L.	Taamalli *et al.,* 2015
Salvianolic acid I	*M. pulegium* L.	Taamalli *et al.,* 2015
Salvianolic acid L	*M. × piperita* L.	Krzyzanowska *et al.,* 2011
	M. longifolia (L.) L.	Krzyzanowska *et al.,* 2011
Sodium lithospermate B	*M. haplocalyx* Briq.	She *et al.,* 2010
	Other organic acids	
Caftaric acid	*M. longifolia* (L.) L.	Benedec *et al.,* 2013
	M. viridis var. crispa	Benedec *et al.,* 2013
Cinnamic acid	*M. × piperita* L.	Rita and Animesh *et al.,* 2011
	M. spicata L.	Igoumenidis *et al.,* 2016
p-Coumaric acid	*M. longifolia* (L.) L.	Benedec *et al.,* 2013
	M. pulegium L.	Fatiha *et al.,* 2015
		Taamalli *et al.,* 2015
	M. × rotundifolia (L.) Huds.	Fatiha *et al.,* 2015
		Marin Pares, 1983
	M. spicata L.	Igoumenidis *et al.,* 2016
		Fatiha *et al.,* 2015
		Kivilompolo and Hyotylainen, 2007
	M. viridis var. crispa	Benedec *et al.,* 2013
Dihydroxybenzoic acid hexoside	*M. pulegium* L.	Taamalli *et al.,* 2015
Ferulic acid	*M. longifolia* (L.) L.	Benedec *et al.,* 2013
	M. pulegium L.	Proestos *et al.,* 2005
	M. × rotundifolia (L.) Huds.	Marin Pares, 1983
	M. spicata L.	Igoumenidis *et al.,* 2016
		Papageorgiou *et al.,* 2008a
		Kivilompolo and Hyotylainen, 2007
	M. viridis var. crispa	Benedec *et al.,* 2013
Gallic acid	*M. spicata* L.	Igoumenidis *et al.,* 2016
		Papageorgiou *et al.,* 2008a
		Kivilompolo and Hyotylainen, 2007
		Proestos *et al.,* 2005
Gentisic acid	*M. × piperita* L.	Zgorka *et al.,* 2001
Hydroxybenzoic acid	*M. × piperita* L.	Zgorka *et al.,* 2001
	M. pulegium L.	Fatiha *et al.,* 2015
	M. × rotundifolia (L.) Huds.	Marin Pares, 1983
	M. spicata L.	Igoumenidis *et al*., 2016
		Fatiha *et al.,* 2015
Oleanolic acid	*M. aquatica* L.	Shen *et al.,* 2011
	M. aquatica ×	Shen *et al.,* 2011

	M. suaveolens	
	M. canadensis L.	Shen *et al.,* 2011
	M. gracilis Sole	Shen *et al.,* 2011
	M. longifolia (L.) L.	Shen *et al.,* 2011
	M. spicata L.	Igoumenidis *et al.,* 2016
		Shen *et al.,* 2011
	M. × smithiana R. Graham	Shen *et al.,* 2011
	M. suaveolens Ehrh.	Shen *et al.,* 2011
	M. × villosa Huds.	Shen *et al.,* 2011
Phloretic acid	*M. spicata* L.	Igoumenidis *et al.,* 2016
Protocatechuic acid	*M. × piperita* L.	Zgorka *et al.,* 2001
	M. spicata L.	Igoumenidis *et al.,* 2016
Sinapic acid	*M. longifolia* (L.) L.	Benedec *et al.,* 2013
	M. spicata L.	Igoumenidis *et al.,* 2016
	M. viridis var. crispa	Benedec *et al.,* 2013
Syringic acid	*M. pulegium* L.	Taamalli *et al.,* 2015
	M. spicata L.	Igoumenidis *et al.,* 2016
		Kivilompolo and Hyotylainen, 2007
Syringic acid hexoside	*M. aquatica* L.	Shen *et al.,* 2011
	M. aquatica ×	Shen *et al.,* 2011
	M. suaveolens	
	M. canadensis L.	Shen *et al.,* 2011
	M. gracilis Sole	Shen *et al.,* 2011
	M. longifolia (L.) L.	Shen *et al.,* 2011
	M. spicata L.	Igoumenidis *et al.,* 2016
		Shen *et al.,* 2011
	M. × smithiana R. Graham	Shen *et al.,* 2011
	M. suaveolens Ehrh.	Shen *et al.,* 2011
	M. × villosa Huds.	Shen *et al.,* 2011
Vanillic acid	*M. pulegium* L.	Taamalli *et al.,* 2015
	M. × piperita L.	Proestos *et al.,* 2005
	M. spicata L.	Zgorka *et al.,* 2001
		Zgorka *et al.,* 2001
		Igoumenidis *et al.,* 2016
		Papageorgiou *et al.,* 2008a
		Kivilompolo and Hyotylainen, 2007
Vanillic acid hexose	*M. pulegium* L.	Taamalli *et al.,* 2015
	Flavones	
Acacetin	*M. arvensis* L.	Salin *et al.,* 2011
Acacetin-acetylglucoside-rhamnoglycoside	*M. arvensis* L.	Salin *et al.,* 2011
Acacetin rutinoside	*M. pulegium* L.	Taamalli *et al.,* 2015
		Salin *et al.,* 2011
Apigenin	*M. × piperita* L.	Misan *et al.,* 2011

		Zaidi *et al.,* 1998
	M. aquatica L.	Kosar *et al.,* 2004
	M. arvensis L.	Dorman *et al.,* 2003
	M. australis R. Br.	Tang *et al.,* 2016
	M. longifolia (L.) L.	Benedec *et al.,* 2013
	M. pulegium L.	Fatiha *et al.,* 2015
		Taamalli *et al.,* 2015
		Proestos *et al.,* 2005
		Zaidi *et al.,* 1998
	M. rotundifolia L. Huds.	Fatiha *et al.,* 2015
		Marin Pares, 1983
	M. spicata L.	Bimakr *et al.,* 2011
		Dorman *et al.,* 2003
	M. viridis var. crispa	Benedec *et al.,* 2013
Apigenin-5-*O*-glucoside Apigenin-4`-*O*-glucoside	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Apigenin-7-*O*-rutinoside	*M. aquatica* L.	Kosar *et al.,* 2004
	M. arvensis L.	Kosar *et al.,* 2004
		Dorman *et al.,* 2003
	M. × dalmatica Tausch	Dorman *et al.,* 2003
	M. dumetorum	Aksit *et al.,* 2014
	M. haplocalyx Briq.	Dorman *et al.,* 2003
	M. "Morocco"	Kosar *et al.,* 2004
	M. "Native Wilmet"	Kosar *et al.,* 2004
	M. × piperita L.	Reichling *et al.,* 2008
		Fecka and Turek, 2007
		Kosar *et al.,* 2004
		Dorman *et al.,* 2003
		Inoue *et al.,* 2002
		Areias *et al.,* 2001
		Guedon *et al.,* 1994
	M. spicata L.	Dorman *et al.,* 2003
	M. × verticillata L.	Kosar *et al.,* 2004
Biochanin B	*M. australis* R. Br.	Tang *et al.,* 2016
5-Desmethoxynobelitin	*M. spicata* L.	Yamamura et al., 1998
Diosmetin	*M. × rotundifolia* (L.) Huds.	Zaidi *et al.,* 1998
	M. suaveolens Ehrh.	Zaidi *et al.,* 1998
Diosmin	*M. pulegium* L.	Fatiha *et al.,* 2015
		Taamalli *et al.,* 2015
	M. × rotundifolia (L.) Huds.	Fatiha *et al.,* 2015
	M. spicata L.	Fatiha *et al.,* 2015
Ladanein	*M. × piperita* L.	Voirin *et al.,* 1999
		Zaidi *et al.,* 1998
Luteolin	*M. longifolia* (L.) L.	Benedec *et al.,* 2013

	M. pulegium L.	Fatiha *et al.,* 2015
		Taamalli *et al.,* 2015
		Proestos *et al.,* 2005
	M. × rotundifolia (L.) Huds.	Fatiha *et al.,* 2015
		Marin Pares, 1983
	M. spicata L.	Fatiha *et al.,* 2015
		Bimakr *et al.,* 2011
	M. viridis var. crispa	Benedec *et al.,* 2013
Luteolin-*O*-diclucuronide	*M. longifolia* (L.) L.	Krzyzanowska *et al.,* 2011
	M. × piperita L.	Krzyzanowska *et al.,* 2011
Luteolin-*O*-glucuronide	*M. longifolia* (L.) L.	Krzyzanowska *et al.,* 2011
	M. × piperita L.	Krzyzanowska *et al.,* 2011
		Reichling *et al.,* 2008
		Fecka and Turek, 2007
Luteolin-*O*-glucuronide-methyl	*M. longifolia* (L.) L.	Krzyzanowska *et al.,* 2011
	M. × piperita L.	Krzyzanowska *et al.,* 2011
Cirsilineol	*M. spicata* L.	Voirin *et al.,* 1999
Desmethylnobiletin	*M. × piperita* L.	Zaidi *et al.,* 1998
	M. spicata L.	Voirin *et al.,* 1999
Gardenin B	*M. aquatica* L.	Voirin *et al.,* 1999
	M. citrata	Voirin *et al.,* 1999
	M. × piperita L.	Areias *et al.,* 2001
		Voirin *et al.,* 1999
		Zaidi *et al.,* 1998
Luteolin-*O*-glucoside	*M. aquatica* L.	Kosar *et al.,* 2004
	M. arvensis L.	Kosar *et al.,* 2004
		Dorman *et al.,* 2003
	M. × dalmatica Tausch	Dorman *et al.,* 2003
	M. haplocalyx	Dorman *et al.,* 2003
	M. longifolia (L.) L.	Ghoulami *et al.,* 2001
	M. "Morocco"	Kosar *et al.,* 2004
	M. "Native Wilmet"	Kosar *et al.,* 2004
	M. × piperita L.	Krzyzanowska *et al.,* 2011
		Reichling *et al.,* 2008
		Kosar *et al.,* 2004
		Dorman *et al.,* 2003
		Inoue *et al.,* 2002
		Areias *et al.,* 2001
		Guedon and Pasquier, 1994
	M. spicata L.	Dorman *et al.,* 2003
	M. × verticillata L.	Kosar *et al.,* 2004
Luteolin-*O*-rutinoside	*M. dumetorum*	Aksit *et al.,* 2014
	M. pulegium L.	Taamalli *et al.,* 2015
Pebrellin	*M. aquatica* L.	Voirin *et al.,* 1999
	M. citrata	Voirin *et al.,* 1999

	M. × piperita L.	Areias *et al.,* 2001
		Voirin *et al.,* 1999
		Zaidi *et al.,* 1998
Salvigenin	*M. aquatica* L.	Voirin *et al.,* 1999
	M. citrata	Voirin *et al.,* 1999
	M. × piperita L.	Zaidi *et al.,* 1998
Sideritoflavone	*M. spicata* L.	Voirin *et al.,* 1999
		Yamamura *et al.,* 1998
Sorbifolin	*M. × piperita* L.	Zaidi *et al.,* 1998
	M. pulegium	Zaidi *et al.,* 1998
Thymusin	*M. × piperita* L.	Voirin *et al.,* 1999
		Zaidi *et al.,* 1998
	M. spicata L.	Voirin *et al.,* 1999
Thymonin	*M. pulegium*	Zaidi *et al.,* 1998
	M. × piperita L.	Voirin *et al.,* 1999
		Zaidi *et al.,* 1998
	M. × rotundifolia (L.) Huds.	Zaidi *et al.,* 1998
	M. spicata L.	Voirin *et al.,* 1999
		Zaidi *et al.,* 1998
		Yamamura *et al.,* 1998
		Tomas-Barberan *et al.,* 1988
Xanthomicrol	*M. × piperita* L.	Zaidi *et al.,* 1998
	Flavanones	
Eriocitrin	*M. aquatica* L.	Kosar *et al.,* 2004
	M. arvensis var. japanensis	Dorman *et al.,* 2003
	M. × dalmatica Tausch	Dorman *et al.,* 2003
	M. dumetorum	Aksit *et al.,* 2014
	M. haplocalyx Briq.	Dorman *et al.,* 2003
	M. "Morocco"	Kosar *et al.,* 2004
	M. "Native Wilmet"	Kosar *et al.,* 2004
	M. × piperita L.	Krzyzanowska *et al.,* 2011
		Dolzhenko *et al.,* 2010
		Dorman *et al.,* 2009, 2003
		Reichling *et al.,* 2008
		Fecka and Turek, 2007
		Inoue *et al.,* 2002
		Areias *et al.,* 2001
	M. × verticillata	Kosar *et al.,* 2004
Eriodictyol	*M*. "Morocco"	Kosar *et al.,* 2004
	M. "Native Wilmet"	Kosar *et al.,* 2004
	M. × piperita L.	Fecka and Turek, 2007
		Dorman *et al.,* 2003
Eriodictyol-*O*-glucoside	*M. × piperita* L.	Fecka and Turek, 2007
		Areias *et al.,* 2001

		Guedon and Pasquier, 1995
Genkwanin-5-*O*-glucoside Genkwanin-4`-*O*-glucoside Genkwanin-5-*O*-(6``-*O*-malonylglucosideI	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Hesperidin	*M. dumetorum* M. longifolia (L.) L. *M. pulegium* L. *M. × piperita* L.	Aksit *et al.,* 2014 Ghoulami *et al.,* 2001 Taamalli *et al.,* 2015 Dolzhenko *et al.,* 2010 Reichling *et al.,* 2008 Fecka and Turek, 2007 Inoue *et al.,* 2002 Areias *et al.,* 2001 Guedon and Pasquier, 1994
Isosakuranetin-*O*-rutinoside/ Isosakuranetin-*O*-neohesperidin	*M. pulegium* L.	Taamalli *et al.,* 2015
Naringenin	*M. aquatica* L. *M. australis* R. Br *M. pulegium* L. *M. × rotundifolia* (L.) Huds. *M. × piperita* L. *M. spicata* L.	Jaeger *et al.,* 2007 Tang *et al.,* 2016 Fatiha *et al.,* 2015 Proestos *et al.,* 2005 Fatiha *et al.,* 2015 Misan *et al.,* 2011 Fecka and Turek, 2007 Igoumenidis *et al.,* 2016 Fatiha *et al.,* 2015 Bimakr *et al.,* 2011
Naringenin-7-*O*-glucoside	*M. arvensis* L. *M. haplocalyx* Briq. *M. × piperita* L. *M. × verticillata* L.	Kosar *et al.,* 2004 Dorman *et al.,* 2003 Dorman *et al.,* 2003 Misan *et al.,* 2011 Fecka and Turek, 2007 Kosar *et al.,* 2004
Naringenin-7-*O*-rutinoside	*M. × piperita* L.	Dolzhenko *et al.,* 2010 Fecka and Turek, 2007 Inoue *et al.,* 2002 Guedon and Pasquier, 1994
Naringin	*M. spicata* L.	Fatiha *et al.,* 2015
Narirutin	*M. × piperita* L. *M. pulegium* L.	Dolzhenko *et al.,* 2010 Fecka and Turek, 2007 Inoue *et al.,* 2002 Guedon and Pasquier, 1994 Taamalli *et al.,* 2015
	Flavonols and dihydroflavonols	

Dimethyl-myricetin	M. pulegium L.	Taamalli *et al.,* 2015
Quercetin	*M. × piperita* L. *M. spicata* L.	Misan *et al.,* 2011 Igoumenidis *et al.,* 2016
Quercetin-3, 7-*O*-glucoside	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Isoquercitrin	*M. longifolia* (L.) L. *M. viridis var. crispa*	Benedec *et al.,* 2013 Benedec *et al.,* 2013
Jaceidin isomer	M. pulegium L.	Taamalli *et al.,* 2015
Kaempferol	*M. longifolia* (L.) L. *M. pulegium* L. *M. spicata* L. *M. suaveolens* Ehrh.	Zaidi *et al.,* 1998 Zaidi *et al.,* 1998 Igoumenidis *et al.,* 2016 Zaidi *et al.,* 1998
Kaempferol-3-*O*-glucoside	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Kaempferol-3-*O*-(6``-*O*-malonylglucoside)-7-*O*-glucoside; Kaempferol-3-*O*-(6``-*O*-malonylglucoside)-7-*O*-rhamnoside	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Kaempferol-3-*O*-rhamnoside Kaempferol-7-*O*-rhamnoside	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Kaempferol-7-*O*-rutinoside	*M. × piperita* L.	Dolzhenko *et al.,* 2010
4`-methoxykaempferol- 7-*O*-rutinoside	*M. × piperita* L.	Dolzhenko *et al.,* 2010
Kaempferol-3-*O*-sophoroside	*M. longifolia* (L.) L.	Stanisavljević *et al.,* 2012
Myricetin	*M. spicata* L.	Bimakr *et al.,* 2011
Rutin	*M. longifolia* (L.) L. *M. × piperita* L. *M. spicata* L. *M. viridis var. crispa*	Benedec *et al.,* 2013 Misan *et al.,* 2011 Fatiha *et al.,* 2015 Bimakr *et al.,* 2011 Adam *et al.,* 2009 Benedec *et al.,* 2013
Flavanols		
Catechin	*M. canadensis* L. *M. pulegium* L. *M. spicata* L.	Shan *et al.,* 2005 Taamalli *et al.,* 2015 Proestos *et al.,* 2005 Igoumenidis *et al.,* 2016 Bimakr *et al.,* 2011
Catechin-4-ol-*O*-glycopyranoside	*M. pulegium* L.	Taamalli *et al.,* 2015
Epicatechin	*M. spicata* L.	Igoumenidis *et al.,* 2016 Bimakr *et al.,* 2011
Gallocatechin isomer	*M. pulegium* L.	Taamalli *et al.,* 2015
Coumarins		

Esculetin	*M. × rotundifolia* (L.) Huds.	Dobias *et al.,* 2010
Scopoletin	*M. spicata* L.	Adam *et al.,* 2009
	Anthocyanidins	
Cyanidin	*M. × rotundifolia* (L.) Huds.	Marin Pares, 1983
Delphinidin	*M. × rotundifolia* (L.) Huds.	Marin Pares, 1983
Luteolinidin	*M. × rotundifolia* (L.) Huds.	Marin Pares, 1983
Pelargonidin	*M. × rotundifolia* (L.) Huds.	Marin Pares, 1983
Petunidin	*M. × rotundifolia* (L.) Huds.	Marin Pares, 1983
	Stilbenoids	
Resveratrol	*M. spicata L.*	Igoumenidis *et al.,* 2016
	Phenylethanoids	
Tyrosol	*M. spicata* L.	Igoumenidis *et al.,* 2016

APPENDIX 3

Main components of the *Mentha* plants essential oils (Lawrence, 2006b).

Compound	*Mentha* plants	Reference
	Hydrocarbons	
β-Caryophyllene	*M. aquatica* L.	Umemoto,1994
	M. arvensis L.	Lawrence, 1978
	M. × dumetorum Schultes	Lawrence, 1978
	M. longifolia (L.) L.	Lawrence, 1978
	M. × maximilianea F.W. Schults	Lawrence, 1978
	M. × smithiana R. Graham	Lawrence, 1978
	M. × verticillata L.	Lawrence, 1978
Germacrene D	*M. aquatica* L.	Umemoto,1994
Limonene	*M. arvensis* L.	Malingre´, 1971
	Alcohols	
Elemol	*M. aquatica* L.	Baser et al., 1999
Geraniol	*M. arvensis* L.	Malingre´, 1971
Linalool	*M. arvensis* L.	Lawrence, 1978
	M. dahurica Fisch. ex Benth.	Lawrence, 1978
	M. spicata L.	Gora and Kalemba, 1979
	M. longifolia (L.) L.	Baser et al., 1999
Menthol	*M. canadensis* L.	Ikeda *et al.,* 1971
	M. × maximilianea F.W. Schults	Lawrence, 1978
	M. × piperita L.	Lawrence, 1978
	M. × verticillata L.	Maffei, 1990
Neomenthol	*M. × gracilis* Sole	Umemoto and Nagasawa, 1978
3-Octanol	*M. arvensis* L.	Sacco and Shimizu, 1965
	M. × gracilis Sole	Lawrence, 1978
	M. × verticillata L.	Lawrence, 1978
cis-/trans-Sabinene hydrate	*M. arvensis* L.	Lawrence, 1978
	M. × dumetorum Schultes	Baser *et al.,* 1999
	M. × verticillata L.	Lawrence, 1978
α-Terpineol	*M. dahurica Fisch.* ex Benth.	Lawrence, 1978
Terpinen-4-ol	*M. aquatica* L.	Baser *et al.,* 1999
	M. arvensis L.	Tucker *et al.,* 1991
	M. spicata L.	Kuwahara *et al.,* 1979
Viridoflorol	*M. aquatica* L.	Lawrence, 1978
	Esters	
Decyl acetate	*M. × verticillata* L.	Lawrence, 1978
Dihydrocarvyl acetate	*M. × smithiana* R. Graham	Lawrence, 1978
	M. × villosa Huds.	Lawrence, 1978
1,2-Epoxyneomenthyl acetate	*M. suaveolens* Ehrh.	Lawrence, 1978
Menthyl acetate	*M. cervina* L.	Velasco-Negueruela *et al.,* 1987

	M. × dumetorum Schultes	Lawrence, 1978
	M. × maximilianea F. W. Schults	Lawrence, 1978
	M. × piperita L.	Lawrence, 1978
	M. × rotundifolia (L.) Huds.	Kokkini, 1983
	M. × verticillata L.	Maffei, 1990
Neoisomenthyl acetate	*M. pulegium L.*	Lawrence, 1978
Neomenthyl acetate	*M. diemenica* Spreng.	Brophy *et al.,* 1996
3-Octyl acetate	*M. arvensis L.*	Sacco and Shimizu, 1965
α-Terpinyl acetate	*M. × verticillata* L.	Lawrence, 1978
	Ketones	
Carvone	*M. longifolia* (L.) L.	Baser *et al.,* 1999
	M. spicata L.	Sticher and Flück, 1968
	M. suaveolens Ehrh.	De la Torre and Torres, 1977
	M. × villosa Huds.	Lawrence, 1978
	M. × smithiana R. Graham	Lawrence, 1978
cis-/*trans*-Dihydrocarvone	*M. canadensis L.*	Chou and Zhou, 1993
	M. longifolia (L.) L.	Lawrence, 1978
	M. spicata L.	Lawrence, 1978
	M. suaveolens Ehrh.	Lawrence, 1978
	M. × rotundifolia (L.) Huds.	Lawrence, 1978
	M. × villosa Huds.	Lawrence, 1978
Isomenthone	*M. canadensis* L.	Ikeda *et al.,* 1971
	M. cervina L.	Velasco-Negueruela *et al.,* 1987
	M. × dumetorum Schultes	Baser et al., 1999
	M. japonica (Miq.) Makino	Fujita and Fujita, 1970
	M. pulegium L.	Lawrence, 1978
	M. spicata L.	Murray and Lincoln*,* 1972
Menthone	*M. canadensis* L.	Ikeda et al., 1971
	M. cervina L.	Velasco-Negueruela *et al.,* 1987
	M. diemenica Spreng.	Brophy *et al.,* 1996
	M. × gracilis Sole	Ikeda *et al.,* 1963
	M. japonica (Miq.) Makino	Fujita and Fujita, 1970
	M. longifolia (L.) L.	Kapelev and Akimov, 1980
	M. × piperita L.	Kokkini, 1983
	M. pulegium L.	Lawrence, 1978
	M. requienii Benth.	Mucciarelli and Sacco, 1999
	M. spicata L.	Murray and Lincoln*,* 1972
3-Octanone	*M. arvensis* L.	Malingre´, 1971
	M. × gracilis Sole	Lawrence, 1978
	M. × verticillata L.	Lawrence, 1978
Pulegone	*M. diemenica* Spreng.	Brophy *et al.,* 1996

	M. gattefossei Maire	Fujita and Fujita, 1967
	M. × gracilis Sole	Nagasawa *et al.,* 1975a,b
	M. grandiflora Benth.	Brophy *et al.,* 1997
	M. longifolia (L.) L.	Kapelev and Akimov, 1980
	M. × piperita L.	Lawrence, 1978
	M. pulegium L.	Fujita and Fujita, 1967
	M. satureoides R. Br.	Jones and Berry-Smith, 1926
	M. suaveolens Ehrh.	Velasco-Negueruela *et al.,* 1996
Piperitenone	*M. cervina* L.	De Pascual Teresa *et al.,* 1983
	M. × gracilis Sole	Nagasawa and Umemoto, 1976
	M. longifolia (L.) L.	Calvarano and Codignola, 1976
Piperitone	*M. canadensis* L.	Ikeda *et al.,* 1971
	M. dahurica Fisch. ex Benth.	Chou and Zhou, 1993
	M. longifolia (L.) L.	Calvarano and Codignola, 1976
	M. spicata L.	Murray and Lincoln, 1972
	Ethers	
1,8-Cineole	*M. aquatica* L.	Lawrence, 1978
	M. suaveolens Ehrh.	De la Torre and Torres, 1977
	M. × maximilianea F. W. Schults	Lawrence, 1978
	M. × piperita L.	Kokkini, 1983
	M. × smithiana R. Graham	Lawrence, 1978
	M. × verticillata L.	Lawrence, 1978
Menthofuran	*M. aquatica* L.	Sticher and Flück, 1968
	M. × dumetorum Schultes	Murray and Lincoln, 1972
	M. × maximilianea F. W. Schults	Lawrence, 1978
	M. x piperita L.	Kokkini, 1983
	M. × verticillata L.	Lawrence, 1978
	Oxides	
Caryophyllene oxide	*M. aquatica* L.	Baser *et al.,* 1999
Piperitenone oxide	*M. grandiflora* Benth.	Brophy *et al.,* 1997
	M. × rotundifolia (L.) Huds.	Kokkini, 1983
	M. × villosa Huds.	Kokkini, 1983
Piperitone oxide	*M. canadensis* L.	Umemoto and Tsuneya, 1988
	M. suaveolens Ehrh.	Shimizu *et al.,* 1960
	M. × rotundifolia (L.) Huds.	Van Os and Hendriks, 1975
	M. × villosa Huds.	Kokkini, 1983

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