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THE FIRST TRULY INDEPENDENT WATCHDOG FOR THOSE
WORKING WITH NATURAL AROMATIC MATERIALS

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Towards a Melissa (aka Lemon Balm) Bibliography.

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[To be continually updated].

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Cropwatch Introduction.

This bibliography has been rapidly assembled following the initial banning by IFRA of Melissa oil from *Melissa officinalis* L. [CAS 8014-78-9] as a perfumery ingredient "...based on the absence of reports on its use as a fragrance ingredient and inadequate evaluation of possible physiological effects resulting from its use in fragrances." This ban has now been modified to a concentration restriction under IFRA's 44th Amendment (2009), citing evidence privately provided by Robertet, Grasse. A summary of this evidence has been kindly provided to Cropwatch by Catherine Gadras of Robertet, Grasse, which can be seen in the *Toxicological Considerations* section of this bibliography. You can judge for yourselves whether either the previous IFRA ban or the forthcoming IFRA restriction is justified by the sparse evidence cited. Update Sept. 2009 – further experimental details provided by Catherine Gadras of Robertet, Grasse.

Melissa oil / extracts: Biocidal Activity.

Allahverdiyev A., Duran N., Ozguven M. & Koltas S. (2004) "Antiviral activity of the volatile oils of *Melissa officinalis* L. against *Herpes simplex virus type-2*." *Phytomedicine* **11**(7-8), 657-61.
Abstract. *Melissa officinalis* L. (Lamiaceae) has been used in a variety of practical applications in medical science. Our objective in the current study was to determine the effects of the volatile oil components of *M. officinalis* on *Herpes simplex virus type 2* (HSV-2) replication in HEP-2 cells. Four different concentrations (25, 50, 100, 150 and 200 microg/ml) of volatile oils were examined. Experiments were carried out using HEP-2 cells. *M. officinalis* volatile oil was found to be non-toxic to HEP-2 cells up to a concentration of 100 micro/ml. It was, however, found to be slightly toxic at a concentration over of 100 microg/ml. The antiviral activity of non-toxic concentrations against HSV-2 was tested. The replication of HSV-2 was inhibited, indicating that the *M. officinalis* L. extract contains an anti-HSV-2 substance.

Cohen R.A., Kucera L.S., & Herrmann E.C. Jr. (1964). "Anti-viral activity of *Melissa officinalis* (Lemon Balm) extract." *Proc. Society of Experimental & Biological Medicine* **117**, 431-434.

Dikshit A. & Husain A. (1984) "Antifungal action of some essential oils against animal pathogens." *Fitoterapia* **55**(3), 171-176.

Dimitrova Z., Dimov B., Manolova N., Pancheva S., Ilieva D. & Shishkov S. (1993) "Antiherpes effect of *Melissa officinalis* L. extracts." *Acta-Microbiol-Bulg.* 1993, 2965-72

Friedman M., Henika P.R., Levin C.E. & Mandrell R.E. (2004) "Antibacterial activities of plant essential oils and their components against *Escherichia coli* O157:H7 and *Salmonella enterica* in apple juice." *J Agric Food Chem.* **52**(19), 6042-8. [Abstract](#). We evaluated 17 plant essential oils and nine oil compounds for antibacterial activity against the foodborne pathogens *Escherichia coli* O157:H7 and *Salmonella enterica* in apple juices in a bactericidal assay in terms of % of the sample that resulted in a 50% decrease in the number of bacteria (BA(50)). The 10 compounds most active against *E. coli* (60 min BA(50) range in clear juice, 0.018-0.093%) were carvacrol, oregano oil, geraniol, eugenol, cinnamon leaf oil, citral, clove bud oil, lemongrass oil, cinnamon bark oil, and lemon oil. The corresponding compounds against *S. enterica* (BA(50) range, 0.0044-0.011%) were Melissa oil, carvacrol, oregano oil, terpineol, geraniol, lemon oil, citral, lemongrass oil, cinnamon leaf oil, and linalool. The activity (i) was greater for *S. enterica* than for *E. coli*; (ii) increased with incubation temperature and storage time, and (iii) was not affected by the acidity of the juices. The antibacterial agents could be divided into two classes: fast-acting and slow-acting. High-performance liquid chromatography analysis showed that the bactericidal results are related to the composition of the oils. These studies provide information about new ways to protect apple juice and other foods against human pathogens.

Gochnauer T.A., Boch R. & Margetts V.J. (1979) "Inhibition of *Ascospaera apis* by citral and geraniol." *Journal invertebr. Path.* **34**, 57-61.

Herrmann E.C. Jr. & Kucera L.S.. (1967) "Antiviral substances in plants of the mint family (labiateae). II. Nontannin polyphenol of *Melissa officinalis*." *Proc Soc Exp Biol Med.* **124**(3), 869-74.

Kucera L.S., Herrmann E.C. Jr..(1967) "Antiviral substances in plants of the mint family (labiateae). I. Tannin of *Melissa officinalis*." *Proc Soc Exp Biol Med.* **124**(3), 865-9

Kucera, L.S., Cohen, R.A. and Herrmann, E.C. Jr. (1965). "Antiviral activities of extracts of the lemon balm plant." *Ann. N.Y. Acad. Sci.* **130**(1):474-82.

Kucera L.S., Cohen R.A. & Herrmann Jr. E.C. (1965) "Antiviral activities of extracts of the lemon balm plant." *Annals of the New York Academy of Sciences* **130**(1), 474-482.

Larrondo J.V., Gut M. & Calvo-Torras M.A. (1995). "Antimicrobial activity of essences from labiates." *Microbios*, **82**(332), 171-172.

Lis-Balchin M. & Deans S.G. (1997). "Bioactivity of selected plant essential oils against *Listeria monocytogens*." *Journal of Applied Microbiology* **82**(6), 759-762.

Lis-Balchin M., Deans S.G. & Eaglesham E. (1998). "Relationship between bioactivity and chemical composition of commercial essential oils." *Flav & Frag Journal* **13**(2), 98-104.

Maruzzella J.C. & Sicurella N.A. (1960). "Antibacterial activity of essential oil vapors." *Journal of the American Pharm. Association* **49**(10)

Mazzanti G, Battinelli L, Pompeo C, Serrilli A.M., Rossi R., Sauzullo I., Mengoni F. & Vullo V. (2008) "Inhibitory activity of *Melissa officinalis* L. extract on *Herpes simplex virus* type 2 replication." *Nat Prod Res* **22**(16), 1433-40. [Abstract](#). *Melissa officinalis* L. (Lamiaceae) (lemon balm) is used in folk medicine for nervous complaints, lower abdominal disorders and, more recently, for treating Herpes simplex lesions. In this work the antiviral activity of a hydroalcoholic extract of lemon balm leaves against the Herpes simplex virus type 2 (HSV-2) was assessed by the cytopathic effect inhibition assay on Vero cells (ATCC CCL-81), in comparison with acyclovir.

The cytotoxicity of the extract on Vero cells was previously tested by evaluating the cellular death and was confirmed by the Trypan blue test. Lemon balm showed to reduce the cytopathic effect of HSV-2 on Vero cells, in the range of non-toxic concentrations of 0.025-1 mg mL⁻¹ (with reference to the starting crude herbal material). The maximum inhibiting effect (60%) was obtained with 0.5 mg mL⁻¹. The viral binding assay showed that the extract does not prevent the entry of HSV-2 in the cells, thus suggesting a mechanism of action subsequent to the penetration of the virus in the cell. The extract was also chemically characterised by NMR and HPLC analysis; it showed to contain cinnamic acid-like compounds, mainly rosmarinic acid (4.1% w/w). Our experiments support the use of lemon balm for treating Herpes simplex lesions and encourage clinical trials on this medicinal plant.

Mikus J. , Harkenthal M. , Steverding D. & Reichling J. (2000). "In vitro effect of essential oils and isolated mono- and sesquiterpenes on *Leishmania major* and *Trypanosoma brucei*." *Planta Medica* **66**(4), 366-368.

Mose J.R. & Lukas G. (1957). "Studies on the antibacterial action of some ethereal oils and their ingredients." *Arzneimittel-Forsch.* **11**, 687-692.

Mimica-Dukic N., Bozin B., Sokovic M. & Simin N. (2004) "Antimicrobial and antioxidant activities of *Melissa officinalis* L. (Lamiaceae) essential oil." *J. Agric. Food Chem.* **52** (9), 2485–2489. [Abstract](#). with the effects on lipid peroxidation (LP) of *Melissa officinalis* essential oil. The chemical profile of essential oil was evaluated by the means of gas chromatography–mass spectrometry (GC-MS) and thin-layer chromatography (TLC). RSC was assessed measuring the scavenging activity of essential oil on the 2,2-diphenyl-1-picrylhydrazyl (DPPH•) and OH• radicals. The effect on LP was evaluated following the activities on Fe²⁺/ascorbate and Fe²⁺/H₂O₂ systems of induction. The antimicrobial activity was tested against 13 bacterial strains and six fungi. The examined essential oil exhibited very strong RSC, reducing the DPPH radical formation (IC₅₀ = 7.58 µg/mL) and OH radical generation (IC₅₀ = 1.74 µg/mL) in a dose-dependent manner. According to the GC-MS and TLC (dot-blot techniques), the most powerful scavenging compounds were monoterpene aldehydes and ketones (neral/geranial, citronellal, isomenthone, and menthone) and mono- and sesquiterpene hydrocarbons (E-caryophyllene). Very strong inhibition of LP, particularly in the Fe²⁺/H₂O₂ system of induction (94.59% for 2.13 µg/mL), was observed in both cases, also in a dose-dependent manner. The most effective antibacterial activity was expressed on a multiresistant strain of *Shigella sonnei*. A significant rate of antifungal activity was exhibited on *Trichophyton* species.

Munné-Bosch S. & Alegre L. (2000) "The significance of β-carotene, α-tocopherol and the xanthophyll cycle in droughted *Melissa officinalis* plants." *Australian Journal of Plant Physiology* **27**(2) 139 - 146. [Abstract](#). Diurnal variations in pigment composition, α-tocopherol and photosynthesis were measured during the summer drought and recovery after autumn rainfalls in *Melissa officinalis* L. grown under Mediterranean climate. Summer drought caused a drastic decrease in relative water content and water potential of leaves to ca 35% and –3 MPa respectively, indicative of severe stress. Chlorophyll levels decreased progressively in drought, associated with the inability to increase total carotenoids, and especially β-carotene. In contrast, α-tocopherol increased by ca 60% in response to drought and showed a significant decrease at midday in severely stressed plants. The intrinsic efficiency of PSII photochemistry remained unchanged at predawn throughout the experiment and decreased up to ca 65% in plants exposed to the interaction of high light and drought, associated with an enhanced de-epoxidation state of the xanthophyll cycle. Although droughted *M. officinalis* plants showed a significant decrease in the endogenous levels of photosynthetic pigments, the antioxidant function of α-tocopherol and the dissipation of excess excitation energy by the xanthophyll cycle may help to avoid irreversible damage to the photosynthetic apparatus.

Schnitzler P, Schuhmacher A., Astani A. & Reichling J. (2008) "*Melissa officinalis* oil affects infectivity of enveloped herpesviruses." *Phytomedicine*. **15**(9), 734-40. [Abstract](#). Extracts and essential oils of medicinal plants are increasingly of interest as novel drugs of antimicrobial and antiviral agents, since herpes simplex virus (HSV) might develop resistance to commonly used

antiviral agents. *Melissa officinalis* essential oil was phytochemically examined by GC-MS analysis, its main constituents were identified as monoterpenaldehydes citral a, citral b and citronellal. The antiviral effect of lemon balm oil, the essential oil of *Melissa officinalis*, on herpes simplex virus was examined. The inhibitory activity against herpes simplex virus type 1 (HSV-1) and *herpes simplex* virus type 2 (HSV-2) was tested in vitro on monkey kidney cells using a plaque reduction assay. The 50% inhibitory concentration (IC50) of balm oil for herpes simplex virus plaque formation was determined at high dilutions of 0.0004% and 0.00008% for HSV-1 and HSV-2, respectively. At noncytotoxic concentrations of the oil, plaque formation was significantly reduced by 98.8% for HSV-1 and 97.2% for HSV-2, higher concentrations of lemon balm oil abolished viral infectivity nearly completely. In order to determine the mode of antiviral action of this essential oil, time-on-addition assays were performed. Both herpes viruses were significantly inhibited by pretreatment with balm oil prior to infection of cells. These results indicate that Melissa oil affected the virus before adsorption, but not after penetration into the host cell, thus lemon balm oil is capable of exerting a direct antiviral effect on herpes viruses. Considering the lipophilic nature of lemon balm essential oil, which enables it to penetrate the skin, and a high selectivity index, *Melissa officinalis* oil might be suitable for topical treatment of herpetic infections.

Wolbling R.H. & Leonhardt K. (1994) "Local therapy of herpes simplex with dried extract from *Melissa officinalis*" *Phytotherapy* **1**. 25-31.

Melissa oil / extracts: Botany / Agriculture.

The genus *Melissa* comprises several species of perennial herbs, including:

***Melissa axillaris* (Benth.) Bakh.f.**

***Melissa bicornis* Klokov**

***Melissa flava* Benth. ex Wall.**

***Melissa officinalis* L.**

***Melissa romana* Miller**

***Melissa yunnanensis* C.Y.Wu & Y.C.Huang**

Some seventy or more individual species of *Melissa* have been described in the literature, but most of these are synonyms for previously identified species. *M. romana* was previously considered a subspecies of *M. officinalis*, but Pignatti (1982) classified it as a separate species based on studies by Montelucci (through Miceli *et al.* (2004). As previously mentioned by Cropwatch, there is some small commercial production of *Melissa romana* essential oil, estimated at 30 Kg/annum.

***Melissa officinalis* L. is an upright bushy perennial herb with small white or yellowish flowers and fragrant lemon-flavored leaves. It is native to S. Europe & N. Africa, and various subspecies are known:**

***Melissa officinalis* L. subsp. *altissima* (Sibth. & Sm.) Arcang**

***Melissa officinalis* L. subsp. *inodora* (Bornm.) Bornm.**

***Melissa officinalis* L. subsp. *officinalis*.**

As far as Cropwatch can establish, *Melissa officinalis* L. subsp. *officinalis* is the species most commonly cultivated for essential oil; the compositions of essential oils from other subspecies are markedly different.

Binder G. & Abou M.A.A. (2000). "Regeneration of plants and production of volatiles from callus cultures of *Melissa officinalis* L. 5. Investigations on the subspecies *altissima*." *Journal of Applied Botany*. **74**(1-2): 26-31.

Burgett, M. (1980) "The use of lemon balm (*Melissa officinalis*) for attracting honeybee swarms." *Bee World*. **61**: 44-46.

Ceylan, A., Bayram E., Kaya N. & Otan H. (1994) "Ege Bölgesi *Melissa officinalis* L., *Origanum onites* L. ve *Salvia triloba* L. Turlerinde Kemotiplerin Belirlenmesi ve Kulturu Uzerinde Araştırma, TÜBÜTAK Tarm ve Ormancılık Arastirma Grubu, Proje No: TOAG-788, Sonuc Raporu.

Corsi G, Morelli I, Pagni AM, Catalano S. (1979) "Osservazioni morfologiche, isto-anatomiche, cariologiche e fitochimiche su *Melissa officinalis* s.l. (Lamiaceae). (Morphological, histo-anatomical, caryological and phytochemical observations about *Melissa officinalis* s.l. (Lamiaceae).)" *Atti Soc. Tosc. Sci. Nat., Mem. B.* **86**. 331 – 353.

Corsi G., Morelli I. & Pagni A.M. (1980) "Studio cariologico anatomico e fitochimico su *Melissa officinalis* L. ssp. *officinalis* e *Melissa officinalis* L. ssp. *altissima* (Sibth. et Sm.) Arcangeli." *Giorn. Bot. Ital.* **114**. (3 - 4): 98 (1980) - Congresso Sociale 1979, Palermo, 3rd - 6th Ottobre. Anatomy and morphology, Chemotaxonomy.

Dafni H., Lensky Y. & Fahn A. (1988) "Flower and nectar characteristics of nine species of Labiatae and their influence on honeybee visits." *Journal of Apicultural Research* **27**(2), 103-114. **Abstract.** The anatomy of the nectary, the relative amount of nectar secreted, the composition of the nectar and its sugar concentration, were studied in 9 species of the family, Labiatae (*Coridothymus capitatus*, *Melissa officinalis*, *Phlomis viscosa*, *Rosmarinus officinalis*, *Salvia fruticosa*, *S. hierosolymitana*, *S. judaica*, *Satureja thymbra*, *Stachys aegyptiaca*). The visiting rate of the honeybees to the various species was investigated. The nectar is secreted from the asymmetrically thick, disc-like nectary, through modified stomata. These occur on the thicker side of the nectary only. There is a correlation between the volume of the nectary and the amount of nectar secreted. The larger the nectary, the more nectar it secretes. No correlation was found between the type of vascular tissue (phloem, xylem) and the sugar concentration in the nectar. *Rosmarinus officinalis* and *Coridothymus capitatus* were the species most frequently visited by honeybees. The quantitative relationship between sucrose, glucose and fructose differed in the various species examined.

Gorlachova Z.S. (2000) "Vnutrishnovydova minlyvist deyakykh morfolohichnykh oznak *Melissa officinalis* L. (Lamiaceae Lindl.) v umovakh introduktsiyi. (The interspecific variation of some morphological features in *Melissa officinalis* L. (Lamiaceae Lindl.) under the conditions of introduction.)" *Ukr. Bot. Zhurn.* **57** (4): 409-414.

Harshavardhan P.G., Vasundhara M., Sirnivasappa K.N., Biradar S.L., Rao G.G.E. & Gayithri H.N. (2005) "Effect of spacing and integrated nutrient management on biomass and oil yield of *Melissa officinalis*." *J. Indian Perfum.* **49**, 349-354. .

Iauk L., Lo Bue A.M., Milazzo I., Rapisarda A. & Blandino G. (2003) "Antibacterial activity of medicinal plant extracts against periodontopathic bacteria." *Phytotherapy Research* **17**(6), 593-604. **Abstract.** This study was performed to evaluate the antibacterial activity of *Althaea officinalis* L. roots, *Arnica montana* L. flowers, *Calendula officinalis* L. flowers, *Hamamelis virginiana* L. leaves, *Illicium verum* Hook. fruits and *Melissa officinalis* L. leaves, against anaerobic and facultative aerobic periodontal bacteria: *Porphyromonas gingivalis*, *Prevotella* spp., *Fusobacterium nucleatum*, *Capnocytophaga gingivalis*, *Veilonella parvula*, *Eikenella corrodens*, *Peptostreptococcus micros* and *Actinomyces odontolyticus*. The methanol extracts of *H. virginiana* and *A. montana* and, to a lesser extent, *A. officinalis* were shown to possess an inhibiting activity (MIC 2048 mg/L) against many of the species tested. In comparison, *M. officinalis* and *C. officinalis* extracts had a lower inhibiting activity (MIC 2048 mg/L) against all the tested species with the exception of *Prevotella* sp. *Illicium verum* methanol extract was not very active though it had a particular good activity against *E. corrodens*. The results suggest the use of the alcohol extracts of *H. virginiana*, *A. montana* and *A. officinalis* for topical medications in periodontal prophylactics.

Ibarra A., Feuillere N., Roller M., Lesburgere E. & Beracochea D. (2010) "Effects of chronic administration of *Melissa officinalis* L. extract on anxiety-like reactivity and on circadian and exploratory activities in mice." *Phytomedicine*. 2010 Feb 17. **Abstract.** This study aimed to

determine the effects of chronic (15 consecutive days of treatment) per os administration of *Melissa officinalis* L. extract (Cyracos((R)), Naturex) on anxiety-like reactivity in mice. As measured by HPLC, Cyracos((R)) contains significant amounts of rosmarinic acid and the triterpenoids oleanolic acid and ursolic acid, which inhibit gamma-aminobutyric acid transaminase (GABA-T) activity and increase GABA levels in the brain (Awad *et al.*, 2007; Awad *et al.*, 2009). Thus, we evaluated Cyracos((R)) use in independent groups of C57BL/6 mice with regard to anxiety-like reactivity in an elevated plus maze and an open field task. We found that Cyracos((R)) significantly reduced anxiety-like reactivity in the elevated plus maze dose-dependently, but no significant effect was observed in the open field task. Parallel experiments in independent groups of mice showed that the Cyracos((R)) dose at which it exerted anxiolytic-like effects in the elevated plus maze did not alter exploratory or circadian activities. Therefore, our results demonstrate that Cyracos((R)) has anxiolytic-like effects under moderate stress conditions and does not alter activity levels.

Koch H. I., Schultze W., *et al.* (1985). "Investigations on callus cultures of *Melissa officinalis*: 2. Volatile diterpene hydrocarbons in undifferentiated static cultures." *Zeitschrift Fuer Naturforschung Section C Biosciences* **40**(1-2): 13-20.

Kordana S., Mordalski R. & Zalecki R. (1997). „Effect of amount of sown seeds, term of herb harvesting and fertilization on herb crop and quality of lemon balm (*Melissa officinalis* L.).” *Herba Pol.* **43**. 135-144.

Maia V. C. (date?) "A new species of *Clinodiplosis kieffer* (Diptera, Cecidomyiidae) associated with *Melissa officinalis* Linnaeus (Labiatae) in Brazil." *Revista Brasileira de Zoologia* **10**(4): 695-697.

Meszaros A., Bellon A. *et al.* (1999). "Micropropagation of lemon balm." *Plant Cell Tissue and Organ Culture* **57**(2): 149-152.

Micelli A., Negro C. & Tommasi L. (2004?) "Essential oil of *Melissa romana* (Miller) Wild grown in Southern Italy". - see www.sibv.it/congressi/2004/miceli2_2004.pdf

Munoz L.M., Beato M.T.A. & Bobillo M.T.S.. (1998-99) "Plantas medicinales Espanolas - *Melissa officinalis* L. (Labiatae). (Melisa). [Spanish medicinal plants. *Melissa officinalis* L. (Melissa, cure-all).]" *Bol. Soc. Broteriana* **69**, 89-99.

Munne-Bosch. S. & Alegre L. (1999). "Role of dew on the recovery of water-stressed *Melissa officinalis* L. plants." *Journal of Plant Physiology*. **154**(5-6): 759-766.

Putievsky E., Raviv M., *et al.* (1983). "Development and regeneration ability of lemon balm (*Melissa officinalis*) and marjoram (*Marjorana hortensis*) on various media." *Biological Agriculture & Horticulture* **1**(4): 327-334.

Rey C. (1996) "Field seeding compared to planting of lemon balm (*Melissa officinalis* L.)." *Revue Suisse de Viticulture, d'Arboriculture et d'Horticulture*. **28** (6), 361-366.

Sari A.O & Ceylan A. (2006) *Turk J Agric For* **26** (2002) 217-224 [Abstract](#). Eleven lemon balm (*Melissa officinalis* L.) populations originating from different sources in Turkey and European countries were investigated in two ecologically different locations, Menemen and BozdaŰ, in the Aegean region of Turkey over three years to determine the populations having high quality and yield. There were significant variations between locations, years and populations in terms of yield and quality characters. The ecology was highly suitable in Menemen for growing lemon balm successfully and almost all yield and quality characters in Menemen were significantly higher than those in BozdaŰ. The plant height, green herb yield, drug leaves yield and essential oil rate over populations and years were 47.58 cm, 2869 kg.ha⁻¹, 496.9 kg.ha⁻¹ and 0.067% respectively in Menemen while they were 20.73 cm, 416 kg.ha⁻¹, 90.0 kg.ha⁻¹ and 0.036% respectively in BozdaŰ. The growth of populations in this study increased after the first year of the trials in both

locations; therefore all yields were significantly higher in the second and third years of the trials compared to the first year. The populations numbered 9 and 7, originating from Germany and Romania, had high yield and quality and they were the two most promising populations for lemon balm cultivation in the locations studied. The green herb yield, drug leaves yield and essential oil rate of population 9 over three years at Menemen were 3389 kg.ha⁻¹, 593.1 kg.ha⁻¹ and 0.085% respectively while they were 2888 kg.ha⁻¹, 565.1 kg.ha⁻¹ and 0.097% respectively for population 7. The main component of the essential oil of the lemon balm was geranial in both locations and the average geranial rate was 38.13% in Menemen and 53.68% in Bozdağ. Hence, Menemen ecologic conditions were suitable for growing lemon balm with high yield and quality. Populations originating from Romania and Ege University Agricultural Faculty (Germany) are recommended to growers.

Tantos A., Meszaros A. *et al.* (1999). "The effect of tricontanol on micropropagation of balm, *Melissa officinalis* L." *Plant Cell Reports*. **19**(1): 88-91.

Tavares A. C., Pimenta M.C. *et al.* (1996). Micropropagation of *Melissa officinalis* L. through proliferation of axillary shoots. *Plant Cell Reports* **15**(6): 441-444. [Abstract](#). Multiple shoots were differentiated in cotyledonary nodes of 10 d old seedlings of *Melissa officinalis*, cultured on MS medium supplemented with BAP (0-4 mg/l). The production of shoots was further induced in subcultures of the original explant, after the first harvest of shoots (stump), using similar conditions. The highest average number of shoots in the two inoculations was obtained with 2 mg/l of BAP: 24 axillary shoots per explant, 7 in the first inoculation and 17 in the second one. The maximum elongation of shoots was achieved with BAP at 0.2 mg/l, and higher concentrations of the hormone induced a decrease in their size. A range of BAP concentrations between 0.2–0.5 mg/l allowed the production of more shoots with a size suitable for rooting. Roots were induced in 30 d old shoots, transferred to MS medium individually supplemented with IBA or NAA (0–4 mg/l). Micropropagated plants were successfully transferred to soil.

Wolf H.T., van den Berg T., Czygan F.C., Mosandl A., Winckler T., Zündorf I. & Dingermann T. (1999) "Identification of *Melissa officinalis* Subspecies by DNA Fingerprinting." *Planta Med.* **65**(1), 83-5. [Abstract](#). The random amplified polymorphic DNA analysis (RAPD) is a method to study genetic variability within and between populations and species on the basis of the amplification of anonymous fragments from genomic DNA templates by means of polymerase chain reaction (PCR). We applied RAPD analysis in order to distinguish medicinal plant subspecies at the level of their genomes. In this study we investigated various samples of two MELISSA subspecies and showed that RAPD analysis is a fast and reliable method to distinguish subspecies on the pharmaceutical market that have been previously classified according to the distribution pattern of compounds present in the lemon balm oil.

Melissa oil / extracts: Chemistry.

Adinee J., Piri K. & Karami O. (2008) "Essential oil component in flower of Lemon Balm (*Melissa officinalis* L.)." *American Journal of Biochemistry and Biotechnology* **4**(3), 277-278. [Abstract](#). This research focuses on the analysis of the chemical composition lemon balm essential oil. The essential oil of flowers was obtained by steam distillation with a Clevenger apparatus. The chemical components of the essential oil of lemon balm were analyzed by capillary GC and GC/MS and 12 substances were identified. The flower oil contained trans-carveol (28.89%), citronellol (25.24%), δ -3-carene (5.26%), citronellal (4.9%), geraniol (2.2%), 1-octene-3-ol (2.03%) and spathulenol (2.06%). The trans-carveol in flowers was dominant among components.

Adzet T., Ponz R., Wolf E. & Schulte E. (1992) "Content and composition of *M. officinalis* oil in relation to leaf position and harvest time." *Planta Medica* **58**(6), 562-565. [Abstract](#). The content and composition of the essential oil in the leaves of *M. OFFICINALIS* L. (Lamiaceae) cultivated under Mediterranean climatic conditions were investigated. Different leaf positions and different times of harvest during the year and during the day were considered. It was shown that in the terminal leaves, the content of essential oil was more than 0.1% higher than in the others. The results obtained also indicated a variation of the oil composition. The favourable climatic and

environmental conditions of the Ebro-Delta in Spain permitted four harvests per year with a maximum of 0.4% essential oil in September. To reduce losses of volatile terpenoids, a harvest in the morning during summertime is recommended.

Adzet T, Ponz R, Wolf E, Schulte E. (1992) "Genetic variability of the essential oil content of *Melissa officinalis* L." *Planta Med* **58**(6), 558-61. [Abstract](#). The essential oil content of various populations of *MELISSA OFFICINALIS* L. (Lamiaceae), cultivated under Mediterranean climatic conditions (Ebro-Delta, Spain) has been investigated during five years of selection and improvement of the genetic plant material. Starting with an essential oil content of 0.2-0.3%, a content of more than 0.5% was obtained as a result of genetic improvement. A weak negative correlation between the content of essential oil and phenotypical growth parameters such as the number of branches per plant and height was observed. No correlation between biomass production per plant and essential oil content could be found. By the method of hybridization, *M. OFFICINALIS* synthetics with a high yield of biomass and essential oil content were selected.

Agata I, Kusakabe H, Hatano T, Nishibe S, Okuda T. (1993) "Melitric acids A and B, new trimeric caffeic acid derivatives from *Melissa officinalis*.." *Chemical & Pharmaceutical Bulletin* **41**, 1608-1611.

Basta A., Tzakou O., Couladis M. (2005) "Composition of the leaves essential oil of *Melissa officinalis* s.l. from Greece." *Flav. Frag. J.* **20**, 642-644,

Van den Berg T., Freundl E. & Czygan F.C. (1997) "*Melissa officinalis* subsp. *altissima*: characteristics of a possible adulteration of lemon balm." *Pharmazie* **52**(10), 802-808.

Caniova A. & Brandsteterova (2001) "HPLC analysis of phenolic acids in *Melissa officinalis*." *J Liquid Chromatography & Related Techniques* **24**(17), 2647-2659.

Carnat A.P., Carnat A., Fraisse D. & Lamaison J.L. (1998). "The aromatic and polyphenolic composition of lemon balm (*Melissa Officinalis* L. subsp. *Officinalis*) tea." *Pharm Acta Helvetiae* **72**, 301–305. [Abstract](#). The chemical composition of the widely used herbal tea made from lemon balm (*Melissa officinalis* L. subsp. *officinalis*) was previously unknown. The qualitative and quantitative composition of the main aromatic and polyphenolic constituents of the infusion were examined and compared with those of the leaves before and after infusion. The dried lemon balm leaves originally contained 0.32% essential oil of which citral (neral + geranial) 0.13%, total polyphenol compounds 11.8% comprising total hydroxycinnamic compounds 11.3% (rosmarinic acid 4.1%) and total flavonoid compounds 0.5%. The tea contained 10 mg/l of essential oil (extraction yield 31%) with much more citral (74% of the essential oil). It also contained large amounts of polyphenol compounds (about 1.07 g/l) corresponding to a 93% extraction yield.

Cherneva-Pancheva J. & Balinova-alpha-Tzvetkova A. (1992) "Essential oils in *Melissa* plants." *Proceedings of the 12th International Congress Essential Oil - Fragrance and Flavors*.

Chlabicz J. & Galasinski W. (1986). "The components of *Melissa officinalis* that influence protein biosynthesis in vitro." *Journal Of Pharmacy and Pharmacology* **38**(11): 791-794.

Clery R.A. (1992) *An investigation of the variability of essential oil production in plants. Ph.D. Thesis, Univ. Reading, UK.*

Cosge B., Ipek A. & Gurbuz G. (2009) "GC/MS analysis of herbage essential oil from Lemon Balms (*Melissa officinalis* L.) grown in Turkey." *Journal of Applied Biological Sciences* **3**(2), 136-139. [Abstract](#). This study was carried out to investigate the content and chemical composition of essential oil from lemon balm (*Melissa officinalis* L., Labiatae) grown in Turkey. The water-distilled essential oil from aerial parts of plants was analyzed by GC/MS. The essential oils of plant materials investigated ranged from 0.04 to 0.10%. Citronellal (36.62 to 43.78%), citral (10.10 to 17.43%), thymol (0.40 to 11.94%), and β -caryophyllene (5.91 to 7.27%) were recorded as major components. ..

Dawson B.S.W., Franich R.A. & Meder R. (1988). "Essential oil of *Melissa officinalis* L. subsp. *altissima* (Sibth. et Smith) Arcang. *Flavour and Fragrance Journal* **3**, 167-170. [Abstract](#). The essential oil derived by steam distillation of the leaves of *Melissa officinalis* L. subsp. *altissima* (Sibth. et Smith) Arcang. naturalized in New Zealand has been shown by capillary column GLC combined with mass and Fourier-transform infrared spectrometry to comprise -cubebene (39% of the oil) together with lesser amounts of other sesquiterpenes, including - and -copaene, -bourbonene, -caryophyllene, and germacrene-B and -D. Significant amounts of terpene alcohols were identified in the oil, viz. 4-terpineol, -terpineol, and - and T-cadinol, and T-muurolol, together with cis-hex-3-en-1-ol. The fragrance of the essential oil is green and woody (pine-like), with a floral (rosy) top note, probably attributable to the terpenes, terpineols and hexenol. The oil did not contain any geranial, neral, or citronellal typically found in *M. officinalis* L. subsp. *officinalis*.

Fecka I. & Turek S. (2007) "Determination of water-soluble polyphenolic compounds in commercial herbal teas from Lamiaceae: peppermint, melissa, and sage." *J Agric Food Chem.* **55**(26), 10908-17. [Abstract](#). Chromatographic techniques (HPLC and HPTLC) were used for qualitative and quantitative determination of eriocitrin, luteolin 7-O-rutinoside, luteolin 7-O-beta-glucuronide, lithospermic acid, rosmarinic acid, and methyl rosmarinate together with other known compounds in commercial herbal teas from the Lamiaceae family: peppermint leaf (*Menthae piperitae* folium), melissa leaf (*Melissae* folium), and sage leaf (*Salviae officinalis* folium). Contents of analyzed compounds in infusions, the most popular forms, were established using a C18 column with acetonitrile-water-formic acid as a mobile phase. The HPLC method was validated for linearity, precision, and accuracy. Luteolin 7-O-beta-glucuronide and lithospermic acid were identified as new *Mentha x piperita* compounds. The investigated herbal teas delivered polyphenols in high amounts, up to 182.2 mg for the infusion of one peppermint tea bag.

Gbolade A.A. & Lockwood G.B.. (1991) "Growth and production of volatile substances by *Melissa officinalis* and *Petroselinum crispum* cultures." *Fitoterapia* **62**. 237-242.

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Heitz A., Carnat A., Fraisse D., Carnat A.-P. & Jean-Louis Lamaison J.-L. (2000) "Luteolin 3'-glucuronide, the major flavonoid from *Melissa officinalis* subsp. *officinalis*." *Fitoterapia* **71**(2),201-202. [Abstract](#). Luteolin 3'-O-β- -glucuronide (1) was isolated from the leaves of *Melissa officinalis* subsp. *officinalis* and characterized by spectroscopic analysis.

Hener U., Faulhaber S., Kreis P. & Mosandl A. (1995) "On the authenticity evaluation of balm oil (*Melissa officinalis* L.)." *Pharmazie* **50**(1), 60-62.

Holla M. , Svajdenka E. , Tekel J. , Vaverkova S. & Havranek E. (1997) "Composition of the essential oil from *Melissa officinalis* L. cultivated in Slovak Republic." *Journal of Essential Oil Research* **9**(4), 481-484.

Holla M., Vaverkova S. , Tekel J. & Havranek E. (2000). "Content and composition of the oil from *Melissa officinalis* L. after application of Ridomil 72 WP." *Journal of Essential Oil Research* **12**(4), 496-498.

Ozturk A., Unlukara A., Ipek A. & Gurbuz B. (2004) "Effects of salt stress and water deficit on plant growth and essential oil content of lemon balm (*Melissa officinalis* L.)." *Pakistan Journal of Botany* **36**(4), 787-792. [Abstract](#). Studies were carried out to determine the effects of salt stress (0.25, 1.00, 2.00, 4.00 and 6.00 dSm⁻¹) and water deficiency (0, 12.5, 25.0, 37.5 and 50.0 %) on some yield components and essential oil contents of lemon balm (*Melissa officinalis* L.). The results showed moderate tolerance of lemon balm against salt with death of all plants when irrigation water had salinity level of 6 dSm⁻¹. Dry yield per plant under salt stress varied between 4.33-14.87 g with maximum yield at 1 dSm⁻¹ salt concentration. Lemon balm was found highly tolerant against water stress. Dry yield under water deficit varied from 13.05 to 19.20 g per plant. Reduction in yield was not statistically significant till 25 % water deficiency. Each increase in salt stress was accompanied with reduction in essential oil, whereas its ratio increased with each increase in water deficiency.

Hanganu D., Vlase L., Filip L., Sand C., Mirel S. & Indrei L.L. (2008) "The study of some polyphenolic compounds from *Melissa officinalis* L. (Lamiaceae)." *Rev Med Chir Soc Med Nat Iasi*. **113**(2), 525-9. [Abstract](#). We proposed the analyses of polyphenolic compounds from the *Melissa officinalis* L. (Lamiaceae) leaves obtained from Medicinal Plant Collection of USAMV Cluj-Napoca. MATERIAL AND METHOD: The study was performed by using spectrophotometric (I) and HPLC methods (II). RESULTS: The vegetal product contains 0.64% flavonoids expressed in rutoside and 8,962% phenyl-propane derivatives expressed in caffeic acid (I). HPLC analyses (II) were made after extraction of studied compounds from leaves with ethyl-ether, ethyl acetate and 1-butanol. These extracts were analyzed before and after the hydrolysis of compounds. There were identified 6 polyphenolic compounds: caftaric acid, caffeic acid, p-cumaric acid, ferulic acid, luteolin and apigenin. CONCLUSION: The extracted amount of these compounds in chosen solvents depending of their polarity.

Klimek B., Majda T., Gora J. & Patoa J. (2000) "Investigations of the essential oil from lemon catnip (*Nepeta cataria* L. var. *citriodora*) in comparison to the oil from lemon balm (*Melissa officinalis* L.)" *Herba Pol.* **46**, 226-234. 13.

Klimek B., Majda T., Gora J. & Patora J. (1998) "Investigation of essential oil and phenolic compounds of lemon balm (*Melissa officinalis* L.) cultivated in Poland." *Herba Polonica* **44**(4), 324-331.

Kreis P. & Mosandl A. (1994) "Chiral compounds of essential oils. Part XVI. Enantioselective multidimensional gas chromatography in authenticity control of balm oil (*Melissa officinalis* L.)." *Flav & Frag Journal* **9**(5), 249-256. [Abstract](#). Using enantioselective multidimensional gas chromatography (enantio-MDGC) and the column combination polyethylene glycol/heptakis (2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)- β -cyclodextrin in OV 1701-vi, the chiral monoterpenoids *cis/trans*-rose oxides, octan-3-ol, oct-1-en-3-ol, linalol, citronellal, citronellol and citronellic acid methyl ester were stereoanalysed. The method is applied to chirality evaluation of these compounds from balm oils. The enantiomeric distributions are discussed in order to assess the authenticity of this essential oil.

Lawrence B.M. (1978) "Progress in essential oils." *Perf & Flav*, **3**(4), 54-58.

Lawrence B.M. (1985) "A review of the world production of essential oils (1984)." *Perf & Flav*, **10**(5), 1-16.

Lawrence B.M. (1986) "Progress in essential oils." *Perf & Flav* **10**, 29-38.

Lawrence B.M. (1989) "Progress in essential oils." *Perf & Flav* **14**(3), 71-80.

Lawrence B.M. (1996) "Progress in essential oils." *Perf & Flav* **21**(4), 57-67.

Lawrence B.M. (1999) Progress in essential oils. *Perf & Flav* **24**(3), 47-50, 52-56, 58-60, 62, 64.

Lawrence B.M. (2008) "Progress in essential oils. Melissa or Lemon Balm oil." *Perf & Flav*. **33**, (Sept 2008), 66-70.

Mencherini T., Picerno P., Russo P., Meloni M., & Aquino R. (2009) "Composition of the fresh leaves and stems of *Melissa officinalis* and evaluation of skin irritation in a reconstituted human epidermis model. *J Nat Prod* **72**(8), 1512-25. [Abstract](#). The composition of a centrifuged product obtained from the fresh leaves and stems of *Melissa officinalis* and skin irritation in the reconstituted human epidermis (Episkin model) have been investigated in comparison to the EtOH-H₂O (1:1) extract obtained by Soxhlet from the dried plant. Two new sulfated triterpenes (1 and 2) and two ionol derivatives have been isolated for the first time from *Melissa officinalis* together with caffeic and rosmarinic acids. The structures of compounds 1 and 2 were established by analysis of their spectroscopic data. Both the centrifuged material and its major constituents neither affected cell viability nor caused the release of pro-inflammatory mediators or the decrease of trans-epithelial electrical resistance (TEER) in the reconstituted human epidermis.

Mencherini T., Picerno P., Scesa C. & Aquino R. (2007) "Triterpene, antioxidant, and antimicrobial compounds from *Melissa officinalis*." *J Nat Prod.* **70**(12), 1889-94. [Abstract](#). Six new triterpenes (1- 6) and four known compounds have been isolated from dried stems and leaves of *Melissa officinalis*. The known compounds were identified as quadranoside III, salvianic acid A, rosmarinic acid, and luteolin. The structures of compounds 1- 6 were established by analysis of spectroscopic data. Free radical scavenging and antimicrobial activities of the extracts and of rosmarinic acid, the major component, were evaluated.

Meyer, W. & Spiteller G. (1996). "Increase of caryophyllene oxide in ageing lemon balm leaves (*Melissa officinalis* L.): A consequence of lipid peroxidation?" *Zeitschrift fuer Naturforschung Section C Journal of Biosciences* **51**(9-10): 651-656.

Mrljanová M, Tekel'ová D, Felklová M, Tóth J, Musil P, Grancai D. (2001) "Comparison of the quality of *Melissa officinalis* L. cultivar Citra with *Melissas* of European origin]" *Ceska Slov Farm.* **50**(6), 299-302. [Abstract](#). Within two vegetation periods, melissas from 17 European regions and the inland cultivar Citra were examined. Melissas differed in height, foliage, and essential oil content. In the cultivating conditions under study, two collections were possible in one year. In both experimental years at the stage just before blooming, or at the onset of blooming, plants 60-80 cm in height prevailed in the set. The share of leaves in the tops was 35-70%. In the second repeated harvest, plants with newly formed sprouts reached a height of 15-35 cm and had the best foliage (60-95%). The essential oil content in the leaves at the stage just prior to blooming, or at the onset of blooming, ranged from 0.06 to 0.16% (V/m), and the maximal essential oil content was in the plants from the second harvest (0.09-0.45%). The cultivar Citra was characterized by medium height (75-80 cm), stable values of foliage (1st harvest 55-60%, 2nd harvest 70-80%), and essential oil content (1st harvest 0.13%, 2nd harvest 0.23-0.27%).

Mrljanova M., Tekel'ova M., Felklova M., Renohl V. & Toth J. (2001) "The influence of the harvest cut height on the quality of the herbal drugs *Melissa folium* & *Melissa herba*." *Planta Med.* **68**, 178-180. [Abstract](#). Variability in both the content and quality of essential oil was observed in herb and leaf drugs in dependence on the harvest cut height of lemon balm (*Melissa officinalis* L. cv. *Citra*). Three different cuts were carried out on the respective plants. The oil content in the herb was highest in the top third (0.13 % V/m), satisfactory in the herb including both the top and middle thirds (0.08 % V/m) and lowest in the whole herb (0.06 % V/m). The oil content in the leaves of the respective herbs was in the range 0.39 % - 0.14 % V/m (top third part - whole aerial part). The percentage of citrals, linalool and beta-caryophyllene in essential oil decreased in the basipetal direction, whilst the amounts of beta-caryophyllene oxide and citronellal increased in the same direction. Citrals (A and B): 55.79 % in the top third part of the herb, 48.46 % in the whole herb, 59.74 % and 56.87 % in the leaves from that parts, respectively. Similarly, beta-caryophyllene: 5.01 %, 3.87 %, 6.97 %, 5.13 %; beta-caryophyllene oxide: 17.19 %, 24.07 %, 15.64 %, 17.82 %; citronellal: 2.73 %, 5.51 %, 2.82 %, 6.44 %.

Munne, B. S., K. Schwarz, et al. (1999). alpha-Tocopherol protection against drought-induced damage in *Rosmarinus officinalis* L. and *Melissa officinalis* L. *Zeitschrift fuer Naturforschung Section C Journal of Biosciences.* **54**(9-10): 698-703.

Mulkens, A. & Kapetanidis I. (1988). "Eugenylglucoside, a new natural phenylpropanoid heteroside from *Melissa officinalis*". *Journal of Natural Products* **51**(3): 496-498.

Nhu-Trang T.T., Casabianca H., Grenier-Loustalot M.F.. (2006) "Authenticity control of essential oils containing citronellal and citral by chiral and stable-isotope gas-chromatographic analysis." *Anal Bioanal Chem.* **386**(7-8), 2141-52. [Abstract](#). Enantioselective capillary GC on a Supelco beta-DEX 225 column (heptakis(2,3-di-O-acetyl-6-O-tert-butylidimethylsilyl)-beta-cyclodextrin SPB 20poly--20% diphenyl, 80% dimethylsiloxane) and isotope-ratio mass spectrometry, coupled online with capillary GC on an HP5 column have been used for origin-specific analysis and authenticity control of essential oils, for example lemon (*Citrus limon*), lemongrass (*Cymbopogon citratus* and *Cymbopogon flexuosus*), citronella (*Cymbopogon nardus* L. -Ceylon type and *Cymbopogon winterianus* -Java type), *Litsea cubeba*, *Lippia citriodora*, lemon myrtle (*Backhousia*

citriodora), lemon gum (*Eucalyptus citriodora*), and, especially, precious lemon balm oil (*Melissa officinalis* L.). Isotope data ($\delta^{13}\text{C}$ (PDB) and $\delta^2\text{H}$ (V-SMOW)) for citral (neral + geranial) and citronellal from on-line GC-C/Py-IRMS and chiral data for citronellal in these essential oils are reported. The possibility of using these data to determine the origin of these essential oils and to detect adulteration is discussed. Principal-components analysis (PCA) of specific compounds in two essential oils of lemongrass and *Litsea cubeba* was performed as a practical statistical method for distinguishing between these two types of oil.

Munne, B. S. and L. Alegre (2000). "The significance of beta-carotene, alpha-tocopherol and the xanthophyll cycle in droughted *Melissa officinalis* plants." *Australian Journal of Plant Physiology* **27**(2): 139-146.

Nykanen I. & Nykanen L. (1986). "Flavor composition of lemon balm (*Melissa officinalis* L.) cultivated in Finland." *Lebensmittel Wissenschaft & Technologie* **19**(6): 482-485.

Oberhofer A., Nikiforov A., Buchbauer G. Jirovetz L. & Bicchi C. (1999) "Investigation of the alteration of the composition of various essential oils used in aroma lamp applications." *Flav. & Frag. J.* **14**, 293-299.

Patora J, Majda T, Góra J & Klimek B. (2003) "Variability in the content and composition of essential oil from lemon balm (*Melissa officinalis* L.) cultivated in Poland." *Acta Pol Pharm.* **60**(5), 395-400. [Abstract](#). Essential oil from a few different population of *M. officinalis* cultivated in Poland has been investigated. The percentage of essential oil ranged from 0.08 to 0.25 ml/100 g in the leaves and from 0.06 to 0.167 ml/100 g in the herb and was higher in the plant material from experimental patch than that from commercial cultivations. Comparative determinations of the essential oil in fresh and dried material showed slightly higher content of the oil in the fresh one. The analysis of the oil composition has been performed by GC and GC/MS. Great differences in the contents of citral, citronellal, linalool, nerol, geraniol beta-caryophyllene and beta-caryophyllene oxide among the populations has been found. Effect of the harvest time, drying and storage on the composition of lemon balm oil has also been studied.

Patora J & Klimek B. (2002) "Flavonoids from lemon balm (*Melissa officinalis* L., Lamiaceae)." *Acta Pol Pharm.* **59**(2), 139-43. [Abstract](#). Six flavonoids have been isolated from the leaves of lemon balm (*Melissa officinalis* L., Lamiaceae). Their structures were determined on the basis of spectral data (UV, IR, ^1H NMR, ^{13}C NMR and FAB MS) as luteolin, luteolin 7-O-beta-D-glucopyranoside, apigenin 7-O-beta-D-glucopyranoside, luteolin 7-O-beta-D-glucuronopyranoside, luteolin 3'-O-beta-D-glucuronopyranoside and luteolin 7-O-beta-D-glucopyranoside-3'-O-beta-D-glucuronopyranoside. The last three glycosides have been found in lemon balm for the first time and luteolin 7-O-beta-D-glucopyranoside-3'-O-beta-D-glucuronopyranoside is a new compound found in plants.

Pino J.A., Rosado A. & Fuentes V. (1999). "Composition of the essential oil of *Melissa officinalis* L. from Cuba." *Journal of Essential Oil Research* **11**(3), 363-364.

Shalaby *et al.* (1995) "Oil of *Melissa officinalis* L., as affected by storage & herb drying" *J. Essen. Oil Res.* **7**, 667-9. [Abstract](#). The essential oils of the fresh and dried herb of *Melissa officinalis* L., grown in Egypt were subjected to GC/MS investigation. Among the 60 constituents separated, 21 were identified. The oil consisted mainly of geranial, neral, citronellal, caryophyllene oxide, beta-caryophyllene and geraniol. Drying the herb prior to distillation did not change the qualitative composition of the oil, but the relative amount of some constituents was affected...

Sarer E. & Kökdil G. (1991). "Constituents of the essential oil from *Melissa officinalis*." *Planta Medica* **57**(1), 89-90.

Schultze W., Koenig W.A., Hilker A. & Richter R. (1995) "Lemon balm oil. Investigations of authenticity by enantioselective gas chromatography and isotope-ratio mass spectrometry." *Deutsche Apotheker Zeitung* **135**(7), 17-18, 23-24, 27-28, 31-32, 35-36, 39.

Schultze W., Zanglein W., Hose S., Kubeczka K.H., Czygan F.C. (1992) "Volatiles in flowers of Balm (*Melissa officinalis* L.)" in R. Hartley & T. Renolds (eds) *Advances in Labiatae Science* pp 357-366, Royal Botanic Gardens, Kew.

Schultze W., Zanglein A., Klose R. & Kubeczka, K.H. (1989) "Constituents of the essential oil from *Melissa officinalis*." *Planta Med.* **57**, 89-90.

Singh D. , Siddiqui M.S. & Sharma S. (1989). "Reproduction retardant and fumigant properties in essential oils against rice weevil (*Coleoptera: curculionidae*) in stored wheat." *Journal of Economic Entomology* **82**(3), 727-733.

da Silva S., Sato A., Salgueiro Lage C.L., de Silvava San Gil R.A., de Almeida Azevedo D. & Esquibel M.A. (2005) "Essential oil composition of *Melissa officinalis* L. in vitro produced under the influence of growth regulators." *J. Braz. Chem. Soc.* **16**(6b). [Abstract](#). It was investigated the effects of indole-3-acetic acid (11.42 $\mu\text{mol L}^{-1}$), benzylaminopurine (8.87 $\mu\text{mol L}^{-1}$) on essential oil composition and on the growth of *Melissa officinalis* in vitro plants. In vitro plantlets developed on MS media, showed 1.4 times in the proportion of nerol and 4.1 of geraniol, when compared with ex vitro plants. Treatments with 11.42 $\mu\text{mol L}^{-1}$ indole-3-acetic acid plus 8.87 $\mu\text{mol L}^{-1}$ benzylaminopurine led to 1.7 and 2.2 fold in proportion of nerol and geraniol, respectively in 60-day-old whole plants. These increases might be associated with the action of growth regulators which stimulate plant growth (shoot organogenesis and elongation) and delaying the alcohol oxidation to aldehydes.

Tagashira, M. & Ohtake Y. (1998). "A new antioxidative 1,3-benzodioxole from *Melissa officinalis*". *Planta Medica* **64**(6): 555-558.

Tekel J., Holla A., Vaverkova S. & Svajdenka E. (1997) „Determination of uracil herbicide residues and compounds in essential oil of *Melissa officinalis* L. in its development phases." *J. Essen. Oil Res.* **9**, 63-65.

Tittel G., Wagner H. & Bos R. (1982) [Chemical composition of the essential oil from Melissa.] *Planta Med.* **46**(10), 91-8. [Abstract](#). Different oil-samples of *MELISSA OFFICINALIS* L. were analysed by capillary GC/MS, using fused silica columns and E.I.-Mass-spectrometry. Comparing the observed mass-spectra with those of a spectral collection, 70 compounds of the oil were identified. Geranial, neral, 6-methyl-5-hepten-2-one, citronellal, geranyl-acetate, beta-caryophyllene, and beta-caryophyllene-oxide comprise about 96%. The fingerprint of the capillary gas-chromatogram permitted differentiation of the essential oil of *MELISSA OFFICINALIS*, *CYMBOPOGON WINTERIANUS* and *NEPETA CATARIA* var. *CITRIODORA*., as well as a standardisation of pharmaceutical preparations containing Melissa oil.

Topal U., Sasaki M., Goto M. & Otles S. (2008) "Chemical compositions and antioxidant properties of essential oils from nine species of Turkish plants obtained by supercritical carbon dioxide extraction and steam distillation." *International Journal of Food Sciences and Nutrition* **59**(7-8), 619-634. [Abstract](#). Chemical compositions and antioxidant activities of essential oils from nine different species of Turkish plants, namely *Melissa officinalis* L., *Rosmarinus officinalis* L., *Cuminum cyminum* L., *Piper nigrum* L., *Lavandula stoechas* spp., *Foeniculum vulgare*, *Pimpinella anisum* L., *Thymus serpyllum* and *Liquidamber orientalis* Mill., were studied. Essential oils were obtained by supercritical carbon dioxide (SCCO₂) extraction and steam distillation, and were analyzed by gas chromatography–mass spectrometry. The antioxidant activities of SCCO₂ extraction and steam distillation extracts were tested by means of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. Essential oils extracted by SCCO₂ and steam distillation showed different compositions in different species. In the DPPH assay, *R. officinalis*, *C. cyminum*, *P. anisum*, *T. serpyllum* and *L. orientalis* essential oils obtained by SCCO₂ extraction showed higher antioxidant activity than steam distillation extracts, with radical scavenging activities ranging from 87.1±0.23% to 92.0±0.34% compared with the butylated hydroxytoluene positive control (91.4±0.21%).

Vaverková S., Hollá M. & Takeš J. (2001) "[The content and quality of *Melissa officinalis* essential oil after application of Rastim 30 DKV]." *Ceska Slov Farm.* **50**(1), 46-50. [Abstract](#). The paper deals with the evaluation of the content and quality of the essential oil of *Melissa officinalis* in various leaf insertions in the course of the ontogenetic development of the plant. The quality of the drug after the administration of the preparation Rastim 30 DKV in the form of granules was not changed in comparison with control samples. The experimental work, subsequent analysis of samples, and evaluation of results led to conclusions important from the viewpoint of significant changes in the content and composition of the essential oil taking place in the plant in the course of the vegetation period.

Venskutonis P.R., Dapkevicius A. & Baranauskiene M. (1995) "Flavor composition of some lemon-like aroma herbs from Lithuania." *Devl. Food Sci.* **37A**, 833-847.

Melissa oil / extracts: General & Pharmacological Properties.

Abuhamdah S., Huang L., Elliott M.S.J., Howes M.-J.R., Ballard C., Holmes C., Burns A., Perry E.K., Francis P.T., Lees G. & Chazot P.L. (2008) "Pharmacological profile of an essential oil derived from *Melissa officinalis* with anti-agitation properties: focus on ligand-gated channels." *Journal of Pharmacy and Pharmacology* **60** (3), 377-384. [Abstract](#). A dual radioligand binding and electrophysiological study, focusing on a range of ligand-gated ion channels, was performed with a chemically-validated essential oil derived from *Melissa officinalis* (MO), which has shown clinical benefit in treating agitation. MO inhibited binding of [³⁵S] t-butylbicyclophosphorothionate (TBPS) to the rat forebrain gamma-aminobutyric acid (GABA)_A receptor channel (apparent IC₅₀ 0.040 ± 0.001 mg mL⁻¹), but had no effect on N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) or nicotinic acetylcholine receptors. Electrophysiological analyses with primary cultures of rat cortical neurons demonstrated that MO reversibly inhibited GABA-induced currents in a concentration-dependent manner (0.01-1 mg mL⁻¹), whereas no inhibition of NMDA- or AMPA-induced currents was noted. Interestingly, MO elicited a significant dose-dependent reduction in both inhibitory and excitatory transmission, with a net depressant effect on neurotransmission (in contrast to the classical GABA_A antagonist picrotoxinin which evoked profound epileptiform burst firing in these cells). The anti-agitation effects in patients and the depressant effects of MO in in-vitro we report in neural membranes are unlikely to reflect a sedative interaction with any of the ionotropic receptors examined here

Abuhamdah S. & Chazot P.L. (2008) "Lemon balm and lavender herbal essential oils: Old and new ways to treat emotional disorders?" *Current Anaesthesia & Critical Care* **19**(4), 221-226. [Abstract](#). Nature is the best chemist. Novel therapeutics derived from natural sources is clearly a worthwhile strategy and has long historic pedigree. Anxiety, depression and psychotic disorders lack ideal medications based on a limited understanding of the underlying causes of these complaints. Many of the current therapeutics display lack of efficacy and/or multiple side effects. There is growing evidence that essential oils derived from plants have useful properties in relieving emotional disorders, particularly those seen in neurodegenerative diseases. This review focuses on two essential oils derived from *Melissa* and *Lavender* plants, both of which have useful anti-agitation properties in humans, the former having an additional beneficial property of maintaining attention in patients suffering from dementias.

Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. (2003) "*Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial." *J Neurol Neurosurg Psychiatry* **74**(7), 863-6. [Abstract](#). OBJECTIVE: To assess the efficacy and safety of *Melissa officinalis* extract using a fixed dose (60 drops/day) in patients with mild to moderate Alzheimer's disease. DESIGN: A four month, parallel group, placebo controlled trial undertaken in three centres in Tehran, Iran. METHODS: Patients with mild to moderate Alzheimer's disease aged between 65 and 80 years (n = 42; 18 women, 24 men) with a score of ≥ 12 on the cognitive subscale of Alzheimer's disease assessment scale (ADAS-cog) and ≤ 2 on the clinical dementia rating (CDR) were randomised to placebo or fixed dose of *Melissa officinalis* extract. The main efficacy measures were the change in the ADAS-cog and CDR-SB scores compared with baseline. Side effects

were systematically recorded. RESULTS: At four months, *Melissa officinalis* extract produced a significantly better outcome on cognitive function than placebo (ADAS-cog: $df = 1$, $F = 6.93$, $p = 0.01$; CDR: $df = 1$, $F = 16.87$, $p < 0.0001$). There were no significant differences in the two groups in terms of observed side effects except agitation, which was more common in the placebo group ($p = 0.03$). CONCLUSIONS: *Melissa officinalis* extract is of value in the management of mild to moderate Alzheimer's disease and has a positive effect on agitation in such patients.

Ammon H.P.T. (1989) "Phytotherapeutika in der kneipp-therapie." *Therapiewoche* **39**, 117-127.

Anonymous (1999). "Lemon Balm.". *The Review of Natural Products*. St. Louis: Facts and Comparisons, 1999..

Aufmkolk M. , Ingbar J.C. , Amir S.M. , Winterhoff H. , Sourgens H. , Hesch R.D. & Ingbar S.H.I. (1984). "Inhibition by certain plant extracts of the binding and adenylate cyclase stimulatory effect of bovin thyrotropin in human thyroid membranes." *Endocrinology*, **115**(2), 527-534.

Awad R, Muhammad A, Durst T, Trudeau VL, Arnason JT. (2009) "Bioassay-guided fractionation of lemon balm (*Melissa officinalis* L.) using an in vitro measure of GABA transaminase activity." *Phytother Res*. 2009 Jan 22 [Abstract](#). A novel pharmacological mechanism of action for the anxiolytic botanical *Melissa officinalis* L. (lemon balm) is reported. The methanol extract was identified as a potent in vitro inhibitor of rat brain GABA transaminase (GABA-T), an enzyme target in the therapy of anxiety, epilepsy and related neurological disorders. Bioassay-guided fractionation led to the identification and isolation of rosmarinic acid (RA) and the triterpenoids, ursolic acid (UA) and oleanolic acid (OA) as active principles. Phytochemical characterization of the crude extract determined RA as the major compound responsible for activity (40% inhibition at 100 microg/mL) since it represented approximately 1.5% of the dry mass of the leaves. Synergistic effects may also play a role.

Ballard C.G., O'Brien J.T., Reichelt K. & Perry E.K.. (2002) "Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa." *J Clin Psychiatry*. **63**(7), 553-8. [Abstract](#). BACKGROUND: Behavioral and psychological symptoms in dementia are frequent and are a major management problem, especially for patients with severe cognitive impairment. Preliminary reports have indicated positive effects of aromatherapy using select essential oils, but there are no adequately powered placebo-controlled trials. We conducted a placebo-controlled trial to determine the value of aromatherapy with essential oil of *Melissa officinalis* (lemon balm) for agitation in people with severe dementia. METHOD: Seventy-two people residing in National Health Service (U.K.) care facilities who had clinically significant agitation in the context of severe dementia were randomly assigned to aromatherapy with Melissa essential oil (N = 36) or placebo (sunflower oil) (N = 36). The active treatment or placebo oil was combined with a base lotion and applied to patients' faces and arms twice a day by caregiving staff. Changes in clinically significant agitation (Cohen-Mansfield Agitation Inventory [CMAI]) and quality of life indices (percentage of time spent socially withdrawn and percentage of time engaged in constructive activities, measured with Dementia Care Mapping) were compared between the 2 groups over a 4-week period of treatment. RESULTS: Seventy-one patients completed the trial. No significant side effects were observed. Sixty percent (21/35) of the active treatment group and 14% (5/36) of the placebo-treated group experienced a 30% reduction of CMAI score, with an overall improvement in agitation (mean reduction in CMAI score) of 35% in patients receiving Melissa balm essential oil and 11% in those treated with placebo (Mann-Whitney U test; $Z = 4.1$, $p < .0001$). Quality of life indices also improved significantly more in people receiving essential balm oil (Mann-Whitney U test; percentage of time spent socially withdrawn: $Z = 2.6$, $p = .005$; percentage of time engaged in constructive activities: $Z = 3.5$, $p = .001$). CONCLUSION: The finding that aromatherapy with essential balm oil is a safe and effective treatment for clinically significant agitation in people with severe dementia, with additional benefits for key quality of life parameters, indicates the need for further controlled trials.

Bicchi C. , Manzin V. , D'Amato A. & Rubiolo P. (1995) "Cyclodextrin derivatives in GC separation of enantiomers of essential oil, aroma and flavour compounds." *Flavour and Fragrance Journal*, **10**(3), 127-137.

Bobin M.F., Raymond M. & Martini M.C. (1994) "UVA/UVB absorption properties of natural products." *Cosmetics and Toiletries*, **109**(11), 63-70.

Bolkent S., Yanardag R., Karabulut-Bulan O. & Yesilyaprak B. (2005) "Protective role of *Melissa officinalis* L. extract on liver of hyperlipidemic rats: a morphological and biochemical study." *J. Ethnopharmacol.* **99**(3), 391-8. [Abstract](#). In this study, the effects of *Melissa officinalis* L. extract on hyperlipidemic rats were investigated, morphologically and biochemically. The animals were fed a lipogenic diet consisting of 2% cholesterol, 20% sunflower oil and 0.5% cholic acid added to normal chow and were given 3% ethanol for 42 days. The plant extract was given by gavage technique to rats to a dose of 2 g/kg every day for 28, 14 days after experimental animals done hyperlipidemia. The degenerative changes were observed in hyperlipidemic rats, light and electron microscopically. There was a significant increase in the levels of serum cholesterol, total lipid, alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP), a significant decrease in the levels of liver tissue glutathione (GSH), a significant increase in the levels of tissue lipid peroxidation (LPO) in this group. On the other hand, the administration of *Melissa officinalis* L. extract reduced total cholesterol, total lipid, ALT, AST and ALP levels in serum, and LPO levels in liver tissue, moreover increased glutathione levels in the tissue. As a result, it was suggested that *Melissa officinalis* L. extract exerted an hypolipidemic effect and showed a protective effect on the liver of hyperlipidemic rats.

Buchbauer G. & Jirovetz L. (1994) "Aromatherapy - use of fragrances and essential oils as medicaments." *Flavour and Fragrance Journal*, **9**(5), 217-222.

Buchbauer G. (1996) "Aroma therapy. Methods of its investigation." *Deutsche Apotheker Zeitung*, **136**(35), 21-26.

Canadanović-Brunet J., Cetković G., Djilas S., Tumbas V., Bogdanović G., Mandić A., Markov S., Cvetković D. & Canadanović V. (2008) "Radical scavenging, antibacterial, and antiproliferative activities of *Melissa officinalis* L. extracts." *J Med Food*.**11**(1), 133-43. [Abstract](#). The aromatic herb *Melissa officinalis* L. can be used as an easily accessible source of natural antioxidants and as a possible food supplement and as a phytochemical. Radical scavenging, antibacterial, and antiproliferative activities of petroleum ether, chloroform, ethyl acetate, n-butanol, and water extracts of *M. officinalis* L. extracts were investigated. The results of antioxidative activity, obtained by electron spin resonance spectroscopy, confirmed that investigated extracts suppressed the formation of 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl, and lipid peroxy radicals in all investigated systems in a dose-dependent manner. The maximum DPPH and hydroxyl radical scavenging activities (SA(DPPH) = SA(OH) = 100%) were achieved in the presence of n-butanol extract at concentrations of 0.4 mg/mL and 0.5 mg/mL, respectively. The highest lipid peroxy scavenging activity (93.20%) was observed at a higher concentration (5 mg/mL) of n-butanol extract in the lipid peroxidation system. The most effective antibacterial activities were expressed by petroleum ether and ethyl acetate extracts on *Sarcina lutea*. Chloroform extract showed the strongest antiproliferative effect with 50% inhibitory concentration values of 0.09 mg/mL and 0.10 mg/mL for HeLa and MCF-7 cell lines, respectively. The present study demonstrated the high phenolic content and radical scavenging, antibacterial, and antiproliferative activities of extracts of *M. officinalis* L. originating from Serbia.

Capasso R., Savino F. & Capasso F. (2007) "Effects of the herbal formulation ColiMil on upper gastrointestinal transit in mice in vivo." *Phytotherapy Research PTR* **21**(10), 999-1101. [Abstract](#). Clinical evidence suggests that the herbal formulation ColiMil (which contains *Matricaria recutita* flowers extract, *Foeniculum vulgare* fruit extract and *Melissa officinalis* aerial parts extract) is effective in the treatment of breastfed colic in infants. Therefore the effect of this phytotherapeutic formulation and its herbal constituents on upper gastrointestinal transit was investigated in mice in vivo. Oral administration of the herbal formulation (0.4-0.8 mL/mice) dose-dependently delayed upper gastrointestinal transit. Among the herbal components, *Matricaria recutita* extract (0.89 and

1.78 mg/mouse) and *Melissa officinalis* extract (6.46 and 12.92 mg/mouse), but not *Foeniculum vulgare* (8.21 and 16.42 mg/mouse), reduced motility significantly. These results suggest that ColiMil reduces upper gastrointestinal motility in mice, with a major contribution by *Matricaria recutita* and *Melissa officinalis*. These experimental data may be important to better understand the observation that the herbal formulation ColiMil improves colic in breastfed infants.

Cerny A. & Schmid K (1999). "Tolerability and efficacy of valerian/lemon balm in healthy volunteers: a double-blind, placebocontrolled, multicentre study." *Fitoterapia* **70**, 221–228.

Coleta, M., Campos M.G., Cotrim M.D. & Proenca Cunha A. (2001). "Comparative evaluation of *Melissa officinalis* L., *Tilia europaea* L., *Passiflora edulis* Sims and *Hypericum perforatum* L. in the elevated plus maze anxiety test." *Pharmacopsychiatry* **34**, 20-21.

Dastmalchi K., Ollilainen V., Lackman P., Boije af Gennäs G., Dorman H.J., Järvinen P.P., Yli-Kauhahuoma J. & Hiltunen R. (2009) "Acetylcholinesterase inhibitory guided fractionation of *Melissa officinalis* L." *Bioorg Med Chem.* **17**(2), 867-71. [Abstract](#). The plant *Melissa officinalis* L. has been used traditionally in the treatment of cognitive dysfunction. Based on its traditional medicinal use, it was assessed for its clinical efficacy in mild to moderate Alzheimer's patients. The plant was effective in the management of the disease. Therefore, based on this result, a similar plant extract was prepared in order to be screened for bioactivities which are relevant in Alzheimer's disease therapy. The extract was recently screened for antioxidant activity and it showed a wide range of antioxidant properties. Another important bioactivity is acetylcholinesterase inhibition, which the extract was screened for in the current investigation. The extract was capable of inhibiting the enzyme in a time and dose-dependent manner. Activity of the extract at 10 min was estimated as 1.72±0.16 microg equivalents of physostigmine/mg of the extract. Acetylcholinesterase inhibitory guided fractionation of the extract was then carried out. Most of the fractions showed inhibitory activity and were more potent than the extract. The contents of the most potent fraction were identified as cis- and trans-rosmarinic acid isomers and a rosmarinic acid derivative using LC-DAD-ESI-MS and NMR methods.

Dastmalchi K., Dorman HJD., Oinenen PP., Darwin Y, Laakso I & Hiltunen R. (2008) "Chemical composition and in vitro antioxidative activity of a lemon balm (*Melissa officinalis* L.) extract." *LWT - Food Science and Technology* **41**(3), 394-400. [Abstract](#). The leaf material of lemon balm (*Melissa officinalis* L.) was extracted with 450 ml/l aqueous ethanol by medium pressure liquid–solid extraction. The total phenolic content of the extract was estimated as gallic acid equivalents by Folin–Ciocalteu reagent method and a qualitative–quantitative compositional analysis was carried out using high performance liquid chromatography coupled with photodiode array detection. The lemon balm extract contained hydroxycinnamic acid derivatives and flavonoids with caffeic acid, m-coumaric acid, eriodictyol-7-O-glucoside, naringin, hesperidin, rosmarinic acid, naringenin, hesperetin being identified based on their chromatographic behaviour and spectral characteristics. The extract was also investigated for potential in vitro antioxidant properties in iron(III) reduction, iron(II) chelation, 1,1-diphenyl-2-picrylhydrazyl, 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonate), superoxide anion and nitric oxide free-radical scavenging, and inhibition of β-carotene–linoleic acid bleaching assays. The extract demonstrated antioxidant activity in all the assays. However, it was not as potent as the positive controls except in the β-carotene–linoleic acid bleaching assay, where its activity was superior to that of gallic and caffeic acids and statistically indistinguishable from quercetin and BHA. The exceptionally high antioxidant activity and the fact that this assay is of biological relevance warrants further investigation of lemon balm extract in ex vivo and in vivo models of oxidative stress.

DeVincenzi M., Maialetti F. & Dessi M.R. (1995) "Monographs on botanical flavoring substances used in foods. Part IV." *Fitoterapia*, **66**(3), 203-210.

Dimpfel W., Pischel I & Lehnfeld R. (2004) "Effects of lozenge containing lavender oil, extracts from hops, lemon balm and oat on electrical brain activity of volunteers." *Eur J Med Res.* **9**(9), 423-31. [Abstract](#). Within a randomized double blind, placebo controlled trial the electrical activity of the human brain has been monitored using charge mode technology (Laplacian estimates) after exposure to a lozenge containing 4 different herbal preparations (lavender oil, extracts from

hops, lemon balm and oat) or a matching placebo without any active ingredients. Sixteen healthy volunteers (8 males and 8 females) were tested within a crossover design. After baseline recording each subject sucked a lozenge and 2 hours later a second one. Recording was performed immediately after finishing the lozenge and in hourly intervals thereafter. Comparison to reference periods of 10 min eyes open and 5 min eyes closed, respectively, revealed increases in alpha 1, alpha 2 and beta 1 electrical power at the electrode positions Cz, P3, T3 and T5 which were even more pronounced after a second application two hours later. Since alpha 1 changes repeatedly have been attributed to attentional states, increases of this electrical activity must be seen as indicator of a relaxational psychophysiological state. Changes in the alpha2 frequencies have been related to working memory indicating that an increase can be seen as a correlate for attenuating this circuit. Increases of beta1 activity have been seen in the presence of anxiolytic drugs including major and minor tranquilizers. The changes as observed after the application of this herbal composition are therefore in line with the idea of having induced a state of relaxation and regeneration. This interpretation suggests that one could expect from the ingestion of this lozenge to better cope with psychological and emotional stress. The data are further proof that recording computer aided quantitative EEG is a very fruitful and promising approach in psychophysiology.

Dressing H & Riemann D. (1992) "Insomnia: Are Valerian/Melissa combinations of equal value to benzodiazepine?" *Therapiewoche* **42**, 726-36.

Dressing H., Kohler S. & Muller W. (1996) "Improvement in sleep quality with a high dose valerian-melissa preparation." *Psychopharmacotherapie* **3**, 123-130.

Duke J.A. & Beckstrom-Sternberg S.M. (1994). "Acceptable levels of flavoring ingredients?" *Devl. Food Sci.* **34**, 741-757.

EMA (2007) "Community Herbal Monograph on *Melissa officinalis* L. folium." (HMPC). Doc Ref EMA/HMPC/5341/2007.

Elliott M.S.J., Abuhamdah S., Huang L., Perry E.K., Ballard C., Lees G., Chazot P.L., Holmes C., Burns A. & Francis P.T. (2006) *Alzheimer's and Dementia* **2**(3) Suppl 1, S225. .

Ersoy S., Orhan I., Turan N.N., Sahan G., Ark M. & Tosun F. (2008) "Endothelium-dependent induction of vasorelaxation by *Melissa officinalis* L. ssp. *officinalis* in rat isolated thoracic aorta." *Phytomedicine*. **15**(12), 1087-92. [Abstract](#). In the current study, vasorelaxant effect produced by the aqueous extract of *Melissa officinalis* L. ssp. *officinalis* (MOO) (Lamiaceae) and its possible mechanism in isolated rat aortic rings precontracted with phenylephrine were examined. In the first series of experiments, effect of MOO on the baseline and phenylephrine (10(-)5M) precontracted arteries was investigated, while in the second group of experiments, endothelium intact or endothelium denuded effect was determined. The agents used were N(omega)-nitro-L-arginine (L-NAME), an irreversible inhibitor of nitric oxide (NO) synthase, indomethacin (10 microM), a cyclooxygenase (COX) inhibitor, and glibenclamide (10 microM), an ATP-sensitive potassium channel blocker. The extract was found to exert a vasorelaxant effect and rosmarinic acid quantity, the characteristic compound of the plant, was analyzed by reversed-phase high-performance liquid chromatography (18.75%), and was further confirmed by LC-MS analysis giving a prominent [M(+1)] molecular ion peak at m/z 365. Total phenol amount in the extract was determined using Folin-Ciocalteu reagent (0.284 mg/mg extract). Vasorelaxant effect of the extract was entirely dependent on the presence of endothelium and was abolished by pretreatment with L-NAME, whereas pretreatment with indomethacin and glibenclamide reduced the relaxation to a minor extent. Rosmarinic acid was also tested in the same manner as the extract and was found to exert vasorelaxant effect. These results suggest that the aqueous extract of MOO vasodilates via nitric oxide pathway with the possible involvement of prostacycline and endothelium-derived hyperpolarizing factor (EDHF) pathways as well.

Ferreira A., Proença C., Serralheiro M.L. & Araújo M.E. (2006) "The in vitro screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from Portugal." *J.*

Ethnopharmacol. **108**(1), 31-7. [Abstract](#). Essential oil, ethanolic extract and decoction of 10 plant species from interior Portugal were analyzed for their activity towards acetylcholinesterase (AChE) enzyme and their antioxidant activity. Of these, *Melissa officinalis*, *Paronychia argentea*, *Sanguisorba minor*, *Hypericum undulatum* and *Malva silvestris* are used in herbal medicine, *Laurus nobilis* and *Mentha suaveolens* as condiments, and *Salvia officinalis*, *Lavandula angustifolia* and *Lavandula pedunculata* also as aromatics. *Melissa officinalis* and *Mentha suaveolens* showed AChE inhibitory capacity higher than 50% in the essential oil fraction. *Laurus nobilis*, *Hypericum undulatum*, and *Sanguisorba minor* showed a high inhibition value of AChE in the ethanolic fraction, 64% (1 mg ml⁻¹), 68% (0.5 mg ml⁻¹), and 78% (1 mg ml⁻¹), respectively. Higher values of AChE inhibitory activity were found using decoctions of *Lavandula pedunculata*, *Mentha suaveolens* and *Hypericum undulatum*, 68, 69 and 82% (at a concentration of 5mg dry plant ml⁻¹ of assay), respectively. The free radical scavenger activity was higher for the polar extracts. In the water extracts most of the plants showed values around 90%. When antioxidant activity was measured with the beta-carotene-linoleic acid assay high activity (65-95%) was also found in the water extracts. *Hypericum undulatum*, *Melissa officinalis* and *Laurus nobilis* showed both high AChE inhibitory capacity and antioxidant activity

Fisher A.A. (1975) "Patch testing with perfume ingredients." *Contact Dermatitis* **1**, 166-168.

Gazola R., Machado D., Ruggiero C., Singi G. & Alexandre M.M. (2004) "*Lippia alba*, *Melissa officinalis* and *Cymbopogon citratus*: effects of the aqueous extracts on the isolated hearts of rats." *Pharmacological Research* **50**(5), 477-480. [Abstract](#). This research was developed to evaluate the actions of the aqueous extracts of leaves of *Lippia alba*, *Melissa officinalis* and *Cymbopogon citratus* upon contractile force (CF) and cardiac rate (CR). 2. For the experiments in isolated heart, 21 male adult rats were used. The hearts were perfused according to Langendorff's method. The records of CF and CR were obtained in control and after application of the extracts. The extracts were utilized in doses: 0.038, 0.38, 3.8 and 38 mg. Results obtained were compared by statistic analyses. 3. The aqueous extracts provoked significant CR reduction and did not alter the CF. The negative CR effect may have occurred by cardiac muscarinics receptors stimulation.

Gbolade A.A. & Lockwood G.B. (1989) "The constituents of *Melissa officinalis* cell cultures" *Planta Med.* **55**. 228.

Gilsoul J.J. & Jeanfils J (1992). « Antioxidative activity of *Picea-Abies* and *Melissa-officinalis* extracts on peanut oil." *Bulletin de la Societe Botanique de France Lettres Botaniques* **139**, 35-43.

Goldschmiedt H. (1970) "Review of herbal bath preparations." *American Perfumer Cosm.* **85**, 39-42.

Guginski G, Luiz AP, Silva MD, Massaro M, Martins DF, Chaves J, Mattos RW, Silveira D, Ferreira VM, Calixto JB, Santos AR. (2009) "Mechanisms involved in the antinociception caused by ethanolic extract obtained from the leaves of *Melissa officinalis* (lemon balm) in mice." *Pharmacol Biochem Behav.* **93**(1):10-6. [Abstract](#). The present study examined the antinociceptive effect of the ethanolic extract from *Melissa officinalis* L. and of the rosmarinic acid in chemical behavioral models of nociception and investigates some of the mechanisms underlying this effect. The extract (3-1000 mg/kg), given orally (p.o.) 1 h prior to testing, produced dose-dependent inhibition of acetic acid-induced visceral pain, with ID50 value of 241.9 mg/kg. In the formalin test, the extract (30-1000 mg/kg, p.o.) also caused significant inhibition of both, the early (neurogenic pain) and the late (inflammatory pain), phases of formalin-induced licking. The extract (10-1000 mg/kg, p.o.) also caused significant and dose-dependent inhibition of glutamate-induced pain, with ID50 value of 198.5 mg/kg. Furthermore, the rosmarinic acid (0.3-3 mg/kg), given p.o. 1 h prior, produced dose-related inhibition of glutamate-induced pain, with ID50 value of 2.64 mg/kg. The antinociception caused by the extract (100 mg/kg, p.o.) in the glutamate test was significantly attenuated by intraperitoneal (i.p.) treatment of mice with atropine (1 mg/kg), mecamlamine (2 mg/kg) or l-arginine (40 mg/kg). In contrast, the extract (100 mg/kg, p.o.) antinociception was not

affected by i.p. treatment with naloxone (1 mg/kg) or D-arginine (40 mg/kg). It was also not associated with non-specific effects, such as muscle relaxation or sedation. Collectively, the present results suggest that the extract produced dose-related antinociception in several models of chemical pain through mechanisms that involved cholinergic systems (i.e. through muscarinic and nicotinic acetylcholine receptors) and the L-arginine-nitric oxide pathway. In addition, the rosmarinic acid contained in this plant appears to contribute for the antinociceptive property of the extract. Moreover, the antinociceptive action demonstrated in the present study supports, at least partly, the ethnomedical uses of this plant.

Herodez S.P., Hadolin M., Kerget M. & Knez E. "Solvent extraction study of antioxidants from Balm (*Melissa officinalis* L.) leaves." *Food Chem* **80**(2), 275-282. [Abstract](#). In the paper, the extraction of antioxidants from Balm (*Melissa officinalis* L.) leaves with ethanol is presented. Effects of particle size, amount of solvent and temperature on the extraction rates and concentrations of antioxidants in the extracts were studied and kinetics was determined. Individual antioxidants (carnosic, ursolic and oleanolic acids) were identified by high performance liquid chromatography. Results showed that the intraparticle diffusion was the rate-governing step of the extraction process. The extractions all proceeded in three stages: an initial washing stage, a fast stage and a slower stage. Experimental extraction curves were analysed with a mathematical model derived from Fick's second law, and diffusion coefficients of the antioxidants within the particles under different operating conditions in ethanol were determined.

Hohmann J., Zupko I. *et al.* (1999). "Protective effects of the aerial parts, of *Salvia officinalis*, *Melissa officinalis* and *Lavandula angustifolia* and their constituents against enzyme-dependent and enzyme-independent lipid peroxidation." *Planta Medica*. **65**(6): 576-578. [Abstract](#). The antioxidant effects of aqueous methanolic extracts from three medicinal Lamiaceae species were investigated in enzyme-dependent and enzyme-independent lipid peroxidation systems. All these extracts caused a considerable concentration-dependent inhibition of lipid peroxidation. Phenolic components present in the plant extracts were evaluated for antioxidant activity and were found effective in both tests. Their concentrations in each extract were determined by TLC-densitometry.

Huang L, Abuhamdah S, Howes MJ, Dixon CL, Elliot MS, Ballard C, Holmes C, Burns A, Perry EK, Francis PT, Lees G, Chazot PL. (2008) "Pharmacological profile of essential oils derived from *Lavandula angustifolia* and *Melissa officinalis* with anti-agitation properties: focus on ligand-gated channels." *Pharm Pharmacol*. **60**(11), 1515-22. [Abstract](#). Both *Melissa officinalis* (Mo) and *Lavandula angustifolia* (La) essential oils have putative anti-agitation properties in humans, indicating common components with a depressant action in the central nervous system. A dual radioligand binding and electrophysiological study, focusing on a range of ligand-gated ion channels, was performed with a chemically validated essential oil derived from La, which has shown clinical benefit in treating agitation. La inhibited [³⁵S] TBPS binding to the rat forebrain gamma aminobutyric acid (GABA)(A) receptor channel (apparent IC₅₀ = 0.040 +/- 0.001 mg mL(-1)), but had no effect on N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or nicotinic acetylcholine receptors. A 50:50 mixture of Mo and La essential oils inhibited [³H] flunitrazepam binding, whereas the individual oils had no significant effect. Electrophysiological analyses with rat cortical primary cultures demonstrated that La reversibly inhibited GABA-induced currents in a concentration-dependent manner (0.01-1 mg mL(-1)), whereas no inhibition of NMDA- or AMPA-induced currents was noted. La elicited a significant dose-dependent reduction in both inhibitory and excitatory transmission, with a net depressant effect on neurotransmission (in contrast to the classic GABA(A) antagonist picrotoxin which evoked profound epileptiform burst firing in these cells). These properties are similar to those recently reported for Mo. The anti-agitation effects in patients and the depressant effects of La we report in neural membranes in-vitro are unlikely to reflect a sedative interaction with any of the ionotropic receptors examined here. These data suggest that components common to the two oils are worthy of focus to identify the actives underlying the neuronal depressant and anti-agitation activities reported.

Ivanova D., Gerova D., Chervenkov T. & Yankova T. (2004) "Polyphenols and antioxidant capacity of Bulgarian medicinal plants." *Journal of Ethnopharmacology* **96**(1-2),145-150. [Abstract](#). Extracts of 21 plants used in Bulgarian phytotherapy for the treatment of respiratory, gastrointestinal and other inflammatory disorders were screened in vitro for antioxidant activity and phenolic compounds content. Plant extracts were prepared as herbal teas following the ethnic use. The water-phase TEAC (Trolox equivalent antioxidant capacity) of the teas were compared to that of the famous tea-like beverages mate, rooibos and honeybush, and to that of green and black tea, well known for their high antioxidant potential. The content of total phenolics in the teas was determined spectrometrically according to the Folin-Ciocalteu procedure and calculated as quercetin equivalents (QE). Seven Bulgarian medicinal plants were with high phenolics content and antioxidant properties: *Pulmonaria officinalis* L. (Boraginaceae) (TEAC 2.02 ± 0.14 mM/QE 673.39 ± 9.92 μ M), *Hypericum perforatum* L. (Hypericaceae) (TEAC 3.75 ± 0.14 mM/QE 881.93 ± 6.68 μ M), *Agrimonia eupatoria* L. (Rosaceae) (TEAC 3.76 ± 0.5 mM/QE 702.29 ± 6.82 μ M), *Origanum vulgare* L. (Lamiaceae) (TEAC 5.87 ± 0.2 mM/QE 1653.61 ± 11.52 μ M), *Melissa officinalis* L. (Lamiaceae) (TEAC 4.06 ± 0.31 mM/QE 1370.09 ± 41.38 μ M), *Rubus sp. diversa* (Rosaceae) (TEAC 4.23 ± 0.12 mM/QE 608.95 ± 5.95 μ M), *Cotinus coggygria* Scop. (Anacardiaceae) (TEAC 7.05 ± 0.19 mM/QE 923.33 ± 14.19 μ M). Therefore, Bulgarian herbs can be considered to be a rich source of water-soluble antioxidants and/or phenolic compounds as compared to studied foreign plants.

Kanazawa K. (1995) "Strong desmutagenicity of flavonoids against dietary carcinogen, Trp-P-2." *Environ. Mutagen Res. Commun.* **17**(1), 115-122.

Kennedy D.O., Little W., Haskell C.F. & Scholey A.B.. (2006) "Anxiolytic effects of a combination of *Melissa officinalis* and *Valeriana officinalis* during laboratory induced stress." *Phytother Res.* **20**(2), 96-102. [Abstract](#). OBJECTIVE: *Melissa officinalis* (lemon balm) and *Valeriana officinalis* (valerian) have been used both traditionally and contemporaneously as mild sedatives, anxiolytics and hypnotics. Recent research has suggested that both may attenuate laboratory induced stress. As the two herbs are most often sold in combination with each other the current study assessed the anxiolytic properties of such a combination during laboratory-induced stress. METHODS: In this double-blind, placebo-controlled, randomized, balanced cross-over experiment, 24 healthy volunteers received three separate single doses (600 mg, 1200 mg, 1800 mg) of a standardized product containing *M. officinalis* and *V. officinalis* extracts, plus a placebo, on separate days separated by a 7 day wash out period. Modulation of mood and anxiety were assessed during pre-dose and 1 h, 3 h and 6 h post-dose completions of a 20 min version of the Defined Intensity Stressor Simulation (DISS) battery. Cognitive performance on the four concurrent tasks of the battery was also assessed. RESULTS: The results showed that the 600 mg dose of the combination ameliorated the negative effects of the DISS on ratings of anxiety. However, the highest dose (1800 mg) showed an increase in anxiety that was less marked but which reached significance during one testing session. In addition, all three doses led to decrements in performance on the Stroop task module within the battery, and the two lower doses led to decrements on the overall score generated on the DISS battery. CONCLUSIONS: These results suggest that a combination of *Melissa officinalis* and *Valeriana officinalis* possesses anxiolytic properties that deserve further investigation.

Kennedy D.O. & Scholey A.B.. (2006) "The psychopharmacology of European herbs with cognition-enhancing properties." *Curr Pharm Des.* **12**(35), 4613-23. [Abstract](#). Extensive research suggests that a number of plant-derived chemicals and traditional Oriental herbal remedies possess cognition-enhancing properties. Widely used current treatments for dementia include extracts of Ginkgo biloba and several alkaloidal, and therefore toxic, plant-derived cholinergic agents. Several non-toxic, European herbal species have pan-cultural traditions as treatments for cognitive deficits, including those associated with ageing. To date they have not received research interest commensurate with their potential utility. Particularly promising candidate species include sage (*Salvia lavandulaefolia/officinalis*), Lemon balm (*Melissa officinalis*) and rosemary (*Rosmarinus officinalis*). In the case of sage, extracts possess anti-oxidant, estrogenic, and anti-inflammatory properties, and specifically inhibit butyryl- and acetyl-cholinesterase. Acute

administration has also been found to reliably improve mnemonic performance in healthy young and elderly cohorts, whilst a chronic regime has been shown to attenuate cognitive declines in sufferers from Alzheimer's disease. In the case of *Melissa officinalis*, extracts have, most notably, been shown to bind directly to both nicotinic and muscarinic receptors in human brain tissue. This property has been shown to vary with extraction method and strain. Robust anxiolytic effects have also been demonstrated following acute administration to healthy humans, with mnemonic enhancement restricted to an extract with high cholinergic binding properties. Chronic regimes of aromatherapy and essential oil respectively have also been shown to reduce agitation and attenuate cognitive declines in sufferers from dementia. Given the side effect profile of prescribed cholinesterase inhibitors, and a current lack of a well tolerated nicotinic receptor agonist, these herbal treatments may well provide effective and well-tolerated treatments for dementia, either alone, in combination, or as an adjunct to conventional treatments.

Kennedy D.O., Little W. & Scholey A.B. (2004) "Attenuation of laboratory-induced stress in humans after acute administration of *Melissa officinalis* (Lemon Balm)." *Psychosom Med.* **66**(4), 607-13. [Abstract](#). OBJECTIVE: *Melissa officinalis* (lemon balm) is contemporaneously used as a mild sedative and/or calming agent. Although recent research has demonstrated modulation of mood in keeping with these roles, no studies to date have directly investigated the effects of this herbal medication on laboratory-induced psychological stress. METHODS: In this double-blind, placebo-controlled, randomized, balanced crossover experiment, 18 healthy volunteers received two separate single doses of a standardized *M. officinalis* extract (300 mg, 600 mg) and a placebo, on separate days separated by a 7-day washout period. Modulation of mood was assessed during predose and 1-hour postdose completions of a 20-minute version of the Defined Intensity Stressor Simulation (DISS) battery. Cognitive performance on the four concurrent tasks of the battery was also assessed. RESULTS: The results showed that the 600-mg dose of *Melissa* ameliorated the negative mood effects of the DISS, with significantly increased self-ratings of calmness and reduced self-ratings of alertness. In addition, a significant increase in the speed of mathematical processing, with no reduction in accuracy, was observed after ingestion of the 300-mg dose. CONCLUSION: These results suggest that the potential for *M. officinalis* to mitigate the effects of stress deserves further investigation.

Kennedy D.O., Wake G., Savelev S., Tildesley N.T.J., Perry E.K. , Wesnes K.A. & Scholey A.B. (2003) "Modulation of mood and cognitive performance following acute administration of single doses of *Melissa Officinalis* (Lemon Balm) with human CNS nicotinic and muscarinic receptor-binding properties." *Neuropsychopharmacology* (2003) **28**, 1871–1881. [Abstract](#). *Melissa officinalis* (Lemon balm) is a herbal medicine that has traditionally been attributed with memory-enhancing properties, but which is currently more widely used as a mild sedative and sleep aid. In a previous study it was demonstrated that a commercial *Melissa* extract led to dose-specific increases in calmness, and dose-dependent decrements in timed memory task performance. However, the extract utilized in that study did not exhibit in vitro cholinergic receptor-binding properties. The current study involved an initial screening of samples of *M. officinalis* for human acetylcholinesterase inhibition and cholinergic receptor-binding properties. The cognitive and mood effects of single doses of the most cholinergically active dried leaf were then assessed in a randomized, placebo-controlled, double-blind, balanced crossover study. Following the in vitro analysis, 20 healthy, young participants received single doses of 600, 1000, and 1600 mg of encapsulated dried leaf, or a matching placebo, at 7-day intervals. Cognitive performance and mood were assessed predose and at 1, 3, and 6 h postdose using the Cognitive Drug Research computerized assessment battery and Bond–Lader visual analog scales, respectively. In vitro analysis of the chosen extract established IC₅₀ concentrations of 0.18 and 3.47 mg ml⁻¹, respectively, for the displacement of [3H]-(N)-nicotine and [3H]-(N)-scopolamine from nicotinic and muscarinic receptors in the human cerebral cortex tissue. However, no cholinesterase inhibitory properties were detected. The most notable cognitive and mood effects were improved memory performance and increased 'calmness' at all postdose time points for the highest (1600 mg) dose. However, while the profile of results was overwhelmingly favorable for the highest dose, decrements in the speed of timed memory task performance and on a rapid visual information-processing task increased with decreasing dose. These results suggest that doses of

Melissa officinalis at or above the maximum employed here can improve cognitive performance and mood and may therefore be a valuable adjunct in the treatment of Alzheimer's disease. The results also suggest that different preparations derived from the same plant species may exhibit different properties depending on the process used for the sample preparation.

Kennedy D.O., Scholey A.B., Tildesley N.T., Perry E.K. & Wesnes K.A. (2002) "Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm)." *Pharmacol Biochem Behav.* **72**(4) 953-64. [Abstract](#). *Melissa officinalis* (lemon balm) is a traditional herbal medicine, which enjoys contemporary usage as a mild sedative, spasmolytic and antibacterial agent. It has been suggested, in light of in vitro cholinergic binding properties, that *Melissa* extracts may effectively ameliorate the cognitive deficits associated with Alzheimer's disease. To date, no study has investigated the effects on cognition and mood of administration of *Melissa* to healthy humans. The present randomised, placebo-controlled, double-blind, balanced-crossover study investigated the acute effects on cognition and mood of a standardised extract of *M. officinalis*. Twenty healthy, young participants received single doses of 300, 600 and 900 mg of *M. officinalis* (Pharmaton) or a matching placebo at 7-day intervals. Cognitive performance was assessed using the Cognitive Drug Research (CDR) computerised test battery and two serial subtraction tasks immediately prior to dosing and at 1, 2.5, 4 and 6 h thereafter. In vitro IC₅₀ concentrations for the displacement of [3H]-(N)-nicotine and [3H]-(N)-scopolamine from nicotinic and muscarinic receptors in human occipital cortex tissue were also calculated. Results, utilising the cognitive factors previously derived from the CDR battery, included a sustained improvement in Accuracy of Attention following 600 mg of *Melissa* and time- and dose-specific reductions in both Secondary Memory and Working Memory factors. Self-rated "calmness," as assessed by Bond-Lader mood scales, was elevated at the earliest time points by the lowest dose, whilst "alertness" was significantly reduced at all time points following the highest dose. Both nicotinic and muscarinic binding were found to be low in comparison to the levels found in previous studies.

Kim M.Y., Hahm J.C., Park B.Y., Park E.K., Lee H.S., Angiolab Inc. (2009) "Fractionation of *Melissa* leaf extract having angiogenesis & MMP inhibitory activities and composition comprising the same." Patent Cooperation Treaty WO2009025532 (A2) [Abstract](#). The present invention relates to an ethyl acetate fraction of *Melissa* leaf having excellent anti-angiogenesis and MMP inhibitory activities, and a composition comprising the same. In particular, the ethyl acetate fraction of *Melissa* leaf is characterized that *Melissa* leaf is extracted with 50-100% C1-C6 alcohol, and concentrated, and then the concentrated alcohol extract is suspended in water, and fractionated with ethyl acetate, and dried to obtain the ethyl acetate fraction of *Melissa* leaf. The ethyl acetate fraction of *Melissa* leaf of the present invention has strong and excellent anti-angiogenic and MMP inhibitory activities. Therefore, the composition comprising the ethyl acetate fraction of *Melissa* leaf of the present invention can be used as an agent for the treatment or prevention of angiogenesis-related diseases and MMP-mediated diseases.

Kubota M., Ikemoto T., Komaki R. & Inui M. (1992) "Odor and emotion - effects of essential oils on contingent negative variation." *Proceedings of the 12th International Congress Essential Oil - Fragrance and Flavors*, 456-460.

Kurkin V.A., Zapesochnaya G.G. *et al.* (1999). "Qualitative and quantitative analysis of the *Melissa officinalis* L. herb and preparations." *Rastitel'nye Resursy* **35**(3): 116-121.

Lee J., Chae K, Ha J., Park B.Y., Lee H.S., Jeong S., Kim M.Y. & Yoon M. (2008) "Regulation of obesity and lipid disorders by herbal extracts from *Morus alba*, *Melissa officinalis*, and *Artemisia capillaris* in high-fat diet-induced obese mice." *J Ethnopharmacol.* **115**(2), 263-70. [Abstract](#). *Melissa officinalis* L. (Labiatae), *Morus alba* L. (Moraceae), and *Artemisia capillaris* Thunb. (Compositae) are suggested to be involved in the regulation of hyperlipidemia. We hypothesized that Ob-X, a mixture of three herbs, *Morus alba*, *Melissa officinalis* and *Artemisia capillaris* [corrected] improves lipid metabolism, body weight gain and adiposity and that peroxisome proliferator-activated receptor alpha (PPARalpha) is associated with these events. Mice fed a high-fat diet for 12 weeks exhibited increases in body weight gain and adipose tissue mass

compared with mice fed a low fat diet. However, feeding a high-fat diet supplemented with Ob-X significantly reduced these effects. Ob-X treatment also decreased the circulating levels of triglycerides and total cholesterol, and inhibited hepatic lipid accumulation. Ob-X supplementation was found to increase the hepatic mRNA levels of PPARalpha target enzymes responsible for fatty acid beta-oxidation. Moreover, Ob-X elevated the endogenous expression of a luciferase reporter gene containing three copies of a PPAR response element (PPRE) in NMu2Li liver cells. These data demonstrate that Ob-X regulates body weight gain, adipose tissue mass, and lipid metabolism in part through changes in the expression of hepatic PPARalpha target genes

López V, Martín S, Gómez-Serranillos MP, Carretero ME, Jäger AK, & Calvo MI. (2009) "Neuroprotective and neurological properties of *Melissa officinalis*." *Neurochem Res.* **34**(11),1955-61. [Abstract](#). *Melissa officinalis* has traditionally been used due to its effects on nervous system. Both methanolic and aqueous extracts were tested for protective effects on the PC12 cell line, free radical scavenging properties and neurological activities (inhibition of MAO-A and acetylcholinesterase enzymes and affinity to the GABA(A)-benzodiazepine receptor). The results suggest that the plant has a significant ($P < 0.05$) protective effect on hydrogen peroxide induced toxicity in PC12 cells. The radical scavenging properties were also investigated in cells and in cell free systems, where this plant was shown to be a good free radical scavenger. The MAO-A bioassay was also performed to detect possible antidepressant activities demonstrating that both extracts inhibited this enzyme, which has a key role in neurotransmitters metabolism. However, no activity was detected in the acetylcholinesterase and GABA assays. In general, the methanolic extract was more effective than the aqueous.

Marongiu B., Porcedda S. Piras A., Rosa A., Deiana M., Dessì M.A. (2004) "Antioxidant activity of supercritical extract of *Melissa officinalis* subsp. *officinalis* and *Melissa officinalis* subsp. *inodora*." *Phytotherapy Res* **18**(16), 789-792. [Abstract](#). The antioxidant activity of *Melissa officinalis* subsp. *officinalis* and of *Melissa officinalis* subsp. *inodora* extracts, obtained by using carbon dioxide under supercritical conditions was investigated. The samples were prepared in two steps. A preliminary extraction at 90 bar and 50 °C eliminated the essential oil, then a further extraction at 300 bar and 50 °C obtained the high molecular mass extract. These samples were tested for autoxidation and the iron or EDTA-mediated oxidation of linoleic acid at 37 °C in the absence of solvent, in in vitro systems. During linoleic acid autoxidation and its EDTA-mediated oxidation both *M. officinalis* and *M. inodora* extracts showed an antioxidant activity, and no significant differences in their efficacy were observed. None showed any prooxidant activity

Matsumoto T., Matsumoto A. , Tokuda H. & Nishino H. (1997). "Antitumor promoters from plants used as condiments or garnishes. *Food Factors for Cancer Prevention (International Conference)*, 265-269.

Mulder-Krieger T., Verpoorte R. , Svendsen A.B. & Scheffer J.J.C. (1988). "Production of essential oils and flavours in plant cell and tissue cultures. A review." *Plant Cell. Tissue Organ Culture* **13**, 85-154.

Müller S.F & Klement S. (2006) "A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. " *Phytomedicine* **13**(6), 383-387. [Abstract](#). Efficacy and tolerability of a combined valerian/lemon balm preparation¹ were investigated in an open, multicentre study in children less than 12 years suffering from restlessness and nervous dyskoimesis. Patients were dosed individually by the investigators. In total, 918 children were evaluated for therapeutic efficacy and tolerability. A distinct and convincing reduction in severity was found for all symptoms in the investigators' and parents' ratings. The core symptoms dyssomnia and restlessness were reduced from "moderate/severe" to "mild" or "absent" in most of the patients. In total, 80.9% of the patients who suffered from dyssomnia experienced an improvement for this symptom and 70.4% of the patients with restlessness improved clearly. For the other listed symptoms the total improvement was 37.8% on average. Both, parents and investigators assessed efficacy as to be "very good" or "good" (60.5% and 67.7%, respectively). The tolerability of Euvegal® forte was considered as "good" (in 96.7% of the patients it was judged to be "very good" or "good"). No study medication-related adverse events occurred.

Pereira R.P., Fachinetto R., de Souza Prestes A., Puntel R.L., Santos da Silva G.N., Heinzmann B.M., Boschetti T.K., Athayde M.L., Bürger M.E., Morel A.F., Morsch V.M. & Rocha J.B.. (2009) "Antioxidant effects of different extracts from *Melissa officinalis*, *Matricaria recutita* and *Cymbopogon citratus*." *Neurochem Res.* **34**(5), 973-83. [Abstract](#). Considering the important role of oxidative stress in the pathogenesis of several neurological diseases, and the growing evidence of the presence of compounds with antioxidant properties in the plant extracts, the aim of the present study was to investigate the antioxidant capacity of three plants used in Brazil to treat neurological disorders: *Melissa officinalis*, *Matricaria recutita* and *Cymbopogon citratus*. The antioxidant effect of phenolic compounds commonly found in plant extracts, namely, quercetin, gallic acid, quercitrin and rutin was also examined for comparative purposes. Cerebral lipid peroxidation (assessed by TBARS) was induced by iron sulfate (10 microM), sodium nitroprusside (5 microM) or 3-nitropropionic acid (2 mM). Free radical scavenger properties and the chemical composition of plant extracts were assessed by 1'-1' Diphenyl-2' picrylhydrazyl (DPPH) method and by Thin Layer Chromatography (TLC), respectively. *M. officinalis* aqueous extract caused the highest decrease in TBARS production induced by all tested pro-oxidants. In the DPPH assay, *M. officinalis* presented also the best antioxidant effect, but, in this case, the antioxidant potencies were similar for the aqueous, methanolic and ethanolic extracts. Among the purified compounds, quercetin had the highest antioxidant activity followed by gallic acid, quercitrin and rutin. In this work, we have demonstrated that the plant extracts could protect against oxidative damage induced by various pro-oxidant agents that induce lipid peroxidation by different process. Thus, plant extracts could inhibit the generation of early chemical reactive species that subsequently initiate lipid peroxidation or, alternatively, they could block a common final pathway in the process of polyunsaturated fatty acids peroxidation. Our study indicates that *M. officinalis* could be considered an effective agent in the prevention of various neurological diseases associated with oxidative stress.

Ribeiro M.A., Bernardo-Gil M.G. & Esquivel M.M. "Melissa officinalis, L.: study of antioxidant activity in supercritical residues." *Journal of Supercritical Fluids* **21**(1),51-60. [Abstract](#). The supercritical CO₂ extraction of lemon balm (*Melissa officinalis*, L.) at pressures from 10 to 18 MPa and at temperatures of 308–313 K was studied. The antioxidant activity of lemon balm extracts, obtained from solid residues of supercritical extraction and from raw lemon balm leaves, was performed using the Rancimat method. The best protection factor curve was obtained when extracts from the solid residues of supercritical extraction at 10 MPa, 308 K and 4 h of extraction time were used. A spectrophotometric method was used for the determination of the polyphenol compounds in the extraction residues. The highest value of phenol compounds was obtained for the extracts of solid residues of supercritical extraction at 10 MPa, 323 K and 30 min.

Reiter M. & Brandt W. (1985). "Relaxant effects on tracheal and ileal smooth muscles of the guinea pig." *Drug Res.* **35**(1), 408-414.

Sadraei H., Ghannadi A. & Malekshahi K. (2001) "Relaxant effect of essential oil of *Melissa officinalis* and citral on rat ileum contractions." *Fitoterapia* **74**(5), 445-452. [Abstract](#). The relaxant effect of the essential oil of *Melissa officinalis* and its main component, citral, on rat isolated ileum contractions was evaluated. *M. officinalis* essential oil (MOEO) inhibited the response to KCl (80 mM), ACh (320 nM) and 5-HT (1.28 µM) in a concentration-dependent manner with a IC₅₀ of approximately 20 ng/ml. Citral also had a concentration-dependent inhibitory effect on contraction of rat ileum with IC₅₀s comparable to that of MOEO.

Sanchez-Medina A., Etheridge C.J., Hawkes G.E., Hylands P.J., Pendry B.A., Hughes M.J. & Corcoran O. (2007) "Comparison of rosmarinic acid content in commercial tinctures produced from fresh and dried lemon balm (*Melissa officinalis*)." *J Pharm Pharm Sci.* **10**(4), 455-63 [Abstract](#). **PURPOSE:** To measure the rosmarinic acid content of eight commercial tinctures derived from fresh (n= 5) and dried (n=3) *Melissa officinalis* herb. **METHODS:** Rosmarinic acid and the internal standard (esculin) were purchased from Aldrich Chemical Co. The column used was a Luna C18, 5 µm (150 x 4.6 mm I.D., Phenomenex) maintained at ambient room temperature. The HPLC system consisted of a Shimadzu SCL-6B controller, Shimadzu LC-6A pumps, Shimadzu SPD-6A UV single wavelength spectrophotometric detector set to 320 nm and Shimadzu SIL-6B

autosampler. Gradient elution of the samples and standard were performed using ammonium formate (0.02 M; pH 6.25 at 27 °C; eluent A) and methanol (eluent B). The gradient elution initial conditions were 2% of eluent B with linear gradient to 60% at 30 min, followed by linear gradient to 90% of eluent B at 31 min, this proportion being maintained for 4 min. The column was then returned to the initial condition at 36 min and maintained until the end of the run at 43 min. The flow rate was 1 mL/min. The assay was validated for sensitivity, accuracy and reproducibility. RESULTS: The content of rosmarinic acid in commercial tinctures was significantly higher in the tinctures made from dried plant material (2.96 - 22.18 mg/mL) compared to fresh plant tinctures (\leq 0.92 mg/mL). CONCLUSION: These results have implications both for the manufacturers of commercial tinctures and also for herbal practitioners in the choice of tinctures for treating Herpes simplex infection.

Savino F, Capasso R, Palumeri E, Tarasco V, Locatelli E, Capasso F. (2008) "[Advances on the effects of the compounds of a phytotherapeutic agent (COLIMIL) on upper gastrointestinal transit in mice]. *Minerva Pediatr* **60**(3), 285-90. [Abstract](#). AIM: Phytotherapeutic agents, such as herbal formulations containing *Matricariae recutita* flowers (chamomile) extract, *Foeniculum vulgare* fruit (fennel) extract and *Melissa officinalis* aerial parts (lemon balm) extract have beneficial effects on gastrointestinal tract in colicky infants. However, the mechanism is largely unexplored and, particularly, it is not clear if it affects intestinal motility. The aim of this experimental study was to evaluate the effect of different herbal formulations containing *Matricariae recutita* extract, *Foeniculum vulgare* extract and *Melissa officinalis* extract on upper gastrointestinal transit in mice in vivo. METHODS: Gastrointestinal transit was measured in male ICR mice and in croton oil-treated mice after the oral administration of herbal formulations containing chamomile, fennel and lemon balm (ColiMil) and chamomile and lemon balm (ColiMil experimental). RESULTS: The herbal formulations tested (0.4-0.8 mL/mouse) dose-dependently and significantly inhibited gastrointestinal transit both in control and in croton oil-treated mice. Chamomile extract and lemon balm extract reduced significantly intestinal motility, but not fennel. At similar concentration ColiMil evoked a more consistent response than ColiMil experimental. CONCLUSION: Our findings directly demonstrate in vivo the effect of a combination of herbal formulations on intestinal motility. The observed inhibitory effect might be studied with clinical studies to test the efficacy of these compounds in the treatment of colicky infants.

Savino F., Cresi F., Castagno E., Silvestro L. & Oggero R.. (2005) "A randomized double-blind placebo-controlled trial of a standardized extract of *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* (ColiMil) in the treatment of breastfed colicky infants." *Phytother Res.* **19**(4), 335-40. [Abstract](#). OBJECTIVE: The aim of this randomized, double-blind, placebo-controlled trial was to investigate the effectiveness and side effects of a phytotherapeutic agent with *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* in the treatment of infantile colic. METHODS: 93 breastfed colicky infants were enrolled, the diagnosis was made according to Wessel's criteria. After a 3 day observation period, the infants were randomly divided into two groups, one treated with phytotherapeutic agent (PA) and the other with placebo twice a day for 1 week. Crying time and side effects were recorded. RESULTS: 88 infants completed the trial: 41 in the PA group and 47 in the control. The daily average crying time for the PA was 201.2 min/day (SD 18.3) at the baseline and 76.9 min/day (SD 23.5) at the end of the study; for the placebo it was 198.7 min/day (SD 16.9) and 169.9 min/day (SD 23.1) ($p < 0.005$). Crying time reduction was observed in 85.4% subjects for the PA and in 48.9% subjects for the placebo ($p < 0.005$). No side effects were reported. CONCLUSION: The present study shows that colic in breastfed infant improves within 1 week of treatment with an extract based on *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis*.

Scher S.K. (1991) "Botanicals-myth and reality." *Cosmetics and Toiletries* **106**(6), 65-76.

Schimmer O., Kruger A., Paulini H.. & Haefele F. (1994) "An evaluation of 55 commercial plant extracts in the Ames mutagenicity test." *Pharmazie* **49**, 448-51. **Cropwatch comments:** Ethanollic tincture of *M. officinalis* leaves (1:5 in 70% ethanol) showed no mutagenic effects in standard Ames test

Sorensen J.M. (2000) "*Melissa officinalis*." *Int. J. Aromatherapy* **10**(1-2), 7-15.

Soulimani R., Fleurentin J., Mortier F., Misslin R., Derrieu G. & Pelt J.M. (1991) "Neurotropic action of the hydroalcoholic extract of *Melissa officinalis* in the mouse." *Planta Med.* **57**(2), 105-9. [Abstract](#). A lyophilised hydroalcoholic extract of *Melissa officinalis* L. (Lamiaceae) has been evaluated for behavioral effects in mice. According to the traditional use of *M. officinalis*, sedative properties have been confirmed for low doses by the decrease of behavioral parameters measured in a non-familiar environment test (staircase test) and in a familiar environment test (two compartment test). With high doses, a peripheral analgesic activity was obtained by reducing the acetic acid-induced pain (writhing test); moreover, the plant extract induced the sleep in mice after treatment with an infrahypnotic dose of pentobarbital and potentialised the sleep induced by a hypnotic dose of pentobarbital.

Soulimani R., Younos C., Fleurentin J., Mortier F., Misslin R. & Derrieux G. (1993) "Study of the biological activity of *Melissa officinalis* L. on the central nervous system of mice in vivo and the duodenum of rats in vitro." *Plantes Medicinales et Phytotherapie* **26**, 77-85.

De Sousa A.C., Alviano D.S., Blank A.F., Alves P.B., Alviano C.S., Gattass C.R. (2004) "*Melissa officinalis* L. essential oil: antitumoral and antioxidant activities." *Journal of Pharmacy and Pharmacology* **56**(5), 677-681. [Abstract](#). *M. officinalis* (lemon balm) is a traditional herbal medicine used widely as a mild sedative, spasmolytic and antibacterial agent. This paper focuses on the analysis of the chemical composition and the biological activities of *M. officinalis* essential oil obtained under controlled harvesting and drying conditions. An in-vitro cytotoxicity assay using MTT indicated that this oil was very effective against a series of human cancer cell lines (A549, MCF-7, Caco-2, HL-60 and K562) and a mouse cell line (B16F10). This oil possessed antioxidant activity, as evidenced by reduction of 1,1-diphenyl-2-picryl-hydrazyl. These results pointed to the potential use of *M. officinalis* essential oil as an antitumoral agent.

Stahl-Biskup E., Intert F., Holthuijzen J., Stengele M. & Schulz G. (1993) "Glycosidically bound volatiles - A review 1986-1991" *Flav & Frag Journal* **8**(2), 61-80.

Toma C.C., Pancan I.B. Chirita M. & Vata F.M. & Zamfir A.D. (2008) "Electrospray Ionization Tandem Mass Spectrometric Investigation of Essential Oils from *Melissa officinalis* (Labiatae Family) and *Pellargonium* ssp. (Geraniaceae Family)". In: *Applications of Mass Spectrometry in Life Safety: NATO Science for Peace and Security Series A: Chemistry and Biology* pp 213-220. [Abstract](#). In the present work we report upon the development of a novel methodology based on electrospray (ESI) high capacity ion trap (HCT) multistage mass spectrometry (MS/MS), for assessing the composition and structure of essential volatile oils. The method was particularly applied to a native terpenoid mixture extracted from *Melissa officinalis* and different species of *Pellargonium* genus. Optimized ESI HCT MS and MS/MS in positive ion mode allowed the detection of three major components without the need of Chromatographic off- or on-line separation prior to MS. Linalol, citronellol, and citral species could be reliably identified based on accurate mass measurement of their molecular and related sequence ions.

Ulbricht C., Brendler T., Gruenwald J., Kligler B., Keifer D., Abrams T.R., Woods J., Boon H., Kirkwood C.D., Hackman D.A., Basch E., Lafferty H.J; Natural Standard Research Collaboration (2005) "Lemon balm (*Melissa officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother.* **5**(4), 71-114. [Abstract](#). An evidence-based systematic review including written and statistical analysis of scientific analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetic/dynamics, interactions, adverse effect, toxicology, and dosing.

Wolbling R.H. & Leonhardt K. (1994). "Local therapy of herpes simplex with dried extract from *Melissa officinalis*." *Phytomedicine* **1**. 25-31.

Yasukawa K., Yamaguchi A., Arita J., Sakurai S., Ikeda A. & Takido M. (1993) "Inhibitory effect of edible plant extracts on 12-O-tetradecanoylphorbol-13-acetate-induced ear oedema in mice." *Phytotherapy Research* **7**(2), 185-189.

Melissa oil / extracts: Toxicological Considerations.

Bianchi-Santamaria A. , Tateo F. & Santamaria L. (1993) "Antimutagenic action of beta carotene, canthaxanthin and extracts of *Rosmarinus officinalis* and *Melissa officinalis* genotoxicity of basil and tarragon oil." *Royal Society Chem., Spec. Publ.*, **123**, 75-81.

Burfield T. (2000) "Safety of essential oils." *International Journal of Aromatherapy*, **10**(1-2), 16-29.

Hausen B.M. & Schulze R. (1986) "Comparative study of the sensitizing capacity of some commonly used antiviral drugs." *Dermatosen Beruf Und Umwelt* **34**(6), 163-170. **Cropwatch comments:** Authors indicated weak sensitising capacity of *M. officinalis* extracts for guinea-pigs.

Menz J.. & Winkelmann R.K. (1987) "Sensitivity to wild vegetation." *Contact Dermatitis* **16**(3), 169-173. **Abstract.** 74 patients suspected of having allergic contact dermatitis to wild vegetation were patch tested with ether extracts of 13 plants of the family Compositae and 7 other weeds or trees. *Anthemis cotula* (dog fennel) and *Xanthium strumarium* (cocklebur) gave the most frequent positive results, demonstrating a change of frequency in sensitivity compared to the 1950s, when *Ambrosia artemisiifolia* (ragweed) was recognized as the most frequently sensitizing weed. The reasons for these changes of incidence and clinical patterns are examined. **Cropwatch comments:** Patch testing of a series of patients clinically diagnosed as suffering from possible weed dermatitis. Testing included application of *Melissa officinalis* extract described as "sweet clover". No differentiation for possible irritant responses made.

Okabe M. (1994) "The application of the medical plants to the hypo-irritative and hypo-allergic cosmetics - mainly about the Labiatae and the compositae plants." *Fragrance Journal* **22**(8), 74-80.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Human repeated insult patch test. Unpublished study from Robertet, 21 February > Report number 36641. (RIFM, Woodcliff Lake, NJ, USA). Alternative title: "Tolerability study of Balm oil (*Melissa officinalis* L.) according to sensitization protocol described by Marzulli and Maibach in 50 subjects." Unpublished. **Cropwatch comments:** Cropwatch approached both RIFM and Robertet for details of this study – Catherine Gadras of Robertet kindly released a summary to Cropwatch on 15th June 2009. However it appears that a more detailed description of the study is available on the RIFM database..

Human Repeat Insult Patch Test (HRIPT) (Robertet 2001)

Test Protocol : Marzulli-Maibach protocol semi-occlusive

50 subjects

Test Concentration: 2% (w/w) (825µg/cm²)

Carrier Ethanol/DEP (1:3)

Conclusion : No induction of sensitization.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Local Lymph Node Assay Unpublished study from Robertet. (RIFM, Woodcliff Lake, NJ, USA). Unpublished. **Cropwatch comments:** Cropwatch approached both RIFM and Robertet for details of this study – Catherine Gadras of Robertet kindly released a summary to Cropwatch on 15th June 2009..

Robertet (2009) LLNA

Local Lymph Node Assay (LLNA) (OCDE 429) (Robertet 2008)

EC3 calculated = 18% (w/v) 4500µg/cm²

Carrier acetone/Olive oil (4:1)

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Human Repeated insult patch test. Unpublished study from Robertet. (RIFM, Woodcliff Lake, NJ, USA). Unpublished **Cropwatch**

comments: Cropwatch approached both RIFM and Robertet for details of this study – Catherine Gavras of Robertet kindly released a summary to Cropwatch on 15th June 2009..

Robertet (2008) Human Repeat Insult Patch Test (HRIPT).

Test Protocol : Marzulli-Maibach semi-occlusive

100 subjects

Test Concentration: 2 % (w/w) (910µg/cm²)

Carrier Ethanol/DEP (1:3)

Conclusion : No induction of sensitization

Cropwatch comments: Catherine Gavras of Robertet kindly released these details to Cropwatch on 15th June 2009 also.

Repeat Insult Patch Test (HRIPT) (Robertet 2009)

Test Protocol : Marzulli-Maibach semi-occlusive

100 subjects

Test Concentration: 2 % (w/w) (1470µg/cm²)

Carrier Ethanol/DEP (1:3)

Conclusion : No induction of sensitization

Sainio E.-L. & Kanerva L. (1995) "Contact allergens in toothpastes and a review of their hypersensitivity." *Contact Dermatitis* **33**(2)100-105.

Thomson K.F. & Wilkinson S.M. (2000) "Allergic contact dermatitis to plant extracts in patients with cosmetic dermatitis." *British Journal of Dermatology* **142**(1), 84-88.

Tisserand R. & Balacs T. (1995) "Melissa" In : *Essential oil safety : a guide for healthcare professionals*. Churchill Livingstone 1995 p151. **Cropwatch comments:** Essential oil profile (p151) mainly focuses on toxicological consequences of contained citral (stated as 35-55%). Melissa herb toxicology (p219) again focuses on possible adverse effects from citral and "may occasionally give rise to sensitization from aldehyde content". Pros & cons of coumarin content of "Sweet clover" (absolute of *Melissa officinalis*) briefly discussed (p 223). *Cropwatch Newsletter* 4 previously discloses there is 0.9% coumarin on dry weight basis. Wagner (1996) gives coumarin value of 0.25-0.45% in herb, together with umbelliferone, scopolin etc..

Wagner H. & Sprinkmeyer L. (1973) "Über die pharmakologische Wirkung von Melissengeist." *Dt. Apoth. Ztg* **113**(30), 1159-1166. **Cropwatch comments:** LD₅₀ values were determined according to the method of Litchfield and Wilcoxon for "Melissa balm oil spirits" by gavage using 10 BR46 Wistar albino rats. LD50 value (16.2 ml/Kg) was determined for 24 hrs and 14 day periods.

West I. & Maibach H.I.. (1995) "Contact urticaria syndrome from multiple cosmetic components." *Contact Dermatitis* **32**,121.