Lemon balm (Melissa officinalis L.): an evidence-based systematic review by the Natural Standard Research Collaboration

Article *in* Journal of Herbal Pharmacotherapy · February 2005

Source: PubMed

CITATIONS
30

READS
7,836

12 authors, including:

Catherine Ulbricht

97 PUBLICATIONS **2,194** CITATIONS

SEE PROFILE

Thomas Brendler

Plantaphile

35 PUBLICATIONS **281** CITATIONS

SEE PROFILE

Joerg Gruenwald

Analyze & Realize ag

146 PUBLICATIONS **2,240** CITATIONS

SEE PROFILE

Heather Boon

University of Toronto

261 PUBLICATIONS **7,260** CITATIONS

SEE PROFILE

Catherine Ulbricht, PharmD, MBA(C), Column Editor

Lemon Balm (*Melissa officinalis* L.): An Evidence-Based Systematic Review by the Natural Standard Research Collaboration

Thomas Brendler, BA
Joerg Gruenwald, PhD
Benjamin Kligler, MD, MPH
David Keifer, MD
Tracee Rae Abrams, PharmD
Jen Woods, BS
Heather Boon, BScPhm, PhD
Catherine DeFranco Kirkwood, MPH, CCCJS-MAC
Ethan Basch, MD
Hope J. Lafferty, AM
Catherine Ulbricht, PharmD
Dana A. Hackman, BS

for the Natural Standard Research Collaboration

Thomas Brendler is affiliated with PlantaPhile, Berlin. Joerg Gruenwald is affiliated with Phytopharm Consulting. Benjamin Kligler is affiliated with Continuum Center for Health and Healing. David Keifer is affiliated with the University of Arizona. Tracee Rae Abrams is affiliated with the University of Rhode Island. Jen Woods is affiliated with Northeastern University. Heather Boon is affiliated with the University of Toronto. Catherine DeFranco Kirkwood is affiliated with the MD Anderson Cancer Center. Ethan Basch is affiliated with the Memorial Sloan-Kettering Cancer Center. Hope J. Lafferty is affiliated with the Memorial Sloan-Kettering Cancer Center. Catherine Ulbricht is affiliated with Massachusetts General Hospital. Dana A. Hackman is affiliated with Northeastern University.

Journal of Herbal Pharmacotherapy, Vol. 5(4) 2005
Available online at http://www.haworthpress.com/web/JHP
doi:10.1300/J157v05n04_08

ABSTRACT. An evidence-based systematic review including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. Citronellae, English balm, Lamiaceae, *Melissa officinalis* L., sweet balm

SEARCH STRATEGY

To prepare each Natural Standard review, electronic searches are conducted in nine databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, MEDLINE, and NAPRALERT. Search terms include the common name(s), scientific name(s), and all listed synonyms for each topic. Hand searches are conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions are placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) are consulted for access to additional references or ongoing research.

Selection Criteria

All literature is collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria are utilized for selection.

Data Analysis

Data extraction and analysis are performed by *health care professionals* conducting clinical work and/or research at academic centers, using standardized instruments that pertain to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data are verified by a second reviewer.

Review Process

Blinded review of reviews is conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, complementary and alternative medicine (CAM) research, and clinical practice. In cases of editorial disagreement, a three-member panel of the *Editorial Board* addresses conflicts, and consults experts when applicable. Authors of studies are contacted when clarification is required.

Update Process

Natural Standard regularly monitors scientific literature and industry warnings. When clinically relevant new data emerge, best efforts are made to update content immediately. In addition, regular updates with renewed searches occur every 3-18 months, variable by topic.

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Synonyms/Common Names/Related Substances

- Balm, balm mint, bee balm, blue balm, Citra, citronellae, citronmelisse, common balm, cure-all, dropsy plant, English balm, folia citronellae, folia melissae citratae, garden balm, gastrovegetalin, hjertensfryd, honey plant, kneipp melisse pflanzensaft, Labiatae/Lamiaceae (family), lemon melissa, lomaherpan, melissa, *Melissa officinalis*, *Melissa officinalis* L., melissae, melissae folium, Melisse (German and French), melissenblatt, melissengeist, sweet balm, sweet mary, toronjil (Spanish), valverde boutons de fievre crème.

Selected Combination Products

- Abdomilon, Abdomilon N, Absimed, Agua del Carmen, Aktiv Nerven-und Schlaftee, Anevrase, Aponatura Beruhigungs, Aponatura Einschlaf, Aranidorm-S, Arterosan Plus, Avedorm, Baldracin, Baldrian-Elixier, Baldrian-Krautertonikum, Baldriparan, Baldriparan Beruhigungs, Baldriparan stark N, Balsamo Branco, Befelka-Tinktur, Beruhigungstee, Biocarde, Bio-Garten Tee zur Beruhigung, Bio-Garten Tropfen zur Beruhigung, Camomila, Canad, Caramelos Agua del Carmen, Cardalept, Cardiaforce, Colominthe, Cough Drops, Cura, Digestol Sanatorium, Doppelherz Melissengeist, Doppelherz Tonikum, Dormarist, Dormiplant, Dragees pour la detente nerveuse, Elixir Bonjean, Emmenoiasi, Especies Calmante, Euvegal Entspannungs-und Einschlafdragees, Euvegal forte, Euvegal N, Euviterin, Fargestium, Fluxoten, Gastregan, Gastrol S, Gastrosan, Gutnacht, Heumann Beruhigungstee Tenerval N, Herz-und Kreislauftonikum Bioflora, Hyperiforce comp, Iberogast, JuDorm, JuNeuron S, Klosterfrau Melissengeist, Kneipp Krauter Taschenkur Nerven und Schlaf N, Kneipp Nerven-und Schlaf- Tee, Kneipp Nerven- und Schlaf-Tee N, Krauterdoktor Beruhigungstropfen, Krauterdoktor Entspannungs-und Einschlaftropfen, Krauterdoktor Magen-Darmtropfen, Krauterdoktor Nerven-Tonikum, Krauterdoktor Rosmarin-Wein, Krauterhaus Mag Kottas Babytee, Krauterhaus Mag Kottas Magen- und Darmtee, Krauterhaus Mag Kottas Nerven- und Schlaftee, Krauterhaus Mag Kottas Wechseltee, Krautertee Nr 1, Krautertee Nr 141, Krautertee Nr 16, Krautertee Nr 201, Krautertee Nr 209, Krautertee Nr 9, Lindofluid N, Lo-701, Luvased-Tropfen N, Mag Doskar's Magentonikum, Mag Doskar's Nerventonikum, Mag Kottas Beruhigungstee, Mag Kottas Krauterexpress-Nerven-Schlaf-Tee, Mag Kottas Magen-Darmtee, Mag Kottas Nerven-Beruhigungstee, Mag Kottas Schlaftee, Mag Kottas Tee fur stillende Mutter, Mag Kottas Wechseltee, Mariazeller, Mediflor Tisane Calmante Troubles du Sommeil No 14, Mediflor Tisane Circulation du Sang No 12, Mediflor Tisane Pectorale d'Alsace, Melissa comp., Melissa Specie Composta, Melissa Tonic, Melissengeist, Melissin, Nervendragees, Nerven-Tee Stada N, Nervifloran, Nervosana, Nyrene, Oxacnt N, Oxacant-sedativ, Pascosedon, Passedan, Passelyt, Passiflora Composta, Phytoberidin, Phytogran, Phytonoctu, Plantival, Plantival novo, Presselin Blahungs K 4 N, Pronervon Phyto, Relax, Resolutivo Regium, RubieSed, Salus Nerven-Schlaf-Tee Nr.22, Salusan, Santane D5, Santane N9, Schlaf-

und Nerventee, Sedacur, Seda-Grandelat, Sedantol, Seda-Plantina, Sedariston, Sedaselect N, Sedasyx, Sedatol, Sedatruw S, Sedinfant N, Seracalm, Sidroga Herz-Kreislauf-Tee, Sidroga Kindertee, Sidroga Magen-Darm-Tee, Sidroga Nerven-und Schlaftee, Sirmiosta Nerven-elixier N, Sol Schoum, Songha, Songha Night, Soporin, Species nervinae, St Radegunder Beruhigungs-und Einschlaftee, St Radegunder Fiebertee, St Radegunder Herz-Kreislauf- Tonikum, St Radegunder Herz- Kreislaufunterstutzender Tee, St Radegunder Magenberuhigungstee, St Radegunder Nerventee, St Radegunder Nerven-Tonikum, St Radegunder Reizmildernder Magentee, St Radegunder Rosmarin-Wein, Stullmaton, STW 5-II (bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root, and lemon balm), STW-5-S (matricaria flower, peppermint leaves, caraway, licorice root, and lemon balm), SX Valeriana comp, Synpharma InstantNerventee, Teekanne Magen-und Darmtee, Teekanne Schlaf-und Nerventee, The Brioni, The Chambard-Tee, The Franklin, Tisana Arnaldi, Tisana Cisbey, Tisana Kelemata, Tisane antiflatulente pour les enfants, Tisane calmante pour les enfants, Tisane des Familles, Tisane favorisant l'allaitement, Tisane Grande Chartreuse, Tisane pour le coeur et la circulation, Tisane pour le Foie, Tisane pour le sommeil et les nerfs, Tisane pour les enfants, Tisane pour l'estomac, Tisane Purgative, Tisane relaxante, Tisane Touraine, Vagostabyl, Valerina Day Time, Valerina Night- Time, Valverde Dragees pour la détente, Wechseltee.

CLINICAL BOTTOM LINE EFFECTIVENESS

Brief Background

- Lemon balm (*Melissa officinalis*) is an herb with a lemon scent native to southern Europe. Historically lemon balm has been said to possess sedative/tranquilizing, anti-gas, fever-reducing, antibacterial, spasmolytic, hypotensive, memory-enhancing, menstrual-inducing, and thyroid-related effects and has been proposed by some to be an herbal cure-all.[1-3] The plant has been used for centuries in various cultures internationally.[4,5]
- Lemon balm has been used for its tranquilizing properties in Portuguese folk medicine and for anticancer properties in Cuban folk medicine.[1,6]

- Lemon balm is member of the Lamiaceae family.[7-10] Other members of the Lamiaceae family include dittany, mint, sage, siderites, and sweet marjoram.[11]
- *In vitro* data suggest that lemon balm may contain high concentrations of antioxidants.[12]
- Lemon balm has been assigned to the FDA Generally Recognized As Safe (GRAS) list in the United States. No serious side effects have been reported, although there is limited research of long-term effects. See Tables 1 and 2.
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Historical or Theoretical Uses Which Lack Sufficient Evidence

- Analgesic,[13] anorexia, anticholinergic,[14,15] anti-gas,[16] antihistaminic, antihypertensive, antisecretory,[17] antispasmodic,[18-20] antiulcerogenic,[17] antiviral,[7,9,9,19,21-26] anxiolytic,[19,27] aromatic, attention deficit and hyperactivity disorder,[28] cancer,[6,17,29,30] chronic bronchitis, chronic fatigue syndrome, colic, coughs, depression,[19] digestive aid, fever reduction, flatulence, flatulent colic, gastrointestinal disorders, Graves' disease,[31-33] heart conditions, high blood pressure, HIV,[26] influenza, insect bites, insomnia,[19,34-36] irregular menstrual periods,[16] irritable bowel syndrome, intestinal relaxant,[15] memory enhancer,[4,5,14] migraine, nausea, nervous palpitations,[37] nervous stomach,[37] neuralgia,[19] neurasthenia, promoting menstrual flow,[33,38] promoting sweating, restlessness, sedative,[13,19,34-36] shingles, skin irritations, sleep disorders,[19,34-36] tension headache, toothache, tranquilizer, vasodilatation, vomiting, wound healing (topical).

TABLE 1. Scientific Evidence for Common/Studied Uses

Indication	Evidence Grade	
Herpes simplex virus infections	B	 GRADING SYSTEM LINK
Agitation in dementia	C	
Anxiety	C	
Cognitive performance	C	
Colitis	C	
Dyspepsia	C	
Sleep quality	C	

TABLE 2. Natural Standard evidence-based validated grading rationale™

Level of Evidence Grade	Criteria
A (Strong Scientific Evidence)	Statistically significant evidence of benefit from > 2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (Good Scientific Evidence)	Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from ≥ 1 properly conducted meta-analysis OR evidence of benefit from > 1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (Unclear or conflicting scientific evidence)	Evidence of benefit from ≥ 1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥ 1 cohort/case-control/non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (Fair Negative Scientific Evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (Strong Negative Scientific Evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from ≥ 1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of Evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

* Objective criteria are derived from *validated instruments for evaluating study quality*, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (*Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17[1]:1-12*). See Table 4.
† Listed separately in monographs in the "Historical or Theoretical Uses which Lack Sufficient Evidence" section.

Expert Opinion and Folkloric Precedent

- In Europe, lemon balm has been widely used as a topical antiviral treatment for genital and oral herpes, applied at the first sign of a herpes flare-up or regularly for prevention. In Germany, the essential oil placed on the temples has been used to relieve headaches or sleeplessness.
- The German Commission E recommends lemon balm for nervous sleep disorders and functional gastrointestinal complaints. The European Scientific Cooperative on Phytotherapy (ESCOP) recommends its use for tenseness, restlessness, and irritability. Lemon balm has been placed on the FDA Generally Regarded As Safe (GRAS) list.

Brief Safety Summary

- *Likely Safe:* When used topically or orally in recommended doses (up to 30 days) in otherwise healthy adults[34,39] and when consumed in amounts found in foods. Lemon balm has been assigned Generally Regarded As Safe (GRAS) status in the United States with a maximum level of 0.5% in baked goods.
- *Possibly Unsafe:* During pregnancy or lactation or in pediatric patients, and when used in patients with thyroid disorders or in combination with sedatives (theoretical).

DOSING/TOXICOLOGY

General

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

Standardization

- Investigations of lemon balm have suggested that the percentage of essential oil from the leaves can range from 0.08 to 0.25 mL/100 grams, and 0.06 to 0.167 mL/100 grams in the herb.[40] The content and quality of essential oils from lemon balm also may differ depending upon the height and location of the harvest cut of a particular plant, the vegetation period of the plant, and also between different populations of the plant. For example, the oil content in lemon balm appears to be highest in the top third of the plant, and the percentage of the constituents may be highest when the plant is cut in the basipetal direction.[40-47] Clinical trial data suggest that different preparations of lemon balm may result in products, which exhibit different properties depending on the process used for the sample preparation.[2]

- Lomaherpan® is a topical lemon balm extract (70:1) sold in Europe that is standardized by bioassay.[23,24] Herpilyn®, a topical preparation with equivalent standardization to the European products (70:1), is sold in the United States. Doses used in other herbal combinations are variable.
- Studies have demonstrated that analysis of the different constituents of lemon balm may be achieved using methods such as gas chromatography, mass spectroscopy, thin-layer chromatography, plasma optical emission spectrometry and inductively coupled plasma-source mass spectrometry, matrix solid-phase dispersion, UV, 1R, 1H NMR, 13C NMR, and FAB MS.[8,11,40,48-54] Several authors have presented methods for identification,[55-58] determination of herbicide residues,[59] and characteristics of adulterations.[60] A study of residue extraction from the whole leaves of lemon balm by *in vitro* analysis by an isopropanol apparatus suggested that this method is not appropriate for lemon balm.[61]

Adult Dosing (18 Years and Older)

Oral

- *Tea:* A common dose of lemon balm is one cup of tea taken several times per day as needed. Anecdotally, others have suggested 1.5 to 4.5 grams of lemon balm herb taken several times per day as a tea.
- *Tincture:* A dosage of 2-6 mL three times per day (1:5 in 45% alcohol) has been used historically.
- *Liquid extract:* Lemon balm extract in a dose of 60 drops per day has been cited in research on patients with Alzheimer's disease for improvement in cognition.[62]
- *Leaves:* A dosage of 8-10 grams per day has been used.
- *Combination products:* The product Songha Night®, which includes 120 mg *Valeriana officinalis* extract and 80 mg lemon balm extract, has been used as a sleep aid in a dosage of three tablets taken nightly for 30 days.[34] For anxiety, Klosterfrau Melissengeist® [each teaspoonful (5 mL) contains essential oils of lemon balm (27 mg), orange peel (36 mg), cinnamon (16 mg), and myristica (4 mg)] has been taken as 0.23 mL/kg body weight, three times per day for eight weeks.[37] For dyspepsia, Iberogast®, a standardized formula containing *Matricata recutita*, *Iberis amara*, *Angelica archangelica*, *Carum carvi*, *Silybum marianum*, lemon balm,

Chelidonium majus, *Glycyrrhiza glabra*, and *Mentha* × *piperita*, has been taken in a dosage of 20 drops, three times per day for a minimum of four to eight weeks.[63]

Topical

- *Cream:* Cream containing 1% of a standardized 70:1 extract, topically up to four times per day for 5 to 10 days has been studied for the treatment of active viral herpes.[22-24]
- *Tea:* Alternatively, a tea has been applied to herpes lesions with a saturated cotton ball several times per day. The tea is prepared by steeping 2-3 teaspoons (2-3 grams) of the finely cut leaf in 150 mL boiling water for 5-10 min and then straining.

Pediatric Dosing (Younger Than 18 Years)

- Insufficient available data.

Toxicology

- Lemon balm preparations may contain trace amounts of lead. A study evaluating metal dispersion in food crops suggested that the soil in which some plants are grown may be contaminated by lead from environmental pollution and therefore may cause the plant to contain trace amounts of the element.[64]
- The lack of genotoxic effects of aqueous or alcoholic extracts of lemon balm on Aspergillus nidulans D-30 using a plate-incorporation assay has been noted.[6]
- There are insufficient available data on chronic toxicity.

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

Individuals with known allergy/hypersensitivity to lemon balm should avoid its use. Hypersensitivity reactions have been reported, including contact dermatitis.[65] Lemon balm extract had a weak sensitizing effect in guinea pigs.[66]

Adverse Effects/Post Market Surveillance

General: Based on available research, oral forms have been reported to be relatively well-tolerated when taken for up to 8 weeks.[37] Evidence for topical administration of cream suggested minimal side effects for up to 10 days of application.[22,24,39]

Dermatologic: Contact dermatitis,[65] local reddening, burning sensation, paresthesia, residual pigmentation,[23] and dermal irritation[24] on application of cream have been reported. One case of irritation and one case of exacerbation of herpes symptoms were reported when lemon balm was applied topically.[24]

Neurologic: One clinical study reported the occurrence of headache.[37] One study cited that 1200 mg of lemon balm resulted in EEG changes.[67] One trial reported that 900 mg of lemon balm may reduce alertness, so caution should be used when driving or operating heavy machinery.[20] In one clinical trial, the use of a *Valeriana officinalis*/lemon balm combination was reported to cause mild adverse effects in 28.8% of patients, with sleep disturbances and tiredness cited as the most common side effects (although sedative properties of *Valeriana officinalis* alone are well-described and the additional effects of lemon balm are not clear in this combination).[13,34] A *Valeriana officinalis-Humulus lupulus*-lemon balm combination was reported to cause tiredness in isolated cases.[68]

Ocular/Otic: Anecdotal reports note the possibility of lemon balm increasing intraocular pressure.

Cardiovascular: One randomized controlled trial reported the occurence of palpitations.[37]

Endocrine: A pre-clinical study reported that constituents of lemon balm may block the binding of thyroid-stimulating hormone (TSH) to its receptor by acting both on the hormone and the receptor itself.[69] Studies have suggested that patients with thyroid problems such as Graves' disease use caution due to the potential for thyroid hormone inhibition.[27,31-33,38,69] Lemon balm may interfere with thyroid hormone replacement therapy (theoretical).

Gastrointestinal: Cases of nausea and diarrhea have been reported.[37)]

Precautions/Warnings/Contraindications

- Use cautiously in patients with thyroid problems such as Graves' disease due to potential for thyroid hormone inhibition.[27,31-33,38,69]

- Use cautiously in patients with glaucoma as anecdotal reports have suggested that lemon balm may increase intraocular pressure.
- Use caution when driving or operating heavy machinery. Results from one clinical study have suggested that lemon balm may reduce alertness at doses of 900 mg.[20]
- Lemon balm preparations may contain trace amounts of lead. A study evaluating metal dispersion in food crops suggested that the soil in which some plants are grown may be contaminated by lead from environmental pollution and therefore may cause the plant to contain trace amounts of the element.[64]

Pregnancy and Lactation

- Not recommended due to lack of sufficient data.[27] Lemon balm may elicit emmenagogic, antithyrotropic, and antigonadotropic effects (anecdotal).

INTERACTIONS

Lemon Balm/Drug Interactions

- *Alcohol:* In theory, alcohol use with lemon balm may augment the sedative effects of alcohol.[20,27] However, no additive effects of alcohol were shown when combined with a *Valeriana officinalis-Humulus lupulus*-lemon balm combination product.[68]
- *Barbiturates:* Lemon balm has been reported to increase the hypnotic effects of barbiturates in animal studies.[13,27]
- *Sedative agents:* Based on preclinical studies[70] and initial human research,[20] combination use of lemon balm with sedatives may result in additive effects.
- *Glaucoma medications:* Based on anecdotal accounts, lemon balm may increase intraocular pressure, thereby diminishing effects of glaucoma medications.
- *Thyroid agents:* In euthyroid rats, the administration of freeze-dried extracts of lemon balm was reported to reduce pituitary and serum thyroid stimulating hormone (TSH) concentrations.[31-33] One study suggested that constituents of lemon balm may block the binding of TSH to its receptor by acting on both the hormone and the receptor itself.[69] Lemon balm may interfere with thyroid hormone replacement therapy (theoretical).

- *Nicotine and scopolamine:* Lemon balm may displace drugs bound to nicotinic and muscarinic receptors, as demonstrated in clinical trials with the displacement of nicotine and scopolamine from these receptors.[2,14,20]
- *Selective serotonin reuptake inhibitors (SSRIs):* As demonstrated in *in vitro* studies, lemon balm may inhibit concentrations of serotonin and therefore may interact with drugs which affect concentrations of serotonin *in vivo.*[15]

Lemon Balm/Herb/Supplement Interactions

- *Sedative herbs and supplements:* A study examining efficacy and safety of herbal sedatives suggested that combination use of sedative herbs with lemon balm may result in additive effects.[70] Such herbs include ashwaganda root, calamus, calendula, California poppy, capsicum, catnip, celery, cough grass, elecampane, Siberian ginseng, German chamomile, goldenseal, gotu kola, hops (*Humulus lupulus*), Jamaican dogwood, kava, sage, St. John's wort, sassafras, skullcap, shepherd's purse, stinging nettle, valerian (*Valeriana officinalis*), wild carrot, wild lettuce, and yerba mansa.
- *Herbs and supplements used for glaucoma:* Anecdotal accounts suggest that lemon balm may increase intraocular pressure, thereby diminishing effects of glaucoma treatments.
- *Herbs that affect thyroid hormone:* In euthyroid rats, the administration of freeze-dried extracts of lemon balm was reported to reduce pituitary and serum TSH concentrations.[31-33] One study suggested that constituents of lemon balm may block the binding of TSH to its receptor by acting both on the hormone and the receptor itself.[69]

Lemon Balm/Lab Interactions

- *Thyroid Stimulating Hormone:* In euthyroid rats, the administration of freeze-dried extracts of lemon balm was reported to reduce pituitary and serum TSH concentrations.[31-33] One study reported that constituents of lemon balm may block the binding of TSH to its receptor by acting on both the hormone and the receptor itself.[69]
- *Prolactin:* In rats, prolactin serum levels and hypophyseal stores were reduced by 40 mg/100 grams of a freeze-dried extract of lemon balm.[33]

MECHANISM OF ACTION

Pharmacology

- *Constituents:* The known major components of lemon balm are reported to include hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acids, chlorogenic acid, and metrilic acid;[11,38,49,71-73] tannins;[7,9,21,74,75] flavonoids, including luteolin, luteolin 7-O-beta-D-glucopyranoside, apigenin 7-O-beta-D-glucopyranoside, and luteolin 3′-O-beta-D-glucuronopyranoside;[17,32,40,45,48,52,76,77] monoterpene glycosides;[78] sesquiterpenes, including β-caryophyllene and germacrene;[78] triterpenes;[79] and volatile oils, including citronellal, citral a (geranial), citral b (neral), methyl citronellate, ocimene, citronellol, geraniol, nerol, β-caryophyllene, β-caryophyllene oxide, linalool, and ethric oil.[40,45,80-84] The volatile oil comprises 0.5-0.1% of the plant by weight, and citronellal, geranial, and neral constitute about 50-70% of this oil.[80] Eugenylglycoside has been isolated from lemon balm leaves.[85] The chemical composition of lemon balm tea yielded 10 mg/L of essential oil (74% citral) and large amounts of polyphenol compounds.[86] Steam distillates of lemon balm callus cultures yielded dehydroabietane and another diterpene hydrocarbon, with the relative proportion of those two compounds varying considerably during cultivation passage.[87]
- *Antiviral effects:* Studies have reported that aqueous extracts of lemon balm exhibit antiviral effects against Newcastle disease virus, Semliki forest virus, influenza virus, myxoviruses, vaccinia, and herpes simplex virus.[7,9,21,25,51,74] Lemon balm extract and rosmarinic acid have demonstrated antiviral properties against HIV-1.[26] Studies conducted to assess the antiviral effects of lemon balm on Herpes simplex virus 1 have suggested that different extracts of the herb (M1, M2, M3, and M4) exhibit different effects on the virus.[51] Studies conducted to assess the antiviral effects of lemon balm on Herpes simplex virus 2 suggest that the volatile oil components of lemon balm inhibit replication of HSV-2.[88] Lemon balm's antiviral effects are attributed to the tannin and polyphenol constituents. Tannins are reported to possess antiviral properties[7,9,21,25,74] as are rosmarinic, caffeic, and ferulic acids.[7,51]
- *Antibacterial/antifungal effects:* The lemon balm constituent rosmarinic acid was reported to impair *in vivo* activation of mouse macrophages by heat-killed *Corynebacterium parvum*, as mea-

sured by the decreased capacity of the activated macrophages to undergo the oxidative burst.[73] *In vitro* analyses of the antimicrobial properties of lemon balm suggested that at a concentration of 500 microg/mL, the herb completely inhibits the growth of all yeast species including, *Torulaspora delbrueckii*, *Zygosaccharomyces bailii*, *Pichia membranifaciens*, *Dekkera anomala*, and *Yarrowia lipolytica.*[50,89] Data from *in vitro* analyses have suggested that lemon balm may be effective as an antibiotic against anaerobic and facultative aerobic periodontal bacteria including, *Porphyromonas gingivalis*, *Prevotella* spp., *Fusobacterium nucleatum*, *Capnocytophaga gingivalis*, *Veilonella parvula*, *Eikenella corrodens*, *Peptostreptococcus micros*, and *Actinomyces odontolyticus.*[90] Lemon balm oils have been reported to demonstrate highest activity against *S. enterica* (BA50 range, 0.0044-0.011%).[91] Antibacterial activity was reported to be expressed on a multiresistant strain of *Shigella sonei*.[92]

- *Antiinflammatory effects:* The paucity of clinical evidence makes the assessment of the antiinflammatory effect of lemon balm difficult to verify.[73,93] Rosmarinic acid has been reported to reduce paw edema induced by cobra venom factor in rats and to inhibit passive cutaneous anaphylaxis in rats at doses of 1-100 mg/kg by mouth. Rosmarinic acid has been reported not to inhibit t-butyl hydroperoxide-induced paw edema in the rat, indicating selectivity for complement-dependent processes.[73]
- *Antioxidant effects: In vitro* data suggest that lemon balm contains high concentrations of antioxidants (greater than 75 mmol/100 g).[8,11,12,17,72,94] Lemon balm has been reported to demonstrate high phenolics content and antioxidant properties (TEAC 4.06+/−0.31 mM/QE 1370.09+/−41.38 microM).[95] Lemon balm extracts and rosmarinic acid have both been reported to demonstrate antioxidant properties *in vitro,*[8,11,72] and rosmarinic acid and caffeic acid have demonstrated significant antioxidant and immune modulating activities.[10, 11, 72,73,93] During linoleic acid autoxidation and its EDTA-mediated oxidation, lemon balm showed antioxidant activity.[96] An *in-vitro* cytotoxicity assay demonstrated that lemon balm oil was very effective against a series of human cancer cell lines (A549, MCF-7, Caco-2, HL-60, K562) and one mouse cell line (B16F10). Further antioxidant activity of lemon balm has been reported as evidenced by the reduction of 1,1-diphenyl-2- picrylhydrazyl (DPPH).[97] Studies have demonstrated that the cytoprotective effect of lemon balm extracts seen in rats was due in part to

free-radical scavenging properties.[10,17] Immunostimulating effects of a lemon balm extract were also demonstrated.[98] Inhibitory effects of rosmarinic acid from lemon balm on porcine pancreatic amylase were reported *in vitro*.[99]

- *Antiprotozoal effects:* Essential oils, monoterpenes, and sesquiterpenes from lemon balm were tested on bloodstream forms of *Leishmania major* and *Trypanosoma major*. These constituents were reported to be about 50- to 80-fold more toxic to *T. major* than were human HL-60 cells. None of the essential oils or terpenes were reported to be more toxic to *L. major* than HL-60.[78] Monoterpene and sesquiterpenes may possess antiprotozoal effects (anecdotal).
- *Antithrombotic effects:* Rosmarinic acid has been reported to demonstrate inhibitory effects on both the classical pathway convertase and the alternative pathway convertase. One study reported that rosmarinic acid inhibited 70% of the immunohemolysis of antibody-coated sheep erythrocytes by guinea pig serum via possible inhibition of the C3 convertase of the classical complement pathway. However, higher concentrations of rosmarinic acid were less effective.[73] Rosmarinic acid was also reported to inhibit C5 convertase in the classical pathway.[73,93]
- *Antithyroid effects:* Studies have shown that freeze-dried extracts of lemon balm were reported to inhibit the binding of bovine TSH to human thyroid plasma membranes and adenylate cyclase. In rat liver microsomes, lemon balm aqueous extract was reported to inhibit the extrathyroidal enzymatic T4-5′-deiodination to both T3- and T4-5′-deiodination.[31,32] The thyroid-stimulating immunoglobulin G (IgG) found in patients with Graves' disease has been reported to resemble TSH in its ability to bind to the thyroid plasma membrane and to activate the thyroid gland. Freeze-dried extracts of lemon balm were reported to exhibit antithyrotropic activity by forming adducts with TSH that bound weakly, if at all, to the TSH receptor. When IgG was incubated with extracts of lemon balm, a dose-dependent decrease was reported in the TSH-binding inhibitory activity. As a result of this reported decrease, adenylate cyclase activity was stimulated (thyroid-stimulating immunoglobulin activity) and thyroid iodine release was enhanced in the McKenzie assay system. Cinnamic acid has been reported to inhibit the binding of TSH to human thyroid membranes.[31,32] In euthyroid rats, the administration of freeze-dried extracts of lemon balm was reported to reduce pituitary and serum TSH concentrations.[33]

- *Emmenagogic effects:* One study suggested that freeze-dried extracts of lemon balm inhibited binding of 125I hCG to rat testis membranes.[38] In rats, prolactin serum levels and hypophyseal stores were reported to be reduced by 40 mg/100 grams of a freeze-dried extract of lemon balm.[33]
- *Spasmolytic effects:* Due to lack of clinical data, lemon balm has not been recommended for use as a spasmolytic agent.[18-20] Using histamine and acetylcholine as spasmogens in guinea pig ileum, no significant antispasmodic activity resulting from lemon balm extracts were reported.(18) Studies on isolated duodenum of rat have reported antispasmodic effects of lemon balm *in vitro.*[100]
- *Sedative effects:* In mice, an aqueous alcoholic extract of lemon balm was reported to produce dose-dependent sedation, inducing sleep and potentiating sub-hypnotic and hypnotic doses of pentobarbital. On the other hand, in the same study the essential oil of lemon balm was reported to have no sedative effect.[13] With high doses, a peripheral analgesic effect was noted.[13] In tests on Wistar strain rats and on laboratory mice, lemon balm dried extract was reported to exert influence on CNS in evoking antiaggressive activity. CNS studies of rat reported sedative, hypnotic, and analgesic effects of lemon balm *in vivo.*[100] An ethanolic extract of lemon balm was tested for affinity to the GABA(A)-benzodiazepine site, and moderate activity was reported.[101] However, a study of a volatile oil-free hydroalcoholic extract reported sedative activity in mice.
- *Cardiovascular effects:* One study demonstrated that aqueous extracts of lemon balm provoked a significant reduction in the cardiac rate in isolated rat hearts, while the contractile force remained unchanged. This was reported to be caused by the stimulation of cardiac muscarinic receptors.[102]

Pharmacodynamics/Kinetics

- Insufficient available data.

HISTORY

- Lemon balm is a delicate, low-growing (1-2 foot) perennial herb with lemon-smelling, pointed, heart-shaped or oval leaves, and small white or yellow flowers. The leaves are used medicinally.

Lemon balm is native to the Mediterranean region, and now is also grown in western Asia, the United States, and Europe.
- Lemon balm is commonly planted in gardens to attract bees. The name comes from the Greek word "melissa" which means "bee," and "balm," a short form of "balsam." The medicinal use of lemon balm has been documented since Ancient Greek and Roman times.

Condition

Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include:

- *Randomized controlled trial (RCT):* An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- *Equivalence trial:* An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- *Before and after comparison:* A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- *Case series:* A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- *Case-control study:* A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary & alternative medicine literature.

- *Cohort study:* A study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary & alternative medicine literature.
- *Meta-analysis:* A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- *Review:* An author's description of his or her opinion based on personal, non-systematic review of the evidence.
- *Systematic review:* A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, Year

Identifies the study being described in a row of the table.

N

The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as N. N includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of drop-outs that are not included in the analysis are considered to be weaker evidence for efficacy. (For systematic reviews the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.)

Statistically Significant?

Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as p values).

Quality of Study

A numerical score between 0-5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (*Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clinical Trials 1996;17[1]:1-12*). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).

- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad Score Calculation	
Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Magnitude of Benefit

This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:

- Large: if > 1 SD;
- Medium: if 0.5 to 0.9 SD;
- Small: if 0.2 to 0.4 SD.

In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation (Effect size = [Mean Treatment − Mean Placebo]/SDp).

Absolute Risk Reduction

This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies [(control event rate − experimental event rate/control event rate)]. Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column.

Number Needed to Treat

This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the absolute risk reduction into 1 (1/ARR).

Comments

When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/sub-groups (age, gender, etc.). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DICUSSION

Herpes Simplex Virus Infections

- *Summary:* Rigorous clinical data are lacking. Preliminary clinical studies demonstrate promising effects. See Tables 3 and 4.
- *Evidence:* Vogt et al. investigated the efficacy of a cream containing lemon balm extract in a randomized, placebo controlled, double-blind trial in 116 patients with Herpes simplex infections.[103] Patients were treated with either Lomaherpan Creme or placebo two to four times per day over a period of up to 10 days. Symptoms were documented after day two and at the end of the treatment period (average five days). Symptoms investigated were reddening, swelling, blisters, erosions, scab, pain, and healing. Severity of symptoms was expressed in a score from one to four. Overall evaluation used a score from one to five. Regression of reddening and reduction of swelling were reported as statistically significant vs. placebo. Overall evaluation of efficacy was reported as significantly positive vs. placebo both by patients and doctors. The authors suggested that Lomaherpan proved effective in the treatment of Herpes simplex infections. Efficacy was greater, the earlier treatment commenced.
- A placebo controlled, double-blind trial was conducted to evaluate the efficacy of lemon balm in the treatment of herpes simplex skin or mucosa infections in 116 patients.[24] To be included into the trial, patients must have had symptoms for no more than 72 hours, could have either skin or transitional mucosa infections, and could not be on any antiviral treatment. Patients could apply placebo or topical Lomahephan® (1% dried lemon balm extract) 2-4 times per day for 5-10 days. Outcome measures assessed redness, swelling, scabs, pain, healing, and vesicles on a one to four point symptom scale, lesion size, and efficacy (globally assessed by patients and physicians). Results reported that at day two, redness and swelling were significantly improved in the lemon balm group ($p = 0.0055$ and $p = 0.25$, respectively) compared to the placebo group. Global assessment of efficacy by patients ("very good" rating 24 times in the treatment group vs. 11 times in the placebo group, $p = 0.022$) and physicians ("very good" rating in 25 times in the treatment group and 10 times in the placebo group, $p = 0.031$) were reported as significantly higher in the lemon balm group vs. the placebo group. Reported side effects included irritation in one patient tak-

ing lemon balm and in two patients taking placebo. Two patients taking placebo also reported a burning sensation. Subgroup analysis of 67 patients demonstrated a quicker decrease in lesion area in the lemon balm group, which was not significant on day two but was significant on day five ($p = 0.012$). One limitation of this trial is the flexibility in dosing regimen.

- Koytchev et al. conducted a randomized, placebo controlled, double-blind trial to examine the effects of lemon balm in 66 patients with a history of recurrent herpes labialis.[22] Patients must have experienced at least four episodes per year to be included in the study. Patients received either placebo or Lomaherpan® (1% cream of freeze-dried lemon balm extract) and were treated topically on the affected area four times per day for five days. The patients were instructed to start the application within four hours of symptoms and return for a physician visit within 24 hours. Symptoms including bother, number of blisters, and size of affected area were scored on a scale developed for acyclovir trials. The primary outcome measure was a symptom score on day two, and secondary endpoints included total scores of symptoms over five days of treatment. Results revealed a symptom score on day two of 4.03 in the lemon balm group vs. 4.94 in the placebo group ($p = 0.042$). According to the authors, the difference between total scores was not significant ($p = 0.16$). Physician assessment was also reported as not significant. Limitations include lack of reporting of side effects and tolerance of treatment.
- A case series was conducted to study the efficacy of lemon balm in the treatment of 115 patients with cold sores. To be included on the study, patients experienced symptoms for less than 72 hours. Cream containing 1% dried lemon balm extract was applied to areas of herpes simplex infection as needed up to five times per day, up to 14 days.[23,24] The primary endpoint was the complete healing of the lesion. Healing was completed in 60% of the patients by day four, 87% by day six, and 96% by day eight. According to the authors, these results suggested that the benefit from using lemon balm was dubious. The effect attributed to lemon balm was reported as no shorter than that of the natural course of the disease. The rate of adverse effects was 2.6% (three patients) and included reddening of the skin, burning sensation, paresthesia, and in one case, residual pigmentation. This study is limited by its lack of a placebo control group.

TABLE 3. Evidence Table

Condition	Study Design	Author, Year	N	Statistically Significant?	Quality of Study 0-2 = poor 3-4 = good 5 = excellent	Magnitude of Benefit	ARR	NNT	Comments
Herpes simplex	Randomized, double-blind trial	Vogt, 1991	116	Yes	4	Medium	26%	4	Cream with 1% lemon balm (70:1) used bid to qid x 10 days. Side effects less than 1%; early treatment improved efficacy.
Herpes simplex	Randomized, placebo controlled, double-blind trial	Wölbling, 1994	116	Yes	3	Small	24.9%	4	Cream with 1% lemon balm (70:1) used bid to qid x 5-10 days.
Herpes simplex labialis	Randomized, placebo controlled, double-blind trial	Koytchev, 1999	66	No	2	NA	NA	NA	Cream with 1% lemon balm (70:1) applied within 4 hours of symptoms, then qid x 5 days.
Herpes simplex	Case series	Wölbling, 1984; Wölbling, 1994	115	No	1	NA	NA	NA	Cream with 1% lemon balm used 5 times per day x 14 days. No placebo control group.
Agitation in dementia	Randomized, placebo controlled, double-blind trial	Ballard, 2002	72	Yes	3	Small	Reduction in Cohen-Mansfield Agitation Inventory (CMAI): 24%	4	Lotion with lemon balm applied to patients' face and arms bid.
Anxiety	Randomized, placebo controlled, double-blind trial	Büchner, 1974	102	Yes	4	NA	NA	NA	Combination product used at 0.23 mL/kg body weight.
Anxiety	Case series	Lagoni, 1998	92	NA	2	NA	NA	NA	Combination product used.
Anxiety	Case series	Schmidt, 1992	1599	NA	2	NA	NA	NA	Combination product used. 1395 patients evaluated.
Cognitive performance	Randomized, controlled trial	Akhondzadeh, 2003	42	Yes	3	Small	NA	NA	Lemon balm extract used at 60 drops/ day.
Cognitive performance	Randomized, placebo controlled, double-blind trial	Herberg, 1996	48	Yes	2	Small	NA	NC	2 tablets of combination product used.

Condition	Study Design	Author, Year	N	Statistically Significant?	Quality of Study 0-2 = poor 3-4 = good 5 = excellent	Magnitude of Benefit	ARR	NNT	Comments
Cognitive performance and mood	Randomized, placebo controlled, double-blind crossover trial	Kennedy, 2001	20	NA	2	NA	NA	NA	300, 600, and 900mg of standardized extract used on alternating days.
Cognitive performance	Randomized, crossover trial	Kennedy, 2003	20	NA	2	NA	NA	NA	600, 1000, and 1600mg dried leaf capsules used at 7-day intervals by healthy volunteers.
Dyspepsia	Multicenter, randomized, placebo controlled, double-blind trial	Madisch, 2004	120	Yes	3	Medium	Relief from gastro-intestinal symptoms: 40%	2.5	Combination product used.
Dyspepsia	Double-blind, placebo controlled trial	Madisch, 2001	60	Yes	3	Medium	NA	NA	Combination product used.
Dyspepsia	Multicenter case series	Borho, 1991	152	NA	1	NA	NA	NA	Combination product used.
Sleep quality, well-being, and tolerability	Multicenter, randomized, placebo controlled, double-blind trial	Cerny, 1999	98	No	4	NA	23.9%	4	Healthy volunteers used combination product, three tablets qd, half-hour before bedtime.
Sleep quality	Randomized, placebo controlled, double-blind trial	Dressing, 1996	68	Yes	3	Medium	40% overall evaluation	3	Combination product used.
Sleep quality	Randomized, controlled, double-blind, crossover trial	Lindahl, 1989	27	Yes	2	Small	NA	NA	Combination product used, short study duration.
Sleep quality, mild to severe insomnia	Randomized, placebo controlled trial	Widy-Tyszkiewicz, 1997	50	Yes	2	Medium	NA	NA	Combination product used.
Sleep quality	Controlled, double-blind trial	Dressing, 1992	20	Yes	1	NA	NA	NA	Healthy volunteers used combination product; not randomized.
Sleep quality	Case series	Orth-Wagner, 1995	225	Yes	1	NA	NA	NA	Combination product used.

TABLE 4. Explanation of Columns in Natural Standard Evidence Table

1	2	3	4	5	6	7	8	9	10
Condition	Study Design	Author, Year	N	Statistically Signifi-cant?	Quality of study 0-2 = poor 3-4 = good 5 = excellent	Magnitude of Benefit	Absolute Risk Reduction	Number Needed to Treat	Comments

Agitation in Dementia

- *Summary:* Limited data are available supporting the use of lemon balm as a treatment of agitation in dementia patients. Additional study is necessary before a conclusion can be drawn. See Table 3.
- *Evidence:* Ballard et al. conducted a randomized, placebo controlled, double-blind trial to determine the value of aromatherapy with essential oil of lemon balm for agitation in 72 patients with severe dementia.[39] Patients with clinically significant agitation in the context of severe dementia were included in the study. Lotion enriched with either lemon balm essential oil or placebo oil was applied to patients' faces and arms twice per day. Measurements of effectiveness included 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). Sixty percent of the active treatment group and 14% of the placebo-treated group reported a 30% reduction of CMAI score, with an overall improvement in agitation (mean reduction in CMAI score) of 35% in patients receiving lemon balm essential oil and 11% in those treated with placebo. Quality of life indices were also reported to improve significantly more in patients receiving the active treatment. No significant side effects were reported. Although the results of this trial are promising, this trial is limited due to a small sample size.

Anxiety

- *Summary:* Preliminary human evidence has been published that supports the use of lemon balm for anxiety, commonly referred to in the literature as psycho-vegetative disturbances. Further research is needed to confirm these results. See Table 3.

- *Evidence:* Büchner et al. conducted a randomized, placebo controlled, double-blind trial to examine the efficacy of lemon balm in 102 patients with anxiety and somatic complaints.[37] Subjects were assigned to take either placebo or Klosterfrau Melissengeist® at a dose of 0.23 mL/kg body weight three times per day for eight weeks. Outcome measures included psychological tests, which were taken before and during the eight-week trial. Results reported a significant improvement of the clinical state, including improvements in symptoms of "vegetative disturbances," including "inner restlessness," blushing, palpitation, and headache ($p < 0.05$). The PF 16 Cattell test demonstrated a significant difference for dimension C = Ego Strength vs. Ego Weakness ($p < 0.05$). Significant differences between the experimental and the control groups were also reported in the FPI test for the dimensions of nervousness ($p < 0.01$) and excitability ($p < 0.02$). The FPI dimension of emotional lability also demonstrated significant differences between the two groups ($p < 0.05$). Pronounced effects were reported in female subjects ($p < 0.01$). Eight patients in the treatment group reported side effects including slight nausea, diarrhea, headache, and palpitations, and five patients in the placebo group reported nausea, diarrhea, and headache. The major limitation of this trial is that it assessed the efficacy of a combination product. Further randomized, controlled trials assessing lemon balm monotherapy are warranted.
- In a multicenter, four-week study involving 92 patients, the herbal compound Seda-Plantinag was tested as an alternative to prescription sedatives.[104] According to the study results, Seda-Plantinag did not lead to any signs of fatigue during the day. Patients reported a clear decrease in the degree of their states of agitation or excitement, as well as improvements with regard to their power of concentration and social efficiency. The authors suggested that a combination of single herbal agents with sedative, psychotropic effects proved to be well tolerated and may serve as an alternative for synthetic tranquillizers, even if prescribed regularly in the practice.
- In a large case series, 1599 patients with symptoms of anxiety were treated with Euvegal coated tablets (a combination product with *Valeriana officinalis* and lemon balm).[105] Patients reporting nervousness, fatigue, and sleep disturbances were included in the study. Patients were given one to two tablets of Euvegal twice per day over a four-week period. After week two and week four, sever-

ity of symptoms and possible adverse effects were documented. A total of 1395 patients completed the observation. In two-thirds an almost complete regression of symptoms was observed. Over 90% of patients reported an improvement. Mild adverse effects were reported in 32 cases. Limitations of this study are that it assessed the efficacy of a combination product and that it was not a randomized, controlled trial.

Cognitive Performance

- *Summary:* Clinical data suggest that the use of standardized lemon balm extract has some effect on particular self-reported measures of mood and cognition through cholinergic activities.[4,5,14] More rigorous studies need to be conducted using patient-relevant outcomes to better assess the validity of these results as they apply to patient care. See Table 3.
- *Evidence:* Akhondzadeh et al. conducted a randomized, controlled trial to assess the efficacy and safety of lemon balm extract in 42 patients with Alzheimer's disease.[62] The study included patients with mild to moderate Alzheimer's disease. Patients were given a fixed dose of 60 drops/day of lemon balm extract. The primary outcome measures were changes in the cognitive subscale of an Alzheimer's disease assessment scale and on the clinical dementia rating. At four months, the results demonstrated that lemon balm extract produced a significantly better outcome on cognitive function than placebo. No significant differences in the two groups in terms of observed side effects were reported, except agitation, which was more common in the placebo group. The authors suggested that from these results lemon balm may be beneficial in the treatment of patients with mild to moderate Alzheimer's disease. Further research is needed to confirm these results.
- In a randomized, placebo controlled, double-blind trial, Herberg et al. investigated the everyday safety of a *Valeriana officinalis-Humulus lupulus*-lemon balm combination in 48 adults aged 30 to 60 years old. Subjects received two tablets (95 mg *Valeriana officinalis*, 15 mg *Humulus lupulus,* and 85 mg lemon balm per tablet) or placebo three times per day for two weeks. Cognitive performance was assessed using a computerized test battery. The combination with alcohol (mean 0.5%) was also investigated. No inhibition of cognitive performance was reported. According to the authors, statistically significant differences vs. placebo concerned improve-

ment of general well-being and cognitive skills only. No significant side effects were reported. The authors reported that the *Valeriana officinalis-Humulus lupulus*-lemon balm combination did not affect the effect of alcohol consumption.

- Kennedy et al. conducted a randomized, placebo controlled, double-blind, crossover trial to examine effects of three doses of lemon balm on cognition and mood in 20 participants.[35] Participants received either 300 mg, 600 mg, or 900 mg of a standardized extract of lemon balm or placebo, on different days, each separated by a seven-day washout period. Outcome measures included the cognitive performance as assessed by Cognitive Drug Research (CDR) computerized test battery and subjective mood rating as assessed by Bond-Lader visual analogue scales. The results demonstrated a sustained increase in "accuracy of attention" after ingesting 600 mg and reductions in "secondary memory" and "working memory" that were time- and dose-dependent. Patients reported reductions in "alertness" after the administration of 900 mg and reported that "calmness" was elevated after the administration of 300 mg. A limitation of this study is the small sample of young, healthy subjects not representative of the population of patients with dementia who may benefit from lemon balm.
- Kennedy et al. conducted a randomized, placebo controlled, double-blind, crossover study which investigated the acute effects on cognition and mood of a standardized extract of lemon balm in 20 healthy adults.[2] Participants received single doses of 600 mg, 1000 mg, and 1600 mg of lemon balm (Pharmaton) or a matching placebo at seven-day intervals. Cognitive performance was assessed using the Cognitive Drug Research (CDR) computerized test battery and two serial subtraction tasks. A sustained improvement in "accuracy of attention" following 600 mg of lemon balm and time- and dose-specific reductions in both "secondary memory" and "working memory" factors were demonstrated in the treatment group. Self-rated "calmness," as assessed by Bond-Lader mood scales, was reported to be elevated at the earliest time points by the lowest dose, and "alertness" was reported to be significantly reduced at all time points after the highest dose. A limitation of this study is the small sample of young, healthy subjects not representative of the population of patients with dementia who may benefit from lemon balm.

Colitis

- *Summary:* Limited clinical evidence is available supporting the use of lemon balm for the treatment of chronic colitis. See Table 3.
- *Evidence:* In a case series, 24 patients with chronic non-specific colitis were treated with a combination of *Taraxacum officinale*, *Hypericum perforatum*, lemon balm, *Calendula officinalis*, and *Foeniculum vulgare.*[106] Primary outcome measures included decrease in symptoms. Results demonstrated the disappearance of spontaneous and palpable pains along the large intestine in 95.83% of the patients by day 15 of treatment, and daily bowel movements in the patients with obstipation syndrome. Although these results are promising, lack of randomized, controlled trials with an adequate sample population prevents meaningful extrapolation of these results to clinical practice.

Dyspepsia

- *Summary:* Clinical evidence of varying quality suggests that lemon balm may help reduce dyspepsia as a component of combination products. However, further research is necessary before a conclusion can be drawn.
- *Evidence:* Madisch et al. conducted a multicenter, placebo controlled, double-blind trial using the commercially available, herbal combination preparation Iberogast®, which contains lemon balm, with and without the ingredient bitter candy tuft in 60 patients with functional dyspepsia.[63] Patients discontinued all medications for seven days and then received either of the Iberogast® preparations or a placebo for four weeks. Gastrointestinal symptom (GIS) score and total scores consisting of ten dyspeptic symptoms rated on a Likert scale measured at baseline, at week two, and at week four were reported as statistically significant compared to baseline at $p < 0.001$. Although the results from this study are promising, it is limited due to the fact that the preparation studied was a combination product and the contribution of the lemon balm component to the effects is not discernable without direct comparisons of each individual component.
- Madisch et al. conducted a multicenter, randomized, placebo controlled, double-blind trial to assess the efficacy and safety of an herbal combination product STW 5-II, which contains extracts from bitter candy tuft, matricaria flower, peppermint leaves, cara-

way, licorice root, and lemon balm, for the treatment of patients with functional dyspepsia.[107] One hundred twenty patients with functional dyspepsia were randomly assigned to one of four treatment groups. The primary outcome measure was the improvement of a standardized gastrointestinal symptom (GIS) score. During the first four weeks, the GIS score was reported to significantly decrease in subjects on active treatment compared to those on placebo. After eight weeks 43.3% on active treatment and 3.3% on placebo reported complete relief of symptoms. Although the results from this study are promising, it is limited due to the fact that the preparation studied was a combination product, and the contribution of the lemon balm component to the effects is not discernable without direct comparisons of each individual component.

- In a multicenter, open case series, the efficacy of Gastrol S (a combination product containing lemon balm) in the treatment of nervous irritable stomach and dyspepsia was tested in 152 patients.[108] A majority (58.5%) of the patients participated in the study for more than eight weeks. In 65.5% a dosage of 20-25 drops three times per day was recommended. Tolerance was reported as "good" by 93.4% of the patients, and the therapy was assessed as "very good" by 75.5%. In 82.2% of all documented cases, a distinct improvement of symptoms was reported. This study is limited due to the fact that the preparation studied was a combination product and the contribution of the lemon balm component to the effects is not discernable without direct comparisons of each individual component.

Sleep Quality

- *Summary:* High-quality clinical evidence supporting the use of lemon balm as a sedative/hypnotic is lacking.[70] The available evidence is conflicting, of low quality, or derived from early-phase trials in humans. A systematic review published in 1998 concluded that the paucity of evidence made the sedative effect of lemon balm difficult to assess given that studies usually employed combination products, most often with *Valeriana officinalis*, which itself possesses sedative properties.[27] Rigorous clinical studies are required to better support use of lemon balm as a sedative/hypnotic. See Table 3.
- *Evidence:* Cerny et al. conducted a multicenter, randomized, placebo controlled, double-blind study to assess tolerance and effi-

cacy of a *Valeriana officinalis*/lemon balm combination product in the treatment of minor sleep disorders in 98 healthy volunteers.[34] Subjects were randomly assigned to receive placebo or three tablets of a combination product (120 mg *Valeriana officinalis,* 80 mg lemon balm) one half-hour before bedtime for 30 days. Outcome measures included rating scales for tolerability, sleep quality, and well-being, as well as laboratory and physical parameters. Results reported a rating of good overall tolerability by 93% of subjects in the *Valeriana officinalis*/lemon balm group vs. 91% of subjects in the placebo group. Incidence of mild adverse effects reported was 28.8% in the *Valeriana officinalis*/lemon balm group vs. 28.1% in the placebo group. Among those taking *Valeriana officinalis*/lemon balm, 33.3% of patients reported an improvement in sleep quality vs. 9.4% in the placebo group ($p = 0.04$). No significant changes were reported in regard to laboratory tests, physical examination, or rating of well-being, even though the *Valeriana officinalis*/lemon balm group reported a higher quality of sleep compared to the placebo group. From these results, the authors reported safety of the *Valeriana officinalis*/lemon balm combination product and possible efficacy in improving sleep quality. Though results may appear to be promising, it is important to note that results reflect efficacy and safety of a combination product. Further randomized, controlled trials assessing monotherapy of lemon balm in improving sleep quality are warranted.

- A multi-center, placebo controlled, double-blind trial studied the therapeutic effect of a high dose standardized *Valeriana officinalis*-lemon balm combination (Euvegal forte) on mild insomnia in 68 patients.[109] Patients with mild insomnia as defined by the DSM-3-R and the ICD10 were included in the study. Outcome measures included quality of sleep, general health, and overall clinical impression. Patients received two tablets twice per day of Euvegal and were examined after two weeks of treatment. All criteria were reported as significantly improved vs. placebo. No hangover or rebound phenomena were reported.
- Lindahl et al. conducted a randomized, double-blind, crossover trial with 27 subjects with sleep difficulties to assess the effects of a combination product containing *Valeriana officinalis*, *Flores humuli,* and lemon balm on sleep quality.[110] Subjects received the combination product (400 mg of *Valeriana officinalis*, 375 mg of *Flores humuli,* and 160 mg of lemon balm) or placebo for the first night and then received the opposite treatment the following night.

Outcome measures including sleep quality were recorded on a patient questionnaire that was completed on the second morning. From the results, the authors reported that 21 out of 27 patients rated the combination product better than placebo. The difference between ratings of the two preparations was reported as statistically significant ($p < 0.001$). In terms of sleep quality, 24 out of 27 subjects reported an improvement, and 12 reported "perfect" sleep. No side effects were noted. Short study duration limits the clinical utility of these results. Long-term trials may be more helpful in evaluating efficacy of a product in sleep disturbances. Longer, well-designed, randomized, controlled trials assessing the monotherapy of lemon balm are warranted.

- In a randomized, placebo controlled trial, the sedative effects of a *Valeriana officinalis-Humulus lupulus*-lemon balm-*Leonurus cardiaca* combination product were examined in 50 male alcohol abusers with sleep disturbances and other withdrawal symptoms.[111] From their evaluation of the results, the authors reported significant improvement in sleep quality and significant decrease in sleep interruption and bad dreams. Morning sleepiness was observed as a side effect.
- Dressing et al. conducted a controlled, double-blind study to assess effects of a *Valeriana officinalis*/lemon balm preparation on sleep in 20 healthy volunteers.[36] Subjects were divided into good and poor sleepers. Subjects received either a *Valeriana officinalis*/lemon balm preparation (Euvegal Forte®: 160 mg *Valeriana officinalis*, 80 mg lemon balm), triazolam (125 mg), or placebo at bedtime. Outcome measures included sleep efficiency, length, time in sleep stages, and delta sleep. From the results, the authors suggested that the use of the *Valeriana officinalis*/lemon balm combination product on the poor sleepers induced a significant increase in sleep efficiency and in sleep stages three and four. A significant increase in delta sleep in the group of poor sleepers was also reported. Rebound effects were not reported for groups taking the *Valeriana officinalis*/lemon balm preparation or the triazolam. Limitations to this study include lack of randomization and the use of a combination product.
- In an open, multicenter study of sleep quality, the efficacy and tolerance of Novo-Baldriparan, containing *Valeriana officinalis*, *Humulus lupulus,* and lemon balm, was investigated in 225 patients.[112] The study included patients that reported difficulties falling asleep and

sleeping through the night and/or states of nervous agitation. The two-week therapy with this product was reported to yield a significant improvement in the severity and frequency of the principal symptoms. According to the reported results, both the nervous agitation, which was identified as the underlying cause of the sleep disorders, as well as the sleep disorders themselves were significantly reduced. Specifically, the authors reported that the difficulties falling asleep improved in 89% of the patients, the difficulties sleeping through the night improved in 80%, and the states of nervous agitation improved in 82% of the patients. The quantity of sleep was reported to increase markedly, while external stressors were reported as being less distressing. A similar improvement in the somatic symptoms, like headache, dizziness, cardiovascular, or gastrointestinal discomfort, was reported. The reduction in heart rate and blood pressure under therapy was reported to be accompanied as a whole by a noticeable improvement in the patients' well being. The tolerability of Novo-Baldriparan was rated positively by both physicians and patients: 96.9% of the physicians and 96.4% of the patients gave the rating "very good" or "good." The primary limitation of this study includes the use of a combination product.

PRODUCTS STUDIED

Brands Used in Clinical Trials

- Euvegal Forte® (Spitzner, Germany)[36,105,109]
- Iberogast® (Phyto Pharmica, Germany)[63]
- Klosterfrau Melissengeist® (Klosterfrau, Germany)[37]
- Songha Night® (Pharmaton Natural Health Products, Bioggio/Lugano, Switzerland)[34]
- Lomaherpan® cream[23,24,103]
- STW 5-II[107]
- STW-5-S[63]
- Baldriparan Stark N Beruhigungs-Dragees[68]
- Seda-Plantina[104]
- Gastrol S[108]

United States Patents

- 6,881,776 Gel compositions
- 6,831,103 Composition comprising theanine
- 6,827,944 Percutaneous administration preparations
- 6,797,284 Phytopharmaceutical food products or integrators
- 6,780,825 Cleansing compositions with milk protein and aromatherapy
- 6,703,022 Composition and method useful for treating colic
- 6,664,225 Single-dose quick-dissolving cleansing agent with medicinal properties
- 6,641,801 Gargle method to reduce the duration of common cold symptoms
- 6,629,835 Combinations of diterpene triepoxide lactones and ditepene lactones or triterpenes for synergistic inhibition of cyclooxygenase-2
- 6,589,566 Composition comprising theanine
- 6,509,042 Antiviral composition
- 6,444,253 Flavor delivery system
- 6,423,336 Chewing gums and method of manufacturing the same
- 6,416,769 Cosmetic compositions comprising exfoliating enzymes and uses thereof
- 6,405,948 Liberating intracellular matter from biological material
- 6,346,250 Composition and method useful for treating colic
- 6,342,208 Oil-in-water emulsion containing C10-C24 fatty acid derivatives for treating skin of mammals
- 6,210,738 Freeze-dried ginseng berry tea
- 6,165,964 Aqueous solution of essential oil, and antimicrobial agents, microbicides and antimicrobial finishes for washing
- 6,060,061 Method for preventing or treating disorders involving an inflammatory process
- 6,024,998 Process for the removal of undesired lipophilic contaminations and/or residues, which are contained in beverages or in vegetable preparations
- 5,958,499 Fluidized fat
- 5,906,848 Process for the removal of undesired contaminations and/or residues contained in beverages or in vegetable preparation
- 5,869,340 Plant clones containing elevated secondary metabolite levels
- 5,720,962 Analgesic lotion for hemorrhoids and method of making such lotion

- 5,472,699 Composition and method for visibly reducing the size of skin pores
- 5,415,861 Composition and method for visibly reducing the size of skin pores
- 5,399,353 Preparations for covering undamaged and/or damaged areas of human or animal skin
- 5,318,503 Method and apparatus for auditory and olfactory relaxation
- 5,176,913 Process for preparing a partial extract containing the volatile in steam components and further lipophilic components of medical plants and/or spice plants
- 5,064,675 Herbal extract composition
- 4,933,177 Cosmetic compositions for the treatment of the hair and skin contain in the form of powder particles resulting from the pulverization of at least one plant substance and a cohesion agent
- 4,767,618 Cosmetic compositions for the treatment of the hair and skin in the form of powder particles resulting from the pulverization of at least one plant substance and a cohesion agent
- 4,569,839 Cosmetic compositions for the treatment of the hair and skin in the form of powder particles resulting from the pulverization of at least one plant substance and a cohesion agent
- 4,358,442 Rosmarinic acid-phospholipide-complex
- 4,354,035 Process for isolating rosmarinic acid from plants
- 4,329,361 Use of rosmarinic acid in the treatment of inflammations and pharmaceutical products used therein

AUTHOR/UPDATE INFORMATION

- Last Updated: August 2005.
- Authors/Editors: Thomas Brendler, BA (PlantaPhile, Berlin); Joerg Gruenwald, PhD (Phytopharm Consulting); Benjamin Kligler, MD, MPH (Continuum Center for Health and Healing); David Keifer, MD (University of Arizona); Tracee Rae Abrams, PharmD (University of Rhode Island); Jen Woods, BS (Northeastern University); Heather Boon, BScPhm, PhD (University of Toronto); Catherine DeFranco Kirkwood, MPH, CCCJS-MAC (MD Anderson Cancer Center); Ethan Basch, MD (Memorial Sloan-Kettering Cancer Center); Hope J. Lafferty,

AM (Memorial Sloan-Kettering Cancer Center); Catherine Ulbricht, PharmD (Massachusetts General Hospital), Dana A. Hackman, BS (c) (Northeastern University).

- Blinded Peer-Review: Natural Standard Editorial Board.

REFERENCES

1. Coleta, M., Campos, M. G., Cotrim, M. D., and Proenca, da Cunha. Comparative evaluation of *Melissa officinalis* L., *Tilia europaea* L., *Passiflora edulis* Sims. and *Hypericum perforatum* L. in the elevated plus maze anxiety test. Pharmacopsychiatry 2001;34 Suppl 1:S20-S21.

2. Kennedy, D. O., Wake, G., Savelev, S., Tildesley, N. T., Perry, E. K., Wesnes, K. A., and Scholey, A. B. 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(10):1871-1881.

3. Kennedy, D. O., Little, W., and Scholey, A. B. Attenuation of laboratory-induced stress in humans after acute administration of *Melissa officinalis* (Lemon Balm). Psychosom. Med. 2004;66(4):607-613.

4. Perry, E. K., Pickering, A. T., Wang, W. W., Houghton, P., and Perry, N. S. Medicinal plants and Alzheimer's disease: Integrating ethnobotanical and contemporary scientific evidence. J. Altern. Complement Med. 1998;4(4):419-428.

5. Perry, E. K., Pickering, A. T., Wang, W. W., Houghton, P. J., and Perry, N. S. Medicinal plants and Alzheimer's disease: From ethnobotany to phytotherapy. J. Pharm. Pharmacol. 1999;51(5):527-534.

6. Ramos, Ruiz A., De la Torre, R. A., Alonso, N., Villaescusa, A., Betancourt, J., and Vizoso, A. Screening of medicinal plants for induction of somatic segregation activity in *Aspergillus nidulans*. J. Ethnopharmacol. 7-5-1996;52(3):123-127.

7. Herrmann, E. C., Jr. and Kucera, L. S. Antiviral substances in plants of the mint family (Labiatae). II. Nontannin polyphenol of *Melissa officinalis*. Proc. Soc. Exp. Biol. Med. 1967;124(3):869-874.

8. Hohmann, J., Zupko, I., Redei, D., Csanyi, M., Falkay, G., Mathe, I., and Janicsak, G. 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. Med. 1999;65(6):576-578.

9. Kucera, L. S. and Herrmann, E. C., Jr. Antiviral substances in plants of the mint family (Labiatae). I. Tannin of *Melissa officinalis*. Proc. Soc. Exp. Biol. Med. 1967; 124(3): 865-869.

10. Lamaison, J. L., Petitjean-Freytet, C., and Carnat, A. [Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid]. Pharm. Acta Helv. 1991;66(7):185-188.

11. Triantaphyllou, K., Blekas, G., and Boskou, D. Antioxidative properties of water extracts obtained from herbs of the species Lamiaceae. Int. J. Food Sci. Nutr. 2001; 52(4):313-317.

12. Dragland, S., Senoo, H., Wake, K., Holte, K., and Blomhoff, R. Several culinary and medicinal herbs are important sources of dietary antioxidants. J. Nutr. 2003; 133(5):1286-1290.

13. Soulimani, R., Fleurentin, J., Mortier, F., Misslin, R., Derrieu, G., and Pelt, J. M. Neurotropic action of the hydroalcoholic extract of *Melissa officinalis* in the mouse. Planta. Med. 1991;57(2):105-109.

14. Wake, G., Court, J., Pickering, A., Lewis, R., Wilkins, R., and Perry, E. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. J. Ethnopharmacol. 2000;69(2):105-114.

15. Sadraei, H., Ghannadi, A., and Malekshahi, K. Relaxant effect of essential oil of *Melissa officinalis* and citral on rat ileum contractions. Fitoterapia 2003;74(5): 445-452.

16. Farnsworth, N. R., Bingel, A. S., Cordell, G. A., Crane, F. A., and Fong, H. H. Potential value of plants as sources of new antifertility agents I. J. Pharm. Sci. 1975; 64(4):535-598.

17. Khayyal, M. T., el Ghazaly, M. A., Kenawy, S. A., Seif-el-Nasr, M., Mahran, L. G., Kafafi, Y. A., and Okpanyi, S. N. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung 2001;51(7): 545-553.

18. Forster, H. B., Niklas, H., and Lutz, S. Antispasmodic effects of some medicinal plants. Planta. Med. 1980;40(4):309-319.

19. Israel, D. and Youngkin, E. Q. Herbal therapies for perimenopausal and menopausal complaints. Pharmacotherapy 1997;17(5):970-984.

20. Kennedy, D. O., Scholey, A. B., Tildesley, N. T., Perry, E. K., and Wesnes, K. A. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). Pharmacol. Biochem. Behav. 2002;72(4):953-964.

21. Kucera, L. S., Cohen, R. A., and Herrmann, E. C., Jr. Antiviral activities of extracts of the lemon balm plant. Ann N.Y. Acad. Sci. 7-30-1965;130(1):474-482.

22. Koytchev, R., Alken, R. G., and Dundarov, S. Balm mint extract (Lo-701) for topical treatment of recurring herpes labialis. Phytomedicine 1999;6(4):225-230.

23. Wolbling, R. H. and Milbradt, R. [Clinical manifestations and treatment of Herpes simplex infections]. Therapiewoche 1984;34:1193-1200.

24. Wolbling, R. H. and Leonhardt, K. Local therapy of herpes simplex with dried extract from *Melissa officinalis*. Phytomedicine 1994;1:25-31.

25. May, G. and Willuhn, G. [Antiviral effect of aqueous plant extracts in tissue culture]. Arzneimittelforschung 1978;28(1):1-7.

26. Yamasaki, K., Nakano, M., Kawahata, T., Mori, H., Otake, T., Ueba, N., Oishi, I., Inami, R., Yamane, M., Nakamura, M., Murata, H., and Nakanishi, T. Anti-HIV-1 activity of herbs in Labiatae. Biol. Pharm. Bull. 1998;21(8):829-833.

27. Wong, A. H., Smith, M., and Boon, H. S. Herbal remedies in psychiatric practice. Arch. Gen. Psychiatry 1998;55(11):1033-1044.

28. Berdonces, J. L. [Attention deficit and infantile hyperactivity]. Rev. Enferm. 2001;24(1):11-14.

29. Galasinski, W., Chlabicz, J., Paszkiewicz-Gadek, A., Marcinkiewicz, C., and Gindzienski, A. The substances of plant origin that inhibit protein biosynthesis. Acta Pol. Pharm. 1996;53(5):311-318.

30. Chlabicz, J. and Galasinski, W. The components of *Melissa officinalis* L. that influence protein biosynthesis *in-vitro*. J. Pharm. Pharmacol. 1986;38(11):791-794.

31. Auf'mkolk, M., Ingbar, J. C., Kubota, K., Amir, S. M., and Ingbar, S. H. Extracts and auto-oxidized constituents of certain plants inhibit the receptor-binding and the biological activity of Graves' immunoglobulins. Endocrinology 1985;116(5): 1687-1693.

32. Auf'mkolk, M., Ingbar, J. C., Amir, S. M., Winterhoff, H., Sourgens, H., Hesch, R. D., and Ingbar, S. H. Inhibition by certain plant extracts of the binding and adenylate cyclase stimulatory effect of bovine thyrotropin in human thyroid membranes. Endocrinology 1984;115(2):527-534.

33. Sourgens, H., Winterhoff, H., Gumbinger, H. G., and Kemper, F. H. Antihormonal effects of plant extracts. TSH- and prolactin-suppressing properties of Lithospermum officinale and other plants. Planta Med. 1982;45(2):78-86.

34. Cerny, A. S. and Schmid, K. Tolerability and efficacy of valerian/lemon balm in healthy volunteers; a double-blind placebo-controlled, multicentre study. Fitoterapia 1999;70(3):221-228.

35. Kennedy, D., Scholey, A., Tildesley, N., and Wesnes, K. Dose-dependent changes in mood and cognitive performance following single doses of *Melissa officinalis* (Lemon Balm) to healthy young adults. Proceedings of the British Psychological Society 2001;9(2):209.

36. Dressing, H. Valerian combination therapy vs. benzodiazepine: Same efficacy in the treatment of sleeping disorders? Therapiewoche 1992;42(12):726-736.

37. Buchner, K.H., Hellings, H., Huber, M., Peukert, E., Spath, L., and Deininger, R. [Double blind study as evidence of the therapeutic effect of Melissengeist on psycho-vegetative syndromes]. Medizinische Klinik 1974;69(23):1032-1036.

38. Auf'mkolk, M., Kohrle, J., Gumbinger, H., Winterhoff, H., and Hesch, R. D. Antihormonal effects of plant extracts: Iodothyronine deiodinase of rat liver is inhibited by extracts and secondary metabolites of plants. Horm. Metab. Res. 1984;16(4): 188-192.

39. Ballard, C. G., O'Brien, J. T., Reichelt, K., and Perry, E. K. 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 2002;63(7):553-558.

40. Patora, J., Majda, T., Gora, J., and Klimek, B. Variability in the content and composition of essential oil from lemon balm (*Melissa officinalis* L.) cultivated in Poland. Acta Pol. Pharm. 2003;60(5):395-400.

41. Adzet, T., Ponz, R., and Schulte E. Genetic variability of the essential oil content of *Melissa officinalis*. 1992;58:558-561.

42. Adzet, T., Ponz, R., Wolf, E., and Schulte, E. Content and composition of *M. officinalis* oil in relation to leaf position and harvest time. 1992;58:562-564.

43. Baerheim-Svendsen, A. and Merkx, IJ. A simple method for screening of fresh plant material for glycosidic bound volatile compounds. 1989;55:38-40.

44. Hose, S., Zänglein, A., Berg, T. van den, Schultze, W., Kubeczka, K. H., and Czygan, F. C. Die Pharmazie. Im. Druck. Ontogenetic variation of the essential leaf oil of *Melissa officinalis* L. 1997; 52(3):247-253.

45. Mrlianova, M., Tekel'ova, D., Felklova, M., Reinohl, V., and Toth, J. The influence of the harvest cut height on the quality of the herbal drugs *Melissae folium* and *Melissae herba*. Planta Med. 2002;68(2):178-180.

46. Mrlianova, M., Tekel'ova, D., Felklova, M., Toth, J., Musil, P., and Grancai, D. [Comparison of the quality of *Melissa officinalis* L. cultivar Citra with Mellissas of European origin]. Ceska. Slov. Farm. 2001;50(6):299-302.

47. Vaverkova, S., Holla, M., and Takel, J. [The content and quality of *Melissa officinalis* essential oil after application of Rastim 30 DKV]. Ceska. Slov. Farm. 2001;50(1):46-50.

48. Patora, J. and Klimek, B. Flavonoids from lemon balm (*Melissa officinalis* L., Lamiaceae). Acta Pol. Pharm. 2002;59(2):139-143.

49. Ziakova, A., Brandsteterova, E., and Blahova, E. Matrix solid-phase dispersion for the liquid chromatographic determination of phenolic acids in *Melissa officinalis*. J Chromatogr. A 1-3-2003;983(1-2):271-275.

50. Araujo, C., Sousa, M. J., Ferreira, M. F., and Leao, C. Activity of essential oils from Mediterranean Lamiaceae species against food spoilage yeasts. J. Food Prot. 2003; 66(4):625-632.

51. Dimitrova, Z., Dimov, B., Manolova, N., Pancheva, S., Ilieva, D., and Shishkov, S. Antiherpes effect of *Melissa officinalis* L. extracts. Acta Microbiol Bulg. 1993; 29:65-72.

52. Heitz, A., Carnat, A., Fraisse, D., Carnat, A. P., and Lamaison, J. L. Luteolin 3'-glucuronide, the major flavonoid from *Melissa officinalis* subsp. officinalis. Fitoterapia 2000;71(2):201-202.

53. Palma, S. D., Manzo, R. H., and Allemandi, D. A. Dry plant extracts loaded on fumed silica for direct compression: Preparation and preformulation. Pharm. Dev. Technol. 1999;4(4):523-530.

54. Hener, U., Faulhaber, S., Kreis, P., and Mosandl, A. On the authenticity evaluation of balm oil (*Melissa officinalis* L.). 1995;50:60-62.

55. Schultze, W., König, W.A., Hilkert, A., and Richter, R. Melissenöle/Untersuchungen zur Echtheit mittels enantioselektiver Gaschromatographie und Isotopenverhältnis- Massenspektrometrie. 1995;135:557, 563 567, 571, 577-557, 564, 568, 574, 577.

56. Schultze, W., Zänglein, A., Klose, R., and Kubeczka, K. H. Die Melisse/ Dünnschichtchromatographische Untersuchung des ätherischen Öles. 1989;129: 155-163.

57. Tabatabai, A. S., Buchbauer, G., Jirovetz, L., and Nikiforov, A. Vergleichende Untersuchungen verschiedener Proben von Melissen-und Citronell-Ölen mittels GC-FID und GC-FTIR-MS sowie Multivar Datenanalayse. 1995;63(4):352.

58. Wolf, J. Melissenblatter/Mikro-Dunnschichtchromatographie. 1996;141(25): 2316.

59. Tekel, J., Vaverkova, S., Kovacicova, J., Hola, M., and Havranek, E. A screening method for the determination of the residues of uracil herbicides in *Melissa officinalis* L. 1994;49(899):901.

60. Berg, T. van den, Freundl, E., and Czygan, F. C. *Melissa officinalis* ssp. altissima: Characteristics of a possible adulteration of lemon balm. 1997;52(10): 802-808.

61. Nakashima, M. J. and Glaze, L. E. Extraction of light filth from whole leaves of alfalfa, lemon balm, papaya, and spearmint: collaborative study. J. Assoc. Off. Anal. Chem. 1987;70(6):997-999.

62. Akhondzadeh, S., Noroozian, M., Mohammadi, M., Ohadinia, S., Jamshidi, A. H., and Khani, M. *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 2003;74(7):863-866.

63. Madisch, A., Melderis, H., Mayr, G., Sassin, I., and Hotz, J. [A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study]. Z Gastroenterol. 2001;39(7):511-517.

64. Ward, N. I. and Savage, J. M. Metal dispersion and transportational activities using food crops as biomonitors. Sci. Total Environ. 5-23-1994;146-147:309-319.

65. West, I. and Maibach, H. I. Contact urticaria syndrome from multiple cosmetic components. Contact Dermatitis 1995;32(2):121.

66. Hausen, B. M. and Schulze, R. [Comparative studies of the sensitizing capacity of drugs used in herpes simplex]. Derm Beruf. Umwelt. 1986;34(6):163-170.

67. Schulz, H., Jobert, M., and Hubner, W. D. The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam. Phytomedicine 1998;5:449-458.

68. Herberg, K. W. Nebenwirkungen pflanzlicher Beruhigungsmittel/Leistung und Befinden nach Einnahme einer Baldrian-Hopfen-Kombination. Z. Allg. Med. 1996; 72:234- 240.

69. Santini, F., Vitti, P., Ceccarini, G., Mammoli, C., Rosellini, V., Pelosini, C., Marsili, A., Tonacchera, M., Agretti, P., Santoni, T., Chiovato, L., and Pinchera, A. *In vitro* assay of thyroid disruptors affecting TSH-stimulated adenylate cyclase activity. J. Endocrinol. Invest. 2003;26(10):950-955.

70. Gyllenhaal, C., Merritt, S. L., Peterson, S. D., Block, K. I., and Gochenour, T. Efficacy and safety of herbal stimulants and sedatives in sleep disorders. Sleep Med. Rev. 2000;4(3):229-251.

71. Agata, I., Kusakabe, H., Hatano, T., Nishibe, S., and Okuda, T. Melitric acids A and B, new trimeric caffeic acid derivatives from *Melissa officinalis*. Chem. Pharm. Bull. 1993; 41(9): 1608-1611.

72. Tagashira, M. and Ohtake, Y. New antioxidative 1,3-benzodioxole from *Melissa officinalis*. Planta. Med. 1988;64(6):555-558.

73. Englberger, W., Hadding, U., Etschenberg, E., Graf, E., Leyck, S., Winkelmann, J., and Parnham, M. J. Rosmarinic acid: A new inhibitor of complement C3- convertase with anti-inflammatory activity. Int. J. Immunopharmacol. 1988;10(6): 729-737.

74. Cohen, R. A., Kucera, L.S., and Herrmann, E. C. Antiviral activity of *Melissa officinalis* (lemon balm) extract (29600). Proceedings of the Society for Experimental Biology and Medicine 1964;117:431-434.

75. Felklova, M., Natherova, L., and Duskova, K. [Tannin compounds in leaves of *Melissa officinalis* L., invaded by Septoria melissae Desm]. Cesk. Farm. 1969;18(9): 457-460.

76. Mulkens, A. and Kapetanidis, I. [Flavonoids of the leaves of *Melissa officinalis* L. (Lamiaceae)]. Pharm.Acta Helv. 1987;62(1):19-22.

77. Thieme, H. and Kitze, C. [Occurrence of flavonoids in *Melissa officinalis* L]. Pharmazie 1973;28(1):69-70.

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

79. Brieskorn, C. H. and Krause, W. [Further triterpenes from *Melissa officinalis* L. (author's transl)]. Arch Pharm.(Weinheim) 1974;307(8):603-612.

80. Tittel, G., Wagner, H., and Bos, R. [Chemical composition of the essential oil from Melissa]. Planta Medica 1982;46:91-98.

81. Hefendehl, F. W. [Composition of etheric oil of *Melissa officinalis* L. and secondary changes of oil composition]. Arch Pharm. Ber. Dtsch. Pharm. Ges. 1970;303(4): 345-357.

82. Mulkens, A. and Kapetanidis, I. Eugenylglucoside, a new natural Phenylpropanoid Heteroside from *Melissa officinalis*. J. Nat. Prod. 1988;51:496-498.

83. Mulkens, A., Stephanou, E., and Kapetanidis, I. Heterosides a genines volatiles dans les feuilles de *Melissa officinalis* L. (Lamiaceae). Pharma Acta Helv 1985;60: 276-278.

84. Sarer, E. and Kökdil, G. Constituents of the essential oil from *Melissa officinalis*. Planta Med 1991;57:89-90.

85. Mulkens, A. and Kapetanidis, I. Etude de l'huile essentielle de *Melissa officinalis* L. (Laminaceae). Pharm Acta Helv. 1988;63:266-270.

86. Carnat, A. P., Carnat, A., Fraisse, D., and Lamaison, J. L. The aromatic and polyphenolic composition of lemon balm (*Melissa officinalis* L., subsp officinalis) tea. 1998; 72:301-305.

87. Koch-Heitzmann, I. and Czygan, F. C. Über wasserdampfflüchtige Diterpenkohlenwasserstoffe in nicht differenzierten Oberflächenkulturen/Untersuchungen an Kalluskulturen von *Melissa officinalis* L. 1985;II(40c):13-20.

88. Allahverdiyev, A., Duran, N., Ozguven, M., and Koltas, S. Antiviral activity of the volatile oils of *Melissa officinalis* L. against Herpes simplex virus type-2. Phytomedicine. 2004;11(7-8):657-661.

89. Larrondo, J. V., Agut, M., and Calvo-Torras, M. A. Antimicrobial activity of essences from labiates. Microbios 1995;82(332):171-172.

90. Iauk, L., Lo Bue, A. M., Milazzo, I., Rapisarda, A., and Blandino, G. Antibacterial activity of medicinal plant extracts against periodontopathic bacteria. Phytother. Res. 2003;17(6):599-604.

91. Friedman, M., Henika, P. R., Levin, C. E., and Mandrell, R. E. Antibacterial activities of plant essential oils and their components against Escherichia coli O157:H7 and Salmonella enterica in apple juice. J. Agric. Food Chem. 9-22-2004;52(19): 6042-6048.

92. Mimica-Dukic, N., Bozin, B., Sokovic, M., and Simin, N. Antimicrobial and antioxidant activities of *Melissa officinalis* L. (Lamiaceae) essential oil. J. Agric. Food Chem. 5-5-2004;52(9):2485-2489.

93. Peake, P. W., Pussell, B. A., Martyn, P., Timmermans, V., and Charlesworth, J. A. The inhibitory effect of rosmarinic acid on complement involves the C5 convertase. Int. J. Immunopharmacol. 1991;13(7):853-857.

94. Dimpfel, W., Pischel, I., and Lehnfeld, R. Effects of lozenge containing lavender oil, extracts from hops, lemon balm and oat on electrical brain activity of volunteers. Eur. J. Med. Res. 9-29-2004;9(9):423-431.

95. Ivanova, D., Gerova, D., Chervenkov, T., and Yankova, T. Polyphenols and antioxidant capacity of Bulgarian medicinal plants. J. Ethnopharmacol. 1-4-2005;96(1-2): 145-150.

96. Marongiu, B., Porcedda, S., Piras, A., Rosa, A., Deiana, M., and Dessi, M. A. Antioxidant activity of supercritical extract of *Melissa officinalis* subsp. officinalis and *Melissa officinalis* subsp. inodora. Phytother. Res. 2004;18(10):789-792.

97. de Sousa, A. C., Alviano, D. S., Blank, A. F., Alves, P. B., Alviano, C. S., and Gattass, C. R. *Melissa officinalis* L. essential oil: Antitumoral and antioxidant activities. J. Pharm. Pharmacol. 2004;56(5):677-681.

98. Drozd, J. and Anuszewska, E. The effect of the *Melissa officinalis* extract on immune response in mice. Acta Pol. Pharm. 2003;60(6):467-470.

99. McCue, P. P. and Shetty, K. Inhibitory effects of rosmarinic acid extracts on porcine pancreatic amylase in vitro. Asia Pac. J. Clin. Nutr. 2004;13(1):101-106.

100. Soulimani, R., Younos, C., Fleurentin, J., Mortiert, F., Misslin, R., and Derrieux, G. Recherche de l'Activit, biologique de Melissa officinalis L. sur le Systéme nerveux central de la souris *in vivo* et le Doudenum de Rat *in vitro*. Plant Med Phytother 1993;26:77-85.

101. Salah, S. M. and Jager, A. K. Screening of traditionally used Lebanese herbs for neurological activities. J. Ethnopharmacol. 2-10-2005;97(1):145-149.

102. Gazola, R., Machado, D., Ruggiero, C., Singi, G., and Macedo, Alexandre M. Lippia alba, *Melissa officinalis* and Cymbopogon citratus: Effects of the aqueous extracts on the isolated hearts of rats. Pharmacol. Res. 2004;50(5):477-480.

103. Vogt, M., Tausch, I., Wölbling, R. H., and Kaiser P. M. [Melissa extract in herpes simplex: A double-blind placebo-controlled study]. Der Allgemeinarzt 1991; 13:832-841.

104. Lagoni, N. Wirksamkeitsprüfung eines pflanzlichen Tagessedativums in einer multizentrischen Studie. 1998;39(3):166-169.

105. Schmidt, U., Krieger, W., Frerick, H., and Schenk, N. Psychosomatische und psychische Störungen/Baldrian und Melisse statt synthetischer Psychopharmaka. 1992; 14:15-19.

106. Chakurski, I., Matev, M., Koichev, A., Angelova, I., and Stefanov, G. [Treatment of chronic colitis with an herbal combination of *Taraxacum officinale*, *Hipericum perforatum*, *Melissa officinalis*, *Calendula officinalis* and *Foeniculum vulgare*]. Vutr.Boles. 1981;20(6):51-54.

107. Madisch, A., Holtmann, G., Mayr, G., Vinson, B., and Hotz, J. Treatment of functional dyspepsia with a herbal preparation. A double-blind, randomized, placebo-controlled, multicenter trial. Digestion 2004;69(1):45-52.

108. Borho, B. Biologische Therapie von funktionellen Magenerkrankungen. 1991;6: 501-509.

109. Dressing, H., Kohler, S., and Muller, W. E. Improvement in sleep quality with a high dose valerian-melissa preparation. Psychopharmakotherapie 1996;3:123-130.

110. Lindahl, O. and Lindwall, L. Double blind study of a valerian preparation. Pharmacol. Biochem. Behav. 1989;32(4):1065-1066.

111. Widy-Tyszkiewicz, E., and Schminda, R. A randomized double blind study of sedative effects of phytotherapeutic containing valerian, hops, balm and motherwort versus placebo. Herb Polon. 1997;2:154-159.

112. Orth-Wagner, S., Ressin, W. J., and Friedrich, I. Phytosedativum gegen Schlafstörungen/Klinische Wirksamkeit und Verträglichkeit eines Phytosedativums mit Auszügen aus Baldrianwurzel, Hopfenzapfen und Melissenblättern. 1995; 16(147): 156.