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File: ■ Lemon Balm (*Melissa officinalis*, Lamiaceae)

HC 071645-561

Date: January 31, 2017

RE: Review of the Uses, Chemistry, and Pharmacology of Lemon Balm

Shakeri A, Sahebkar A, Javadi B. *Melissa officinalis* L. – a review of its traditional uses, phytochemistry and pharmacology. *J Ethnopharmacol*. July 21, 2016;188:204-228.

Lemon balm (*Melissa officinalis*, Lamiaceae) is widely used in European traditional medicine and Iranian traditional medicine (ITM) for various diseases, as well as being consumed as a salad vegetable and food flavoring. The authors searched unpublished old texts and several databases of published literature to review the botanical characteristics, traditional uses, phytochemistry, pharmacology, pharmacokinetics, and toxicity of lemon balm.

Lemon balm, also commonly known as balm and beebalm, is a perennial lemon-scented herb. The Eastern Mediterranean region, Western Asia, Southern Europe, Caucasus, and northern Iran are considered its areas of origin, but it grows worldwide. Its medicinal properties were first documented by Dioscorides (40-90 CE), who recommended a leaf decoction for spider, scorpion, and dog bites, and for amenorrhea, dysentery, mushroom poisoning, scrofulous tumors, and other indications. Paracelsus (1493-1541) prescribed lemon balm for nervous system disorders. Since 1984, it has been listed in the German Commission E monographs, and is included in several pharmacopeias. In Danish folk medicine, lemon balm is used for sleeplessness caused by heartbreak or melancholy; in Austria, its essential oil (LBEO) is used for gastrointestinal, nervous, hepatic, and biliary problems. Lemon balm was used by Avicenna (981-1037) for all diseases caused by black phlegm and black bile. He attributed its antidepressant effects to its aroma. The plant has also been reported to be used as a cardiac and gastric tonic, memory enhancer, wound disinfectant, and for certain eye diseases. It is most often used in multiherb preparations, with varying dosages. It is a component of about 400 ITM medicinal preparations.

Lemon balm's main active components are volatile compounds, triterpenes, and phenolics. LBEO, widely used in the pharmaceutical and food industries, is considered to be responsible for lemon balm's antibacterial and antifungal effects. Obtained from fresh or dried flowers, leaves, and branches, LBEO is expensive due to its low yield; it comprises only 0.02-0.30% of plant material. While its composition varies by region and climate, most studies report that LBEO contains oxygenated monoterpenes, including the citral isomers geranial and neral, as well as citronellal, geraniol, and geranyl acetate. The main triterpenes in lemon balm are ursolic and oleanolic acids, with reported biological effects including antifungal, cytotoxic, and hemolytic activities. Antioxidant and

antimicrobial effects also are attributed to its triterpenes. Phenolic compounds in lemon balm, including derivatives of benzoic and caffeic acids, likely exert antioxidant and free radical scavenging effects. Lemon balm's rosmarinic acid (RA) component, with four hydroxyl groups, may be a stronger antioxidant than vitamin E or Trolox. Many flavonoids, including flavones, flavanones, flavonols, and flavanols, are found in lemon balm, with numerous biological effects.

Traditional uses of lemon balm have been supported by its pharmacological anxiolytic effects, possibly due to gamma-aminobutyric acid transaminase (GABA-T) inhibition and/or reduced levels of corticosterone. In vivo studies were supported by two human clinical trials; however, more randomized clinical trials (RCTs) are needed to better understand its mechanisms of action. While animal studies support lemon balm's use as an antidepressant, studies to date used doses so large as to be unfeasible for clinical use. Antidepressive effects of lemon balm need more study, especially the monoamine oxidase A (MAO-A) inhibitory activity of compounds other than RA. Neuroprotective effects of various fractions of lemon balm have been demonstrated in vitro and in vivo, with significant protection against oxidative stress and amyloid beta (Aβ)-induced toxicity. Benefits to mood, cognition, and memory also have been supported in vitro, with acetylcholinesterase (AChE) inhibition seen as especially relevant. RCTs confirmed lemon balm's benefit for some symptoms of Alzheimer's disease and cognitive impairment. Lemon balm's cardiovascular, cytotoxic, anti-inflammatory, antinociceptive, hypoglycemic, hypolipidemic, antioxidant, antimicrobial, antiviral, antispasmodic, antiangiogenic, and antiepileptic effects all have support in various research models, with the general proviso that many doses used in animal trials cannot realistically be applied in clinical practice. Results need to be supported using lower doses of lemon balm extracts.

There are few pharmacokinetic studies of lemon balm, with most focusing on its hydrocinnamic acid derivatives, especially RA, absorbed via paracellular diffusion. Much remains unknown about the bioavailability of lemon balm extracts and components. Microbial metabolites of RA may account for many of its activities. While lemon balm has been reported to be relatively well tolerated in humans when used for up to eight weeks, some adverse effects have been noted with both oral and topical administration. Care should be exercised with regard to high dosage or prolonged use until in-depth evidence from toxicity and dose-escalation studies are available. Current evidence suggests that a daily oral dose of 600 mg lemon balm extract is possibly safe and effective in treating memory, mood, and cognition problems, and topical formulations containing 1% lemon balm are effective in treating very early stages of herpes simplex virus 1 and 2.

Future research needs include mechanisms of action, efficacy, and proper dosages for other ethnomedical uses of lemon balm, as well as proof-of-concept clinical trials evaluating its usefulness as an adjunct to conventional treatment for depression. In vitro studies reveal lemon balm's inhibition of several human cancer cell lines, but a great deal of research needs to be conducted before any clinical applicability could be assessed.

—Mariann Garner-Wizard

The American Botanical Council has chosen not to reprint the original article.