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File: ■ Tulsi (*Ocimum tenuiflorum* syn. *O. sanctum*, Lamiaceae)
■ Safety
■ Systematic Review

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RE: Single-ingredient Clinical Trials with Tulsi—Systematic Review of the Evidence

Jamshidi N, Cohen MM. The clinical efficacy and safety of tulsi in humans: a systematic review of the literature. *Evid Based Complement Alternat Med*. 2017;2017:9217567. doi: 10.1155/2017/9217567.

Tulsi (holy basil; *Ocimum tenuiflorum* syn. *O. sanctum*, Lamiaceae) and ram tulsi (East Indian basil; *O. gratissimum*) are aromatic culinary and medicinal herbs indigenous to India, and have been used in the Ayurvedic medical system for over 3000 years. While tulsi includes two botanically and phytochemically diverse cultivars and ram tulsi has six times the DNA of tulsi, they are distinguished from other *Ocimum* spp. by bright yellow pollen, high levels of eugenol, and a smaller number of chromosomes. Also, they are traditionally used for similar ailments. This systematic review includes both species and all three phenotypes of tulsi. The Indian *Materia Medica* lists tulsi leaf extracts for bronchitis, rheumatism, and fever; other reported uses include treatment of epilepsy, asthma, hiccups, skin and blood diseases, parasitic infestations, neuralgia, headache, wounds, inflammation, and mouth diseases. Leaf juice has been used as a drop for earache; leaf infusions, for stomach and liver disorders. Roots and stems are used on mosquito and snake bites and for malaria.

Since 2007, tulsi has been the subject of over 100 publications. In vitro and in vivo studies support tulsi leaf's adaptogenic, metabolic, immunomodulatory, anticancer, anti-inflammatory, antioxidant, hepatoprotective, radioprotective, antimicrobial, and antidiabetic effects. In vivo, tulsi boosts swimming survival time and has anti-stress effects like those of antidepressant drugs. Aqueous and ethanolic leaf extracts were shown to protect rats from stress-related cardiovascular changes; the leaf extract also has anticonvulsant and anxiolytic properties. Studies of tulsi leaf in polyherbal formulas for humans have been systematically reviewed. This is the first critical systematic review of tulsi as a single herbal agent in human clinical trials. The authors searched electronic databases from inception through November 2016 for reports on human intervention studies involving ingestion of any form of tulsi alone with at least one clinical outcome. Only English-language reports were included. Studies were excluded if they reported only on topical application. After screening 1553 reports, 31 met inclusion criteria. Of these, four were not accessible, one reported on two independent clinical trials, and another clinical trial was reported in three separate publications, leaving 26 trials for review. [Note: The abstract, article text, and flow chart (Figure 1) state there are 24 trials; however, Tables 1-3 appear to list a total of 26 trials.]

Included trials involved 1111 subjects aged 10-80 years; eight had subjects aged ≥40. Only three studies had ≥100 subjects. Study durations ranged from two to 13 weeks. Tulsi dosage

and frequency used were aqueous leaf extract, 300-3000 mg one to three times daily; methanolic leaf extract, 300-1000 mg twice daily; whole plant aqueous extract, 6-14 g daily; fresh leaf aqueous extract, 10 g daily in four equal doses; and tincture, 30 drops daily in three equal doses. Only eight studies had a placebo group. Studies were randomized controlled trials (RCTs), non-placebo-controlled trials, or clinical trials lacking randomization or control information. Jadad scores for study quality were generally low, from 0-3 points; only three studies had high scores of 4-5. Two studies described the tulsi used (Krishna, the purple-leafed cultivar of *O. tenuiflorum*); all others referred to tulsi as *O. sanctum*. Four studied tulsi alone and with, respectively, food, a hypoglycemic drug, curry (*Murraya koenigii* syn. *Bergera koenigii*, Rutaceae) leaves, and neem (*Azadirachta indica*, Meliaceae). Most had populations with acute or chronic illnesses; three used healthy subjects. Outcome measures included blood glucose (BG) levels (eight studies), lipid profiles (six studies), immune response (six studies), neurocognitive changes (four studies), mood (three studies), fatigue (two studies), uric acid levels (two studies), secondary symptoms of diabetes (one study), and sleep (one study). A majority of reports stated that no adverse events (AEs) occurred; one reported mild, occasional nausea; and the rest did not mention AEs.

Of 17 studies on metabolic conditions, 10 reported on type 2 diabetes (T2D) or metabolic syndrome, measuring BG, lipids, and blood pressure (BP); only one reported on clinical symptoms of T2D. One reported on obesity; two, uric acid changes in gouty arthritis. Six studies on metabolic syndrome were RCTs, and six were from 12-13 weeks long; the rest, shorter. Trials lasting 12-13 weeks showed more dramatic changes in fasting BG (FBG) and postprandial glucose (PPG) than trials of four to five weeks. Hemoglobin A1c was significantly decreased with tulsi and hypoglycemic medication compared to the drug alone. Studies reported significant improvements in FBG, PPG, urine glucose, uric acid levels, and lipid profiles in clinical and healthy subjects with various tulsi preparations, alone and combined with curry leaves or neem. Improved BP was reported in some but not all studies. Improved body mass index was reported in obese subjects.

Five studies reported enhanced immune response. Two studies of patients with acute viral infections, one involving encephalitis and the other hepatitis, reported better survival after four weeks in the former and symptom relief after two weeks in the latter. In patients with asthma, tulsi improved vital capacity and relieved symptoms in three days. Four studies of neurocognitive effects found significant improvement in mood and/or cognition regardless of age, gender, formulation, dose, or study quality. Significant reductions in anxiety and stress occurred at higher tulsi doses used for longer periods in three studies.

Eugenol has been suggested to lower BG levels but it is likely that tulsi has many active secondary metabolites that act alone or synergistically on inflammatory pathways. Its effectiveness across diverse clinical domains suggests an adaptogenic effect. The Ayurvedic tradition of consuming tulsi daily may be an effective lifestyle measure to combat stress-related chronic illnesses. More and better-designed RCTs are needed.

One of the authors (Cohen) receives remuneration as a consultant and advisor to Organic India Pty. Ltd. (Lucknow, India), a company that manufactures and distributes tulsi products. Organic India did not have input into the article's content or the decision to publish it.

—Mariann Garner-Wizard

Referenced article can be accessed at https://www.hindawi.com/journals/ecam/2017/9217567/.

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