Supplemental Digital Content 1
Appendix to
Coriander: Overview of Potential Health Benefits
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Antioxidant actions

The essential oil, and lipophilic and hydrophilic extracts of coriander exhibit antioxidant activity *in vitro* (1-10). For example, the radical scavenging activity of coriander seed oil was superior to that of black cumin and niger seed oils, suggesting that polar lipids may be important contributors to antioxidation (11). In another report, cilantro essential oil had one of the strongest protective effects against lipid peroxidation compared to four other essential oils and two synthetic antioxidants (12). One study reported that hydrophilic extracts of coriander leaves showed stronger antioxidant activity than that of the seeds (2). In two human cell-based assays, hydrophilic extracts of coriander seeds and leaves protected lymphocytes and keratinocytes from oxidative stress (13,14). This effect of the extracts was due in part to increasing activities of oxidative defense enzymes and levels of glutathione. Evidence for linalool's effectiveness in suppressing oxidative stress is limited and potency varies according to the assay used (15-17).

Antimicrobial actions

Essential oils of aromatic plants have been long considered important sources of antimicrobial agents (18,19). Although reportedly not as potent as those from other spices (20) oils and extracts from *Coriandrum sativum* have antibacterial activity of varying potency depending on the fraction evaluated. In general the essential oils from both the seeds and leaves (cilantro) show some of the strongest action against bacterial strains. The essential oils can inhibit both gram (+) and gram (-) bacteria and specific human pathogens including *Bacillus* species, *Salmonella* species, *Listeria monocytogenes*, *Escherichia coli*, *Staphylococcus* species, and *Streptococcus pyogenes,* although there is variability in specificity of inhibition and potency

of individual coriander constituents. The inhibitory potency of coriander against the pathogen *Pseudomonas aeruginosa* is inconsistent (21-28). One report concluded that cilantro essential oil exerted a much more potent inhibitory effect against gram (+) bacteria, compared to that of the essential oil of seeds (21). On the other hand gram (-) were reported to be more sensitive than gram (+) bacteria to growth inhibition by the coriander seed oil (29) an effect not consistently observed (22). The profiles of inhibitory chemicals in coriander samples vary considerably, complicating the identification of the most potent constituents. For example, the essential oil of seeds was reported to consist primarily of linalool (65-90%) with lesser amounts of α-pinene, camphor and other volatiles. Yet, the essential oil of cilantro leaf in one study was reported to be composed of 26% linalool, 28% decenals and 8% 2-decen-1-ol (21), and, in another study to have 77% aliphatic alcohols and 12% aliphatic aldehydes (30). Linalool was reported to be effective against 8 periodontopathic and cariogenic bacterial strains (28,31), while a coriander essential oil fraction rich in α-pinene was more potent than one rich in linalool against the pathogens *Pseudomonas, Salmonella, Listeria* and *Staphylococcus* (21). Linalool has little antimicrobial action against *P. aeruginosa* (32). Aliphatic alcohols and aldehydes in essential oils also have antibacterial actions (33,34). For example, (2E)-dodecenal and (2E)-undecenal from the volatile oil of coriander leaves were most bactericidal against *Salmonella* among those similar compounds tested (35). Taken together, these studies indicate that several oil constituents are likely to contribute to inhibition of bacterial growth. Coriander essential oil has been reported to synergize with antibiotics such as ciprofloxacin and tetracyclin against *Acinetobacter baumanii* (36). The essential oil is antibacterial by compromising cell permeability which degrades general cell functions and metabolism (26). Essential oils have played a historical role in treating respiratory tract infections because of their secretolytic actions

(25). Thus, evaluating the impact of coriander essential oil in appropriate experimental models on respiratory tract infections via inhalation or oral delivery (25) would be an additional avenue for future research. In contrast to essential oils, aqueous and alcoholic extracts have much less antibacterial efficacy against a variety of pathogenic bacterial isolates (37-42).

Essential oils of coriander seeds, leaves and stems demonstrate antifungal efficacy *in vitro*. Organisms inhibited include *Aspergillus*, *Rhodotorula*, *Rhizopus*, *Geotrichum*, *Saccharomyces* and *Candida* (21,23,25,28,30,43-46). In one report, coriander oil showed the highest level of overall fungal inhibition compared to the oils of other spices (21). Coriander seed oils contained predominantly linalool (64-90%), whereas leaf essential oil consisted of less linalool (26%) and more alcohols and aldehydes (20%). Differences in oil composition have been responsible for some disparities among coriander species in inhibiting *Aspergillus niger* and *Candida tropicalis* (25,30). Some antifungal constituents identified by bioactivity-guided fractionation include linalool, α-pinene, hexen-1-ol, and cyclodexane (21,45,46). Although the fungus *Kluveromyces* was inhibited by a coriander essential oil, it was not by an equivalent amount of linalool (28). Thus the antifungal capacity of this oil depends on the organism and the composition of the oil investigated. Antifungal mechanisms of the oil include damage to the cytoplasmic membrane leading to an impairment of all cellular functions, inhibition of germ tube formation, and interference with the morphological switch and biofilm formation (43,45,46).

There is very limited information about the inhibitory activity of coriander toward viruses and parasites (19,47,48).

Taken together these results suggest that coriander essential oil has substantial efficacy against a broad range of bacteria and fungi. Substantiation of the antimicrobial actions observed in cell culture studies needs to be rigorously confirmed in animal models of infection, and in

appropriate human interventions. Coriander has been reported to suppress growth of food spoilage organisms and human pathogens in foods (26,43,49-58).

Neurological actions

Linalool affects anxiety, analgesia and cognition in animal models when administered by injection. Both antidepressant and genotoxic actions of linalool treatment (10,50,100 or 200 mg/kg; i.p.) were evaluated in mice (59). Compared to controls, linalool showed anti-depressant-like activity in the tail suspension test at doses of 100 and 200 mg/kg. Furthermore, linalool did not show any genotoxic effects as measured *in vitro* using samples of peripheral blood and brain tissue. In another study in mice (60), compared to controls, linalool significantly improved performance in the forced swim (FST), rotarod and traction tests, and the open field (OFT) and exploratory cylinder (ECT) tests of anxiolytic behavior. However, the dose-responses of linalool treatments (54.8, 100 and 173.2 mg/kg, i.p.) were not consistent among the tests, and the 54.8 mg/kg dose was ineffective in all tests. In rats, linalool dosing (125 mg/kg, i.p.) showed anxiolytic actions as measured by the elevated plus maze (EPM) test (61). In a recent report there is evidence of gender-specific effects when linalool was administered to rats at a lower dose (3 mg/kg, i.p.) for 7 days prior to evaluation in the OFT and EPM (62). Gender did not affect linalool's influence on anxiety-related behavior in the OFT. In contrast, in the EPM, linalool treatment attenuated anxiety-related behavior of males but not females. The basis for this gender-based difference was not characterized.

Inhalation of linalool and calming behavior also have been examined. Linalool treatment of mice (inhalation chamber saturated with linalool at 1% or 3%) for 60 min (63) produced sedation without significantly impairing motor control (63,64). In one report inhalation of linalool (27mg vapor) by female and male mice for 30, 60 or 90 min resulted in plasma

concentrations of linalool of 1.0, 2.7 and 3.0 ng/ml, respectively, which correlated with the efficacy of sedation of each dose (65). Another inhalation study (66) using additional testing models characterized that linalool treatment (1% or 3% vapors) resulted in anxiolytic responses, increased social interaction, and decreased aggressive behavior, compared to controls, although the effective doses differed among the tests. However, a concern was that memory acquisition was impaired at the higher dose of linalool. Impaired memory acquisition also was reported (67) for rats injected with linalool (50 or 100 mg/kg, i.p.). The authors suggested that the impairment was likely due to antagonism by linalool of the NMDA glutamatergic receptor. This memory impairment effect of linalool needs to be further characterized to determine how the method of administration, dose and duration of exposure, and circulating plasma levels relate to this adverse response.

Linalool has antinociceptive actions in a variety of experimental pain models. For example, linalool was administered to mice (25 to 100 mg/kg, s.c.) 30 min prior to evaluating behavior in both chemically-induced writhing and heat-induced pain tests, which model inflammatory pain and supraspinal analgesia, respectively (68). Compared to controls, the 25 to 75 mg/kg doses inhibited the chemically-induced pain response and only the 100 mg/kg dose suppressed heat-induced pain. Similar results were observed in subsequent evaluation of linalool in formalin-induced and heat-induced pain models (69,70). Improving the delivery and efficacy of linalool *in vivo* also was studied in two reports by the same group. Mice were treated with linalool (20 mg/kg and 40 mg/kg, p.o.) prior to administering chemically-induced and heat-induced pain tests (71). Linalool also was administered (25 mg/kg, p.o.) to mice in a model of chronic non-inflammatory muscle pain that mimics human fibromyalgia (72). In both studies the analgesic efficacy of linalool alone was compared to that of β-cyclodextrin-complexed linalool,

with β-cyclodextrin complexing being a means to improve the circulating half-life and the pharmacological properties of the lipophilic linalool. In both reports linalool demonstrated significant anti-hyperalgesic properties, compared to controls, and the β-cyclodextrin complex significantly improved linalool's antinociceptive effect.

The mechanisms identified for linalool's actions on the nervous system are diverse. For example, in one injection study, the antidepressant-like activity of linalool was due to interactions with the monoaminergic system (73). Using freshly isolated preparations of hemidiaphragm muscles of mice (74), it was reported that exposure to linalool reduced acetylcholine release and changed nicotinic receptor-ion channel kinetics at the neuromuscular junction. In an inhalation study, the effects of linalool treatment on the plasma levels of ACTH, catecholamine and gonadotrophin were determined in ether-sedated, menopausal rats (75). Ether-sedation produced an increase in plasma ACTH levels, which were decreased in rats inhaling linalool, and linalool inhalation restored catecholamine levels to near normal after decreases due to ether sedation. Ether sedation also elevated luteinizing hormone levels, which were lowered for rats inhaling linalool. The authors suggested that linalool inhalation may relieve the tension of menopausal disorders. Two studies characterized the linalool inhalation-induced changes in gene expression profiles in rats. In one study rats were exposed to R-(-)-linalool during 2 hr of restraint stress (76). Restraint stress increased plasma ACTH and corticosterone levels, which were suppressed in those rats also inhaling linalool. Similarly, the stress-associated changes in numbers of circulating neutrophils and leukocytes were returned to normal for the linalool-inhaling rats. Holistic changes in whole blood mRNA expression measured by microarray showed that linalool inhalation repressed restraint-induced changes in the expression levels of 109 genes and enhanced the changes in 6 other genes. The authors

suggested that the changes in stress-induced gene expression profiles by linalool could be due to changes in cell subsets in the whole blood and/or to effects on transcription regulation. In a subsequent study by the same authors using the same experimental model (77), changes in the expression of over 600 genes in the hypothalamus were associated with R-(-)-linalool inhalation. Linalool inhalation enhanced expression of genes related to neuron differentiation under stress conditions, specifically those regulating hypothalamic neural conductivity and synapse formation. There also was up-regulation of genes involved in cellular defense responses and those involved in the TGF-β signaling pathway. The authors suggested that further characterization of these changes in gene expression is warranted to better understand the influence of linalool inhalation on stress responses, and, in light of the role of the hypothalamus in regulating satiety, on feeding behavior (77,78).

Linalool was examined in injection models of chemical-, thermal- or mechanically-induced pain for any antinociceptive efficacy (79-87). Linalool treatment effectively inhibited inflammation and neuropathic pain in these reports. Several neural mechanisms of linalool action were identified in these *in vivo* studies and include activation of the opoidergic and cholinergic systems (68,69,71,79,80-84,87), modulation of A_1 and A_{2A} receptor activities (70), increasing Fos protein expression (72), decreasing extracellular signal-related protein kinase (ERK) activation (85), and inhibition of pro-inflammatory cytokines (82,86).

Antidiabetic actions

Linalool treatment (25 mg/kg, p.o., for 45 days) was evaluated in streptozotocin (STZ)-injected diabetic rats (88). Compared to diabetic controls, rats given linalool showed a significant decrease in STZ-elevated plasma glucose and insulin levels, and a return of kidney carbohydrate-metabolizing enzymes and glycogen content to near normal levels. Moreover, in

the kidney, linalool restored normal GLUT-1 expression, mitigated nephrin loss, suppressed oxidative stress and inflammation, and attenuated kidney damage and nephrotoxicity associated with STZ treatment. The authors suggested that linalool be considered as a potential therapy for renal damage in diabetics. Dyslipidemia is associated with diabetes and the metabolic syndrome. Oral administration of linalool (0.57 mg/d, 120 mg/d) for 6 weeks to mice fed a high-fat diet resulted in significantly lower plasma total and low-density lipoprotein cholesterol levels, compared to controls (89). Linalool also was evaluated for its hypotriglyceridemic action in mice fed a Western-diet (90). Compared to controls, mice administered linalool (100 mg/kg, p.o.) for 3 weeks showed a decrease in cumulative food intake, and a significant decrease in plasma triglyceride levels and saturated fatty acids. Additionally, compared to controls, linalool treatment significantly increased liver peroxisome proliferator-activated receptor (PPAR)α expression as well as that of several PPARα target genes. In *in vitro* assays, linalool was identified as a PPARα agonist through interaction with the PPARα ligand binding domain. The authors concluded that linalool can "rewire" the liver transcriptome and plasma metabolome. In a subsequent review (91) the authors proposed that linalool and other bioactive compounds can exert hypolipidemic and antiobesogenic effects by regulating PPARs.

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