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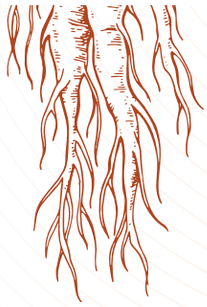
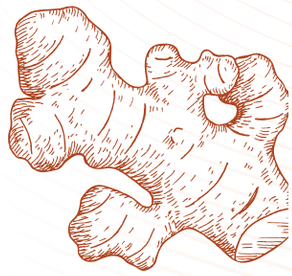


A Brief Review of the Effects of Ginseng and Ginger in Respiratory Tract Infections



1. INTRODUCTION

Infectious diseases are the leading cause of morbidity and mortality worldwide. They are primarily caused by either viral or bacterial infections.[1] Viruses are the most common cause of respiratory infections and facilitate secondary bacterial infections by aiding bacterial adherence, colonization, and translocation through the epithelial barrier of respiratory cells. This is called superimposed infection.[2]

By end of 2019, an outbreak of respiratory disease caused by SARS-CoV-2 virus occurred in China. COVID-19 was declared by the WHO a Public Health Emergency of International Concern in January 2020, and a pandemic in March 2020. Because of the importance of pulmonary infection associated with COVID-19, the present article will review the medicinal benefits of two species of plants, ginseng and ginger, in the management of upper and lower respiratory tract infections (URTI; LRTI), knowing that many food supplements and nutraceutical products contain ingredients originating from them.

2. GINSENG

The name 'ginseng' is widely understood to refer to the *Panax* species which belongs to the family Araliaceae. The *Panax* species is mostly found and cultivated in temperate zones particularly in North America and Asia. *P. ginseng* C.A. Meyer is the most widely used since it is considered as one of the most important tonic drugs.[3]

Different ginseng plants share in common their content of numerous pharmacologically active ingredients mainly ginsenosides, saponins, phytosterols, polyacetylenes, vitamins, nitrogenous substances, and minerals. Ginsenosides are the main active ingredients in ginseng known to possess enhanced therapeutic activity.[4] Ginseng has been shown to play a significant role in the protection from and treatment of many diseases and has been accepted as a natural product for health promotion,[4] enhancement of physical performance, and improvement of vitality and increase in resistance to stress and aging.[5-7] Ginsenosides have been shown to have different pharmacological effects, such as anti-diabetes,[8] anti-inflammatory,[9] anticancer,[10,11] and neuroprotective activity.[12,13] This paper will focus on the effects of ginseng on RTIs.

The literature relating to the use of ginseng extracts for the prevention and treatment of RTIs is exhaustive. Several in-vitro and preclinical and clinical studies have demonstrated the antiviral activity of ginseng on RTIs

arising from influenza virus, respiratory syncytial virus (RSV), rhinoviruses or of bacterial origins, example, *Streptococcus pneumoniae*.[14] Different observational studies have demonstrated the efficacy of ginseng on the course of respiratory diseases. The following are some examples.

Two randomized double-blind placebo-controlled studies in a cohort of patients aged 16-65 years,[15] and elderly subjects (81-84 years)[16] in an assisted living setting, including nursing homes investigated the relationship between ginseng and the incidence of influenza and cold symptoms. A significant decrease in severity of symptoms, occurrence of less cold or influenza episodes and shorter duration of the disease was observed in those who received ginseng versus placebo.

Predy et al.[15] found that the mean number of cold episodes per person was lower in the ginseng group than in the placebo group (0.68 v. 0.93, difference 0.25%, 95% confidence interval [CI] 0.04-0.45). The proportion of subjects with two or more verified colds during the 4-month period was significantly lower in the ginseng group than in the placebo group (10.0% v. 22.8%, 12.8% difference, 95% CI 4.3-21.3), as were the total symptom score (77.5 v. 112.3, difference 1.5%, 95% CI 1.2-2.0) and the total number of days cold symptoms were reported (10.8 v. 16.5 days, difference 1.6%, 95% CI 1.3-2.0).

In keeping with the above, McElhaney et al.[16] found that the incidence of influenza was greater in the placebo group (7 cases/101 subjects) than the ginseng-treated (1/97) groups (odds ratio (OR)=7.73, P=0.033). The combined data for influenza and RSV illness was also greater in the placebo groups (9/101) than ginseng-treated (1/97) groups (OR=10.50, P=0.009), for an overall 89% relative risk reduction of acute respiratory illness in the ginseng groups.

Another study aiming at determining the effect of ginseng administration on the potentiation of influenza vaccination showed that those who received the vaccine together with ginseng had a statistically lower incidence of influenza compared to the group who received a placebo with the influenza vaccine (13% vs 37%, p <0.001). Also, when measuring antibody titers at week 8 post-vaccination, these increased by 59% in the ginseng group vs. placebo group (171 units vs 272, p<0.0001). Natural killer (NK) activity levels at weeks 8 and 12 were nearly twice as high in the ginseng group as compared to the placebo group (p < 0.0001), indicating a higher early antiviral activity.[17]

There are currently two ongoing clinical trials registered in the EU Clinical Trials register [clinicaltrialsregister.eu] relating to ginseng. These are:

1. **EudraCT number:** 2017-003271-61 - Phase IIa (therapeutic exploratory), multicenter, randomized, double-blind, placebo-controlled, 2-stage, 4-arm study exploring the effect of BST204 [ginseng extract] on cancer-related cachexia in patients with gastrointestinal or non-small-cell lung cancer.
2. **EudraCT Number:** 2010-020504-30 - GATAC: Asian ginseng (Panax Ginseng) for the treatment of cancer-related fatigue: a randomized, double-blind controlled study.

Mechanism of Action

Some of the plausible mechanisms for ginseng-mediated viral inhibition are improvements in systemic and mucosa-specific antibody responses, serum hemagglutinin inhibition which is indicative of a good antibody response, lymphocyte proliferation, cell survival rate, and viral clearance in the lungs. Moreover, ginseng reduces the expression levels of proinflammatory cytokines, including IFNγ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL-8 implicated in the triggering of the cytokine storm that is responsible for the development of acute respiratory distress syndrome (ARDS) and subsequent mortalities such as the one seen in complicated COVID-19 infection.[14] In the case of bacterial infections, ginseng acts by lessening pro-inflammatory cytokine production and activating phagocytes and NK cells responsible for the killing of the infecting microorganism. In addition, ginseng inhibits biofilm formation and induces the dispersion and dissolution of mature biofilm making the eradication of infectious bacteria more vulnerable to antibiotic activity.[14]

3. GINGER

Ginger, scientifically known as *Zingiber officinale* is a commonly consumed dietary condiment in many culinary cultures. The plant has a long history of cultivation in the Asian subcontinent[18] and is generally considered to be safe even in pregnant women where it is given to treat morning sickness.[19]

Numerous active ingredients are present in the rhizome including terpenes and phenolic compounds.

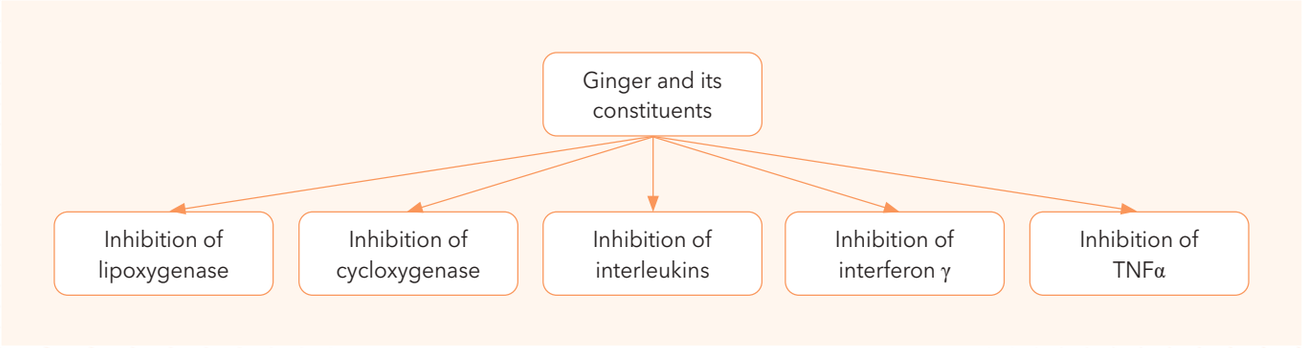


Figure 1: Summarization of the Immunomodulatory and Anti-inflammatory Effect of Ginger and Ginger constituents. Adapted from Rahmani AH (2014).[20]

Terpene components of ginger include zingiberene and α-curcumene. Phenolic components include gingerol, zingerone, gingerdione, paradol and shogaol. Taken together, these components are known to possess preventive and curative properties against various diseases. A review conducted by Rahmani et al (2014) concluded that the main biological effects of ginger, studied in-vitro as well as through preclinical and clinical studies, demonstrate anti-oxidant, anti-tumor, anti-inflammatory, anti-infectious, anti-obesity and antidiabetic activity. The review also discusses the beneficial hepato-, gastro- and neuroprotective effects of ginger.[20]

Similar to ginseng, this scientific review on ginger will focus on its effect on RTIs. As discussed, it is wellestablished that increased circulating levels of proinflammatory cytokines correlate to the severity of an infection.[21] In keeping with this, strenuous exercise, stress hormones and oxidative stress are examples of physiological stimuli that modulate cytokine production. The systemic inflammatory response which arises from prolonged aerobic exercise in athletes may lead to URTIs due to a suppression of the immune system.[21] The use of ginger extracts for a period of 12 weeks in healthy athletic volunteers who undergo intense exercise has been found to significantly reduce the production and release of IL-1β and IL-6 as well TNF-α compared to athletes who received placebo.[21] Interventions to dampen increases in cytokines implicated in inflammatory processes would seemingly justify their use to prevent or decrease infection.

A study conducted by Vahdat Shariatpanahi et al. (2013) concluded that the addition of ginger to the diet of ARDS patients for ten days led to a significant improvement of their respiratory illness, when compared to ARDS patients who were not given ginger. Patients taking ginger had a significant improvement in their oxygenation ($p<0.003$) and static compliance of their lungs (low lung stiffness -$p<0.01$) with a decrease in the duration of mechanical ventilation ($p=0.02$) and a shorter stay in intensive care units ($p=0.04$). This correlated with a significant decrease in pro-inflammatory cytokines IL-1, IL-6, and TNFα and an increase in glutathione ($p<0.05$).[22]

With regards to bacterial infections, the susceptibility of 17 bacteria species associated with RTIs was tested in-vitro against specific ginger extracts. Gram-positive bacteria resistant to cloxacillin, co-amoxiclav, tetracycline and erythromycin and gram-negative bacteria resistant to co-amoxiclav, tetracycline and amoxicillin were shown to be all susceptible to 200 - 400 mg/ml of ginger extract preparation but more to the methanolic than the aqueous extracts. While the mechanism of action needs to be further elucidated, ginger could show benefit in patients with lower RTI.[23]

There is currently one ongoing clinical trial registered in the EU Clinical Trials register [clinicaltrialsregister.eu] relating to ginger, i.e. Ginger, ginger-avocado-soy, glucosamine sulfate and ginger-ibuprofen in relation to chronic low back pain - a randomised double-blind, placebo-controlled clinical trial with parallel groups for 3 months to illustrate joint health [**EudraCT Number:** 2005-002691-1].

Mechanism of action

Many studies have demonstrated that ginger possesses antioxidative properties and plays a role in scavenging superoxide anions, hydroxyl radicals and other free radicals.[20] Figure 1 summarizes the immunomodulatory and anti-inflammatory effect of ginger. In animal studies, gingerol inhibited lipid peroxidation in liver microsomes.[20] Shogaol and gingerdione exert potent inhibition of nitric oxide (NO) synthesis in activated macrophages.[24] While NO plays a beneficial role in normal physiologic situations, increased NO production and release from macrophages is involved in the pathogenesis of inflammatory disorders of the joint, gut and lungs hence the benefits of curbing these effects.[25,26]

4. FROM PLANTS TO CONSUMPTION IN FOOD SUPPLEMENTS AND NUTRACEUTICALS

Many cultures recognize the benefits of ginseng and ginger plant extracts and use them in traditional medicine. The European Food Safety Authority (EFSA) has developed the "Qualified Presumption of Safety (QPS)" approach for

the assessment of botanicals or botanical preparations in food supplements or nutraceuticals.[27] The aim of this assessment is to help manufacturers produce and deliver products with tested ingredients, safe and free of contaminants. EFSA imposes stringent quality checks on compounds before being manufactured into supplements. These relate to the screening for contaminants such as radioactive material, heavy metals (i.e. cadmium, mercury, lead, arsenic, etc.), high potency carcinogens (i.e. aflatoxin-like), inorganic components, proteins and steroids, all substances known or predicted to bioaccumulate, nanomaterials, solvent residues or any other known chemical structure with unknown toxicity profile. Also, the analysis comprises looking for contamination with microorganisms, including yeasts and molds, Salmonella, *E. coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*. Manufacturers should also include analyses on the physical properties of the product such as the appearance, odor, solubility, and moisture levels. Reference specification values for specific methods of analyses exist for each contaminant. Levels of contaminants should always remain below the reference value otherwise the produced batch is discarded by the manufacturer in accordance to Good Manufacturing Practice.

Herbal supplements always pose issues relating to safety. In this case, both ginseng and ginger have shown a very good safety profile in population studies. Taking ginger as an example, this has been safely administered to pregnant women for the treatment of nausea[19] and a review on the adverse events seen with short- and long-term use of ginseng show a similar safety profile between those who received the plant and those who received placebo.[28] In Malta, specific legislation governs the marketing of food supplements on the Maltese market. The main legislative tools are Subsidiary Legislation 449.36 (Food Supplements Regulations) and Subsidiary Legislation 449.46 (Labelling, Presentation and Advertising of Foodstuffs Regulation). These include the maximum permitted levels and guidance levels for vitamins and minerals. Of note is that the labelling, presentation, and advertising must not attribute to food supplements the property of preventing, treating, or curing a human disease or refer to such properties.[29]

5. CONCLUSION

This review on ginseng and ginger focused on their effects in preventing and treating RTIs in view of the fact that since March 2020, the world is living the pandemic of SARS-CoV-2. However, these products have undeniable proven benefits on other diseases like cancer and related conditions such as cachexia, and metabolic diseases. Whereas multiple in-vitro, pre-clinical and clinical testing have proven the efficacy and safety of these two compounds in RTIs, further investigation is needed to assess their possible or potential role in the protection against respiratory infections associated with COVID-19.

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