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File: ■ Rooibos (*Aspalathus linearis*, Fabaceae)
■ COVID-19

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RE: The Potential Therapeutic Role of Rooibos in Addressing Covid-19

Abdul NS, Marnewick JL. Rooibos, a supportive role to play during the COVID-19 pandemic? *J Funct Foods*. November 2021;86:104684. doi: 10.1016/j.jff.2021.104684.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (Covid-19), confirmed at this writing in > 150 nations, continues to spread. Elders and patients with lung, heart, or kidney disease; type 2 diabetes (T2D); or hypertension (HT) have been associated with higher Covid-19 mortality. Symptoms vary, but often feature rapid progression to acute respiratory distress syndrome (ARDS). CoV spike proteins facilitate entry to host cells via angiotensin (Ang)-converting enzyme 2 (ACE2) receptors on cell surfaces. It had been hypothesized that ACE2-stimulating drugs might raise risks of severe or fatal Covid-19. The Council on HT of the European Society of Cardiology has said there is no evidence that Ang-converting enzyme inhibitors (ACEIs) or Ang receptor blockers (ARBs) should be discontinued due to Covid-19, recommending that patients with HT continue treatment. Some data suggest that ACEIs or ARBs may reduce severe lung injury by SARS-CoV-2.

When this article was written, no vaccines for Covid-19 had been deployed. By June 2021, many candidates were in development, and > 10 were being distributed in various areas. This unprecedented vaccine development and distribution, however, have also been inconsistent. Phytomedicines, some used in prior CoV epidemics, may help prevent and/or alleviate Covid-19 symptoms, reducing demands on healthcare systems. In nations with major barriers to widespread inoculation, poor healthcare access, and "rampant" Covid-19 infection, such approaches are especially needed. Bioactive plant polyphenols and their metabolites have reported antioxidant, anti-inflammatory, and immunomodulating activity. Epidemiological, pre-clinical, and clinical studies point to protective effects of polyphenol-rich diets against T2D, obesity, and cardiovascular (CV) problems.

A tisane of rooibos (*Aspalathus linearis*, Fabaceae) leaves and stems, used since at least the late 1700s, has been used to improve health. It is known to have antidiabetic and antiviral properties along with cardiometabolic and organ protective activity. Polyphenol flavonoids in rooibos include its unique aspalathin and nothofagin, rutin, orientin, vitexin, isovitexin, isoorientin, luteolin, and quercetin. In preclinical studies, these compounds have been shown to have antioxidant, anti-inflammatory, and antimutagenic activity. Rooibos has been shown to reduce HT by inhibiting ACE. The authors explore its potential relevance in the Covid-19 pandemic.

Relationships between ACE2, ACEIs/ARBs, HT, and SARS-CoV-2 are not well known. It was suggested that Ang receptor I blockers may be effective against Covid-19; studies are needed. Fermented rooibos significantly inhibited ACE, with maximum effect 30-60 min after an acute dose. It used mixed inhibitor mechanisms, including the enzyme kinetic mechanism

used by the ACEI enalaprilat. Rooibos flavonoids, as metal chelators, may bind to Zn^{2+} at ACE sites, inhibiting conversion of inactive Ang I to harmful Ang II. ACE on type II alveolar cells is a main path for SARS-CoV-2 entry, perhaps explaining the prevalence of ARDS in Covid-19. Rooibos could reduce lung damage in these patients.

Rooibos' anti-inflammatory effects may help modulate the immune dysregulation often seen in Covid-19 as hyperinflammation or "cytokine storms." With no effective treatment, care is supportive. An interleukin (IL)-6 receptor blocker licensed for cytokine release syndrome was in clinical trials in China when this article was written. Preclinically, rooibos reduces cytokines and inflammatory responses. There is little research on its mechanisms, likely involving reduced pro-inflammatory cytokine signaling and increased anti-inflammatory IL-10 secretion. Nothofagin and aspalathin lowered IL-6 and other pro-inflammatory cytokines preclinically, while orientin lowered those and inflammatory enzymes. A study of supportive dietary strategies in Covid-19 focused on adiponectin, an important metabolic regulator. Pro-inflammatory IL-6 is produced by adipose tissue in some viral lung infections. Interventions boosting adiponectin may calm cytokine storms. Aspalathin maintained adiponectin in diabetic mice and raised levels. ACE inhibitors are indirect means to raise adiponectin levels. Oxidative stress (OS) furthers viral replication and subsequent associated diseases. OS and hyperinflammation are firmly linked. While clinical evidence of a link between OS and Covid-19 is lacking, preclinical data point to compromised antioxidant defenses and higher production of cellular oxidants. Jointly, OS and hyperinflammation can cause severe lung injury. In patients at risk for CV disease, drinking rooibos tisane daily for six weeks significantly improved glutathione redox status and significantly reduced damage due to circulating oxidative lipids. Rooibos' potent antioxidants are likely to reduce Covid-19-induced OS and inflammation.

Several comorbidities increase Covid-19 morbidity and mortality. The mechanism of these associations is not established. Patients may die of multiorgan failure, shock, ARDS, or heart or kidney failure. Simple, inexpensive interventions like rooibos, widely available and used, which support organ health and act against comorbidities, are important tools in the pandemic, according to the authors.

Rooibos' direct antiviral activity is attributed to quercetin and luteolin. Each acted against SARS-CoV-2 in vitro and in silico. Vitexin and orientin may target SARS-CoV-2 protease residues needed for viral replication, a possible basis of new treatments. Patients with Covid-19 often show gut microbiome dysregulation. Colonic expression of ACE2, regulated by gut microbiota, has been inhibited by rooibos. Aspalathin and both fermented and unfermented rooibos boosted beneficial gut bacterial strains in vivo. Rooibos may reduce intestinal SARS-CoV-2 targets. Rooibos bioavailability and bioactivity, and potential herb-drug interactions, are also discussed. The report argues for inclusion of rooibos in daily health regimes and in management Covid-19. Regrettably, no systematic literature search is reported. The authors state that they had no competing financial interests.

—Mariann Garner-Wizard

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