Oregano Oil: Updates on Molecular Mechanisms

Oregano oil (*Origanum vulgare*) has been used traditionally for a variety of health-promoting reasons, ranging from gastrointestinal to respiratory support. It has well-establishedantioxidant, antimicrobial, anti-fungal effects, as well as offering support for a healthy inflammatory response. In recent years, anti-neuroinflammatory and neuroprotective effects of carvacrol (the primary constituent of oregano oil) were observed, with activation of nuclear factor E2-related factor (Nrf2) as the likely mechanism of action. Here we review this finding in more detail and provide an update into other recent insights into oregano oil's multiple mechanisms of action.

Antimicrobial Activity

Oregano oil is comprised of many biologically active compounds, including flavonoids, tannins, terpenoids, and phenolics (most notably carvacrol and thymol, both monoterpene phenols) which help to explain its broad physiological effects. For example, carvacrol and thymol have demonstrated broad antimicrobial activity against both gram-negative and gram-positive bacteria, causing disintegration of the outer bacterial membrane and hyperpermeability of the cell membrane. They have also been shown to inhibit biofilm formation, even in multiple strains of treatment resistant bacteria. Both of these

compounds have also proven to have fungicidal activity toward Candida species, interfering with ergosterol synthesis and targeting fungal cell antioxidant systems and proton pumps. Carvacrol specifically has shown anti-viral activity, targeting the viral capsid of the murine norovirus (a surrogate for the human norovirus, one of the more common causes of viral gastroenteritis).

Cell Cycle Activity

Other mechanisms of action have been uncovered which suggest oregano oil may provide support for heathy cell function; in several cell-based studies, carvacrol has been shown to inhibit the transient receptor potential melastatin-like 7 channel (TRPM7), an important channel for calcium and magnesium transit, with overexpression of this channel associated with abnormal cell growth and proliferation. An *in vitro* study published in *Life Sciences* found that carvacrol was able to regulate the cell cycle in part by inhibition of TRPM7, specifically arresting the proliferation phase of an abnormal cell cycle. The authors suggest that at higher doses apoptosis through a second mechanism may also occur, but cell cycle regulation occurred at lower doses. Apoptosis as well as inhibition of abnormal proliferation by carvacrol were both observed in other *in vitro* studies, in several cell lines.

Nrf2: Antioxidant and Inflammatory Response

Several animal-based studies have been published supporting an additional effect of oregano oil, specifically carvacrol, as an activator of Nrf2. Nrf2 is a transcription factor which induces a number of cytoprotective enzymes; for example, multiple genes needed for glutathione synthesis are upregulated, as well as antioxidant and phase 2 detoxification enzymes, highlighting Nrf2's important role in maintaining cellular homeostasis in response to oxidative and inflammatory stress. Nrf2 activators have significant potential to provide not only an upregulation of cellular antioxidant defenses, but also as enhancers of mitochondrial function, critical to healthy cellular activity. It follows that activation of Nrf2 may support the health of multiple body systems, including the neurological, respiratory, gastrointestinal, and cardiovascular systems. For example, Nrf2 activation may play a role in maintaining healthy intestinal cell permeability and immune function; it has been shown to help with intestinal oxidative stress and the inflammatory response, influence tight junction proteins, and modulate T cell differentiation.

In a study published April 2021 in the *Journal of Inflammation Research*, an *in vivo* animal-based study found that carvacrol activated Nrf2 and mitigated the adverse effects of lipopolysaccharide (LPS)-induced neuroinflammation. In

addition, a molecular docking analysis was completed, with detailed analysis of the proposed binding site of carvacrol to Keap1, leading to Nrf2 activation. Nrf2 activation was associated with increases in the antioxidant enzymes catalase, glutathione, and glutathione-S-transferase levels, as well as reduced production of LPS induced inflammatory mediators, such as TNF-α and p-NFkB. This is consistent with a second animal study, which found carvacrol had a protective effect in a streptozotocin-induced model of diabetes, helping with oxidative stress and the inflammatory response while boosting antioxidant enzyme activity, including not only Nrf2, but catalase and glutathione peroxidase. A third study published in *Nutritional Neuroscience* found that carvacrol not only activated Nrf2, but this was associated with an inhibition of the NLRP3 inflammasome. This is an important finding, as the NLRP3 inflammasome functions as a damage sensor from a variety of sources (such as oxidative stress and infection), and overactivation has been associated with aging and impaired function across a variety of chronic conditions.

Multiple studies demonstrating diverse mechanisms of action point to oregano oil as potentially having broader health promoting benefits, in addition to its well known antimicrobial effects. While more human clinical trials are needed, controlled trials do suggest a favorable modulation of the gut microbiota, as well as a positive influence on markers of inflammation, such as hs-C-reactive protein, and TNF-α, vascular endothelial growth factor, and epidermal growth factor in select populations.

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