Chapter 19

Anti-Inflammatory Effect of Essential Oils

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ABSTRACT

Essential oils (EOs) are complex combinations of aromatic compounds found in various plant species, renowned for their therapeutic properties and potential as agents for inflammation reduction. Originating from the plant's secretory organs, EOs are extracted through pressing or distillation methods, offering unique energetic and therapeutic benefits. The chemical composition of EOs, comprising terpenes, phenylpropanoids, and other volatile compounds, contributes to their diverse medicinal properties. Inflammation, the body's response to tissue damage or infection, is a complex biological method regulated by intricate indicating pathways and inflammatory mediators. Essential oils have shown promise in modulating inflammatory pathways, including NF-κB, MAPK, and JAK-STAT, thereby mitigating the release of pro-inflammatory cytokines and reducing tissue damage. Topical use of certain essential oils, such as chamomile, lavender, and eucalyptus oils, has demonstrated anti-inflammatory effects in preclinical studies, offering potential therapeutic benefits for conditions like rheumatism, arthritis, dermatitis, and eczema. Experimental models, both in vivo and in vitro, have provided insights into the mechanisms underlying the anti-inflammatory properties of essential oils, highlighting their potential as novel therapeutic agents. However, while preclinical evidence is promising, further clinical trials are warranted to assess the efficacy and safety of essential oils in human therapy. Clinical studies have shown promising results in conditions such as chronic periodontitis and dental plaque accumulation, but more research is needed to explain the precise tools of action and determine optimal dosage regimens. In conclusion, essential oils hold significant potential as natural remedies for inflammation-related disorders, but their therapeutic utility requires further exploration through rigorous clinical investigation.

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INTRODUCTION

Essential oils are important part of the plant's defense mechanism; they are aromatic compounds that are present in certain plants' specialized cells or glands and that the plant uses to attract pollinators and protect it from pests and predators. The eminent Swiss physician, physicist, astrologer, theologian, and alchemist Paracelsus is credited with naming essential oils by coining the term "quinta essentia," which refers to the plant's essence (Jahan et al., 2015). Essential oils are volatile, very concentrated substances that are taken out from different parts of specific plant species. Each essential oil has unique energetic and therapeutic properties. These volatile liquids are incredibly complex molecules with incredibly strong and targeted actions. Since essential oil doesn't contain any fat, it isn't considered oil. It comes from the essence that the cells of specific plant parts secrete, which is rich in naturally occurring flavors, and active ingredients. Precious liquids can be attained by pressing or distilling the secretory organs. e.g. citrus skin is distilled, and the remaining plant components stem and leaves are flowers, root, and wood are cold pressed (Moghadam et al., 2018). These procedures produce an authentic source of active ingredients as well as an aromatic concentrate. Volatile oil and ethereal oil are other names for essential oils (Branch, 2016). Because a lot of raw materials are needed to extract just a few milliliters of oil, the process can be costly. This explains why authentic essential oils are so expensive. For instance, about 60 roses are needed to produce one drop of essential rose oil (Interfaces et al., 2018). But because there are a lot of low-cost resources and great productivity, there are also less expensive oils. These oils include tea tree oil, lemongrass oil, orange, bergamot, lime, and lemon. As such, EO is very valuable, but a drop is required for valuable effects, and a dose exceeding 2% is hazardous and has unfavorable things (Righi et al., 2017).

Essential Oil Biosynthesis

Majority of offensive compounds are biosynthesized in the leaves, where they stay until flowering. Some of the essential oils that are consumed during fertilization migrate into the flowers during flowering. After fertilization, it either gathers in fruits and seeds or migrates to leaves, bark, and roots (Nikolova and Georgieva, 2022).As plants get older, their essential oil composition changes. These oils are mainly made up of simpler molecules and terpenic hydrocarbons in young plants, while the reproductive structures of plants hold etheric oils, which are higher in oxygenated mixtures. Though their precise role within the plant is unknown, the ethereal oils have a multitude of uses. Out of the over 3,000 essential oils that have undergone chemical and physical characterization, around 150 are produced on an industrialized basis (Rezzoug et al., 2019).

The Chemical Make-Up of Essential Oil

Essential oils are complex combinations made up of 5000–7000 different chemical constituents. The majority of these constituents are mono- and sesquiterpenes, but they also contain aromatic compounds, which are sometimes diterpenes and frequently derivatives of phenyl propane. Terpenic compounds include hydrocarbons, oxygenated products (alcohols, alcohols, aldehydes, ketones, acids), and their reaction yields (ethers, esters). Plant-based mixtures known as terpenic compounds naturally combine with other molecules to form molecular mixtures that eventually form volatile (etheric, essential) oils. Essential oils and aromatic waters can only be obtained with the right raw materials, plant products, and quality. To ensure that the plant material is not contaminated with other plant species, it is important to harvest it carefully (Butnariu and Sarac, 2018). The primary constituents of essential oils can belong to the aliphatic, aromatic, or terpenic series, although their chemical makeup is extremely diverse. Volatile products contain terpenes aromatics, aldehydes, ketones, phenols, unstable acids, esters, and more. The plant's substantial focus to hydrodynamics is not always pick up after harvesting. Typically, plant which is fresh produce more pleasing scents and have a stronger healing effect; the exceptions are dried lavender, lime, and cinnamon flowers. When it comes to dry plants, morphological and chemical changes brought on by air pressure, heating, gramme accumulation, and possibly modification can occasionally result in lower volatile urine levels (Zerkaoui et al., 2018).

Inflammation

The body's natural reaction to tissue impairment caused by a range of possibly hazardous incentives that are brought by biological, chemical, and physical aspects is known as inflammation (Kolaczkowska and Kubes, 2013). If the stimulus is not removed or treated sufficiently, chronic inflammation develops, which puts the host at risk for a variety of illnesses, such as cancer and neurological disorders. Researchers have been motivated to study and create new medications in recent years due to the need for more potent medications that have fewer adverse effects when treating inflammation. The quest for naturally occurring plant-based products is a likely endeavor, and among the compounds with a pharmacological perspective are essential oils. This review aims to discuss the application of essential oils in management of inflammation (Zuo et al., 2020).

Mechanism of Inflammation

The term "inflammatory response" refers to the harmonized initiation of indicating paths that set the amounts of the inflammatory mediators in neighborhood cells of tissue as well as inflammatory cells isolated from blood (Lawrence, 2009). An inflammatory etiology is shared by a number of chronic illnesses, with diabetes, cancer, bowel and cardiovascular diseases, and arthritis (Libby, 2007). The nature of the inflammation response's procedures depends on the details of the early stimulus and where it is located in the body, but share a parallel mechanism expressed as follows: 1) Triggering of inflammatory pathways 2) Release of inflammatory markers 3) Recruitment of inflammatory cells and 4) Identification of pathogenic stimuli by the cell surface sequence receptors.

Inflammatory Pathway Activation

Inflammatory pathways affect many prolonged diseases and involve common inflammatory guiding pathways. Inflammatory stimuli begin intracellular indicating pathways, which in order cause the synthesis of inflammatory. Significant intracellular signaling networks including the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, nuclear factor kappa-B (NF κB), and mitogen-activated protein kinase (MAPK) pathways, are triggered by receptor activation. Main inflammatory stimuli, which include products of microbe and cytokines like TNF-α (TNFR), IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), interact with TLRs to mediate inflammation (E. K. Kim and Choi, 2010).

The NF-κB Pathway

The record aspect NF-κB is intricate in response to immune, survival, inflammation, and apoptosis, among other important procedures. NF-κB activity can be triggered by a variety of chemicals, such as those that come from infectious agents, intercellular inflammatory cytokines, and multiple enzymes. In physiological situations, cytoplasmic IκB proteins inhibit NF-κB. PRRs activate IκB kinase (IKK) via analogous sign transduction pathways. IKK is composed of one regulatory subunit, IKKγ, and two subunits of kinase, IKKα and IKKβ. IKK phosphorylates IκB to regulate the NF-κB pathway's stimulation. The proteasome degrades phosphorylated IκB, freeing NF-κB, which subsequently triggers nuclear translocation and gene transcription. The inflammatory cells recruitment and the generation of pro-inflammatory cytokines, which together augment the inflammatory response, are governed by this pathway (L. Chen et al., 2018).

MAPK Pathway

The response of cells to various stimuli, including thermal shock, mitogens, osmotic stress (OS), and cytokines associated with inflammatory processes like IL-1, TNF-α, and IL-6, which impact the survival of cells, their proliferation, differentiation, and apoptosis, is regulated by a family of serine/threonine protein kinases called MAPKs. The mammalian MAPKs are c-Jun N-terminal kinases (JNK), p38 MAP kinase, and extracellular signal-regulated kinase (ERK1/2) (E. K. Kim and Choi, 2010). The three components of any MAPK signaling pathway are, at minimum, MAPK, MAPK kinase (MAPKK), and MAPK kinase (MAPKKK). Through MAPKKKs, phosphorylating and activating MAPKKs phosphorylates and activates MAPKs. ERKs are usually activated by mitogens and signals of differentiation. However, JNK and p38 are started in response to stress and inflammatory factors. MKK4 and MKK7 activate ERK1/2, MKK1 and MKK2 initiate JNK and MKK3 and MKK6 initiate p38. Phosphorylation and the beginning of MAPKs, for example, Erk1/2 and JNK, present in cytoplasm or nucleus, initiates the response inflammation and activates p38 transcription elements (Raingeaud et al., 1996).

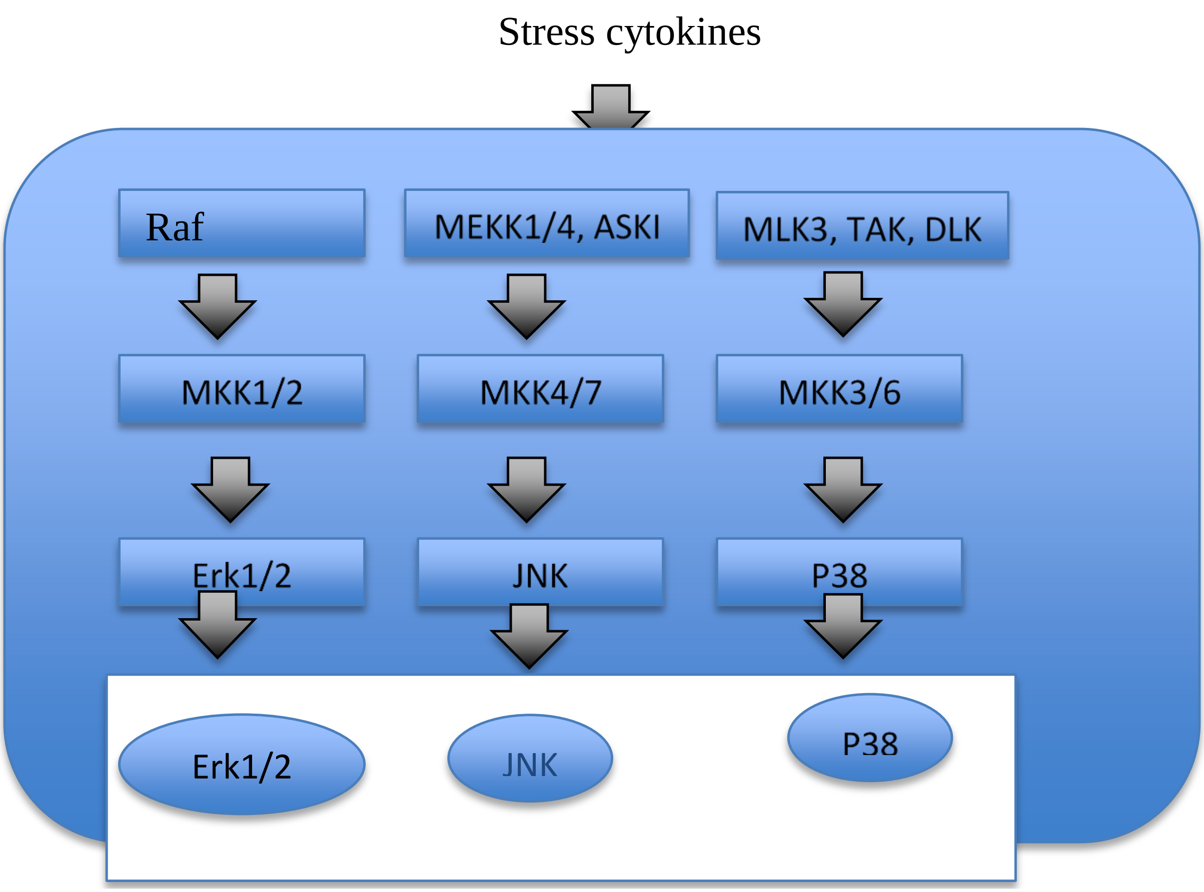

Fig. 1: MAPK PATHWAY

The JAK-STAT Pathway

The greatly evolved JAK-STAT pathway, an indicating process that includes a range of factors of growth, cytokines, interferon's associated molecules like growing hormone and leptin, allows extracellular factors to regulate gene expression (Pengse et al., 2017). Latent cytoplasmic transcription factors known as STATs have docking sites created by receptor-linked JAKs that are stimulated by ligands and phosphorylate one another. When cytoplasmic STATs are attracted to these locations, they undergo dimerization and phosphorylation before moving into the nucleus (Walker and Smith, 2005). Tyrosine phosphorylation is required for DNA binding and STAT dimerization (Ivashkiv and Hu, 2003). Thus, JAK/STAT signaling enables the direct translation of an outside of cell signal into a transcriptional response. For example, JAK-STAT proteins are triggered when IL-6 family members attach to plasma membrane receptors. Target gene promoter regions are bound by translocating STAT proteins into the nucleus to regulate the transcription of inflammatory genes. Inflammatory diseases, cancer, autoimmune, and digestive disorders are all associated with irregularities of JAK-STAT, MAPK, or NF-κB activity Signaling through transcription factors causes the release of cytokines. Numerous transcription factors regulate an abundance of inflammatory genes, such as IL-1, TNF-α, IL-6, interferon's growth factors such as transforming growth factor (TGF), colony stimulating factor (CSF), and chemokine's (Oeckinghaus et al., 2011).

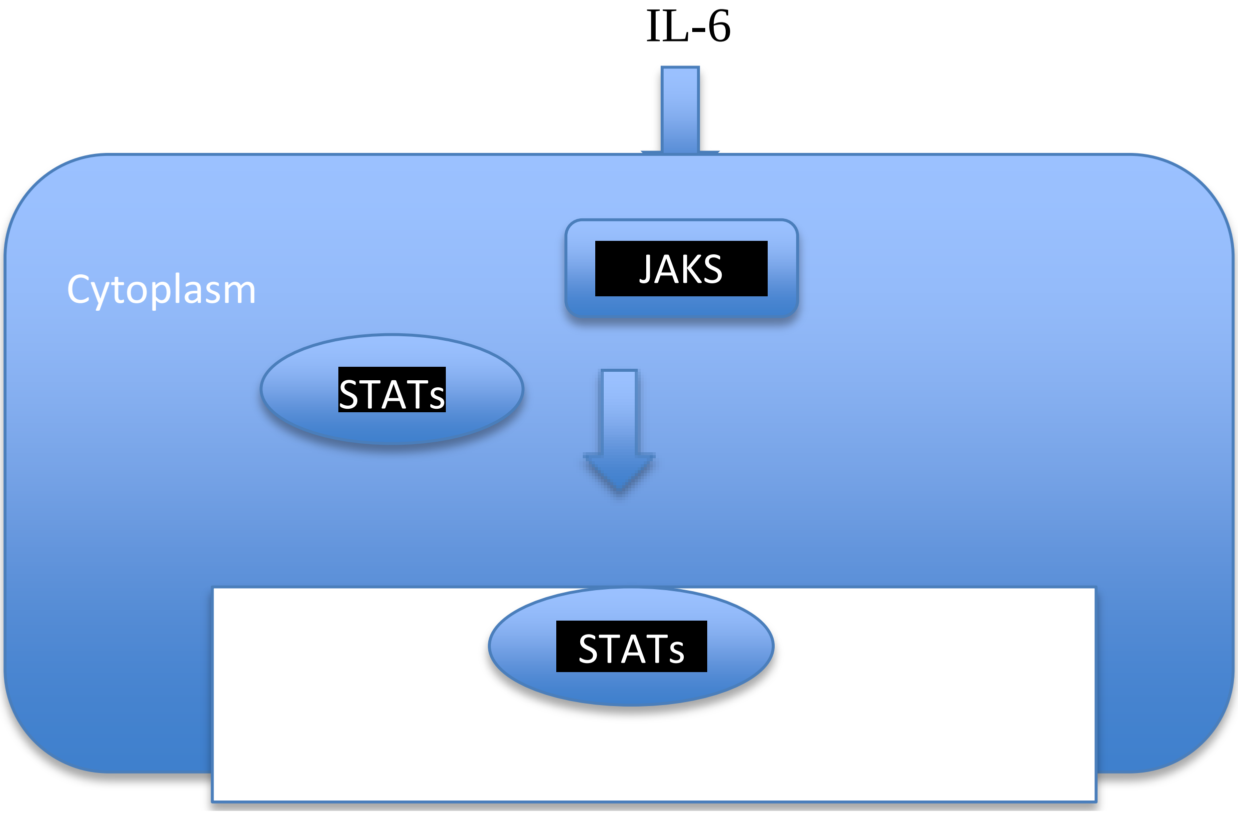

Fig. 2: The JAK-STAT Pathway

Markers of Inflammation

Markers are employed in clinical settings to assess the effectiveness of healing interventions and to distinguish between biological processes that are healthy and unhealthy. Inflammatory markers have been discovered to be associated with the reasons and concerns of a range of inflammatory diseases (Ivashkiv and Hu, 2003) like infections, endothelial disorders, and heart conditions, and to be predicting of inflammatory diseases (Carrero et al., 2008). Stimuli not only trigger the production of inflammatory proteins and enzymes but also cause the release of inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as the activation of inflammatory cells such as macrophages and adipocytes. These substances could serve as biomarkers for the diagnosis, prognosis, and choice of suitable therapies(Goldstein et al., 2009).

Proliferating Cytokines

Cytokines are released by most immune cells, including lymphocytes, macrophages, and monocytes. Pro-inflammatory cytokines support inflammation while anti-inflammatory cytokines stop it. Leukocyte assembly at the site of damage or infection is the principal role of cytokines that are inflammatory (Turner et al., 2014), which include ILs, colony-stimulating factors (CSF), IFNs, TNFs, TGFs, and chemokines. Cytokines regulate inflammatory processes and the response of immune system's to inflammation or infection via an intricate network of interactions. Conversely, excess production of inflammatory inflammatory mediators can cause tissue damage, changes in hemodynamics, failure of organs, and eventually death. A deeper knowledge of cytokine pathway regulation would enable treatment of inflammatory conditions and accurate determination of agent-mediated inflammation (Czaja, 2014).

Additional Inflammatory Indicators

Defense mechanisms of antioxidants, such as antioxidant enzymes, have an impact on oxidative stress. Reactive oxygen species (ROS), AP-1, isoprostanes, and other chemicals can be produced as a result of increased oxidative stress (Lopresti et al., 2014) (Huang et al., 2010). A range of factors transcription, including NF-κB, AP-1, p53, and STAT, can be activated by these substances. Consequently, this cascade could up-regulate the gene expression encoding factors growth, inflammatory cytokines, and chemokines (Park et al., 2015). Oxidative stress is linked with amount of diseases, for example, aging, cancer, heart disease, hypertension, diabetes, and atherosclerosis. As a result, oxidative stress-connected products could be markers of the reaction that is inflammatory.

Essential Oils as Agents of Inflammation Reduction

Inflammation is the natural defensive response of the body to injury or infection; it rids the body of dead or damaged host cells and combats foreign invaders. The inflammatory response results in elevated endothelial lining permeability of cells, blood leukocytes, influxes into the interstitium, an oxidative burst, and the release of cytokines. Furthermore, it raises the activity of several enzymes and the metabolism of arachidonic acid. In clinical settings, aromatic oils have recently been used for treating inflammatory diseases like rheumatism and arthritis (Zaman et al., 2020).

Evidence suggests that some essential oils can scavenge free radicals while also having anti-inflammatory qualities. For example, essential chamomile oil has been used for several centuries to treat severe irritations such as dermatitis and eczema by reducing inflammation (Kamatou and Viljoen, 2010). In blended formulations, essential oils such as eucalyptus, rosemary, lavender, and mille folia, as well as other plants like pine, clove, and myrrh, have also been used as anti-inflammatory agents (Darshan and Doreswamy, 2004).

Potential Health Benefits of Applying Essential Oils Topically to the Skin

Olive Oil

The fruits of the *Olea europaea* tree are used to make olive oil. It is mostly made up of the oleic acid, with trace amounts of further fatty acids like palmitic and linoleic acid. Olive oil contains over 200 different chemical compounds, such as phenolic compounds, triterpenic alcohols, carotenoids, and sterols (Nasopoulou et al., 2014).

Oil of Eucalyptus

Compounds found in eucalyptus include cineole (70–85%), limonene, terpinene, cymene, phellandrene, and pinene. Its antibacterial, anti-inflammatory, anti-proliferative, and antioxidant properties have been demonstrated by eucalyptus oil, and studies have conclusively shown that it is extremely effective in treating a wide range of infectious and metabolic disorders. The essential oils of this plant have a well-established history of treating rheumatoid arthritis as well as aches and pains in the muscles and joints (Mulyaningsih et al., 2011).

Eucalyptus oil's Medicinal Benefits and its Anti-inflammatory Qualities

The anti-inflammatory effect of the eucalyptus species is demonstrated by the edema caused in rats by the combination of dextran and carrageenan; neutrophil migration into the peritoneal cavity causes the combination of histamine and carrageenan to induce vascular permeability. The outcome does not follow the same pattern that we saw in the parameters that should be assessed; these will be assessed in terms of activities and dependent on dose relationships. For the study, the assay condition and oil were used. The information utilized for the oil extracts of EG, EC, and ET, which have both independent and dependent anti-inflammatory properties and central and peripheral effects of anti-inflammatory goods due to their phenolic content.

Lavender Oil

The essential oil of *Lavender augustifolia* and its principal components, linalyl acetate and linalool, showed in rats the anti-inflammatory propertie. Many investigated studies have the anti-inflammatory properties of compounds present in lavender oil. These studies investigated the special properties of unlike constituents found in EO, such as α pipine, α-terpinene, terpin-4-ol, α-terpineol, linalyl acetate, and linalool. According to the results of these studies, the compounds present in lavender oil may possess anti-inflammatory or ant nociceptive properties (H.-M. Kim and Cho, 2010).

Clove Oil

The essential oil known as clove oil is derived from *Syzygium aromaticum*. Because eugenol has analgesic, anti-inflammatory, and antiseptic qualities, it is an oil that is frequently used in dental products. The most significant components of cloves are eugenol, sesquiterpenes, and gallotannic acid. Other significant ingredients include vanillin, crategolic acid, betacaryophyllene, eugenin, kaempferol, and rhamnetin (Schmuth et al., 2015).

Clove oil's Medicinal Ability to Treat

- acne
- They eliminate parasites.
- To Increase Circulation of Blood
- In order to lessen gum disease
- To Increase Vitality
- They have natural anti-inflammatory properties.
- They eradicate fungi and mould

Turpentine in Oil

The resin of some pine trees is used to make turpentine oil. Turpentine oil is topically applied to relieve joint pain, toothaches, muscle soreness, and the nerve pain (Aswandi and Kholibrina, 2021).

Camphor

Camphor is a white, clear solid with a waxy consistency and a potent scent. With the chemical formula $C_{10}H_{16}O$, it is a terpenoid. Rosemary leaves from the *Rosemary officinalis* family contain camphor. Rosemary has a melting point of 175–177˚C and contains 10–20% camphor.

The Medical Advantages of Camphor

Camphor easily absorbed through the skin and give off a feeling of warmth or coolness. Serve as a mild local anaesthetic and antibacterial agent.

Experimental Models with Anti-inflammatory Properties

In Vivo

Mice are inoculated with different chemical agents to induce inflammation, which is one of the main in vivo models used to assess the anti-inflammatory capabilities of PEOs. Notably, the model contains common disease like animal models with allergic rhinitis, colitis, wound infection, tissue edema, skin inflammation, and anxiety. The anti-inflammatory qualities of PEOs have been assessed in a range of stimuli-induced inflammation models. Mice with colitis caused by dextran sodium sulphate were helped by cinnamon (Cinnamomum verum J.Presl) EO by correcting the imbalance in intestinal flora (Z. Chen et al., 2020). Tea tree (*Melaleuca alternifolia* (Maiden and Betche) EO decreases cell apoptosis, TNF-α expression, and IL-6 in the Lipopolysaccharides (LPS)-induced mastitis model, thereby reducing the damage brought on by inflammation. Oral PEO administration in vivo models is not feasible due to its inherent volatility and instability. Orally administering PEOs to animals also induces anxiety and discomfort. This results in abnormal behaviors like smearing and grabbing, which negatively impact the outcomes (Yuan et al., 2021). On day 7 of the pathogen-infected mice model of wounds, Mentha piperita L. EO treatment bigger IL-1β levels in the diseased wound tissue while lowering the levels of fibroblast growth factor-2 (FGF2) and vascular endothelial growth factor (VEGF). The exact mechanism of action of this effect is yet unknown; however, it contradicts the anti-inflammatory response that PEOs mediate (Modarresi et al., 2019).

In vitro

The structure and biological function of the cells can be evaluated in in-vitro experiments. Human keratinocytes, BV-2 microglia, HaCaT cells, THP-1 macrophages, and RAW264.7 cells triggered with LPS or other reagents are a few of the frequently used invitro inflammatory models. To lessen harmfulness and irritability, PEOs are usually used at lower focuses for in vitro research than for in vivo studies. The recommended PEO application range for in vitro studies is 1–100 μg/kg. On the other hand, 100 mg/kg is the recommended PEO dose for in vivo research. Leukocyte chemotaxis in the white blood cells chemotaxis model is markedly suppressed when 1–60 μg/mL PEOs are administered (dos Santos et al., 2021). For skin inflammation, ginger-grass extract has been shown to have therapeutic benefits. PEO concentrations of 0.001–0.1% and 0.1–0.3%, respectively, were utilized for topical application and incubation. PEOs are unstable at 37 ◦C, and the in vitro research the lines of the cell are protected at this temperature. As such, it is challenging to determine a relationship between both in vitro and in vivo models' bio-accessibility and bioavailability (Singh et al., 2022).

Clinical Trials

Although PEOs' have been shown anti-inflammatory effects in models in vitro and in vivo, more investigation in the form of epidemiological and also clinical studies is compulsory to evaluate the anti-inflammatory PEOs' potential applications in therapy and prevention. Studies show that PEOs are used to treat inflammatory conditions such as rheumatoid arthritis, migraines, and anxiety (Bahr et al., 2018). When PEOs are applied topically or inhaled, patients report reduced pain and tension; however, more research is required to decide the precise mechanism responsible for PEOs' anti-inflammatory effects. Clinical studies have shown that breath fresheners with PEOs can effectively minimize the incidence of chronic periodontitis and stop dental plaque from accumulating (Anusha et al., 2019). It is first essential to determine whether PEOs are effective in treating humans, either only or in combination (with natural or artificial drugs). Clinical trials evaluate PEOs' anti-inflammatory properties mainly in the context of aromatherapy and stomatitis treatment; comparatively few studies focus on PEOs' absorption and digestion. Patients with type II diabetes experience fewer complications and reduced levels of TNF-α and CRP when they take 100 mg of Cuminum cyminum L. EO pills. Although inflammation-linked signs were not the focus of this study, more inflammatory models will therefore be required in the upcoming to provision the clinical use of PEO (Jünger et al., 2020).

Conclusion

Essential oils have gained attention for their potential anti-inflammatory properties, notably chamomile, lavender, clove, and eucalyptus oils. Experimental studies reveal their modulation of inflammatory pathways, enzyme inhibition, and cytokine regulation. Clinical trials show promise in managing inflammatory conditions like rheumatoid arthritis. However, further research, especially in human trials, is necessary to understand their efficacy, safety, and interactions with medications. Overall, while essential oils offer potential as natural anti-inflammatory remedies, ongoing scientific exploration is crucial to confirm their benefits and refine their application

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