INTRODUCTION

Inflammation is the immune system’s protective reaction to complex processes involving numerous biochemical and molecular mechanisms. Although the overlap is strictly controlled, chronic or excessive inflammation is a hallmark of many diseases, including atherosclerosis, diabetes, dermatitis, arthritis, obesity, and cancers in some organs. Classic indicators of inflammation are redness, heat, swelling, and pain.

Many natural anti-inflammatory were found in flavonoid groups. Flavonoids have a 15-carbon skeleton of two benzene rings linked by heterocyclic pyran rings named A, B, and C in the C6-C3-C6 structure. Flavonoids work to inhibit cyclooxygenase or lipoxygenase and inhibit the accumulation of leukocytes in the affected area. Plants produce a group of bioactive molecules known as flavonoids. Eriocitrin (C27H32O15/eriodictyol trihydroxy 7,3,4-trihydroxy 6-one, as seen in the following image)

Figure 1: The chemical structure of eriocitrin

Potential Anti-Inflammatory Effects of Eriocitrin: A Review

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Abstract

Background: Inflammation is a natural reaction that the body has when exposed to physical damage. Inflammation in numerous organs implies atherosclerosis, diabetes, dermatitis, arthritis, obesity, and cancer. The review’s objective was to summarize the currently known eriocitrin's anti-inflammatory effects. Methods: A review was conducted on a study of the anti-inflammatory effects of eriocitrin conducted from January 2010 to April 2021. Results: Based on eligibility criteria, six studies were included in this study consisting of in vitro and in vivo studies. Some pharmacological studies have suggested that eriocitrin has the potential to treat diseases involving inflammatory responses. Nitric Oxide (NO), IL-1β, IL-6, IL-8, TNF-α, NF-κB, MPO, MAPK, and MMP-9 secretion were reduced by eriocitrin, inhibiting cell apoptosis, and the production of pro-inflammatory cytokines, but increases the content of IL-10, Nrf2, DUSP14, HO-1, and NQO1. Conclusions: Eriocitrin has been shown to have anti-inflammatory effects in both in vitro and in vivo studies.

Keywords: eriocitrin; flavonoids; inflammation

METHODS

The method used in this review is a literature review of secondary data obtained from scientific publications in journal articles. The articles used were taken from the databases of Google Scholar, ScienceDirect, Scopus, PubMed, and Web of Science.
RESULT AND DISCUSSION

The immune system’s homeostasis was maintained through the inflammatory response, a significant biological activity. Inflammation and oxidative stress are two pathophysiological activities with a lot in common. One may appear before or after the other, but once one does, the other will almost certainly follow, and both will contribute a pathogenic role to various abnormalities. Long-term low-level inflammatory processes were thought to have a key role in the pathogenesis of many chronic diseases. Acute inflammation is defined as inflammation that lasts for a few hours to several days and is characterized by the exudation of plasma fluids and proteins and the emigration of leukocytes (mainly neutrophils). Inflammation has a significant influence on health. The rapid demand for granulocytes (neutrophils, eosinophils, and basophils) in the body defined the process of acute inflammation. Mononuclear phagocytes detect pathogen-related molecular damage or patterns as the first line of defense, activating a series of intracellular signals and inducing the expression of pro-inflammatory mediators and cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6).

Acute inflammation was caused by primary immune cells such as macrophages and T lymphocytes, which release cytokines and enzymes and cause tissue damage, as shown in tissue fibrosis symptoms. Excessive inflammation can lead to chronic or systemic diseases, while inadequate inflammation can lead to persistent pathogenic infection. Chronic inflammation, including atherosclerosis, can be caused by an improper activation of ongoing inflammation or stage ablation.

Macrophages play a crucial role in the onset and progression of inflammation. Pro-inflammatory mediators such as cytokines (TNF-α and interleukins), histamine, nitric oxide (NO), leukotrienes, and prostaglandins were released by activated macrophages. Mast cells were responsible for the release of histamine. Endothelial cells were responsible for the release of NO. Endothelial cells made prostaglandins and leukotrienes from the phospholipids of damaged membranes.

A series of studies on the potential of eriocitrin have been conducted by different mechanisms. As many as six studies have been conducted as intended, as shown in table 1.

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Figure 2: Flow chart of the literature search
Potential eriocitrin was carried out on experimental animals using different mechanisms, as shown in table 1. According to Liu et al., eriocitrin investigation combined with resveratrol significantly inhibits the secretion of IL-1β, NO, and TNF-α induced lipopolysaccharides (LPS). Furthermore, eriocitrin, in combination with resveratrol, inhibited NF-κB, phosphor-STAT3, phosphor-AKT factors, and phosphorylation in the mitogen-activated kinase protein (MAPK) signaling pathway 30. It can also diminish the edema and inflammation generated by 12-O-tetradecanoylphorbol-13-acetate (TPA) in the subcutaneous tissue in vivo. Furthermore, the pro-inflammatory cytokines TNF-α and IL-1β were reduced due to eriocitrin and resveratrol administration. The MAPK signaling pathway was moderately reduced in RAW 264.7 cells treated with eriocitrin alone, COX-2, NF-κB, and iNOS. Eriocitrin inhibits the production of IL-1β, NO, and TNF-α by a moderate amount. These findings suggest that eriocitrin works by inhibiting inflammation via a signaling mechanism 30.

According to Guo et al., eriocitrin 30mg/kg treatment for induced colitis animals reduces myeloperoxidase (MPO) activity in experimental animals. Compared to the colitis-induced group, eriocitrin treatment resulted in a substantial reduction in MPO activity. Eriocitrin considerably reduced-sodium sulfate-induced dextrose inflammation in experimental mice. Treatment with eriocitrin 30 mg/kg lowered levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) in acute colitis-induced Dextran Sulfate Sodium (DSS) 31.

He et al. also investigated the effects of eriocitrin on inflammatory reactions by detecting inflammatory cytokines content in the blood and tissues. At 16 and 32 mg/kg doses, the pro-inflammatory variables TNF-α and IL-6 increased significantly in the cerebral reperfusion group. In mice with cerebral ischemia-reperfusion, the inflammatory response was altered by eriocitrin 32. The inflammatory cytokines modulated the reperfusion-induced inflammatory pathways 35, IL-6 was engaged in neuron death and inflammatory cytokine medication in the pathogenesis of cerebral ischemia 36. TNF-α is a pro-inflammatory cytokine linked to brain loss 37.

Meanwhile, IL-10, as an anti-inflammatory cytokine, is essential for regulating the inflammatory response. The inflammatory response may be modulated by the expression of IL-10, IL-6, and TNF-α. Inflammatory responses may be regulated by the expression of IL-6, IL-10, and TNF-α. In this study, eriocitrin decreased the inflammatory response in mice with cerebral reperfusion by decreasing IL-6 and TNF-α levels while improving IL-10 expression. The findings imply that Eriocitrin inhibited oxidative injury and inflammatory responses in mice with cerebral ischemia-reperfusion via the Nrf2/HO-1/NQO1/NF-κB signaling pathway 32.

NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways controlled the production of inflammatory cytokines and inflammatory response enzymes like iNOS and COX-2. MAPK signaling pathways, in particular, have a significant impact on signals that go from extracellular stimulus to intracellular responses. In response to stimulation, these kinases are activated by phosphorylation, and active kinases phosphorylate particular proteins in the cytosol and nucleus. The transcription factor NF-κB was activated as a result. Through activation of NF-κB and MAPK, many activated glial cells display enhanced secretion of pro-inflammatory cytokines such as iNOS, IL-1β, COX-2, and TNF-α 38,39. NF-κB activation was linked to oxidative stress 40 and inflammatory conditions 41. Signals and modulators of the nuclear factor kappa B (NF-κB) were thought to be potential therapeutic targets for inflammatory diseases 42. In neuroinflammatory diseases, NF-κB activation is related to increased ROS
production in activated microglia. Microglia that have been triggered produce more pro-inflammatory cytokines \(43,44\). The activation of NF-κB in microglia generated a large amount of iNOS, resulting in a high NO and cytokine level. COX-2 expression is affected by NF-κB activation, which results in the formation of prostaglandins in activated astrocytes \(45-47\). Activated astrocytes or glia produce pro-inflammatory cytokines \(\text{TNF-}\alpha, \text{IL-1}\beta, \text{IL-6}, \text{IL-8}\), and other substances. TNF-α, for example, can cause cell death by attaching to several TNF receptor families and causing apoptosis. Overproduction of NO triggers cell death by causing the X-related protein BCL2 (BAX) and the homologous antagonist killer BCL2 (BAK1) to activate, causing the release of cytochrome c from mitochondria \(46\).

**CONCLUSION**

Eriocitrin is found mainly in citrus lemons and limes, particularly on the peel, but not all oranges possess it. The importance of eriocitrin as a natural anti-inflammatory was highlighted in this review. Some pharmacological studies have found that eriocitrin has the potential to treat diseases correlated with inflammatory responses. Eriocitrin has been shown to inhibit the secretion of TNF-α, NO, IL-6, IL-1β, IL-8, NF-κB, MMP-9, MPO, MAPK, and cell apoptosis, while increasing the level of IL-10, Nrf2, DUSP14, HO-1, and NQO1.

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