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Review Article

Potential Anti-Inflammatory Effects of Eriocitrin: A Review

Muhanifa Rustam, Ifora Ifora, Fitra Fauziah*

Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences Padang (STIFARM Padang), West Sumatera, Indonesia, 25147

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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 NQ01. **Conclusions:** Eriocitrin has been shown to have anti-inflammatory effects in both in vitro and in vivo studies.

Keywords: eriocitrin; flavonoids; inflammation

*Address for Correspondence: Fitra Fauziah, School of Pharmaceutical Sciences Padang (STIFARM Padang), West Sumatera, Indonesia 25147

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 [1-5]. Classic indicators of inflammation are redness, heat, swelling, and pain [6].

Many natural anti-inflammatories 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 [7]. 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-7-O-rutinoside) is a flavonoid group of the flavanone subgroup IUPAC (2S)-2-(3,4-dihydroxy phenyl)-5-hydroxy-7-[(2S,3R,4S,5S,6R).)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3-dihydrochromen-4-one, as seen in the following image:

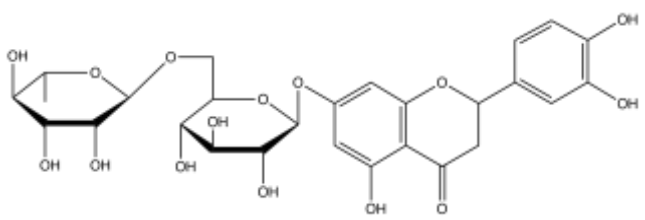

Figure 1: The chemical structure of eriocitrin [8]

Flavonoids are among the categories of secondary plant metabolites, including glycosides, aglycons, and polymers with flavanones, which are among the most widely distributed sub-classes in the genus *Citrus* [9]. Flavanone eriocitrin was contained in citrus lemon [10], especially on a fresh lemon peel, but not in all oranges [11,12]. Flavanone eriocitrin was also found in several other oranges, such as tangelo, grapefruit, sweet orange, lime, mandarin [10], and bergamot [6]. Citrus fruits have been found to provide medical benefits in several recent epidemiological and clinical research [13], and their components against potent antioxidants, oxidative stress, inflammation, and dysmetabolic diseases [12,14], the most common flavonoid subtype in fruits [15], especially *Citrus lemons* [10]. Numerous studies have shown that *Citrus* derivatives effectively prevent and treat chronic inflammatory diseases such as inflammatory bowel disease, type 2 diabetes, and even cancer [16-18]. Through mechanisms involving NF-κB kinase pathways and mitogen-activated proteins (MAP), anti-inflammatory activity was confirmed in mouse intestinal ischemia/reperfusion injury [19].

Eriocitrin (eriodictyol-7-O-rutinoside) and its aglycon eriodyctiol are the main flavanones extracted from the lemon peel (*Citrus limon*) as antioxidants and anti-inflammatory agents. [12,20]. Citrus flavonoids have proven valuable for commercial products such as medicines, foods, health products, dyes, and even cosmetics [21]. This review of the article was intended to show information related to the potential of eriocitrin as an anti-inflammatory.

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 published from January 2010 to April 2021. The keywords used are "inflammation," "anti-inflammatory," "flavonoids," and "eriocitrin." All abstracts and full-text articles are collected, grouped, summarized, and concluded according to the relevant theme. There are 1068 articles obtained from search results using keywords (994 articles from Google Scholar, 64 articles from ScienceDirect, six articles from Scopus, one article from PubMed, and three articles from Web of Science). After screening the full text, six articles meet the requirements used in this review. The flow chart for the literature search is shown in Figure 2.

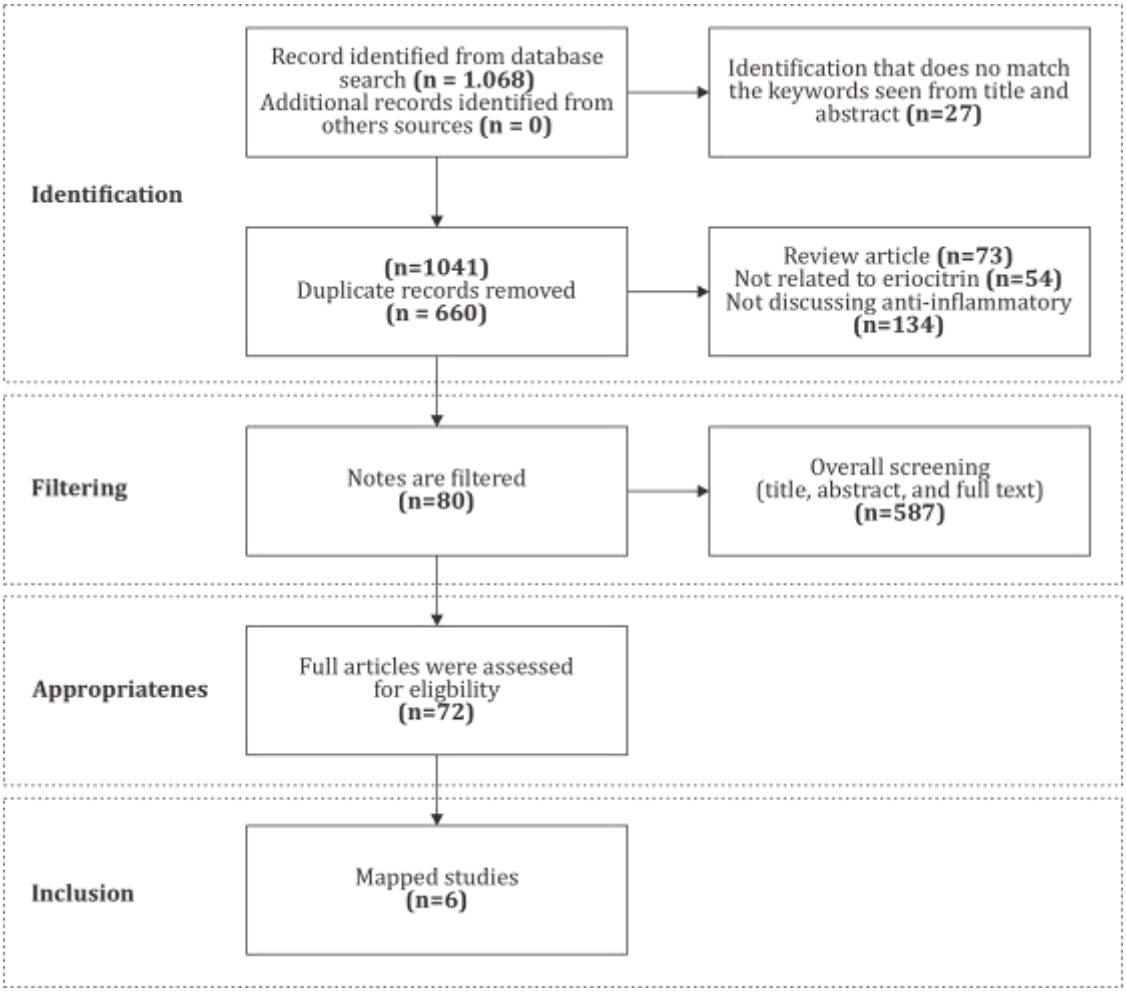

Figure 2: Flow chart of the literature search

RESULT AND DISCUSSION

The immune system's homeostasis was maintained through the inflammatory response, a significant biological activity [22]. 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 [6]. 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) [6]. Inflammation has a significant influence on health [23]. The rapid demand for granulocytes (neutrophils, eosinophils, and basophils) in the body defined the process of acute inflammation [24]. 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)[22,25].

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 [26]. Excessive inflammation can lead to chronic or systemic diseases, while inadequate inflammation can lead to persistent pathogenic infection [27]. Chronic inflammation, including atherosclerosis, can be caused by an improper activation of ongoing inflammation or stage ablation [24].

Macrophages play a crucial role in the onset and progression of inflammation [28]. 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 [29].

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.

Table 1: Anti-inflammatory activity of eriocitrin

Dose/ Conc.	Experimental Model	Animal or Disease Models or Cell/ Specimen	Reported activity	Region	Ref
12.5, 25, 50, 100, 200, and 400 µM Eriocitrin and resveratrol (50 and 10 mg/kg)	LPS-induced RAW264.7 cells (in vitro) and a mouse model of ear edema (in vivo)	RAW 264.7 cells	Eriocitrin combined with resveratrol strongly inhibits the secretion of NO, IL-1β, TNF-α, NF-κB, and MAPK (in vitro). It also reduces edema and inflammation of subcutaneous tissue (in vivo).	China	(30)
30 mg/kg	Dextran Sulfate Sodium (DSS) induced experimental colitis in a murine model	Mice (male breed)	Eriocitrin effectively decreases MPO production, activates MMP-9 and NF-κB, inhibits the production of pro-inflammatory cytokines, iNOS, and COX-2 expression, and protects the colon from inflammation.	China	(31)
8, 16, and 32 mg/kg	Middle cerebral artery occlusion (MCAO)/ reperfusion model	Male Sprague-Dawley (SD) rats	Eriocitrin effectively lowers TNF-α, IL-6 and NF-κB, increasing IL-10, Nrf2, HO-1, and NQO1.	China	(32)
25 ng/mL	Caco-2 transwell model (In Vitro)	Caco-2 cells	Eriocitrin decreases the release of IL-6, IL-8, and NO.	Italy	(33)
10, 30, and 60 mg/kg	OGD/R of HK-2 cell in vitro and a rat model of AKI in vivo	Adult male Sprague-Dawley (SD) rats	Eriocitrin increases DUSP14, and Nrf2 decreases NF-κB phosphorylation, promotes Nrf2 expression, and inactivates NF-κB, thereby lowering inflammation regulation and oxidative stress.	China	(34)
25 and 50 mg/kg	LPS-induced periodontal disease in mice	BALB/c male mice	Eriocitrin inhibits IL-1β and TNF-α gingiva and increases secondary IL-10 due to periodontitis.	Brazil	(11)

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, phosphorus-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 were 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 (TNF-α, IL-1β), glutamate, NO, ROS, 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].

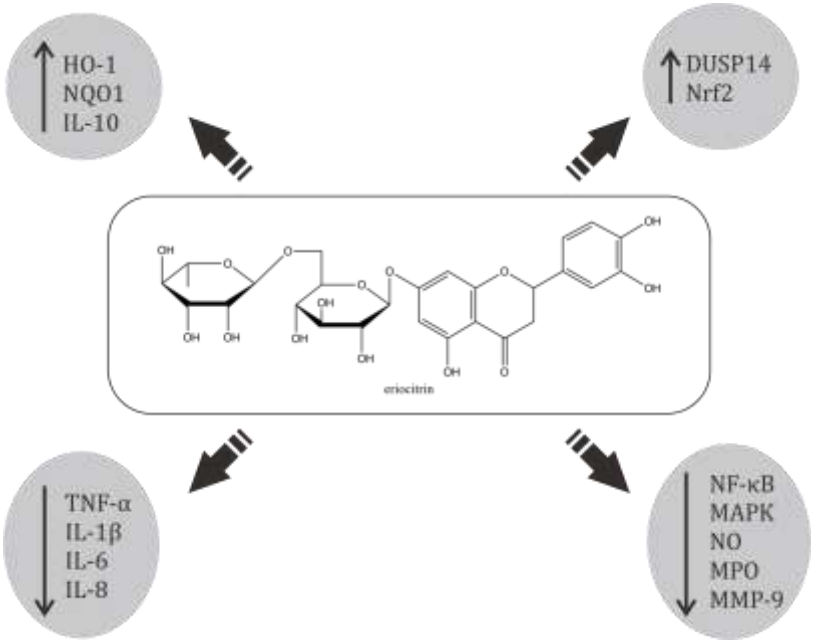

Figure 3: Anti-inflammatory mechanism of eriocitrin

Recent findings from Denaro et al. suggest that eriocitrin is the most potent anti-inflammatory compound among the orange flavanones investigated. The compound's unique structural characteristics protect it from enzymatic reactions or hydrolytic events during digestive processes, allowing it to be available at the gut level and exerting a potent anti-inflammatory effect. In additional research, orange flavanones were mixed with cell-free trials in vitro and then investigated the most potent equimolar ratio to find the potential for synergistic activity. The flavanone combination will be exposed to simulated digestion in vitro. Finally, anti-inflammatory activity was studied in a Caco-2 cell-based model activated by IL-1β, which revealed a more potent antioxidant and anti-inflammatory effect than a single flavanone and synergistic activity. The results obtained from the flavanone mixture can reduce the release of IL-6, IL-8, and nitric oxide, where the results are similar to reference anti-inflammatory drugs [33].

Xu et al. claim that eriocitrin inhibits the expression of malondialdehyde (MDA) oxidation factors and increases levels of antioxidant superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) factors in acute kidney injury in vivo and in vitro experiments, preventing acute kidney injury induced reperfusion [34]. Eriocitrin also inhibits apoptosis in human tubular epithelial cell lines caused by a shortage of oxygen-glucose/reperfusion in a dose-dependent manner by suppressing inflammation and oxidative stress. Eriocitrin significantly enhanced DUSP14 and Nrf2 phosphorylation while decreasing NF-κB phosphorylation. Eriocitrin enhances dormant Nrf2 and NF-κB expression by increasing DUSP14, reducing inflammation and oxidative stress control. Furthermore, blocking DUSP14 expression using inhibitors of the inhibitor IV tyrosine-protein (PTP) reverses the kidneys' protective function against eriocitrin. Finally, eriocitrin protects against acute kidney injury-induced ischemia-reperfusion by reducing oxidative stress and inflammation through enhanced DUSP14, giving a theoretical basis for treating ischemia-reperfusion caused by acute kidney injury [34].

According to the inflammatory response stage caused by LPS from *Escherichia coli*, eriocitrin was associated with granulocyte downregulation and mononuclear infiltration into the gingival mucosa in another study. The effectiveness of eriocitrin to prevent periodontal inflammatory exacerbation may be partly due to the inhibition of cytokine generation and the biochemical parameters measured. To avoid periodontal disease and promote dental health, it was suggested that dentists pay attention to natural foods or dietary supplements containing flavonoids [11].

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 NQ01.

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