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Anti-inflammatory effects of luteolin: A review of in vitro, in vivo, and in silico studies

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Luteolin-5-O-glucoside (PubChem CID: 44258061)
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Luteolin-8-C-glucoside (PubChem CID: 5281675)
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ABSTRACT

Ethnopharmacological relevance: Luteolin (3′, 4′, 5,7-tetrahydroxyflavone) has been identified as commonly present in plants. Plants with a high luteolin content have been used ethnopharmacologically to treat inflammation-related symptoms. Both isolated luteolin and extracts from luteolin-rich plants have been studied using various models and exhibited anti-inflammatory activity.
Aim of the review: This paper uses recent research findings with a broad range of study models to describe the anti-inflammatory activity of luteolin, particularly its mechanisms at the molecular level; provide guidance for future research; and evaluate the feasibility of developing luteolin into an anti-inflammatory drug.
Materials and methods: We summarize reports about the anti-inflammatory activity of luteolin published since 2009, which we found in MEDLINE/PubMed, Scopus, Web of Knowledge, and Google Scholar. To acquire broad information, we extended our search to online FDA documents.
Results: Luteolin is a flavonoid commonly found in medicinal plants and has strong anti-inflammatory activity *in vitro* and *in vivo*. Some of its derivatives, such as luteolin-7-O-glucoside, have also shown anti-inflammatory activity. The action mechanism of luteolin varies, but Src in the nuclear factor (NF)-κB pathway, MAPK in the activator protein (AP) − 1 pathway, and SOCS3 in the signal transducer and activator of transcription 3 (STAT3) pathway are its major target transcription factors. A clinical trial with a formulation containing luteolin showed excellent therapeutic effect against inflammation-associated diseases.
Conclusion: In silico, *in vitro*, *in vivo*, and clinical studies strongly suggest that the major pharmacological mechanism of luteolin is its anti-inflammatory activity, which derives from its regulation of transcription factors such as STAT3, NF-κB, and AP-1. Much work remains to ensure the safety, quality, and efficacy of luteolin before it can be used to treat inflammation-related diseases in humans.

1. Introduction

Luteolin is a flavone compound present in many medicinal plants. The flavones are a class of flavonoids, some of the most abundant secondary metabolites in plants, and are widely known to be responsible for various pharmacological activities. Structurally, luteolin has a hydroxyl (-OH) group attached at the 5-, 7-, 3′-, and 4′- positions of the flavone backbone structure. The presence of a hydroxyl group at the 3′- position distinguishes this flavone from apigenin, which has been studied for many years. Flavones are characterized by the presence of a double bond between C2 and C3, following a ketone at the 4-position on the C-ring. The absence of a hydroxyl group on C3

Abbreviations: NF-κB, nuclear factor kappa B; AP-1, activator protein; STAT3, signal transducer and activator of transcription 3; NK cells, natural killer cells; TNF-α, tumor necrosis factor-α; NO, nitric oxide; iNOS, inducible nitric oxygen synthase; ROS, reactive oxygen species; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; ATP, adenosine triphosphate; Syk, spleen tyrosine kinase; Src, proto-oncogene tyrosine-protein kinase; IL-1β, interleukin-1β; CCL2, chemokine (C-C motif) ligand 2; CXCL2, chemokine (C-X-C motif) ligand 2; LDH, lactate dehydrogenase; LPS, lipopolysaccharides; SOD, superoxide dismutase; GSH, glutathione; IFN-β, interferon-β; HMGB1, high mobility group B1; PGE_2, prostaglandin E_2; COX-2, cyclooxygenase enzyme-2; BMMCs, bone marrow-derived mast cells; LTC4, leukotriene C4; MIP, macrophage inflammatory protein; JAK, Janus tyrosine kinase; PI3K, phosphatidylinositide 3-kinases; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; IκB, inhibitor of kappa B; IKK, IκB kinase; PRV, pseudorabies virus; PMA, phorbol 12-myristate 13-acetate; HUVECs, human umbilical vein endothelial cells; HAT, histone acetyltransferase; HDAC, histone deacetylase; IP-10, interferon gamma-induced protein 10; TLR, toll like receptor; GFP, green fluorescent protein; IRF, interferon regulatory transcription factor; MyD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; TBK1, TANK-binding kinase 1; JNK, c-Jun N-terminal kinase; NFAT, nuclear factor of activated T-cells; PKC, protein kinase C; HSP90, heat shock protein 90; CREB, cAMP response element-binding protein; SIRT1, NAD-dependent deacetylase sirtuin-1; SOCS, suppressor of cytokine signaling; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinases; HO-1, heme oxygenase-1; VCAM-1, vascular cell adhesion protein 1; ICAM-1, intercellular adhesion molecule 1; TIMP, tissue inhibitors of metalloproteinases

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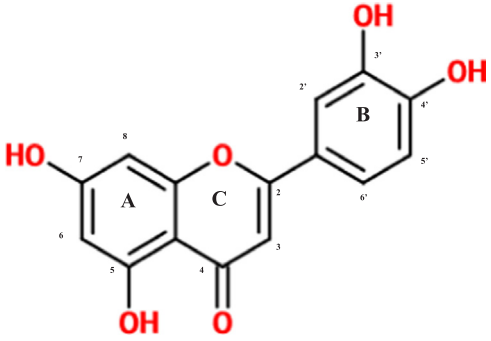

Fig. 1. Chemical structure of luteolin.

distinguishes flavones from flavonols. The chemical structure of luteolin is shown in Fig. 1.

Luteolin is present in vegetables, fruits, and medicinal herbs, including broccoli, onion leaves, carrots, peppers, cabbages, apple skins, *Chrysanthemum indicum* var. albescens flowers, *Codariocalyx motorius* (Houtt.) H. Ohashi, and *Artemisia asiatica* Nakai (also known as *Artemisia dubia* var. *asiatica* Pamp., as at http://mpns.kew.org/mpns-portal). High luteolin content has also been reported in parsley, thyme, peppermint, basil, celery, and artichoke (Jeong et al., 2014; Kim et al., 2014a, 2014b; Li et al., 2012; Pandurangan and Esa, 2014; Wall et al., 2013; Yang et al., 2017). Luteolin has been reported to have antioxidant, anti-microbial, anti-inflammatory, chemopreventive, chemotherapeutic, cardioprotective, anti-diabetic, neuroprotective, and anti-allergic properties (Baek et al., 2017; Baek et al., 2016; Choi et al., 2017; Lopez-Lazaro, 2009; Yu et al., 2017). Similarly, plants with a high luteolin content have been used for a long time in Irani, Brazilian, and Chinese traditional medicines to treat inflammation-related diseases (Farzaei et al., 2013; Ferrari et al., 2013; Ramezani et al., 2009). For example, *Zygophyllum simplex* L. (also known as *Tetraena simplex* (L.) Beier & Thulin as accepted in http://mpns.kew.org/mpns-portal), *Chrysanthemum indicum* var. albescens, *Vernonia condensata* Baker (also known as *Acmella ciliata* (Kunth) Cass. as accepted in http://mpns.kew.org/mpns-portal), *Cymbopogon citratus* (DC). Stapf, *Salvia plebeia* R. Br., and *Codariocalyx motorius* (Houtt.) H. Ohashi, which all have high luteolin content, have been prescribed for inflammatory diseases, including gout, asthma, skin psoriasis, and erythema, as summarized in Table 1. Some researchers have provided non-specific or non-accepted plant names, including *Chrysanthemum indicum* var. albescens, *Artemisia asiatica* Nakai, and *Lychnophora trichocarpha* Spreng. (not included in http://mpns.kew.org/mpns-portal)

Inflammation is a complex biochemical reaction carried out by immune and non-immune cells in a highly coordinated fashion (Chen et al., 2016). Inflammation occurs as a natural response to harmful stimuli, such as tissue stress, injury, and microbial invasion, to maintain homeostasis. The main purpose of the inflammatory reaction is to eliminate harmful stimuli, mainly through the actions of immune cells, such as natural killer (NK) cells and macrophages, upon activation of various molecular signaling pathways. A cascade of molecular events in inflammatory cells promotes the production of inflammatory mediators. Some of these mediators, such as nitric oxide (NO) and tumor necrosis factor (TNF)-α, are cytotoxic to the invading pathogens and also to the host cells, leading to tissue injury. Although inflammation is an important defense mechanism in the human body, inflammatory responses can also lead to serious problems when the reactions persist, i.e., *chronic* inflammatory conditions. Indeed, prolonged inflammation is thought to be associated with many chronic diseases, including rheumatoid arthritis, asthma, multiple sclerosis, and even cancer. Therefore, inflammatory responses must be controlled to prevent immune cells from causing further tissue injury and to prevent the development of progressive, inflammation-associated diseases. For these reasons, anti-inflammatory agents are highly desirable.

Natural sources are often part of drug development. In fact, more than 100 natural product-derived drugs are currently in clinical trials (Katiyar et al., 2012). Flavonoids, particularly luteolin, are derived from a variety of plants with traditional uses that have long been studied for their anti-inflammatory activity. In addition to their many pharmacological benefits, luteolin and its derivatives are relatively tolerable to various cell types. Moreover, because luteolin exhibits anti-inflammatory activity at micromolar concentrations (Seelinger et al., 2008), it has emerged as a potentially promising compound for further development. Some studies have reported structure–activity relationships for luteolin in the context of its anti-inflammatory activity with the goal of confirming its mechanism of action.

Luteolin is considered non-toxic. Unlike quercetin, however, luteolin has not been granted Generally Recognized as Safe status by the U.S. FDA. We provide a compilation of available LD_{50} data for luteolin in Table 2. Because no reports have been made about its toxicological parameters in dogs or rabbits, further studies are needed.

The anti-inflammatory activity of luteolin was comprehensively reviewed in 2008 (Seelinger et al., 2008). They reported that the anti-inflammatory action of luteolin has been attributed to inhibition of inducible nitric oxygen synthase (iNOS), iNOS expression, and NO production; scavenging of reactive oxygen species (ROS); inhibition of ROS production and activation of antioxidant enzymes; inhibition of leukotriene production and release; suppression of pro-inflammatory cytokine expression; inhibition of the NF-κB pathway, protein kinase B (AKT), and the mitogen-activated protein kinase (MAPK) pathway; inhibition of adhesion molecule membrane binding, hyaluronidase activity, and elastase activity; stabilization of mast cells; reduction of vascular permeability; and modulation of cell membrane fluidity. However, the review by Seelinger *et al.* was published more than a decade ago, and this compound has continued to be studied intensely. We previously found that luteolin acts partly by preventing adenosine triphosphate (ATP) from binding to spleen tyrosine kinase (Syk) or proto-oncogene tyrosine-protein kinase (Src) and confirmed that mechanism of action using a docking analysis (Lee et al., 2015a, 2015b). In this review, we summarize current knowledge about the anti-inflammatory activity of luteolin from *in vitro*, *in vivo*, and *in silico* studies published since 2009.

2. *In vitro* anti-inflammatory activity of luteolin

2.1. Regulation of inflammatory mediators

During the inflammatory response, immune cells secrete many types of mediators, including cytokines (e.g., interferons, interleukins, and TNF-α), chemokines (e.g., monocyte chemoattractant protein 1), and eicosanoids (e.g., prostaglandins and leukotrienes) (Azab et al., 2016). Those mediators of inflammation are responsible for eliminating the invading pathogen and initiating repair processes. Failure to resolve acute inflammation leads to the development of chronic inflammation, which is characterized by excessive levels of pro-inflammatory mediators (Serhan, 2009) and can mediate tissue injury. Inhibiting the production or function of inflammatory cytokines and mediators is thought to be important in regulating inflammation (Liu et al., 2016). The ability to regulate inflammatory mediators is thus a potential prerequisite for an anti-inflammatory agent.

Luteolin exerts its anti-inflammatory effects partly by regulating inflammatory mediators and has been shown to regulate various cytokines in *in vitro* and *in vivo* models. Cytokine regulation is thought to be crucial because cytokines are key modulators of both acute and chronic inflammation (Turner et al., 2014). Luteolin can inhibit interleukin (IL)−1β, IL-2, IL-6, IL-8, IL-12, IL-17, TNF-α, interferon (IFN)-β, and granulocyte-macrophage colony-stimulating factor (all pro-inflammatory cytokines) and increase the level of IL-10 (an anti-inflammatory cytokine). Some of these effects have been observed on the mRNA level. On the other hand, chemokines [e.g., chemokine (C-C