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Review

Kaempferol and inflammation: From chemistry to medicine

Kasi Pandima Devi[a], Dicson Sheeja Malar[a], Seyed Fazel Nabavi[b], Antoni Sureda[c], Jianbo Xiao[d,e], Seyed Mohammad Nabavi[b,**,1], Maria Daglia[f,*,1]

[a] Department of Biotechnology, Science Campus, Alagappa University, Karaikudi 630 004, Tamil Nadu, India
[b] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, PO Box 19395 5487, Tehran, Iran
[c] Research Group on Community Nutrition and Oxidative Stress, University of Balearic Islands, and CIBERobn (Physiopathology of Obesity and Nutrition), E-07122 Palma de Mallorca, Balearic Islands, Spain
[d] State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Taipa, Macau
[e] Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany
[f] Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, 27100 Pavia, Italy

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ABSTRACT

Inflammation is an important process of human healing response, wherein the tissues respond to injuries induced by many agents including pathogens. It is characterized by pain, redness and heat in the injured tissues. Chronic inflammation seems to be associated with different types of diseases such as arthritis, allergies, atherosclerosis, and even cancer. In recent years natural product based drugs are considered as the novel therapeutic strategy for prevention and treatment of inflammatory diseases. Among the different types of phyto-constituents present in natural products, flavonoids which occur in many vegetable foods and herbal medicines are considered as the most active constituent, which has the potency to ameliorate inflammation under both *in vitro* and *in vivo* conditions. Kaempferol is a natural flavonol present in different plant species, which has been described to possess potent anti-inflammatory properties. Despite the voluminous literature on the anti-inflammatory effects of kaempferol, only very limited review articles has been published on this topic. Hence the present review is aimed to provide a critical overview on the anti-inflammatory effects and the mechanisms of action of kaempferol, based on the current scientific literature. In addition, emphasis is also given on the chemistry, natural sources, bioavailability and toxicity of kaempferol.

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* Corresponding author. Tel.: +39 0382 987388; fax: +39 0382 422975.
** Corresponding author. Tel.: +98 21 88617712; fax: +98 21 88617712.
E-mail addresses: Nabavi208@gmail.com (S.M. Nabavi), maria.daglia@unipv.it (M. Daglia).
[1] These two authors share the senior authorship.

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1. Introduction

Inflammation is one of the most important biological responses in the vascular tissues caused by different pathogens, irritants or cell damages [1,2]. Inflammation is associated with pain, redness and heat, which usually reduces the normal functions of affected tissues [3]. It is considered as a protective mechanism of living organisms against pathogen-induced tissue damage [4,5]. Inflammation is classified into two major groups: acute and chronic, and it is well known that chronic inflammation is associated with different diseases such as arthritis, allergy, atherosclerosis, cancer, *etc.* [6–9]. Inflammation is the consequence of immune system activation as well as unwanted immune response in which, different immune cell types such as mast cells, T cells, B cells, NK cells, and neutrophils are involved [10–14]. It has also been reported that activities of some regulatory enzymes such as protein kinase C (PKC), phosphatidylinositol kinase (PIK), phosphodiesterase, phospholipase A2 (PLA2), tyrosine kinases, lipoxygenases (LOX) and cyclooxygenases (COX) play important roles in the initiation and progression of inflammation and immune response [14–16]. These regulatory enzymes have a crucial role in the endothelial cell activation which is also involved in the inflammatory response [14,16]. COX is known to be one of the most important inflammatory mediators that release arachidonic acid (AA), a precursor of eicosanoids like prostaglandins and prostacyclins, which have crucial roles in the progression and regulation of inflammation [17–19]. It has also been reported that, nitric oxide synthesized by the different isoforms of the inducible nitric oxide synthase (iNOS) and phosphorylation of protein kinases also play a key role in inflammation [20,21]. Furthermore, phosphodiesterases cause cell activation *via* changing the intracellular 3′,5′-cyclic monophosphate levels through which it alters the expression of pro-inflammatory cytokines and chemokines [22–24].

Both steroidal and non-steroidal anti-inflammatory drugs are currently used for the treatment of acute inflammation [25,26]. However, these drugs are not entirely effective in the treatment of chronic inflammation and related disorders [27,28] and show adverse effects [27,29]. Therefore, the search and discovery for new effective anti-inflammatory substances with low adverse effects are mandatory [27].

During the last two decades, much attention has been focused on dietary products as a rich source for drug discovery and development [30–32]. Special emphasis has been given to fruits and vegetables, which are rich sources of natural bioactive compounds, that can reduce the severity of inflammatory diseases through regulating the expression of pro-inflammatory cytokines as well as eicosanoid production [33–35]. Apart from fruits and vegetables, herbal medicines are also under high consideration because of their richness in natural bioactive compounds including phenols and flavonoids [31,36–39]. Based on the traditional medicinal practices, much attention has been paid in examining the biological effects of herbs, plants, especially edible species, due to their negligible adverse effects [32,40–43].

Several flavonoids have been reported to suppress inflammation both *in vitro* and *in vivo* [44–46]. It has been reported that flavonoids reduce the production of eicosanoids through inhibition of the activities of PLA2, COX and LOX [16,47–49]. In addition, flavonoids are inhibitors of phosphodiesterases, protein kinases, histamine releasing, and modulators of the transcription of genes resulting in anti-inflammatory activities [15,16,50]. Kaempferol, a flavonol widely found in different vegetables is known to be one of the most active and important natural anti-inflammatory compounds [51–54]. Though numerous scientific reports are available on the anti-inflammatory activities of kaempferol, only negligible number of review articles are available on the anti-inflammatory role of kaempferol. Therefore, in the present article, we critically review the available information on anti-inflammatory actions of kaempferol and its possible mechanisms of action.

1.1. Chemistry of kaempferol

According to Fig. 1, kaempferol contains diphenylpropane structure, which is responsible for its hydrophobic property [55]. Kaempferol is synthesized through 4-coumaroyl-CoA condensation with three malonyl-CoA under the catalytic action of chalcone synthase producing naringenin chalcone [55,56]. Thereafter, under the catalytic effects of chalcone isomerase, naringenin-chalcone is transformed into the flavanone called naringenin [55]. In the next step, a hydroxyl group is added to naringenin (at C3 position) to produce dihydrokaempferol, under the activity of flavanone 3-dioxygenase [55,56]. In the final step, kaempferol is produced through the introduction of a double bond at the C2–C3 position in the dihydrokaempferol skeleton by the activity of flavonol synthase [55] (Fig. 2). In plants, different sugars such as rutinose, rhamnose, glucose, and galactose are bonded to kaempferol to produce glycosidic form of kaempferol such as astragalin (kaempferol-3-O-glucoside) [55,57].

1.2. Sources of kaempferol

Kaempferol is widely distributed in different genera such as *Delphinium*, *Camellia*, *Berberis*, *Citrus*, *Brassica*, *Allium*, *Malus*, *etc.* [58–65]. In these plants, kaempferol is bonded to different glycoside moieties [55]. It has been also identified in different medicinal plants like *Acacia nilotica* (L.) Delile, *Aloe vera* (L.) Burm.f., *Crocus sativus* L., *Euphorbia pekinensis* Rupr., *Ginkgo biloba* L., *Hypericum perforatum* L., *Phyllanthus emblica* L., *Ribes nigrum* L., and *Rosmarinus officinalis* L, which are the most common medicinal plants which contain high amounts of kaempferol [55,66–73]. In addition, kaempferol is widely identified in different edible plants [63,72,74]. Table 1 summarizes the most important and common edible plant sources of kaempferol.

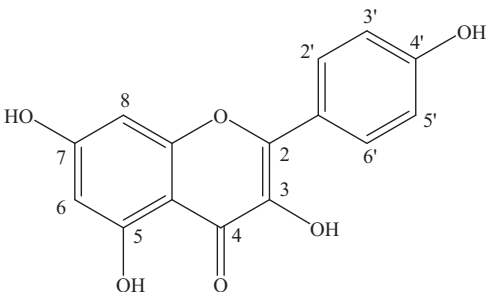

Fig. 1. Chemical structure of kaempferol.