Pharmacological Research 135 (2018) 122–126

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Invited Review

Naringenin as a potential immunomodulator in therapeutics

Wenfeng Zeng[a], Lingtao Jin[b,*], Fayun Zhang[a], Chunling Zhang[a], Wei Liang[a,*]

[a] Protein & Peptide Pharmaceutical Laboratory, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China
[b] Department of Hematology and Medical Oncology, Emory University, Atlanta, Georgia, USA

ARTICLE INFO

Keywords:
Naringenin
Citrus flavonoids
Inflammation
Apigenin

ABSTRACT

Naringenin, a citrus flavonoid that possesses various biological activities, has emerged as a potential therapeutic agent for the management of a variety of diseases. Studies using cell culture system have shown that naringenin can inhibit inflammatory response in diverse cell types. Moreover, research using various animal models has further demonstrated therapeutic potentials of naringenin in the treatment of several inflammation-related disorders, such as sepsis, fulminant hepatitis, fibrosis and cancer. The mechanism of action of naringenin is not completely understood but recent mechanistic studies revealed that naringenin suppresses inflammatory cytokine production through both transcriptional and post-transcriptional mechanisms. Surprisingly, naringenin not only inhibits cytokine mRNA expression but also promotes lysosome-dependent cytokine protein degradation. This unique property of naringenin stands in sharp contrast with some widely-studied natural products such as apigenin and curcumin, which regulate cytokine production essentially at the transcriptional level. Therefore, naringenin may provide modality for the development of novel anti-inflammatory agent. This review article summarizes our recent studies in understanding how naringenin acts in cells and animal models. Particularly, we will discuss the anti-inflammatory activities of naringenin in various disease context and its potential use, as an immunomodulator, in the treatment of inflammatory related disease.

1. Introduction

Naringenin (Fig. 1), a natural predominant flavanone, possesses a broad range of biological and pharmacological activities [1–3]. Accumulating evidence has suggested that naringenin is capable of modulating acute and chronic inflammatory responses and therefore may be used for therapeutic purpose. Indeed, several recent studies have shown that naringenin is effective in controlling several inflammation-related diseases such as sepsis, acute hepatis, fibrosis and cancer [4–6]. In addition, it has been shown that naringenin regulates lipoprotein metabolism and may be used in the management of diabetes, atherosclerosis and insulin resistance, which was extensively discussed in a previous review [1]. In this review article, we will focus on the anti-inflammatory activities of naringenin and discuss its therapeutic potential, as an immunomodulator, in several inflammation-related diseases.

2. Mechanism of action of naringenin in regulating inflammation

2.1. Transcriptional regulation of inflammation

Cytokines such TNF-α, IL-6, IFN-γ play a central role in the development of both acute and chronic inflammation. These inflammatory cytokines serve in host defense but, paradoxically, also induce inflammatory tissue injury. Understandably, in immune cells there are several transcriptional and post-transcriptional mechanisms coordinated to fine-tune the production of cytokines, in order to limit their undesirable consequences [7,8]. Signaling pathways such as NF-κb and MAPK, are the master regulators of inflammatory response essentially through transcriptional regulation of cytokines production, Indeed, several plant polyphenols including naringenin have been shown to regulate inflammation through inhibiting pro-inflammatory signaling pathways in multiple cell types (Table 1) [3,9]. For example, Dou et al. reported that naringenin treatment reduced TNF-α and IL-6 mRNA in the colon mucosa through inhibiting NF-κb p65 activation in macrophage [10]. Yoshida et al also found that naringenin inhibits tumor necrosis factor-α (TNF-α)-induced TLR2 expression by inhibiting the activation of NF-κB and c-Jun NH2-terminal kinase pathways in differentiated adipocytes [11]. In hepatocytes, naringenin has been shown to decrease the pro-inflammatory cytokines including tumor necrosis factor-α, interlukin-6, and interleukin-1β by suppressing NF-κb pathway [12]. Naringenin also inhibits hyperalgesic cytokines (IL-33, TNF-α, and IL-1β) production and NF-κB activation in the paw skin [13].

* Corresponding authors.
E-mail addresses: LJIN4@emory.edu (L. Jin), weixx@sun5.ibp.ac.cn (W. Liang).

https://doi.org/10.1016/j.phrs.2018.08.002
Received 31 July 2018; Accepted 2 August 2018
Available online 03 August 2018

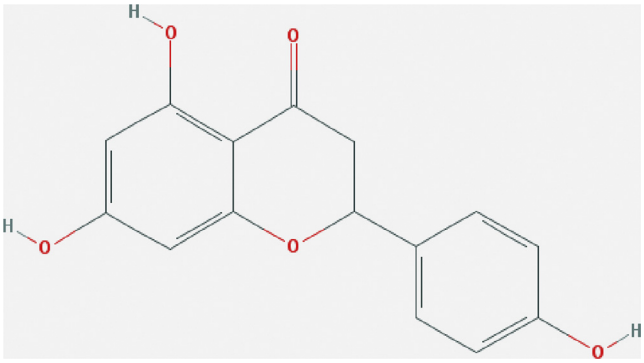

Fig. 1. Chemical structure of naringenin.

In addition to NF-κB, several studies have found that naringenin can modulate MAPK signaling pathway not only in immune cells but also in cancer cells. Naringenin showed protective effect against LPS-induced injury in normal human bronchial epithelium *via* suppression of phosphorylation of ERK1/2, c-Jun NH(2)-terminal kinase (JNK), and p38 MAPK [14]. Li et al. reported that naringenin treatment, in a murine model of collagen-induced arthritis, inhibited lipopolysaccharide (LPS)-induced DC maturation and subsequent pro-inflammatory cytokine production through decreasing LPS-induced MAPK and NF-κB signaling activation [15]. In a murine model of endotoxemia, naringenin has been shown to ameliorate inflammatory response and confer protection against endotoxic shock *via* suppressing MAPK activation in macrophage [16]. Naringenin has also been shown to modulate inflammatory mediators produced by mouse J774 macrophages infected with live C. trachomatis [17]. In addition to immune cells, several studies have shown that naringenin regulates MAPK signaling pathway in cancer cells. For example, naringenin treatment suppressed MAPK activation and consequently induced apoptosis in lung, prostate and breast cancer [18–21].

Naringenin has also been reported to regulate other signaling pathways that may directly or indirectly contribute to inflammation. For example, naringenin promoted AMPK signaling pathway in macrophages [16] and skeletal muscle cells [22]. Also, naringenin treatment activated PPARα, leading to a decrease in vLDL production in hepatocytes [23].

2.2. Post-transcriptional regulation of inflammation

Although transcriptional regulation of cytokine production is important during inflammation, given that every cytokine needs to be secreted out of the cell to exert its effects, it is conceivable that further control mechanisms may exist during the intracellular transport of cytokines. Indeed, recent studies have identified additional control

mechanisms for the cytokine production in post-transcriptional level such as cytokine transport and degradation, which can provide further regulation of the inflammatory response [24–30]. For example, Murray et al. have reported that several exocytosis pathways are involved in the regulation of TNF-α and IL-6 trafficking and secretion [28]. Another report also showed that TNF-α production in macrophage is regulated through lysosome-mediated protein degradation [31]. Therefore, targeting the transport or degradation steps of inflammatory cytokines represents novel therapeutic means to control inflammation. We recently reported that naringenin, through promoting cytokine degradation, ameliorates inflammatory response in several acute inflammation animal models [4]. Mechanistically, we found that naringenin enhanced lysosome-mediated cytokine degradation through a TFEB-dependent mechanism. One unexpected feature of naringenin-mediated inhibition of cytokine production is that naringenin exerts its effect through post-transcriptional mechanism (Fig. 2). This unexpected finding stands in sharp contrast with some widely used anti-inflammation agents, such as glucocorticoids, and natural products, such as apigenin and curcumin, which majorly regulate cytokine production at transcriptional level [3,32]. This diversity in the regulation of cytokine production may be due to the structure variations of flavonoids. Interestingly, the flavonoids that transcriptionally inhibits expression of pro-inflammatory cytokines are generally characterized by certain structure features, such as four hydroxylations at positions 5, 7, 3' and 4', double bond at C2-C3, and the position of the B ring at C2 [33]. In contrast, naringenin has no double bond between C2 and C3, indicating that the form of chemical bond between C2 and C3 may determine the mechanism of action of these flavonoids. Accordingly, further structure and activity relationship study will be critical to understand better the mechanism of action of these natural products. Whether other flavonoids have similar effect certainly warrants further investigation. More importantly, given that detailed mechanism of post-translational regulation of cytokines is yet to be fully discovered, we expect that additional small molecular modulators targeting this newly discovered process will be identified in the near future.

3. Therapeutic potential of naringenin

Given the impressive anti-inflammatory activities of naringenin *in vitro*, multiple studies have tested the efficacy of naringenin in animal models of inflammation-related disease such as sepsis and endotoxic shock [4,16], hepatitis [23,34,35], pulmonary fibrosis [5], atherosclerosis [36], radiation-induced lung Injury [37], obesity [38], diabetes [11,39] and cancer [6]. These preclinical studies have demonstrated the potential of therapeutic use of naringenin in several inflammation-related disease settings with minimal systemic toxicity. Further clinical study would be certainly warranted given the promising pre-clinical results.

3.1. Sepsis and endotoxic shock

Upon recognition of microbial products by specific receptors, the innate and adaptive immune systems are well coordinated to mount immune responses to control the infection. If allowed unchecked, however, the response would cause acute inflammatory disorders, such as endotoxemia. Since TNF-α and other inflammatory cytokines are critical during acute inflammation, there is enthusiasm about the development of anti-cytokine agents. However, potential adverse effects of protein-based anti-TNF-α therapies have been observed in clinical settings [40], encouraging the quest for novel therapeutic strategies to control acute inflammation and restore immune homeostasis. Small molecule inhibitors that target the specific step of cytokines synthesis would potentially offer great benefits. Indeed, development of such agents is ongoing at both the preclinical and clinical stages [41]. Administration of naringenin protected mice against LPS-induced endotoxemia and Con-A induced fulminant hepatitis [4,16]. Naringenin showed no effect in the mouse model of acute liver injury induced by anti-Fas antibody, further demonstrating that naringenin acts through reducing the cytokine production rather than ameliorating organ damage induced by inflammation [4]. Unexpectedly, naringenin not only inhibited cytokine transcription, but also reduces cytokine protein level by inducing their degradation [4]. Given its unique target, naringenin may also be a promising candidate in combination with other anti-inflammation drugs used in the clinic.

3.2. Fibrosis

In addition to acute inflammation, naringenin has been found to be effective in managing other diseases where inflammation is involved such as fibrosis. We previously found that oral administration of naringenin greatly ameliorated bleomycin-induced pulmonary fibrosis [5]. Further mechanistic studies showed that naringenin inhibits TGF-β secretion and thereby suppresses regulatory T cells (Tregs).