REVIEW

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Bioactivity of naringin and related mechanisms

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Naringin is a flavonoid compound, which can be used to treat or prevent various diseases, such as obesity, heart disease, diabetes, and metabolic syndrome. The medicinal value of naringin is mainly reflected in its antioxidant and anti-inflammatory functions, and it has a protective effect on pathophysiology. Furthermore, naringin has shown potential to become an alternative as traditional anti-inflammatory drug, because it exerts less side effects than chemically synthesized compounds. In this paper, we are reviewing the specific molecular mechanisms of anti-inflammatory and antioxidant properties of naringin. We analyze and discuss the primary role of naringin in the treatment of diseases such as acute and chronic liver injury, lung injury, bowel disease, and neurodegenerative diseases. Besides, the bactericidal effect of naringin is also reviewed.

1. Introduction

Naringin is a natural flavonoid glycoside extracted from grapefruit and oranges (Chen et al. 2018). It belongs to a group of flavonoids with a C6-C3-C6 fifteen-carbon structure which are widely demonstrated to have anti-inflammatory effects (Medzhitov 2008) and avoid active oxidants' action. Thus, these agents can be used as drugs for the prevention and treatment of cancer, and chronic diseases (Liu et al. 2017; Suzuki et al. 2013). Many studies have shown that naringin exhibits potent anti-inflammatory and antioxidant activities (El-Desoky et al. 2018; Shirani et al. 2020). However, the specific mechanisms of anti-inflammatory and antioxidant effects of naringin in different diseases are still under discussion (Kim et al. 2004; Ma 2014). In this paper, the research progress on naringin and on its anti-inflammatory, antioxidant, and antibacterial biological activity mechanism are reviewed.

1. Anti-inflammatory mechanism of naringin

1.1. The occurrence of inflammatory reaction

Inflammation plays an essential role in many diseases. The occurrence of inflammation is due to blood changes, vascular permeability, entry and accumulation of leukocytes into the injured tissue, as well as the release of inflammatory mediators (Chen et al. 2018). The disease occurs when the immune system fails to regulate parts of the inflammatory pathway (Rathee et al. 2009). It is generally believed that this is related to the changes in three typical pathways (Harrison 2012; Molina et al. 2006; Sun 2017), as well as changes in cytokines and inflammatory proteases. During the transformation of monocytes into macrophages, a variety of pro-inflammatory and anti-inflammatory factors are produced, and some enzymes are abnormally activated. The most common factors are IL-1 β, IL-6, TNF-α (Tarique et al. 2015), and the abnormal activation of enzymes includes high mobility group protein B1 (HMGB1) (Dong et al. 2015), superoxide dismutase (SOD) (Luo et al. 2012), glutathione peroxidase (GPX), NADPH oxidase (NOx), inducible nitric oxide synthase (Peng et al. 2009), and cyclooxygenase (COX) 2 (Chen et al. 2018; Peng et al. 2009). In unstimulated cells, NF-κB is covalently bound to the inhibitor protein IκB and sequestered in the cytoplasm (Ghosh et al. 1998). The exposure of cells to various stimuli, such as inflammatory cytokines, oxidative stress, UV irradiation, or bacterial endotoxins, will lead to the activation of NF-κB by stimulating phosphorylation and degradation of IκBα. Activated NF-κB then translocates to the nucleus where it binds to the cis-acting κB enhancer element of the target gene, and then activates the expression of pro-inflammatory mediators (Hawiger 2001). At the same time, TNF-α is an important pro-inflammatory chemokine and cytokine that plays a key role in adaptive and innate immunity (Ernandez et al. 2009). Due to its pro-inflammatory properties, TNF-α is involved in the recruitment and activation of inflammatory cells at the site of injury (Lee et al. 2003).

Macrophages, as an essential part of the mononuclear phagocytic system, play a crucial role in the occurrence, maintenance, and regression of inflammation. They participate in all inflammatory processes through the production of chemokines, cytokines and growth factors (Lee et al. 2003). Neutrophils are then able to induce the second wave of inflammatory response, which is essential for the recruitment and function of monocytes / macrophages (Prame Kumar et al. 2018). In addition, research on the anti-inflammatory effects of drugs has focused on the study of macrophage subtypes, which are distinguished by their phenotype and unique gene expression patterns. Among them, M1 macrophages (stimulated by lipopolysaccharide and interferon-γ) are pro-inflammatory cells which are responsible for inflammatory signal transduction, while M2 macrophages are anti-inflammatory macrophages which are involved in the anti-inflammatory process (stimulated by IL-4/IL-136). M2 macrophages produce anti-inflammatory cytokines, which contribute to tissue healing (Saqib et al. 2018). The balance between these two cellular models is thought to be necessary for the regression of inflammation (Mills et al. 2016).

1.2. Common mechanism of naringin in anti-inflammation

Naringin shows some common anti-inflammatory mechanisms in many diseases. Many studies have shown that naringin plays an anti-inflammatory role in diseases including hepatitis, pneumonia, and ulcerative colitis by blocking NF-kB and MAPK pathways. Naringin can also reduce the expression of interleukin and TNF-α in cells. For example, naringin can reduce the intracellular expression levels of IL1 and IL10 in liver injury (Hernandez-Aquino et al. 2017). As we know, hepatitis is also triggered by the production of pro-inflammatory cytokines, including IL-6, IL-12 produced by adipocytes, hepatic macrophages, and lipid-laden hepatocytes, which can promote activation of stellate cells and contribute to liver

fibrosis and apoptosis in NASH, it was found that naringin could inhibit this process (Manne et al. 2018). It also has been shown to block the synthesis of TNF-α by downregulating MMP-13 in liver injury (Adil et al. 2015). Naringin can inhibit the release of TNF-α, IL-8, IL-1 β, IL-6 and leukotriene B4 by increasing the release of IL-10 and preventing the infiltration of neutrophils, thus playing an anti-inflammatory role in the inflammation of pulmonary neutrophils in rats with chronic obstructive pulmonary disease (Chanput et al. 2010; Drummond et al. 2013; Luo et al. 2012; Nie et al. 2012). Other studies have found that naringin also has an effective colon targeting effect, as well as a cytoprotective effect on anti-inflammatory painful colitis in rabbits, and it can also reduce TNF-α significantly (El Naggar et al. 2020).

Previous studies have shown that naringin has significant inhibitory effects on the synthesis of arachidonic acid derivatives, prostaglandin E2 (PGE2), F2 (PGF2), thromboxane A2 (TXA2) and other pro-inflammatory factors, and naringin has been shown to block phospholipase A2 and the key enzymes (cyclooxygenase and lipoxygenase) in the biosynthesis of arachidonic acid analogues (Manthey et al. 2001). In addition, naringin can downregulate the pro-inflammatory gene expression and cytokine synthesis by activating the nuclear factor kappa light chain enhancer (NF-kB), mitogen activated protein kinase (MAPK), and JAK-STAT pathways of B cells (Chen et al. 2018), and inhibiting the lactating animal targets of phosphatidylinositol 3-kinase/protein kinase B (PI3K / Akt) and rapamycin complex 1 (mTORC1) (Yahfoufi et al. 2018), so as to play an anti-inflammatory role. In terms of material metabolism, naringin can counteract the upregulation of glycolysis (Tannahill et al. 2013), TCA cycle remodeling (Dunster 2016), antioxidant capacity (Tannahill et al. 2013), and membrane modification (Mendes et al. 2019) on phospholipid catabolism (Dunster 2016) in M1 macrophage model to a certain extent.

1.3. Different mechanisms of naringin in anti-inflammation of different diseases

In addition to the common anti-inflammatory mechanism, a number of *in-vivo* studies and clinical trials have shown that naringin has unique molecular mechanisms of anti-inflammatory effects in specific diseases.

Toll-like receptors (TLRs) can detect pathogen-associated molecules and induce pro-inflammatory protein molecules, trigger innate and adaptive immunity. Naringin is associated with the downregulation of TLR2 and TLR4 expression in blocking inflammatory responses (Hua et al. 2007; Kim et al. 2013; Wu et al. 2017) Besides, the antioxidant effect of naringin is reflected in the treatment of nonalcoholic fatty liver disease by modulating the TLR/CCL signaling pathway (Wu et al. 2017). Some studies suggested that naringin can inhibit the activation of the mitogen-activated protein kinase (MAPK) family which can be activated by oxidative stress and inflammatory cytokines (Iida et al. 2007; Kim et al. 2011; Taniguchi et al. 2004). Naringin has been shown to block the synthesis of transforming growth factor-b (TGF-b) by downregulating MMP-13 in liver injury (Wu et al. 2017). TGF-b is a protein involved in a variety of cellular processes, including differentiation, growth, immunosuppression, angiogenesis, carcinogenesis, and extracellular matrix formation (Dong et al. 2015), and it is produced by normal hepatocytes (Bissell et al. 2001).

It has been found that naringin causes a slight increase of anti-inflammatory chemokine CCL17 in lung diseases (Drummond et al. 2013). It is well known that the abnormal activity of the host immune system is a significant aspect of the pathogenesis of ulcerative colitis (UC) (Kim et al. 2017). Studies have shown that PPARγ is an indispensable mediator in UC, and its activation inhibits the NF-κB signalling pathway and reduces pro-inflammatory cytokines (Dubuquoy et al. 2002). Also, naringin is associated with the activation of PPARγ, and it maintains the expression of ZO-1 by significantly inhibiting the activation of NLRP3 inflammasome induced by DSS. NLRP3 inflammasome is a molecular platform, its activation can combine with ASC, and then cause the activation of pro-caspase-1, leading to the maturation and release of IL-1β. Unlike other cytokines, the secretion of biologically active IL-1β depends on the activation of inflammasomes (Latz et al. 2013; Lu et al. 2014). Tight junction (TJ) architecture in naringin is also maintained by regulating zonula occludens-1 (ZO-1) expression (Cao et al. 2018). In neurodegenerative diseases, naringin attenuates the inflammatory response through the downregulation of the TLR4 pathway and modulation of P2X7 receptors (Chen et al. 2017; Wang et al. 2017).

Many studies have found that naringin can reverse stress-induced oxidative stress in striatum, prefrontal cortex, and hippocampus by increasing the expression of Nrf2, upregulating the expression of nuclear factor kappa B, and increasing the expression of p53 protein (Ben-Azu et al. 2019; Bisht et al. 2016; Golechha et al. 2014; Gopinath et al. 2012; Jeong et al. 2015). P53 protein is a transcription factor and plays a key role in regulating cell cycle progression and activating DNA repair, it is involved in initiating processes leading to programmed apoptosis when the genetic material of the cell is extensively damaged. p53 acetylation and increased transcription lead to the induction of pro-apoptotic genes, ultimately leading to apoptosis (Chtourou et al. 2015; Miyashita et al. 1995).

2. Antioxidant mechanism of naringin

2.1. Key factors related to oxidative response in the body

In oxidative stress response, reactive oxygen species (ROS) play an important role in many diseases and biological processes (Camhi et al. 1995). There are two ways to produce ROS: one is that the reaction of ions leaked from respiratory chain with oxygen to produce superoxide anion and hydrogen peroxide, the other is that the production of extracellular toxic substances and microbial stimulation (Ma 2010). The role of ROS is to regulate cell proliferation, inflammation, immune response, and other important cellular processes, but the excessive production of ROS will lead to oxidative stress (Buchner et al. 2020). When antioxidants' free radical scavenging system is overwhelmed, it may lead to inflammation, hypersensitivity reactions, and autoimmune conditions (Mates et al. 1999). A complex antioxidant network implements the regulation of the ROS system. Human antioxidants consist of the low-molecular-weight antioxidant glutathione (GSH), noncatalytic antioxidant proteins thioredoxin (Trx) and glutaredoxin (Grx), and ROS-metabolizing enzymes such as superoxide dismutase (SOD), catalase, peroxiredoxin (Prx), and glutathione peroxidase (GPx) (Ma 2013; Raghunath et al. 2018; Santos-Sánchez et al. 2019). Elevated oxidative stress induces the production of ROS, malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine (8-OHdG), and isoprostane, each of them can activate various transcription factors including NF-κB , AP-1, p53, and STAT (Jiang et al. 2019).

2.2. Antioxidant mechanisms of naringin

In the light of the important role of antioxidant enzymes in maintaining normal cell physiology, resisting injury, inflammation, and cancer, naringin plays an antioxidant role mainly by regulating various antioxidant enzymes (Mates et al. 1999). But the regulation factors are slightly different in various diseases. For example, it has been shown that naringin can counteract the decrease of antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), glutathione (GSH), and glutathione thiotransferase (GST) (Thangavel et al. 2012) during liver carcinogenesis. Meanwhile, naringin can diminish the increase of oxidizing agents nitric oxide(NO), inducible nitric oxide synthase, oxidized glutathione (GSSG) during acute liver injury (Wang et al. 2017). Moreover, naringin can reduce the activity of MPO and MMP-9, improve the activity of SOD and increase the content of lipoxin A4 (LXA4) in lung tissue (Luo et al. 2012). Among them, LxA4 is a vital mediator to alleviate inflammation. It can inhibit the recruitment and activation of neutrophils and eosinophils, stimulate the non-inflammatory phagocytosis of apoptotic cells, and reduce the biological activity of angiogenesis and blood brain barrier fibrosis (Maderna et al. 2009). Like interleukin-6 (IL-6),

MPO is synthesized and secreted by neutrophils, it can catalyze the formation of hypochlorous acid and tyrosine radicals during respiratory bursts (Klebanoff et al. 1984). Elevated concentrations of MPO in tissues and plasma are commonly used as a marker of polymorphonuclear leukocytosis in inflammatory conditions (Faith et al. 2008). Additionally, naringin also significantly alleviated LPS-induced acute lung injury in mice *via* the suppression of myeloperoxidase and iNOS (Liu et al. 2011).

In addition, it has been shown that naringin increases the production of the antioxidant enzyme SOD, xanthine oxidase GSH, as well as the precursor substance that produces SOD called XO. Superoxide dismutase plays a key role in scavenging harmful free radicals by reducing O_2- to H_2O (Kruidenier et al. 2003), while glutathione is also an essential member of the family of antioxidant free radical scavengers that converts H_2O_2 to H_2O. They both have the function of protecting cells and tissues from free radical damage (Sies 1999). On the contrary, naringin can downregulate the levels of these substances, such as MPO, NO, and lipid peroxidation (LPO) (Kumar et al. 2014). Notably, the production of inducible nitric oxide synthase leads to the increase of nitric oxide levels, which in turn promotes the production of reactive oxygen metabolites, leading to the increase of intestinal inflammation (Grisham et al. 2002). Similarly, the increase of LPO level is a marker of free radical-induced tissue damage (Perez et al. 2002).

However, in neurodegenerative diseases, naringin can reduce the level of intracellular ROS through the downregulation of cytochrome P450 2E1 (CYP2E1) expression directly, rather than through the upregulation of antioxidant-related protein expression, progressively maintaining the balance of the pro-oxidant and antioxidant enzyme system (Wang et al. 2017)

3. The bactericidal effect of naringin

3.1. Common antibacterial mechanism of flavonoids

Numerous studies have shown that the antimicrobial mechanisms of flavonoids are as follows: inhibition of nucleic acid synthesis; inhibition of cytoplasmic membrane function by affecting biofilm formation; pore proteins; permeability and interactions with certain key enzymes (Barbieri et al. 2017; 9; Khameneh et al. 2019; Xie et al. 2015). Flavonoids are usually more effective against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) than Gram-positive bacteria (*Enterococcus faecalis* and *Staphylococcus aureus*), on the other hand, benzene rings A (C-5, C-7) and B (C-3', C-4') do not usually affect the activity level of flavonoids. A significant increase in the activity of the hydroxyl derivatives of flavonoids is observed only in the case of *Staphylococcus aureus*. Similarly, the presence and position of glycosyl groups in flavonoid glycosides usually did not affect MIC values (Adamczak et al. 2019). In addition, flavonoids have a wide range of ability to inhibit the germination of plant pathogen spores, so it has been proposed to be used to resist human fungal pathogens (Alam et al. 2014). A number of studies have found that there are synergistic effects between natural flavonoids and other antimicrobial agents, which can resist bacterial resistance. However, there are also differences among many reports of antibacterial activity of flavonoids. In particular, the determination relying on the diffusion of flavonoids may not be able to give reliable quantitative antibacterial activity, because the effective diffusion rate of antibacterial flavonoids may be very low, and even using the same detection method, contradictory results can be obtained (Cushnie et al. 2005). In some cases, the antibacterial activity of flavonoids is six times that of standard drugs on the market, some synthetic derivatives of flavonoids also showed significant antibacterial activity, 20 to 80 times higher than that of standard drugs against multi-drug-resistant gram-negative and gram-positive bacteria (Farhadi et al. 2019). Although there are relatively few studies on the potential mechanism of flavonoid antibacterial activity, the information in the published literature indicates that different compounds in this kind of phytochemicals may target different compositions and functions of bacterial cells, including inhibition of cell membrane function, inhibition of energy metabolism, inhibition of nucleic acid synthesis (Cushnie et al. 2005).

3.2. Antibacterial mechanism of naringin

In 2008, Tsui et al. found that naringin had significant antibacterial properties against periodontal pathogens *in vitro*, naringin also has an inhibitory effect on certain common oral microorganisms at low concentrations (Tsui et al. 2008). Another study found that naringin has a significant antibacterial effect on the growth of gram-positive *Bacillus subtilis* (Das et al. 2014). Naringin potentiates the efficacy of both ciprofloxacin and tetracycline on *P. aeruginosa* biofilm in comparison to their solo treatment (Dey et al. 2020). The anti-osteosarcoma and antibacterial assay showed that the delivered naringin and Zn^{2+} can induce a remarkable increase of oxidative stress in bacteria (*E. coli* and *S. aureus*) and osteosarcoma (Saos-2 cells) by producing ROS. Accumulation of ROS results in damage of bacterial biofilm and bacterial membrane, leading to the leakage of bacterial RNA and DNA. Meanwhile, the increase of ROS induces osteosarcoma cell apoptosis by activating ROS/extracellular signal-regulated kinase signaling pathway (Yang et al. 2020). Naringin can mitigate biofilm formation of *Pseudomonas* isolates up to 57%, successfully inhibit the formation of biofilm, and in addition, can also remove the pre-formed biofilm and show strong binding affinity towards biofilm associated proteins (Husain et al. 2021). However, the low antibacterial effect of naringin observed in this study was consistent with the earlier reports (Yu et al. 2020). Therefore, it is more valuable to study the antibacterial function of synthetic or semi-synthetic naringin derivatives. In recent years, the antibacterial effect of naringin has been studied more deeply.

One study confirmed that Nari-cos formed by hydrogen bond between A, B rings of naringin and COS was successfully synthesized. Compared with naringin, Nari-cos has better water solubility, less bitter taste, stronger antioxidant capacity, and stronger antibacterial activity (Cao et al. 2021). In addition, it is possible to obtain NAR derivatives with important antimicrobial activity, especially for Gram-positive pathogenic bacteria, linking saturated aliphatic chains with 10-12 carbon atoms to the A ring of flavonoids (or sugars attached to the ring) seems to be the most promising modification, alkyl linin esters with the chain length of C10-C12 have high anti-*Listeria* and anti-*Staphylococcus* activities, it also provides guidelines for structural modification in similar molecules to enhance antimicrobial activity. Thus, they have broad prospects as antibacterial agents (Celiz et al. 2011).

The role of pure polyhydroxylated plant secondary metabolites in the bioreduction of silver ions to AgNPs was investigated, and it was found that naringin can be used for the synthesis of silver nanoparticles, and that a hydroxyl group participated in the reaction process. Eventually, AgNPs synthesized using naringin as reducing agent showed better antibacterial activity and higher stability, the synthesized nanoparticles behaved as mild antimicrobial agents (Sahu et al. 2016). Rao et al. (2017) used gold nanoparticles (AuNPs) as cargo for naringin loading. An increased bactericidal potential of naringin was observed after loading on AuNPs against various tested bacterial strains, which was further authenticated by the surface morphological analysis, showing enhanced membrane destabilizing effects of loaded naringin. Jaradat et al. (2018) found that compound **2a** showed the best antibacterial activity with a minimum inhibitory concentration value of 62.5 g/mL among three new hydrazone and oxime compounds which were semi-synthesized from naringin. Even so, the molecular mechanism of antibacterial activity of naringin and the bacteria on which it acts deserve to be further investigated. Moreover, the appropriate molecular modification of naringin to enhance its antibacterial effect and co-dosing of naringin with other agents also deserve further exploration.

Naringin, as a type of herbal medicine, is a drug with great prospect and research value. Because of the advantage of less side effects, it can replace chemically synthetic drugs in the future or supplement the use of chemical synthetic drugs to a certain extent. In recent years, studies on naringin's anti-inflammatory effects have been conducted mainly from the perspective of inflammatory cells, inflammatory receptors, inflammogenic pathways, cytokines, inflammatory proteases and inflammation-related enzymes. Although the exploration of naringin as a drug is not entirely

perfect, the anti-inflammatory effects of naringin on a molecular level has been demonstrated from multiple perspectives.

Conflicts of interest: None declared.

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