Biomedical Journal of Indonesia
Journal Homepage: https://bji-fk.ejournal.unsri.ac.id

Flavonoids and Their Role As Anti-Inflammatory Agents

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ARTICLE INFO

Keywords:
Flavonoids
Anti-inflammation

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/BJI.v10i2.187

ABSTRACT

The human civilizations have been using plants and herbs for their rich sources of phytonutrients and bioactive compounds. Polyphenols are one of the groups of beneficial compounds found naturally, they include a wide variety of molecules and are divided into 4 main categories, which are flavonoids, phenolic acids, lignans, and stilbenes. It is estimated that more than 10,000 flavonoid compounds have been isolated and then identified, with the results finding that the majority of flavonoids are widely accepted as therapeutic agents. It is found in various flowers, fruits, and leaves such as red peppers, celery, parsley, chamomile, mint, and ginkgo biloba. Flavonoids are known for their anti-inflammatory properties using a mechanism that is thought to be different. The mechanism used may include an enzyme inhibition mechanism for enzymes that regulate transcription factors. This has a very important role, one of the roles being the control of mediators involved in an inflammatory process. The study for this systematic review was conducted without a time constraint using scientific databases such as Google Scholar and ScienceDirect, with 5 years' time limitation. Previous research has validated the pharmacological characteristics of some flavonoids and their potential health advantages.

1. Introduction

Flavonoids are one of the secondary metabolites found in plants, the constituents of flavonoids consist of a benzopyrone ring which contains phenolic or polyphenol groups in different locations. Fruits, herbs, stalks, grains, nuts, vegetables, flowers, and seeds are common sources of these flavonoids. It is estimated that more than 10,000 flavonoid compounds have been isolated and after that distinguished, with the comes about finding that the larger part of flavonoids is broadly acknowledged as therapeutic agents. We can find flavones in various flowers, fruits, and leaves like ginkgo biloba red peppers, celery, parsley, chamomile, and mint. The flavones that are most discussed and explained further and sometimes research is carried out on these substances are luteolin, apigenin, and tangeritin. Fruits such as oranges, lemons, and grapes are examples of fruits that are rich in flavanones, in this case, the compounds referred to as the main compounds are hesperitin, naringenin, and eriodictyol.[1,2]

Inflammation is a form of reaction carried out by the body to substances or objects that are foreign or unusual for the body's normal functions. The body's immune cells can recognize several types of foreign objects such as bacteria, viruses, antigenic substances, parasites, or chemicals using the receptors of cells. Once foreign substances that enter the body are recognized, various pro-inflammatory pathways will be activated, which will then lead to the cytokines manufacturing process and immune cell activation, including lymphocytes and macrophages which are tasked with eliminating foreign objects. However, when the body comes up short to eliminate the foreign substances in the initial phase, an inflammatory process will increase, this is further known as the chronic phase, in this phase the process will be mediated by excessive production of cytokines, chemokines, and inflammatory enzymes.[6] Inflammation can also be interpreted as a form of response that protects the body in a complex and very important way which is often caused by infection by microbes. Apart from infection, inflammation can also occur due to injury or injury to tissue or trauma can occur without the intervention of microbes, this is further known as sterile inflammation. Inflammation is a specific self-controlled immune response in the body designed to repair tissue and wounds or overcome infections. However, in some conditions, inflammation can cause several irregular responses or can even be associated with disturbances in body homeostasis or a form of physiological process that is not directly related to classical inflammatory triggers. If the triggering factors are not resolved quickly and effectively, the inflammatory response will occur irregularly, so this process can cause chronic damage to the system resulting in inflammatory disorders.[3]

Flavonoids have anti-inflammatory properties using a mechanism that is thought to be different. The mechanism used may include an enzyme

inhibition mechanism for enzymes that regulate transcription factors. This has a very important role, one of the roles being the management of the inflammatory process mediators. Besides that, apart from being anti-inflammatory, flavonoids also have other uses, one of which is as an antioxidant, antioxidants can act as an antidote to free radicals. Therefore, flavonoids have a very important effect and need to be discussed further regarding the cells involved in immune factors and what mechanisms occur in the immune process that have a significant impact on the inflammatory process.[3]

2. Method

This article could be an article review executed by a search of literature in the English language from Google Scholar and ScienceDirect. Those articles that met the inclusion criteria were screened. The inclusion criteria in this article include studies of flavonoids as anti-inflammatory agents either in vitro, in vivo, in computation, or in clinical tests dated from January 2018 to February 2024.

3. Result and Discussion

Sources and subtypes of flavonoids

Flavonoids are substances found in particular kinds of plant organs, such as leaves, fruits, roots, and stems, and are products of plant secondary metabolism.[4] Because they contain a huge number of bioactive chemicals, they perform various biological functions. They belong to the phytonutrient class known as polyphenols. Polyphenols have long been utilized in Ayurvedic and Chinese medicine.[5] The Global Healing Center (GHC) states that they have anti-inflammatory and antioxidant properties, as well as being involved in blood pressure and sugar regulation, skin protection, and brain function. A novel material was extracted from oranges in 1930. It was named vitamin P at the time and was believed for one of the recently discovered class of vitamins. This material was subsequently shown to be a flavonoid (rutin), and thus far, more than 4,000 different flavonoids have been known and identified. Flavonoids are one of the main components of plants. Some flavonoids have significant anti-inflammatory activities in vitro and in vivo. There have been many reviews on anti-inflammatory flavonoids and their mechanisms of action.[6]

Polyphenols comprise a broad range of compounds with the traditional phenolic ring structure (i.e., several hydroxyl groups in the aromatic rings). Since tannins are phenolic acids and polymers of flavonoids, polyphenols are classified into four main kinds: phenolic acids, flavonoids, stilbenes, and lignans. Polyphenols based on the number of phenolic rings and the strategy of their bonding, are classified into five kinds. The most prevalent polyphenols found in our regular diets are phenolic acid and flavonoids, which are further classified into several groups according to the oxygen state of the oxygen heterocycle, including flavanols, flavones, flavonones, flavonols, isoflavones, proanthocyanidins, and anthocyanins.[5,8] Flavonoids can be divided into different subgroups depending on the oxidation and degree of unsaturation of the C-ring, as well as the carbon of the C-ring to which the B-ring is bonded (Figure 1). Isoflavones are flavonoids in which position 3 of the B ring is joined to the C ring. Neoflavonoids are those with the B-ring attached at position 4, and there are several subgroups based on the structural characteristics of the C ring for those with the B ring attached at position 2 as flavonols, flavones, flavanols, catechins, or flavanones, are these subclasses, anthocyanins, and chalcones.[9,10] While flavonoids can also be found in certain plants' leaves, petals, and roots, flavonoids are mostly present in the fruits and vegetables of many plants. Table 1 describes the different subtypes of flavonoids and their active compounds, whereas Table 2 lists some dietary sources of flavonoids and their active compounds.

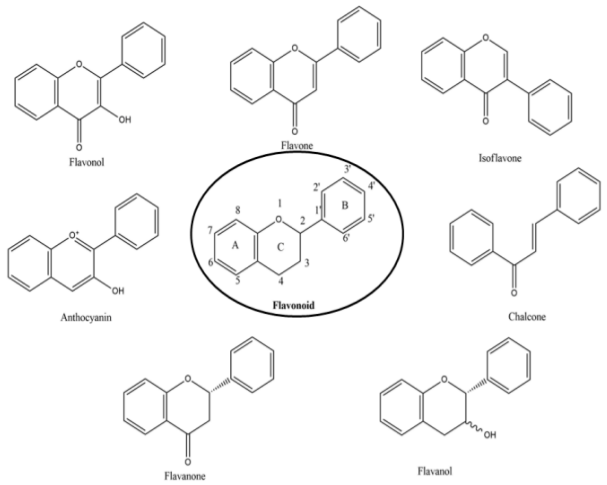

Figure 1. Structure of flavonoid and its subtypes[7]

Table 1. Subtypes of flavonoids and their active compounds.[7,10–13]

Subtypes of flavonoids	Compounds
Flavonol	Kaempferol
	Quercetin
	Myricetin
	Tamariexetin
	Fisetin
	Silibinin
	Rutin
	Isorhamnetin
Flavones	Apigenin
	Wogonin
	Luteolin
	Genistein
	Chrysin
	Glucosedestangeretin
Flavononnes	Naringin
	Naringenin
	Taxifolin
	Eriodictyol
	Hesperetin
Flavanols	Catechin
	Epicathecin
	Epigallocathecin
	Glausan-3-epicathecin
	Proanthocyanidins
	Gallocathecin
	Epicathecingallate
Anthocyanins	Epigallocatechingallate (EGCG)
	Procyanidin
	Cyanidin
	Apigenedin
	Delphinidin
	Pelargonidin
	Malvidin
	Peonidin
Isoflavones	Glycetein
	Daidzein
	Genistein

Biochemical activities and bioavailability of flavonoids

Exogenous antioxidants are flavonoids. It functions by lowering reactive oxygen species, blocking the synthesis of nitric oxide (NO), xanthine oxide synthase, or modulating ion channels. It also regulates the enzymes that are used in the manufacturing procedures. Furthermore, flavonoids lessen the oxidation of low-density lipoprotein (LDL) by peroxynitrite, which is generated when activated macrophages interact with superoxide ions and NO. Moreover, it was shown that apigenin decreased caspase-3 activation and oxidative stress indicators such as glutathione peroxidase, malondialdehyde, and superoxide dismutase. *Ixeris chinensis* (Thunb.) Nakai's luteolin7-glucoside (LUTG) shows strong antioxidant qualities. Flavonoids and phenolic compounds from lentil and parsley plants have been shown to reduce ROS. It also increases the antioxidant enzyme glutathione-S-transferase (GST). [4,7]

Their antibacterial properties enhance with hydroxyl groups at specific locations on the aromatic ring of flavonoids. Flavonoids are known to reduce disease by preventing the production of nucleic acids, energy efficiency, cell membrane function, the formation of biofilms, and pathogenicity. Flavonoid-containing *Anisomeles malavarica* (L.) R. Br. ex. Sims extract showed antibacterial and antioxidant capabilities against *Proteus vulgaris, Staphylococcus aureus,* and *Bacillus subtilis.* [7,24]

The chemicals' absorption and bioavailability determine how different flavonoids are in terms of their action. Research has indicated that flavonoids are either passively absorbed or actively transported out of the stomach and small intestine, where they are subsequently processed by the liver and small intestinal cells. The biological transformation of flavonoids is by adding sulfate, glucuronide, or methyl group. In addition, flavonoids are absorbed by microorganisms in the colon and flavonoids are broken down into phenolic acids and aldehydes. It is converted into the liver and transported to the blood. [7,11]

The bioavailability and absorption of flavonoids are contingent upon their molecular weight,

structure, and capacity for esterification by glycosylation. There are fewer flavonoids in circulation, such as p-coumaric acid, quercetin, and caffeic acid. When given as quercetin glycosides rather than as natural quercetin, quercetin is five times more bioavailable. Additionally, biodiversity differs according to the quercetin-containing dietary supply. For instance, powdered onion extract is more bioactive than apple peel powder, and citrus fruits absorb faster but are less bioavailable. [4,7]

Therefore, the bioavailability of various flavonoids should be improved to obtain better therapeutic effects. Various technologies are used to carry plant extracts or flavonoids to the site of action, such as dispersions of solid, liposomal vesicles, self-nano emulsifying drug delivery systems, micelles, nanoparticle synthesis, and solid dispersions. [4,7]

Flavonoids as an anti-inflammation agent

It is well-known flavonoids provide potent anti-inflammatory activities. The structural makeup of flavonoids has a major impact on their anti-inflammatory qualities. Their structure in a planar ring with a double-bound at C2–C3 and their hydroxyl group positions are crucial in imparting the feature. Without the hydroxyl groups located at the B-ring's 3' and 4' locations, the compound's anti-inflammatory properties are gone. Apigenin, a flavonoid, has been demonstrated to reduce TNF-α-induced steady-state mRNA levels, which in turn decreases the endothelial cells' expression of VCAM-1, E-selectin, and intercellular adhesion molecule-1 (ICAM-1). [6]

Furthermore, it appeared that cells retreated with apigenin had inhibitions of prostaglandin E2, IL-1β, and IL-6 generated by TNF-α. In a guinea pig asthma model, it has been shown that the flavonoid genistein helps reduce ovalbumin-induced broncho-constriction, pulmonary eosinophilia, and hyperresponsiveness of the airways. It showed protective activities in rats against endotoxin-induced organ failure when given intraperitoneally. Additionally, it lessened collagen-induced joint damage and inflammation in mice with arthritis. In an experimental setting, quercetin, hesperidin, and rutin reduced inflammation, both chronic and acute. Rutin was discovered to be significant throughout the long-term phase. In a rat model of colitis produced by trinitrobenzene sulfonic acid (TNBS), diosmin and hesperidin have the potential to decrease the synthesis of Leukotriene B4 (LTB4) and thus prevent colitis. By decreasing leukocyte infiltration and inhibiting cytokines that promote inflammation, including TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, and IL-12, naringenin also has an anti-inflammatory effect (Figure 2). [6]

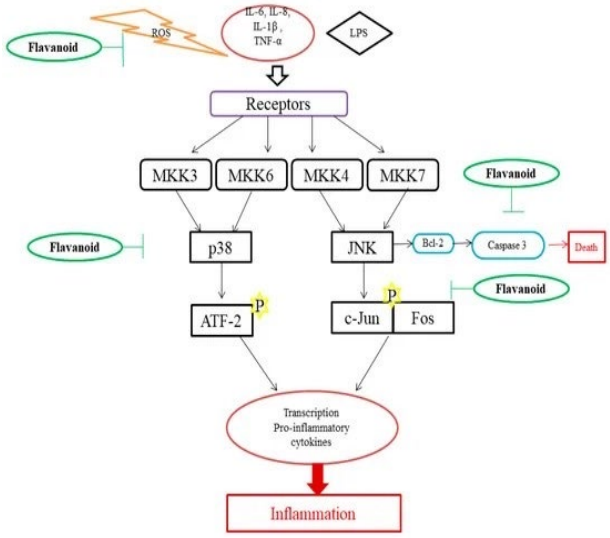

Figure 2. Anti-inflammatory action of flavonoids

Table 2. Dietary source of flavonoids and their active compounds

Dietary Source	Flavonoid	Ref.
Green tea *(Camellia sinensis)*	Epicatechin Epigallocatechin Epicatechin gallate Epigallocatechin gallate	14,15
Black tea *(Camellia sinensis assamica)*	Quercetin 3-O-glucoside Kaempferol-O-glucoside	15
Red wine	Catechin Epicatechin Epigallocatechin Epicatechin 3-O-gallate Proanthocyanidins	16
Onion *(Allium cepa)*	Quercetin Kaempferol Isorhamnetin	17

	Myricetin Anthocyanin (cyanidin, peonidin, pelargonidin, delphinidin, and petunidin) Luteolin	
Potato *(Solanum sp.)*	Anthocyanin (cyanidin, peonidin, malvidin, pelargonidin, delphinidin, and petunidin) Eriodyctiol Kaempferol Glycosides Quercetin Glycosides Catechin Epicatechin Naringenin	18
Apple *(Malus pumila)*	Anthocyanin Cyanidin-3-galactoside	19
Citrus sp.	Hesperetin Naringenin Narirutin Naringin Apigenin Luteolin Nobiletin Tangeretin Quercetin Kaempferol	20
Acalypha indica	Nicotiflorin Naringenin Hesperetin Kaempferol	21
Neem tree *(Azodirachta indica)*	3-*O*-butyl-(-)-epicatechin 3-*O*-butyl-(-) epigallocatechin (−)-epicatechin (+)-gallocatechin (−)-epigallocatechin Azadirachtin A Triolein Octadecanoic acid-tetra- hydrofuran-3,4-diyl ester	22
Cannabis sativa	Apigenin Luteolin Kaempferol Quercetin aglycones Glycosides	23

TBS was more effective in reducing NO and cytokines, such as TNF-α, IL-12, and IL-6. TBS extracts decreased the MAPK and NF-κB pathways by regulating the phosphorylation of ERK, p38, MKK4, and JNK. By blocking c-Jun N-terminal kinase and extracellular signal-regulated kinase, quercetin demonstrated an anti-inflammatory effect by reducing the activities of AP-1, NF-κB, MAPK, and AP-1. Additionally, catechin blocked AP-1, NF-κB, and MAPK via blocking p38 kinase and c-Jun N-terminal kinase. Flavonoids also enhance the activity of cytotoxic T cells and cytotoxic T cells. Hesperidin controls systemic inflammation in rats under intense exercise and training. Fisetin inhibits MAPK phosphorylation and NF-κB transcription, thereby reducing phorbol-12-myristate-13-acetate and calcium ion transporter (PMACI)-stimulated cytokine secretion in rats. Luteolin-8-C-fucopyranoside (LU8C-FP) inhibits IL-6 by focusing on the pathways involved in NF-κB and MAPKs. In a study from *Lonicera japonica* Thunb, luteolin also decreased the production of COX2, TNF-α, and IL-6. It also inhibited the ERK1/2, c-Jun N-terminal kinase (JNK) 1/2, and NF-κB pathways.[6]

A broad class of polyphenolic substances known as flavonoids are used to treat several inflammatory conditions, such as ulcerative colitis, joint inflammation, gastritis, nephritis, hepatitis, Alzheimer's sickness, atherosclerosis, and other hypersensitive responses. This part includes details on different types of flavonoids and their potential mechanisms that have been linked to the treatment of inflammatory illnesses. These substances also control the state of oxidation and guard against harm from oxidative stress, including the antioxidant function. Chronic inflammatory illnesses are associated with elevated tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 levels, among other cytokines. The expression and secretion of cytokines are inhibited by some flavonoids, specifically luteolin, quercetin, and apigenin. It implies that as cytokine modulators, these flavonoids might be beneficial therapeutically for treating illnesses linked to inflammation. An

intrinsic immunological reaction to harmful stimuli, inflammation serves to defend the body against infections. Priming and triggering are the two basic stages of an inflammatory response. While inflammasomes are activated during triggering, which leads to cell death, pro-inflammatory cytokines are released, and inflammatory cells increase the production of pro-inflammatory chemicals during priming. Protein complexes known as inflammasomes are made up of pro-caspase-1, either with or without the bipartite adaptor molecule ASC, and intracellular Gene-binding oligomerization domain-like receptors (NLRs) are an example of a pattern recognition receptor (PRRs), which are lacking in melanoma 2 (AIM2) and caspases-4/5/11. Interleukin (IL)-1b and IL-18 are secreted by caspase-1 and pyroptosis, and diseases. Flavonoids' anti-inflammatory properties and inflammatory cell death are all caused by the activation of the inflammasome. Secondary metabolites called flavonoids are present in many different types of plants and are thought to be essential for maintaining good health and reducing the symptoms of many underlying mechanisms.[25]

4. Conclusion

Vegetables and fruits have many flavonoids and it has benefits for our health. Most flavonoids target the MAPK, NF-κB, ERK, and Akt pathways, reducing oxidative stress, inflammation, and many downstream diseases. Flavonoids can reduce inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-17. Flavonoids can reduce enzymes such as COX2, iNOS, lysozyme, and glucuronidase. It acts on apoptosis and cell viability, enhancing the AMPK and Nrf2 pathways and antioxidant enzymes such as SOD, CAT, glutathione-S-transferase (GST), and Heme-oxygenase-1. They play an important role in reducing diseases related to inflammation. Further research is needed to improve the bioavailability of flavonoids. Furthermore, further human trials are needed to demonstrate its potential as an anti-inflammatory agent.

5. Acknowledgement

None

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