International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Use of Phenolic Compound as Anti-Inflammatory

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ABSTRACT

The most prevalent secondary metabolites in plants are phenolic compounds, which have drawn increasing interest in recent years due to their diverse biological actions.

One significant source of novel bioactive chemicals is natural products. Among these are phenolic chemicals, which are found in large quantities in plants and are reported to have a variety of medicinal uses.

anti-inflammatory properties of phenolic-rich extracts made from round purple beans (RPB) and white kidney beans (WKB), two varieties of common beans. WKB extracts included more phenolic acids than RPB extracts, which had larger quantities of these chemicals. Moreover, RPB extracts demonstrated increased anti-inflammatory efficacy by lowering NO generation and LPS-stimulated macrophage cytokine mRNA expression.

When biological, chemical, or physical agents enter the body and disrupt tissue homeostasis, the immune system releases a number of pro-inflammatory mediators. However, when these mediators are produced excessively, as happens in chronic inflammation, it may lead to further damage. Extraction, isolation of four compounds, namely (1–4), 3-O-coumaroylquinic acid (1), 3-O-feruloylquinic acid (2), 4-O-feruloylquinic acid (3), and 5-O-feruloylquinic acid (4) from *Pleioblastus amarus* shoots for phenolic compound.

The body's immune system produces a number of pro-inflammatory mediators when biological, chemical, or physical agents disrupt tissue homeostasis. However, when this happens repeatedly, as in chronic inflammation, the immune system's overproduction of these mediators can result in the development of a number of chronic diseases.

INTRODUCTION

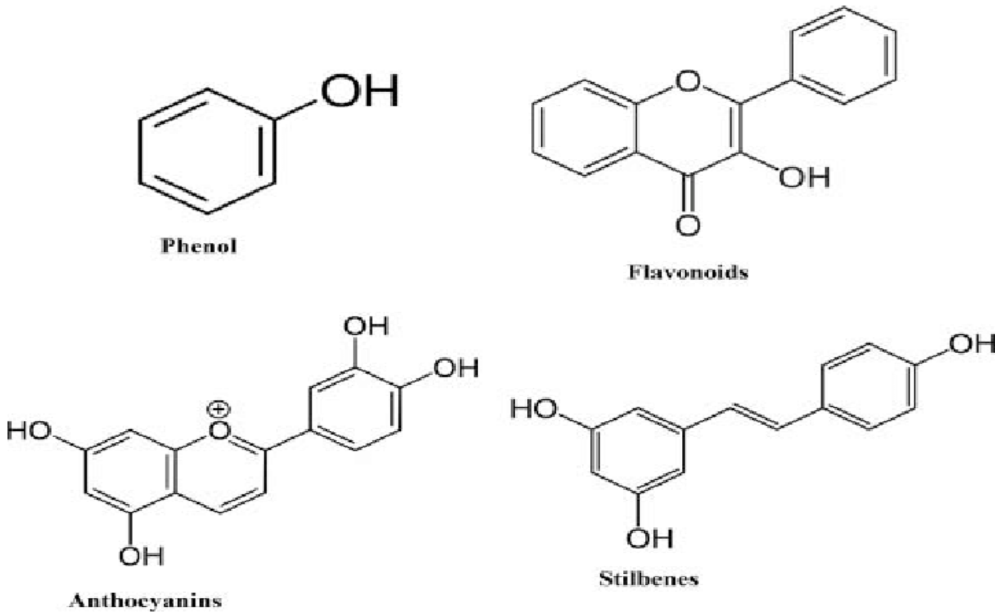
PHENOLIC COMPOUND : A vast class of secondary metabolites found in many higher plant organs, including grains, legumes, nuts, and fruits, vegetables, and legumes, are called **phenolic compounds.** These compounds are important for a variety of physiological processes, including stress resistance, colour, flavour, and plant quality. Nowadays, phenolic compounds' inherent anti-inflammatory, antibacterial, anticarcinogenic, and antioxidant properties are much sought-after in terms of application and study. A common structural feature of phenolic compounds is an aromatic ring with one or more hydroxyl substituents. These compounds can be classified into many classes, with flavonoids, phenolic acids, tannins, stilbenes, and lignans.[1] As their bioactivity has gained more attention in recent years, phenolic compounds have been shown to have a variety of effects, including anti-oxidant, antimicrobial, anticarcinogenic, anti-inflammatory, and preventive effects on diabetes, cancer, cardiovascular disease, and diseases linked to oxidative stress. As an illustration, four marker compounds from Dendrobii herb have anti-inflammatory properties because they target various cytokines linked to inflammation.Thirteen. With IC50 values ranging from 30.4 to 75.2 μM, the isolated phenolic compounds (syringaresinol, isoferulic acid, and anillic acid) from Taraxacum coreanum roots exhibit radical scavenging action. The combination of protocatechuic, vanillic, and catechin acids can prevent uropathogenic Escherichia coli from adhering to silicone surfaces.[1]

INFLAMMATION : As a biological defence mechanism, inflammation arises when biological, chemical, or physical agents disrupt tissue homeostasis within the body. The immune system generates a range of pro-inflammatory mediators, but excessive production of these mediators, as seen in chronic inflammation, may cause a number of chronic disorders to emerge. Because of this, it is critical to slow down the inflammatory process.[2]

Phenolic substances have the capacity to prevent pro-inflammatory mediators from being produced or from acting.resulting in the ability to reduce inflammation.[7]

PHENOLIC ACIDS

Plants contain both free and bound forms of phenolic acids, which are members of a significant class of phenolic chemicals. The two subclasses of phenolic acids are hydroxycinnamic acid (HCA) and hydroxybenzoic acid (HBA). HBAs, which comprise p-HBA, protocatechuic, vanillic, gallic, and syringic acids, are based on a C6–C1 structure. However, HCAs, which include coumaric, caffeic, ferulic, and sinapic acids, are aromatic molecules having a 3-carbon side-chain (C6–C3). Oilseeds, cereals, coffee, cowpea, black currant, raspberry, squash shells and seeds, and blackberries are rich sources of HBAs. Coffee, cherries, cereals, peaches, spinach, citrus fruits and juices, plums, tomatoes, potatoes, and almonds are the main sources of HCAs.[3]Research has indicated that phenolic acids serve a variety of biological purposes. Two significant components of HCA with inherent antioxidant and cardioprotective qualities are caffeic acid (CAA) and chlorogenic acid (CHA). In rats given cyclosporine, CAA and CHA show blood pressure-lowering effects and decrease the activity of important enzymes connected to the etiology of hypertension.35 Research on adipose tissue has revealed that gallic acid selectively targets this tissue to reduce excessive lipid accumulation in obese subjects, improve insulin signalling, and simultaneously combat elevated proinflammatory response and oxidative stress.[3]



CHEMICAL STRUCTURE OF DIFFERENT PHENOLIC COMPOUND[19]

PLANT-BASED IDENTIFICATION OF PHENOLIC COMPOUNDS

Flavonoids

Diphenylpropanes (C6–C3–C6) make up the basic skeleton of flavonoids, which are a class of molecules having two aromatic rings joined by a central 3-carbon bridge. Currently, flavonoids are the most varied class of phenolic compounds. They are directly linked to the production of plant color in flowers and are vital in the interaction between plants and their environment, as seen in their ability to resist disease, prevent ultraviolet damage, and influence the formation of legume root nodules, among other things. Anthocyanins, flavones, flavonols, flavanones, isoflavones, flavanonols, and other subclasses are the most prevalent flavonoids in nature.

Herbs like Flos sophorae Immaturus, Crateagus pinnatifida Bunge, Hypericum japonicum Thunb, and Folium Mori, for instance, contain quercetin and rutin.24 A flavonoid called epicatechin that was extracted from the Mexican medicinal plant Geranium mexicanum HBK may have an impact on a pathogen's ability to infect humans.25 Kaempferol, another important flavonoid, has antiherpes properties and is derived from Kalanchoe blossfeldiana Poelln.26 The main flavonoids in citrus are called flavanones, and they can be found in oranges, lemons, and grapefruit as hesperitin, eriodictyol, and aglycones naringenin. There are 40–140 mg of flavanone glycosides in a glass of orange juice.

As a subgroup of flavonoids, isoflavones have structural characteristics with estrogens. Often called "phytoestrogens," isoflavones are particularly prevalent in soybeans. According to studies, they can be utilized to improve intestinal health and prevent certain serious illnesses including cancer and hypertension. The greatest class of water-soluble vacuolar pigments, known as anthocyanins, are found in all plant tissues, including flowers, stems, leaves, roots, and fruits. They can have red, blue, or purple hues. [1]

Lignans

A broad class of naturally occurring compounds known as lignans are produced when two phenyl-propane units oxidatively dimerize. They eat a variety of foods, including vegetables, fruits, nuts, oilseeds, garlic, olive oil, wine, tea, beer, and coffee—linseed being perhaps the richest of all. They have long been utilized in both traditional and ethnic medicine, but study in recent years has focused on their biological activities, which range from antioxidant, anticancer, anti-inflammatory, to antiviral properties47. Solanum melongena L. roots contain 16 different types of lignans, which Yang et al identified. Based on their findings, S. melongena L. is a significant source of lignans' varied structures and may have biological activity values for other biological activities that warrant further study.[5]

Stilbenes

A class of phenolic chemicals known as stilbenes can be found in nature in many different food sources, including red wine, peanuts, berries, grapes, and various medicinal plants. However, wines, peanuts, grapes, and peanut products are the primary dietary sources. Resveratrol, pterostilbene, and 3′-hydroxypterostilbene are a few of the well-known stilbenes.42 1,2-diphenylethylene makes up the fundamental chemical structure of stilbene molecules. Stilbenes have garnered significant interest and attention recently because of their many health benefits, including their anti-inflammatory, anti-carcinogenic, antidiabetic, and anti-dyslipidaemia properties.43 The most representative substance is resveratrol, which has been shown to have antioxidant properties in the cardiovascular system44 and the ability to make a range of malignant cells more susceptible to chemotherapeutic treatments, thus reversing multidrug resistance.[1]

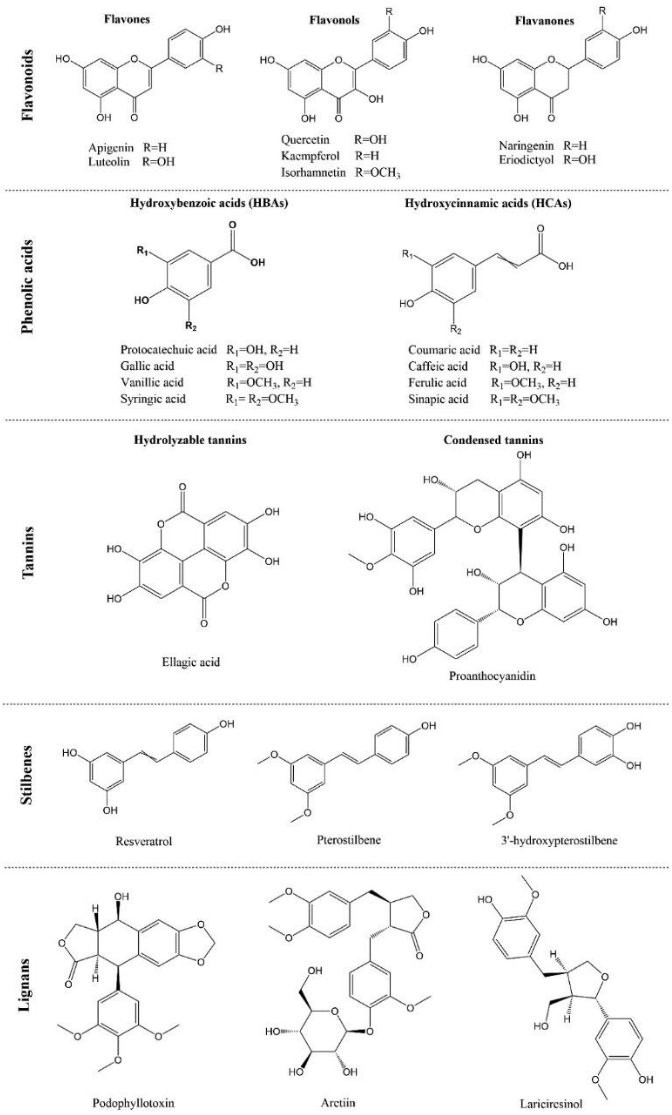
Tannins

Tannins are a class of high molecular weight (500–3000 Da) water-soluble polyphenols. This particular phenolic class substances are further classified as hydrolysable tannins or condensed tannins based on the units of 3-flavanols or phenolic acids, respectively. Tannins are commonly found in fruits, vegetables, cereals, wine, tea, and chocolate. They are primarily found in complexes with alkaloids, polysaccharides, and proteins . [6]

Coumarins

Coumarins are lactones that belong to the phenolic group and are produced through the cyclization of hydroxycinnamic acids. Their main structural elements are C6–C3. Plants contain coumarins in free as both glycosides and form. The primary chemical diversity among coumarins is attributed to variations in the degree of oxygenation of their benzopyrane molecule. Simple hydroxylcoumarins (such as esculetin and scopoletin), furocoumarins and isofurocoumarins (such as psoralen and isopsoralen), pyranocoumarins (such as xanthyletin, xanthoxyletin, selin, and praeuptorin A), bicoumarins, dihydro-isocoumarins (such as bergenin), and others (such as wedelolactone) are the main components of coumarins. Dietary sources of coumarins include olive oil, fruits, vegetables, herbs, wine, and tea. [7]

TYPICAL PHENOLIC COMPUND IDENTIFIED FROM PLANTS[1]



EXTRACTION OF PHENOLIC COMPOUNDS

1. **ANTI-INFLAMMATORY PROPERTIES OF PHENOLIC-RICH EXTRACTS FROM ORDINARY WHITE AND RED BEANS (*in vitro)***

Phenolic compounds have garnered significant interest in recent times owing to their diverse biological properties, including but not limited to anti-inflammatory, anti-tumour, and anti-atherogenic effects.

SAMPLE : From IGP Judía de El Barco de Ávila (Spain), bean samples were acquired. They belonged to the Phaseolus vulgaris genus and were identified as round purple bean (RPB) for red beans and white kidney bean (WKB) for white beans. They were kept in storage at -20 °C until they were needed to make methanolic extracts.

CHEMICALS AND REAGENT : HPLC (high-performance liquid chromatography) grade methanol, acetonitrile and sodium carbonate were obtained from VWR-International (Darmstadt, Germany) while acetic acid (96%) and Folin–Ciocalteau reagent were used.

RESULT : Phenolic compounds have been shown to have anti-inflammatory activity by different mechanisms including modulation of the inflammatory cascade.[8]

2. EXTRACTION, ISOLATION AND IDENTIFICATION OF FOUR PHENOLIC COMPOUNDS FROM *PLEIOBLASTUS AMARUS* SHOOTS AND THEIR ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES *IN VITRO*

Shoots of Pleioblastus amarus, or P. amarus, are a traditional green vegetable in China and members of the Gramineae family of grasses. They are rich in nutrients and have a number of health benefits. For the first time, four chemicals were isolated from Pleioblastus amarus shoots: 1-4), 3-O-coumaroylquinic acid (1), 3-O-feruloylquinic acid (2), 4-O-feruloylquinic acid (3), and 5-O-feruloylquinic acid (4). Infrared (IR) spectroscopy, high resolution electrospray ionization mass spectrometry (HR-ESI-MS), and comprehensive spectroscopic (1D/2D NMR) were used to determine the structures of the isolated chemicals. .. 3-O-feruloylquinic acid (2) demonstrated a higher inhibitory rate of 60.92 percent at 400 µg/mL, demonstrating a better anti-inflammatory effect than the other compounds. It considerably reduced the generation of nitric oxide (NO) by lipopolysaccharide (LPS)-induced RAW 264.7 cells. In addition, 3-O-feruloylquinic acid (2) suppressed the expression of nuclear factor-κB (NF-κB), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and interleukin-1β (IL-1β). This compound may have applications in the development of novel antioxidant and anti-inflammatory drugs.[9]

INFLAMMATION PROCESS

Depending on the type of stimulus and the effectiveness of the body's response to eliminate it or heal damaged tissues, inflammation can either be acute or chronic. Acute inflammation is characterized by leukocyte emigration (mostly neutrophils) and fluid and plasma protein exudation. It starts fast (within minutes) and lasts for a few hours or days. Acute inflammation resolves when the immune system successfully gets rid of the harmful substances causing it; but, if the response is unable to do so, a chronic phase may result. Vascular growth, fibrosis, tissue damage, and the presence of lymphocytes and macrophages are all linked to chronic inflammation.[10]

PHENOLIC SUBSTANCES AND INFLAMMATORY PROCESSES

A heterogeneous class of chemicals called phenols is produced by plants' secondary metabolism. Phenolic compounds are structurally composed of at least one aromatic ring that is connected to one or more hydroxyl groupings have aliphatic or aromatic structural bonds. Flavonoids and non-flavonoids are two categories of phenolic chemicals

1. Two aromatic rings connected by an oxygen heterocycle make up flavonoids. Anthocyanins, flavonols, flavones, isoflavones, flavanols, flavanones, and so on can be subclassified based on the degree of hydrogenation and the replacement of the heterocycle. Glycosides are the predominant form of flavonoids in nature .
2. Non-flavonoids. Known by their common name, phenolic acids, benzoic and cinnamic acid are two of the most representative chemicals of this sort A heterogeneous class of chemicals called phenols is produced by plants' secondary metabolism. Phenolic compounds are structurally composed of at least one aromatic ring that is connected to one or more hydroxyl groupings have aliphatic or aromatic structural bonds. Flavonoids and non-flavonoids are two categories of phenolic chemicals .
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4. Non-flavonoids. Known by their common name, phenolic acids, benzoic and cinnamic acid are two of the most representative chemicals of this sort . A few other common phenolic acids are stilbenes, tannins, and lignins.[8]

SYNTHETIC APPROACH TO PHENOLIC COMPOUNDS

Researchers have worked to create novel compounds with certain anti-inflammatory properties from the phytochemicals that are already known in recent decades. Synthetic compounds of gingerol were developed into a class of possible anti-inflammatory medicines. Enhancing COX-2 inhibition in A549 cells appears to depend on side chain lipophilicity, ring hydroxylation, and/or methoxylation . Another is curcumin illustration of how to improve the structure of a raw plant product. Curcumin's fundamental skeleton has undergone numerous alterations, and surprisingly, three distinct strategies result in three distinct target interactions. Three distinct target interactions result from the use of separate techniques. Through NF-B and MAPK, 1,7-bis(3,4-dimethoxyphenyl)-5-hydroxy-heptatrien-3-one, also known as dimethoxycurcumin, had a strong anti-inflammatory effect inhibition in lymphocytes activated by concanavalin . In mouse macrophages, 3,5-bis(2-pyridinylmethylidene)-4-piperidone, another curcumin derivative, demonstrated a strong suppression of NF-B DNA-binding activity and nuclear translocation . Another cyclic synthetic analogy, (2E, 5E)-2,5-bis(4-(3-(dimethylamino)-propoxy)benzylidene)cyclopentanone, decreased the amount of carrageenan-induced paw oedema and inhibited the expression of inflammatory mediators, including NO, IL-6, IL-1, and TNF-. [8]

PHENOLIC COMPOUNDS' MODE OF ACTION AS ANTI-INFLAMMATORY AGENTS

Similar to how NSAIDs function, phenolic substances can also block pro-inflammatory mediators other than COX by preventing their activity or gene expression. Additionally, certain phenolic compounds have the ability to alter the expression of transcriptional factors involved in inflammatory and antioxidant pathways, such as nuclear factor-kB (NF-kB) or Nrf-2.[11]

The anti-inflammatory activity mechanisms of phenolic compounds are significantly influenced by their structural makeup. For instance, the intermediate radical species is stabilized by resonance when the C ring is unsaturated. Additionally, a double bond in C2-C3 causes rings A and C to coplanarize, which promotes the flavonoid's interaction with the enzyme's active site.[1]

The B ring's catechol group aids in enzymatic oxidation, which causes electrophilic species to develop and permits nucleophilic addition. Lastly, phenolic compound ligands contribute to the creation of covalent connections between macromolecules and flavonoids. [13]

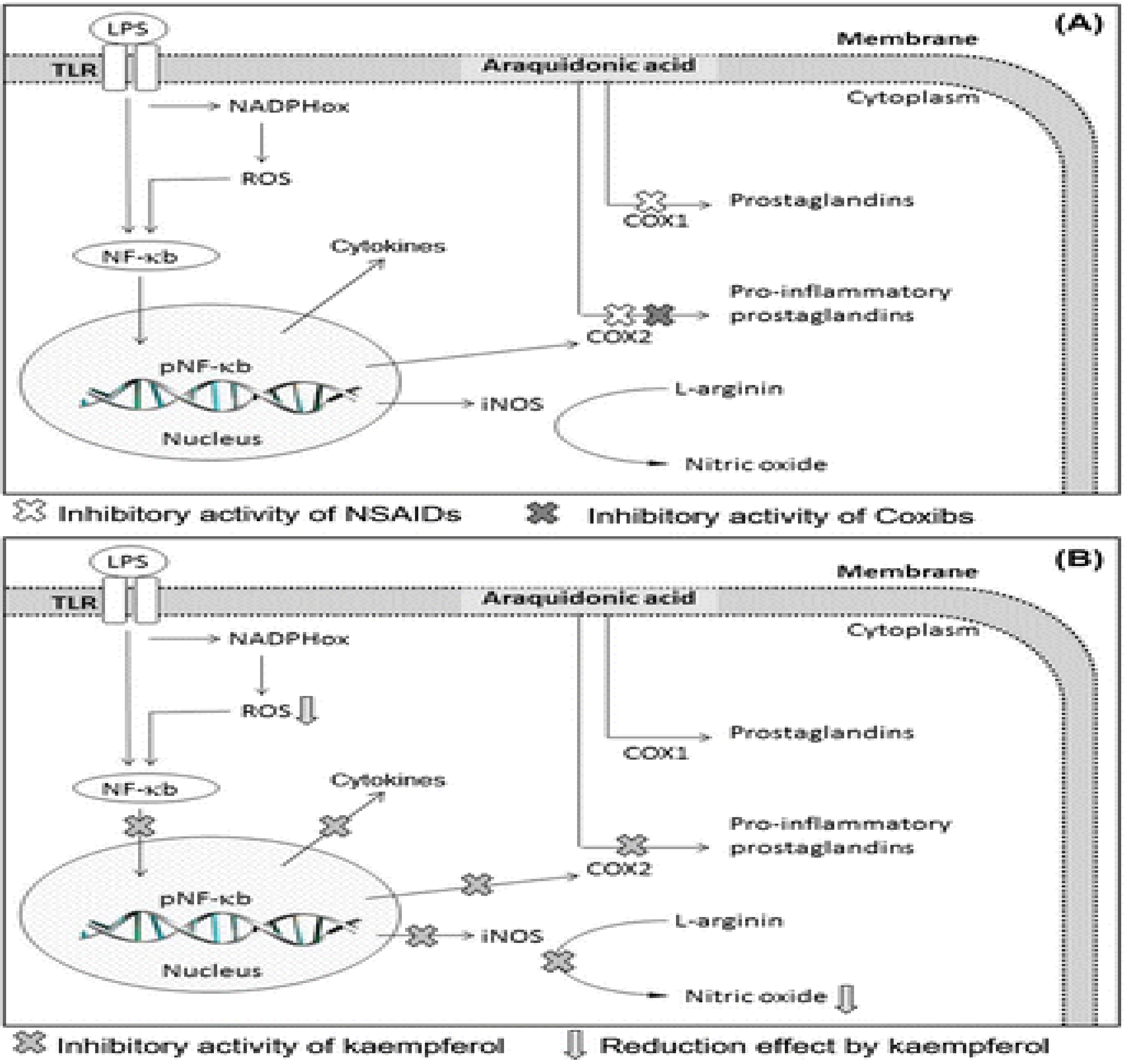
It has been demonstrated that certain dietary flavonoids affect inflammatory mediators like IL- Here, it has been demonstrated that the flavonoid content of cocoa and tea, known as flavonols, influences the level of IL-6 in blood plasma in a dose-response. The health benefits of cocoa phenolic compounds have garnered attention. Studies on the epidemiology have linked modest use of cocoa products to inflammation.[14]

However, Mathur et al. reported no effect on intake of cocoa phenolics and inflammation markers (IL-1β, 1L-6, TNF-α). Nevertheless, a reduction in LDL oxidation was shown, which can lead to a decreased vascular inflammation, oxidative stress, reduction of nitric oxide, and prevention of platelet aggregation, which translates in prevention of cardiovascular diseases. Some studies demonstrate a positive effect in inhibition of inflammation markers.[15]

Also, grapes and red wine consumption have also been the focus of numerous studies on the anti-inflammatory properties of phenolic compounds. In vitro and *in vivo* studies have been performed using grape phenolic extracts; and it has been reported that procyanidins show inhibition of inflammatory mediators. Results showed decreased in nitric oxide concentration, prostaglandins E2 and ROS. This effect was mainly attributed to the antioxidant properties of phenolic compounds[16]

Phenolic chemicals work by inhibiting pro-inflammatory mediators through a variety of mechanisms, including gene expression. While medications work in a single method, phenolic compounds alone or in combination can exert their anti-inflammatory effect in multiple ways. The flavonol kaempferol has demonstrated inhibitory effect against the following: aldosterone signaling and aldosterone-driven gene expression (indirect cytokine-inhibition), iNOS expression and NO generation, COX-2 expression and PGE2 production, and cytokines (TNF-α, IL-1β) production triggered by LPS. [17]

The way that anti-inflammatory drugs work. (A) How NSAIDs and coxibs reduce inflammation. (B) A theoretical model that explains kaempferol's anti-inflammatory effects.[18]



REFERENCE

1. 1.Zhang Y, Cai P, Cheng G, Zhang Y. A Brief Review of Phenolic Compounds Identified from Plants: Their Extraction, Analysis, and Biological Activity. Natural Product Communications. 2022;17(1). doi:10.1177/1934578X211069721
2. Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature*, *454*, 428–435.10.1038/nature07201
3. Zhang Z, Wu XY, Cao SY,. et al. Caffeic acid ameliorates colitis in association with increased Akkermansia population in the gut microbiota of mice. *Oncotarget*. 2016;7(22):31790-31799.
4. Agunloye OM, Oboh G, Ademiluyi AO, et al. Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. *Biomed Pharmacother*. 2019;109(0753-3322):450-458.
5. Yang BY, Yin X, Liu Y,. et al. Terpenes and lignans from the roots of *Solanum melongena* L. *Nat Prod Res*. 2020;34(3):359-368.
6. 6.Rangkadilok, N.; Sitthimonchai, S.; Worasuttayangkurn, L.; Mahidol, C.; Ruchirawat, M.; Satayavivad, J. Evaluation of free radical scavenging and antityrosinase activities of standardized longan fruit extract. Food Chem. Toxicol., 2007, 45(2), 328-336.
7. Huang, W.Y.; Cai, Y.Z.; Zhang, Y. Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. Nutr. Cancer, 2009, 62(1), 1-20.
8. : García-Lafuente, A., Moro, C., Manchón, N., Gonzalo-Ruiz, A., Villares, A., Guillamón, E., Rostagno, M. and Mateo-Vivaracho, L., 2014. In vitro anti-inflammatory activity of phenolic rich extracts from white and red common beans. *Food Chemistry*, *161*, pp.216-223.
9. Ao, X., Yan, J., Liu, S., Chen, S., Zou, L., Yang, Y., He, L., Li, S., Liu, A. and Zhao, K., 2022. Extraction, isolation and identification of four phenolic compounds from Pleioblastus amarus shoots and their antioxidant and anti-inflammatory properties in vitro. *Food Chemistry*, *374*, p.131743.
10. Kumar, V., Abbas, A. K., Fausto, N., & Mitchell, R. N. (2012). *Robbins basic pathology*. Philadelphia, PA: Elsevier Health Sciences.
11. Maroon, J. C., Bost, J. W., & Maroon, A. (2010). Natural anti-inflammatory agents for pain relief. *Surgical Neurology International*, *1*, 1–80. doi:10.4103/2152-7806.73804
12. Lättig, J., Böhl, M., Fischer, P., Tischer, S., Tietböhl, C., Menschikowski, M., … Pisabarro, M. T. (2007). Mechanism of inhibition of human secretory phospholipase A2 by flavonoids: Rationale for lead design. *Journal of Computer-Aided Molecular Design*, *21*, 473–483. doi:10.1007/s10822-007-9129-8
13. Lago, J. H., Toledo-Arruda, A. C., Mernak, M., Barrosa, K. H., Martins, M. A., Tibério, I. F., & Prado, C. M. (2014). Structure-activity association of flavonoids in lung diseases. *Molecules*, *19*, 3570–3595.
14. Stote, K., Clevidence, B., Novotny, J., Henderson, T., Radecki, S., & Baer, D. (2012). Effect of cocoa and green tea on biomarkers of glucose regulation, oxidative stress, inflammation and hemostasis in obese adults at risk for insulin resistance. *European Journal of Clinical Nutrition*, *66*, 1153–1159.10.1038/ejcn.2012.101
15. Allgrove, J., & Davison, G. (2014). *Dark chocolate/cocoa polyphenols and oxidative stress polyphenols in human health and disease* (Vol. 1, pp. 241–251). Elsevier. ISBN 978-0-12-398456
16. Rodrigo, R., Miranda, A., & Vergara, L. (2011). Modulation of endogenous antioxidant system by wine polyphenols in human disease. *Clinica Chimica Acta*, *412*, 410–424.10.1016/j.cca.2010.11.034

17. Nair, V., Bang, W. Y., Schreckinger, E., Andarwulan, N., & Cisneros-Zevallos, L. (2015). Protective role of ternatin anthocyanins and quercetin glycosides from butterfly pea (Clitoria ternatea Leguminosae) blue flower petals against lipopolysaccharide (LPS)-induced inflammation in macrophage cells. *Journal of Agricultural and Food Chemistry*, *63*, 6355–6365. doi:10.1021/acs.jafc.5b00928
18. Kong, L., Luo, C., Li, X., Zhou, Y., & He, H. (2013). The anti-inflammatory effect of kaempferol on early atherosclerosis in high cholesterol fed rabbits. *Lipids in Health and Disease*, *12*, 115. doi:10.1186/1476-511x-12-115
19. Image Souza, Evandro & Albuquerque, Thatyane & Santos, Aldeir & Massa, Nayara & Alves, José. (2018). Potential interactions among phenolic compounds and probiotics for mutual boosting of their health-promoting properties and food functionalities – A review. Critical Reviews in Food Science and Nutrition. 59. 1-15. 10.1080/10408398.2018.1425285.ss