Available online on 15.07.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2011-2022 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited

Open Access Full Text Article

Review Article

Anti-Inflammatory Properties of Quercetin: A Review

*, [1]Chibuzo Carole Nweze, [2]Wandoo Tseaa & [3]Ini Patrick Ekpe

[1,2] Department of Biochemistry and Molecular Biology, Nasarawa State University, Keffi, Nigeria

[3] Department of Biochemistry, Faculty of Natural and Applied Sciences, Veritas University Abuja, Nigeria

Article Info:

Article History:

Received 03 May 2022
Reviewed 29 May 2022
Accepted 11 June 2022
Published 15 July 2022

Cite this article as:

Nweze CC, Tseaa W, Ekpe IP, Anti-Inflammatory Properties of Quercetin: A Review, Journal of Drug Delivery and Therapeutics. 2022; 12(4):205-210

DOI: http://dx.doi.org/10.22270/jddt.v12i4.5453

*Address for Correspondence:

Chibuzo Carole Nweze, Department of Biochemistry and Molecular Biology, Nasarawa State University, Keffi, Nigeria

Abstract

Quercetin, one of the most taken flavonoid with diet, belongs to the family of flavonols. Quercetin occurs as a glycoside or as an aglycone and is gotten from various dietary sources such as apples, berries, onions, kale. Quercetin is being reviewed based on its bioavailability, metabolism and anti-inflammatory properties. Inflammation is the body's immune response to an irritant; this could be a pathogen or foreign object. An inflammatory response is either acute or chronic depending on the duration of inflammation and prolonged inflammatory response can lead to various diseases that are harmful to the body. Studies have shown that quercetin exerts good anti-inflammatory, antioxidant and anti-allergic activity by acting on leukocytes, targeting signaling kinases as well as membrane proteins crucial for an inflammatory response and acts as a scavenger of free radicals. Quercetin also down regulates the expression of pro-inflammatory factor while up regulating the expression of anti-inflammatory factor and this aids in maintaining homeostasis. Although poorly bioavailable due to its rapid metabolism, quercetin is an effective modulator of inflammation.

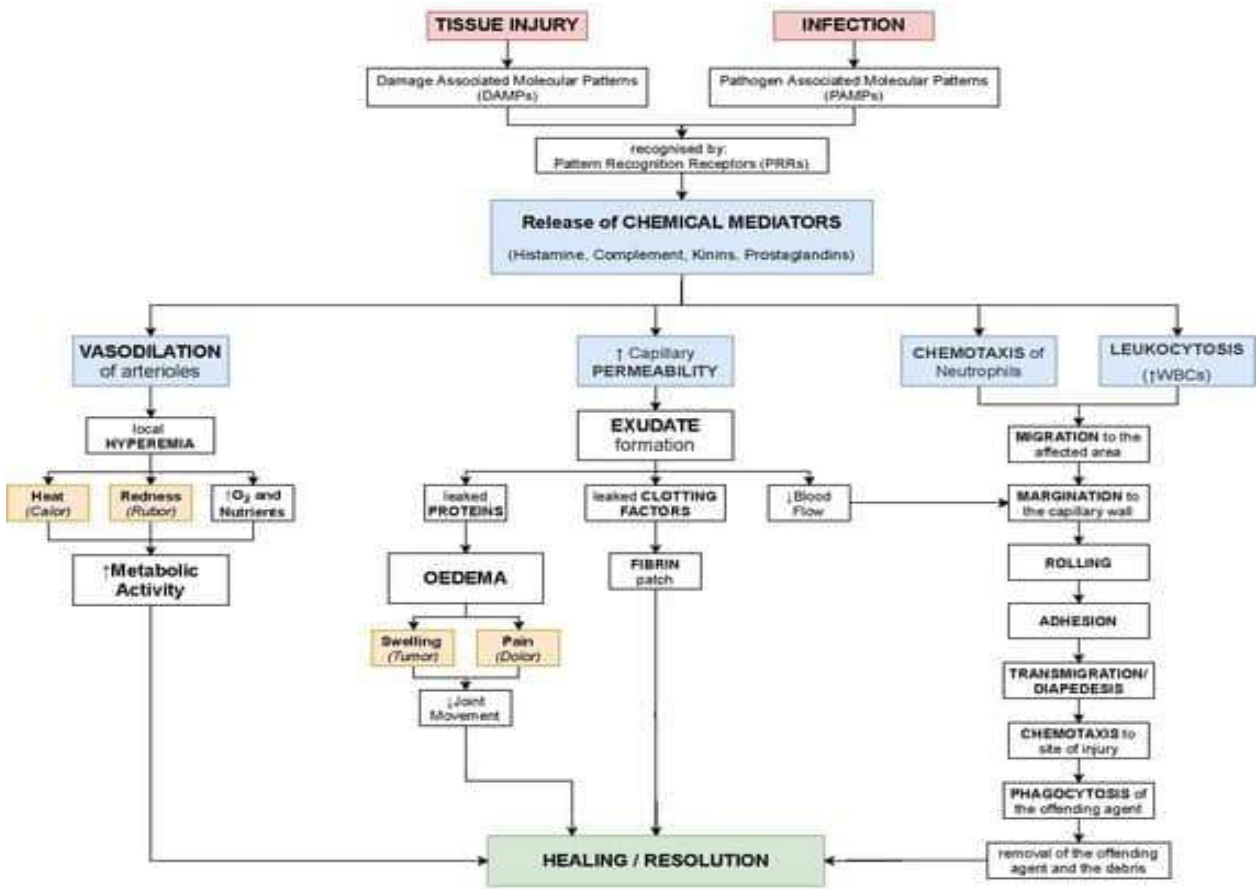
Keywords: Quercetin, inflammation, antioxidants, flavonols, free-radicals

Introduction

An organism's ability to fight infection and heal damage depends on its metabolic and immune systems. Inflammation is a self-protecting measure taken when the body experiences damaging or troublesome stimuli[1]. An inflammatory response is a defense mechanism in higher organisms to protect them from infection and injury. Its purpose is to localize and eliminate the injurious agent and to remove damaged tissue components so that the body can begin to heal. The normal inflammatory response relies upon metabolic support, and energy redistribution, particularly the mobilization of stored lipid, plays an important role in fighting infection during the acute-phase response[1]. These events are controlled by a host of extracellular mediators and regulators, including cytokines, growth factors, eicosanoids (prostaglandins, leukotrines, etc), complement and peptides[2]. The aim of this process is removing of the injured cells, pathogens, or other adverse stimuli, while beginning the treatment procedure. Inflammatory conditions are not essentially equal to infection. Infection is usually resulted from a viral, bacterial, or fungal source, but inflammatory processes include the reaction of the human body toward healing itself. Inflammation can be linked to a wide range of diseases such as allergy, cancer, Alzheimer's disease and many others[2].

Mechanism of Inflammatory Response

Inflammation involves a cascade of events. The first step of an inflammatory response involves the detection of an infection signal or damaged tissues which is mediated by the pathogen-associated molecular patterns (PAMPs) that recognize molecules expressed by the pathogens and the damage-associated molecular patterns (DAMPs) that recognize cells committed to death[1]. Thisleads to the activation of the immune system via interaction with pattern recognition receptors[2]. In response to successful recognition of these signals, transmembrane toll-like receptors or inflammasomes activate specific immune signaling pathways that lead to the activation of nuclear factor kappa-light-chain-enhancer of activated B (NF-κB). NF-κBas a result dissociates from IkB and translocates to the nucleus, where transcription occurs[3]. These events subsequently lead to the secretion of pro-inflammatory cytokines that recruit immune cells such as monocytes and neutrophils at the site of injury. The termination of neutrophils recruitment will lead to wound healing and homeostasis while continuous recruitment of neutrophils to the site of injury will result in the generation of reactive oxygen and nitrogen species that may lead to oxidative stress or damage of macromolecules[3].



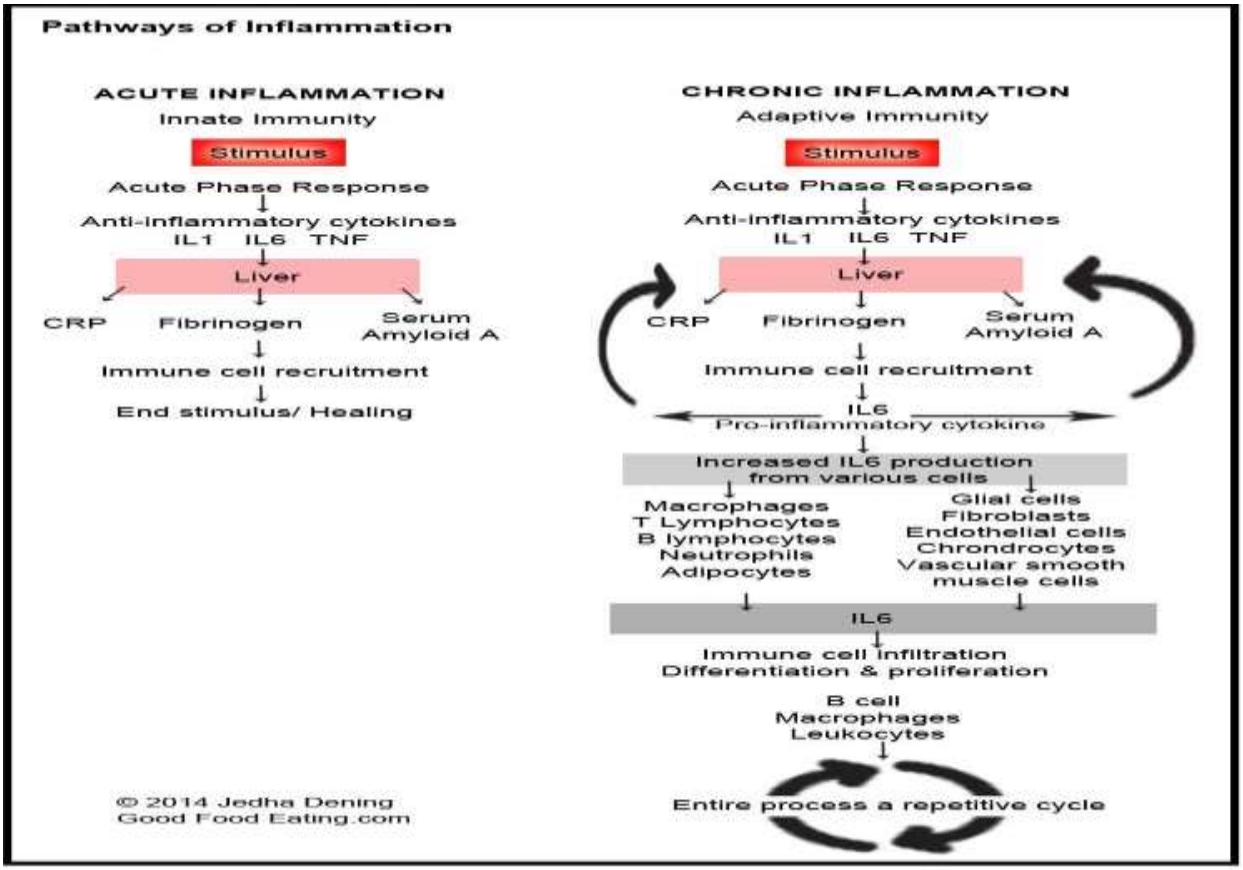
Robbins S, Cotran R, Kumar V, Abbas A, Aster J, Pathologic basis of disease , 2020; 10.

Figure 1 Overview of Inflammatory Response

Types of Inflammation

Inflammation can be acute or short term inflammation when it lasts only a few days. Signs of an inflammation may include; redness caused by the dilation of small blood vessels at the site of injury, heat that results from the increased blood flow through the affected area, swelling which is caused by fluid accumulated outside the blood vessels due to the release of chemicals by white blood cells that make the capillaries permeable and finally pain that is as a result of tissue distortion caused by chemical mediators of inflammation[3]. Some factors that can lead to acute inflammation include acute bronchitis, appendicitis, in grown toe nail, a sore throat from cold or flu and physical trauma or wound[4].

Inflammation can also be chronic and this type of inflammation has a longer duration. Macrophages, lymphocytes and plasma cells are predominating in chronic inflammation compared to the neutrophils that predominate in acute inflammation[4]. Chronic inflammation is harmful and it can lead to various diseases. Chronic inflammation occurs when the body is hypersensitive and this can lead to allergy. Long term, low level exposure to an irritant, such as industrial chemicals can result in chronic inflammation. Also persistent acute inflammation can lead to chronic inflammation. Macrophages, lymphocytes and plasma cells are predominating in chronic inflammation compared to the neutrophils that predominate in acute inflammation[4]. Chronic inflammation is harmful and it can lead to various diseases. A defect in the cells responsible for mediating inflammation leads to persistent inflammation[4]. Chronic inflammation causes a significant amount of diseases that lead to death in the world. Worldwide, 3 of 5 people die due to chronic inflammatory diseases like stroke, chronic respiratory diseases, heart disorders, cancer, obesity and diabetes[4].



https://www.pininterest.com/pin/pathwaysofacuteinflammationandchronicinflammation--298574650274900056/

Figure 2 Pathways of Inflammation

Quercetin

Quercetin is categorized as a flavonol, one of the six subclasses of flavonoid compounds. The name has been used since 1857, and is derived from quercetum (oak forest), after Quercus. It is a naturally occurring polar auxin transport inhibitor[5]. The International Union of Pure and Applied Chemistry (IUPAC) nomenclature for quercetin is 3, 31, 41, 5, 7-pentahydroxyflvanone (or its synonym 3, 31, 41, 5, 7-pentahydroxy-2-phenylchromen-4-one). This means that quercetin has an OH group attached at positions 3, 5, 7, 31, and 41. Quercetin is a unique bioflavonoid that is found in abundance in various types of vegetables and fruits[5]. It exhibits numerous beneficial effects on the human health, and acts as a potent antioxidant, anti-carcinogenic, anti-inflammatory, anti-infective, neuroprotective, and psycho stimulant agent[6].

Quercetin (C15H10O7) is an aglycone, lacking an attached sugar. It is a brilliant citron yellow needle crystal and entirely insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol and lipids[7]. A quercetin glycoside is formed by attaching a glycosyl group (a sugar such as glucose, rhamnose, or rutinose) as a replacement for one of the OH groups (commonly at position 3) [7]. The attached glycosyl group can change the solubility, absorption, and in vivo effects. As a general rule of thumb, the presence of a glycosyl group (quercetin glycoside) results in increased water solubility compared to quercetin aglycone[7].

Nutritional Quercetin is present mainly as glycosides rather than as aglycones. It shows a relatively higher bioavailability than other phytochemicals, with its main sources being grapes, berries, cherries, apples, citrus fruits, onions, buckwheat, kale, tomatoes, red wine, and black tea[8].

Bioavailability, Absorption and Metabolism of Quercetin

Bioavailability of quercetin is very low, mostly due to its extensive metabolism. Quercetin is present in plants mainly in its highly hydrophilic glycosylated forms, primarily as β-glycosides of various sugars[7]. The estimated absorption of quercetin glycoside, the naturally occurring form of quercetin, ranges from 3% to 17% in healthy individuals receiving 100 mg[7]. Quercetin glycosides might be differently absorbed based on the type of sugar attached. Due to the different sugar types and sugar group conjugation sites will result in absorption variation. Average daily flavonoid intake is estimated between 50 - 800mg of which quercetin intake is dependent on the consumption of foods rich in quercetin[9].

When quercetin glycosides are ingested, they are absorbed near the intestinal wall. Quercetin glycosides are first hydrolyzed by lactase-phlorizin hydrolyze enzyme to an aglycone before entering the enterocyte[10]. This is the first step because its glycosides form cannot pass through the enterocyte cell membrane due to its high hydrophilic nature. Quercetin aglycone on the other hand undergoes passive diffusion through the phospholipids' bilayer of enterocytes due to its lipophilic nature[10]. After absorption, quercetin becomes metabolized in various organs including the small intestine, colon, liver and kidney. It undergoes biotransformation which involves two phases. The phase I includes oxidation and O-demethylation while the phase II includes methylation, sulfation or glucuronidation[11]. Resulting

conjugates of quercetin are absorbed into the bloodstream via passive diffusion or bisolateral ATP binding cassette (ABC) transporters[7]. These ABC transporters enable ATP to be hydrolyzed and use the energy harnessed for active efflux transport of molecules[12]. When these metabolites of quercetin are absorbed in the bloodstream they may bind to albumin and then they can be transported to the liver via the portal vein[13].Further biotransformation takes place in the liver and subsequently quercetin metabolites can be transported from the liver to other sites such as the kidney where they are excreted in urine[7]. Consequently, after the intake of food rich in quercetin glycosides and aglycone, methylated, glucuronidated, sulfated and combined derivatives of quercetin, such as isorhamnetin-3-glucuronide, quercetin diglucuronide, quercetin glucuronide sulphate, methyl quercetin diglucuronide, etc., have been found in the human plasma[7].

Functional Properties of Quercetin

Numerous studies have been carried out in order to ascertain the various effects of quercetin in the body.

Studies have reviewed the effects of quercetin as an antioxidant that scavenges oxygen free radicals responsible for oxidative stress thereby reducing cellular damage[14]. Free radicals such as nitric oxide as well as reactive oxygen species act as regulatory mediators in signaling processes[15]and they are generated from immune cell activation, inflammation, infection, cancer, stress, air pollution and radiation[16-17]. Excess production of these free radicals alters cellular functions and induces chronic diseases[15].

Cellular damage can result to lipid peroxidation that causes damage to organs. Quercetin shows antioxidant action through the decrease in lipid peroxidation and increase in detoxification enzymes[18]. Studies also reported that quercetin reduces lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophages. Nitric oxide (NO) is produced by endothelial cells for vasodilation. However, when a high amount of NO is produced, it can cause oxidative damage[19].

Oxidative stress plays an important role in the development of behavioral impairment[20]. Several investigations have revealed that depressive-like behavior associated with brain oxidative stress is as a result of enhanced glutathione transferase activity and lipid peroxidation[21]. Lipid peroxidation causes cytotoxic damage in different organs, especially in the brain, leading to cognitive impairment and neurodegenerative diseases[22].

Studies have reported evidence of the action of quercetin-rich fruits and vegetables on improved spatial learning and memory impairment in Moris water maze test associated with decrease in reactive oxygen species production and an increase in antioxidant enzyme activity[23]. Another study reported quercetin's ability to pass through blood-brain barrier in certain models, which suggests that quercetin, could be a potential neuroprotective approach to slow down degenerative disease progression[18] leading to an improvement of cognitive and behavioral impairment in Parkinson's disease.

Basophils are blood granulocytes involved in hypersensitivity and anaphylactic reactions. They promote chronic allergy inflammation[24]. When activated basophils degranulate to release histamine, proteglycans and proteolytic enzymes. They also secrete lipid mediators like leukotrienes as well as several cytokines[25]. Basophils are motile cells and they migrate from the blood to inflamed tissues and act as allergic inflammatory cells. Studies have reported that basophils play an important role in inflammation related angiogenesis through the expression of several forms of vascular endothelial growth factors and their receptors[26]. In vitro studies about the action of quercetin aglycone reported its ability to inhibit histamine release in human basophils when they are activated and also inhibit peptide presentation in antigen presenting cells[27].Quercetin is also known as a natural inhibitor of mast cells exocytosis. It can induce the down regulation of the degranulatory response in mast cells[28].

Over the years most In vivo and In vitro studies have investigated the effect of quercetin on leukocyte and smooth muscle contraction[29]. A study hypothesized that quercetin blocks airway epithelial cells chemokine expression via phosphatidylinositol (PI) 3 kinase-dependent mechanism. They showed that quercetin (3,3,4,5,7 pentahydroxyflavone) blocks the airway epithelial cell IL-8 and monocyte chemoattractant protein (MCP)-1 expression by attenuating the signaling through a PI-3 kinase/Akt/NF-κB pathway and also inhibits chemokine expression via transcriptional and posttranscriptional ways[29]. Another study involved the effect of quercetin on cytokine levels and smooth muscle contraction, in vitro and its therapeutic potential effect on a murine model of asthma[30]. The study showed the reduction of inflammatory cytokines production, tracheal ring relaxation and also reduction of eosinophil peroxidase in the lungs by treatment with quercetin[30]. In 2017, the effects of several herbs investigated revealed that quercetin could be used to develop new bronchodilators to treat obstructive lung diseases such as asthma and chronic obstructive pulmonary disease[31].

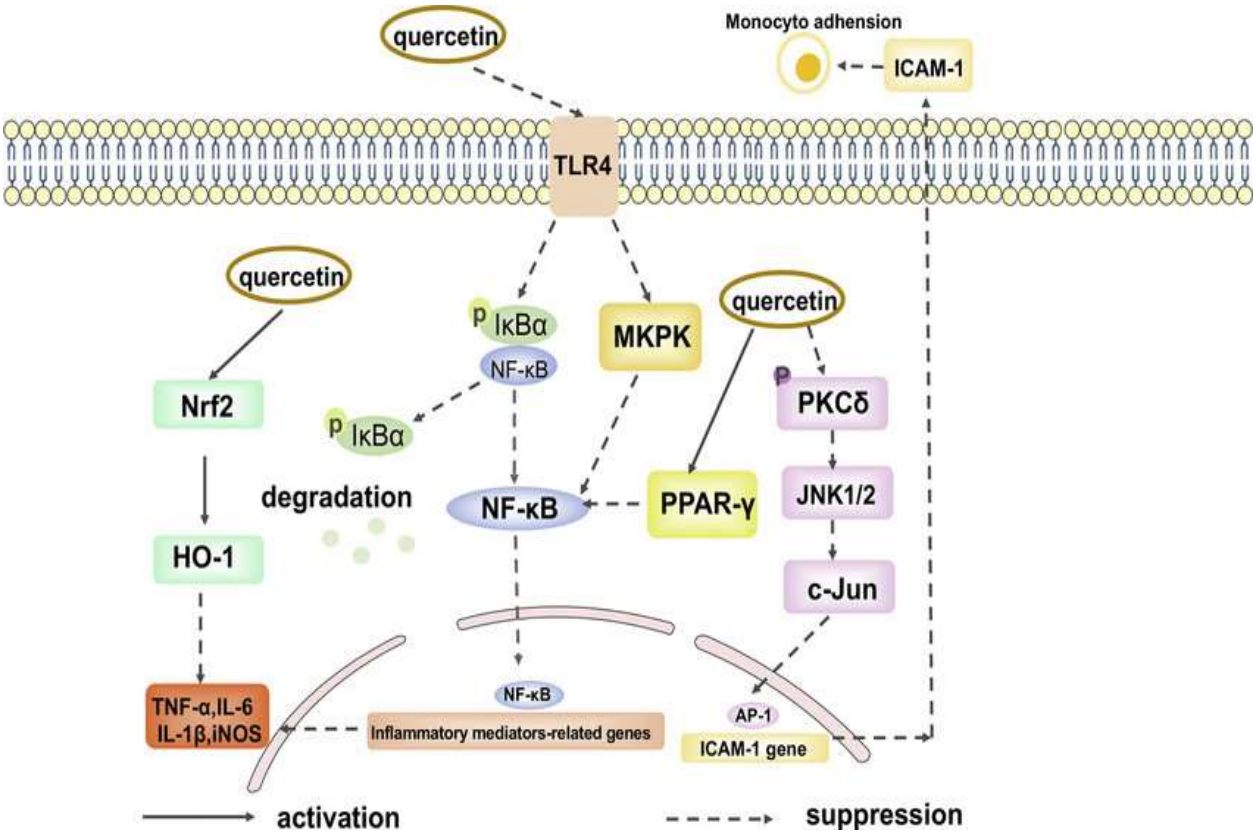
Quercetin affects immunity and inflammation by acting mainly on leukocytes and targeting many intracellular signaling kinases, enzymes, phosphatases and membrane proteins. A study involving an in vitro treatment of activated T cells with quercetin revealed the inhibition of IL-12-induced tyrosine phosphorylation of JAK2, STAT3, and STAT4, resulting in a decrease in IL-12-induced T cell proliferation[32]. Several In vitro studies have also shown that quercetin prevents the development of lipopolysaccharide (LPS)-mediated tumor necrosis factor-α (TNF-α) in macrophages and the development of IL-8 induced by inhibiting the activation of p38[33]. In addition, quercetin can inhibit TNF-α and Interleukin (IL)-1α levels of LPS-induced mRNA, which results in reduced apoptotic neuronal cell death caused by microglial activation. The potential of quercetin in modulation of inflammation is one of its critical and considerable features as inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenase can be inhibited by this agent and consequently inflammatory mediators including prostaglandins as well as leukotrienes can reduced[34].

Quercetin substantially stimulates the gene expression and the development of interferon-γ (IFN-γ) derived from T helper cell-1 (Th-1) and down-regulates IL-4 derived from Th-2 by normal peripheral blood mononuclear cells (PBMC). Quercetin is also known to have inhibitory activity against nuclear factor-kappa B (NF-κB), activator protein 1 (AP-1), mitogen-activated protein kinase (MAPK), expression that causes inflammation[35]. Quercetin inhibits the nuclear translocation of NF-κB by suppression of the inhibitor of kappa B-protein degradation[36].As noted earlier, upon activation NF-κB dissociates from IkB and translocates into the nucleus where it can act as a transcription factor for pro-inflammatory genes. Activator protein-1 is another transcription factor capable of regulating the expression of pro-inflammatory and adhesion molecules. LPS stimulation induces MAPK cascade that results in the activation of AP-1[36].

Studies also reported that quercetin has the ability to counteract the LPS mediated up regulation of the protein expression of NF-κBp65 subunit, toll-like receptor 4, MyD88

and down regulates of IkB in eat intestinal microvascular endothelial cells[35].

A study was designed to determine the effect of quercetin on the indicators of chronic systemic inflammation in coronary artery disease (CAD) patients[32]. The study involved 85 CAD patients, stable angina pectoris, functional class II, and heart failure. Thirty patients received quercetin at a daily dose of 120 mg for 2 months, while the remaining 55 patients considered as the control group received β-blockers, statins, and aspirin[32]. An increase in the levels of IL-1β and tumor necrosis factor-α (TNF-α) and a moderate increase in IL-10 levels were detected in the serum of patients with CAD. Under the influence of quercetin, levels of IL-1β and TNF-α were reduced and IL-10 levels tended to decrease[32].



Yu W, Tao B, Yao W, Yue S, Drug delivery based pharmacological enhancement and current insight of quercetin with therapeutic potential against oral diseases, Biomedicine & Pharmacotherapy, 2020; 128:110372.

Figure 3 Mechanism of Action

In addition, quercetin may indirectly prevent inflammation by increasing peroxisome proliferator-activated receptor c (PPARγ) activity, which inhibits cytokine induced expression of vascular cell adhesion molecule-1 in endothelial cells[37]. This action blocks TNF-α-mediated induction of inflammatory cascades[37]. Quercetin also has the ability to up-regulate nuclear factor 2 erythroid related factor 2 mediated transcription of anti-inflammatory and antioxidant gene such as for hemeoxygenase-1[37] which inhibits AP-1 activity and adhesion molecule expression[38]. Hence the antagonizing effect NF-κB and Nrf2 have on each other[38].

Conclusion

Inflammation is a defense mechanism of the body that protects against infection and injury. Though it is a part of the body's immune response, persistent inflammation can cause harm to the human body ranging from allergies to various chronic respiratory diseases. Quercetin is an important flavonoid that needs to be incorporated into our daily diet. Several studies have demonstrated its anti-inflammatory properties by down regulating pro-inflammatory factors and up-regulating anti-inflammatory factors inorder to maintain homeostasis.

The health benefits of quercetin in the body are vast but limited due to its poor bioavailability. Therefore, several studies have been conducted to modify its structure to increase its water solubility and bioavailability and thereby enhance its antioxidant and anti-inflammatory activity.

Abbreviations: STAT: Signal Transducers and Activators of Transcription, COX-2: Cyclooxygenase-2, MAPK: Mitogen Activated Protein Kinase, JNK: Jun-N-Terminal Kinase, AP-1: Activated Protein-1, ICAM-1: Intracellular Adhesion Molecule-1, PPAR: Peroxisome Proliferator-Activated Receptors, Nrf2: Nuclear Factor 2 Erythroid Related Factor 2, HO-1: Heme Oxygenase-1, Nf-kB: Nuclear Factor Kappa B.

References

[1]Janeway CA, Travers P, Walport M, Shlomchik MJ, Immunobiology: The Immune System in Health and Disease, Garland Science: NewYork, NY, USA, 2005.

[2]Yang WS, Jeong D, Nam G, Yi YS, Yoon DH, Kim TW, Cho JY, AP-1pathway-targeted inhibition of inflammatory responses in LPS-treated macrophages and EtOH/HCl-treated stomach by Archidendronclypearia methanol extract, Journal ofEthnopharmacol., 2013; 146(2):637-644. https://doi.org/10.1016/j.jep.2013.01.034

[3]Sarmistha S, Brigitta B, Emiliano P, Elisabetta, P, Luciano S, An Overview of Nrf2 Signaling Pathway and Its Role in Inflammation, Molecules, 2020; 25:5474. https://doi.org/10.3390/molecules25225474

[4]Pahwa R, Goyal A, Bansal P, Jialal I, "ChronicInflammation". StatPearls, 2020. PMID29630225

[5]Khan H, Ullah H, Aschner M, Cheang WS, Akkol EK, Neuroprotective effects of quercetin in Alzheimer's disease, Biomolecules, 2020; 10(59). https://doi.org/10.3390/biom10010059

[6]Tavana E, Mollazadeh H, Mohtashami E, Modaresi SMS, Hosseini A, Sabri H, Quercetin: a promising phytochemical for the treatment of glioblastomamultiforme, BioFactors, 2020; (46):356-366. https://doi.org/10.1002/biof.1605

[7]Dabeek WM, Marra MV, Dietary quercetin and kaempferol: Bioavailability and potential cardiovascular-related bioactivity in humans, Nutrients, 2019; 11:2288. https://doi.org/10.3390/nu11102288

[8]Wiczkowski W, et al. Quercetin from shallots (Allium cepa L. var. aggregatum) is more bioavailable than its glucosides, Journal of Nutrition, 2008; 138(5):885-888. https://doi.org/10.1093/jn/138.5.885

[10]Murota K, Terao J, Antioxidative flavonoid quercetin: implication of its intestinal absorption and metabolism, Archives of Biochemistry and Biophysics, 2003; 417(1):12-17. https://doi.org/10.1016/S0003-9861(03)00284-4

[11]Phang-Lyn S, Llerena VA, Biochemistry, Biotransformation. In StatPearls. Treasure Island (FL).2020.

[12]Speer JE, Gunasekara DB, Wang Y, Fallon JK, Attayek PJ, Smith PC, Allbritton NL, Molecular transport through primary human small intestinal monolayers by culture on a collagen scaffold with a gradient of chemical cross-linking, Journal of Biological Engineering, 2019; 13(1):36. https://doi.org/10.1186/s13036-019-0165-4

[13]Manach C, Regerat F, Texier O, Agullo G, Demigne C, Remesy C, Bioavailability, metabolism and physiological impact of 4-oxo-flavonoids, Nutrition Research, 1996; 16(3):517-544. https://doi.org/10.1016/0271-5317(96)00032-2

[15]Anand David AV, Arulmoli R, Parasuraman S, Overviews of biological importance of quercetin: a bioactive flavanoid, Pharmacogn Rev., 2016; 18:84-89. https://doi.org/10.4103/0973-7847.194044

[16]Pham-Huy LA, He H, Pham-Huy C, Free radicals, antioxidants in disease and health, International Journal ofBiomedical Science, 2008;4:89-96.

[17]Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J, Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem Cell Biol., 2007; 39:44-84. https://doi.org/10.1016/j.biocel.2006.07.001

[18]Enrico G, Alessio FP, Ramona D, Patrizia L, Rosalia C, Evaluation of Neuroprotective effects of quercetin against Aflatoxin B1-intoxicated mice, Animals, 2020; 10(5):898. https://doi.org/10.3390/ani10050898

[19]Le HN, Shin SA, Choo GS, Anti-inflammatory effect of quercetin and galangin in LPS-stimulated RAW264.7 macrophages and DNCB-induced atopic dermatitis animal models, International Journal ofMolecular Medicine, 2018; 41:888-898.

[20]Brocardo PS, Boehme F, Patten A, Cox A, Gil-Mohapel J, Christie BR, Anxiety-and depression-like behaviors are accompanied by an increase in oxidative stress in a rat model of fetal alcohol spectrum disorders: Protective effects of voluntary physical exercise, Neuropharmacology, 2012; 62:1607-1618. https://doi.org/10.1016/j.neuropharm.2011.10.006

[21]Merzoug S, Toumi ML, Tahraoui A, Quercetin mitigates Adriamycin-induced anxiety and depression-like behaviors, immune dysfunction, and brain oxidative stress in rats. Naunyn, Schmiedebergs, Arch. Pharmacol., 2014; 387:921-933. https://doi.org/10.1007/s00210-014-1008-y

[22] Sultana R, Perluigi M, Butterfield DA, Protein oxidation and lipid peroxidation in brain of subjects with Alzheimer's disease: Insights into mechanism of neurodegeneration from redox proteomics, Antioxid. Redox. Signal, 2006; 8: 2021-2037. https://doi.org/10.1089/ars.2006.8.2021

[23]Dong F, Wang S,Wang Y, Yang X, Jiang J, Wu D, Qu X, Fan H, Yao R, Quercetin ameliorates learning and memory via the Nrf2-ARE signaling pathway galactose-induced neurotoxicity in mice, Biochem. Biophys. Res. Commun., 2017; 491:636-641.

https://doi.org/10.1016/j.bbrc.2017.07.151

[24]Mukai K, Obata K, Tsujimura Y, Karasuyama H, New insights into the roles for basophils in acute and chronic allergy, Allergol. Int., 2009; 58:11-19. https://doi.org/10.2332/allergolint.08-RAI-0059

[25]Min B, Paul WE, Basophils and type 2 immunity, Current Opinions in Hematology, 2008; 15:59-63. https://doi.org/10.1097/MOH.0b013e3282f13ce8

[26]Crivellato E, Travan L, Ribatti D, Mast cells and basophils: a potential linkin promoting angiogenesis during allergic inflammation, Int. Arch. Allergy Immunol., 2010; 151:89-97. https://doi.org/10.1159/000235998

[27]Gong J, Chen SS, Polyphenolic antioxidants inhibit peptide presentation by antigen-presenting cells, Int. Immunopharmacol., 2003; 3:1841-1852. https://doi.org/10.1016/j.intimp.2003.08.010

[28]Haggag EG, Bou-Moustafa MA, Boucher W, Theoharides TC, The effect of a herbal water-extract on histamine release from mast cells and on allergic asthma, J. Herb. Pharmacother., 2003; 3:41-54. https://doi.org/10.1080/J157v03n04_03

[29]Nanua S, et al., Quercetin blocks airway epithelial cell chemokine expression. Am J Respir Cell Mol Biol., 2006; 35(5):602-610. https://doi.org/10.1165/rcmb.2006-0149OC

[30]Oliveira TT, et al., Potential therapeutic effect of Allium cepa L. and quercetin in a murine model of Blomiatropicalis induced asthma, Journal of Pharmacological Science, 2015;23(1):18. https://doi.org/10.1186/s40199-015-0098-5

[31]Luo X, et al., Polygonumaviculare L. extract and quercetin attenuate contraction in airway smooth muscle, Sci Rep., 2018; 8(1):3114. https://doi.org/10.1038/s41598-018-20409-x

[32]Chekalina N, Burmak Y, Petrov Y, Borisova Z, Manusha Y, Kazakov Y, Kaidashev I, Quercetin reduces the transcriptional activity of NF-kB in stable coronary artery disease, Indian Heart Journal, 2018; 70:593- 597. https://doi.org/10.1016/j.ihj.2018.04.006

[33]Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, Yin Y, Quercetin, Inflammation and Immunity, Nutrients, 2016; 8(3):167. https://doi.org/10.3390/nu8030167

[34]Bian Y, Zhong J, Hu Y, Zhuang S, Fan K, Liu Z,Quercetin Attenuates Adhesion Molecule Expression in Intestinal Microvascular Endothelial Cells by Modulating Multiple Pathways. Dig DisSci, 2018. https://doi.org/10.1007/s10620-018-5221-2

[35]Yang D, Han Z, Oppenheim JJ, Alarmins and immunity, Immunol. Rev., 2017; 280:41-56. https://doi.org/10.1111/imr.12577

[36]Ahmed SM, Luo L, Namani A, Wang XJ, Tang X, Nrf2 signaling pathway: Pivotal roles in inflammation, Biochimica et biophysicaacta, Molecular basis of disease, 2017; 1863(2):585-597. https://doi.org/10.1016/j.bbadis.2016.11.005

[37]Lingappan K, NF-kappaB in Oxidative Stress, Current opinion in toxicology, 2018; 7:81-86. https://doi.org/10.1016/j.cotox.2017.11.002