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Review

An overview on immunoregulatory and anti-inflammatory properties of chrysin and flavonoids substances



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ABSTRACT

Inflammation and the pro-inflammatory cytokines are associated with numerous chronic diseases. Studies suggest that flavonoids, plant polyphenolic compound derivatives from natural origin, have a wide range of putative biological activities. Similar to other flavonoids, chrysin (CH) by its anti-oxidative and anti-inflammatory effects is a potential prophylactic agent in immunopathological and physicochemical injuries. This is an overview on putative immunomodulatory activities of flavonoids and beneficial health effects of these substances particularly, CH in the immune system. CH possesses potent immune-protective effects and suppresses inflammation in innate immune system which results to avoid damages induced by neutrophils and macrophages and suppresses immuno-inflammatory responses.

Furthermore, beneficial effects of chrysin on inhibition of serum levels nuclear transcription factor κ B (NF- κ B) p65 unit, tumor necrosis factor alpha (TNF- α), interleukin-1 β (IL-1 β), IL-6, IL-12, IL-17A, interferon gamma (IFN- γ) was reported. Moreover, CH has been known as the antagonist of NF- κ B and the agonist of peroxisome proliferator-activated receptor gamma (PPAR- γ) which in down regulation of the key pro-inflammatory enzymes such as myeloperoxidase (MPO), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), phospholipase A2, and prostanoids. Therefore, CH can improve immune system and neurodegenerative diseases. In recent years, there has been an increasing interest in compound derivatives from natural origin. Taken together, evidences show that flavonoids may have health-promoting and disease-preventing dietary compounds with important benefits in modern life styles.

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Abbreviations: AHR, airway hyper responsiveness; BALF, bronchoalveolar lavage fluid; Casp-1, caspase-1; CH, chrysin; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; EAN, experimental autoimmune neuritis; ERK, extracellular signal-regulated kinase; GVHD, graft-vs-host disease; HAHs, halogenated aromatic hydrocarbons; HCB, hexachlorobenzene; HUVECs, human umbilical vein endothelial cell; IBD, inflammatory bowel disease; ICAM-1, intercellular adhesion molecule-1; IKK, I- κ B kinase; IL, interleukin; IL-6R, IL-6 receptor; INF- γ , Interferon gamma; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; JNK, c-Jun NH2-terminal kinase; KC, chemoattractant; LPS, Lipopolysaccharide; MAPKs, Mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MCP-1, chemoattractant protein-1; MPO, myeloperoxidase; NO, nitric oxide; -OH, hydroxyl group; OVA, ovalbumin; PAHs, Polycyclic aromatic hydrocarbons; PBBs, polybrominated biphenyls; PBMC, peripheral blood mononuclear cells; PCBs, polychlorinated biphenyls; PMNs, polymorphonuclears; PPAR- γ , peroxisome proliferator-activated receptor gamma; RA, rheumatoid arthritis; RANTES, regulated on activation, normal T cell expressed and secreted; ROR γ t, retinoic acid-receptor-related orphan receptor- γ t; SCI, spinal cord injury; STAT-3, signal transducer and activator of transcription 3; TCDD, Tetrachlorodibenzo-p-dioxin; TGF- β , transforming growth factor beta; Th, T helper; TNF, Tumor necrosis factor; TNFR2, Tumor necrosis factor receptor 2; TNF α , tumor necrosis factor alpha; VAM, vascular adhesion molecules; VCAM-1, vascular cell adhesion molecule-1.

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1. Introduction

Humans live in a world that is heavily polluted by many toxic or allergenic substances that threaten normal bodies. The immune system known as a sophisticated network is not only responsible for protecting the body against diseases and foreign materials but also protects the host from toxic and allergenic substances that enter through body [1]. In summary, immunotoxicity is an inappropriate immune response that can consequently result in the manifestation of immunopathologic reactions. Many studies have pointed to the developing immune system as a remarkably sensitive toxicological target for environmental chemicals and drugs [2]. Exposure to asbestos, benzene [3], heavy metal [4], halogenated aromatic hydrocarbons (HAHs) such as polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs), and dioxins (TCDD), hexachlorobenzene (HCB) [5], can cause severe immunopathological responses in humans [6]. Also, polycyclic aromatic hydrocarbons (PAHs) [7], therapeutic substances and abused recreational drugs, such as ethanol, cocaine, isobutyl nitrites and diphenylhydantoin can alter immune function toward disease manifestation [8] or autoimmune diseases [9]. Environmental exposures are responsible for more than 1/3 of diseases in children less than 5 years. Childhood diseases such as allergic disorders, cancers and diabetes have been linked to environmental exposures [10].

Flavonoids are plant polyphenolic compound derivatives from natural origin that found in fruits, grains, vegetables, roots, bark, flowers, stems, tea, and wine. These compounds according to hydroxylation patterns and the degree of unsaturation of their backbone are classified into six groups [11]. The flavonoids consist of several classes including flavonols, flavones and flavans (Fig. 1) [12].

Chrysin (C₁₅H₁₀O₄), is found in propolis, honey and extracted from numerous plants [13]. Also, it is found in passion flowers such as *Passiflora caerulea*, *Passiflora incarnata* and *Oroxylum indicum* [11]. Recently, several studies *in vitro* and *in vivo* models have shown that selected flavonoids for example CH has multiple putative biological activities, such as antitumor activity [14,15], anti-inflammatory [16], antioxidant [17–19], anti-allergic [20], anti-aging [21] anti-hypertensive [22], anti-angiogenesis [23], antiviral [24], anti-atherogenic [25], antibacterial [26], anti-diabetic [27,28], neuroprotective [29], hepatoprotective [30], nephroprotective [31] and positively effect on reproductive system [32]. CH could inhibit serum levels of major inflammatory cytokines (NF- κ B p65 unit, TNF- α , IL-1 β and IL-6) and activity of iNOS, plasma NO level in rats [33]. Moreover, there is growing evidence that CH exhibits various biological effects on immune

system. CH exhibited anti-inflammatory activities and suppressing immuno-inflammatory responses. In many studies, protective effects and molecular mechanisms of CH on the immune system have been confirmed. The aim of this review is to give an overview on the immune system and recent findings on potential valuable activities of flavonoids on the immune system. In the last part of this review, immunomodulatory mechanisms of flavonoids especially CH are discussed.

2. Chemistry of flavonoids

Flavonoids belong to a group of plant origin compounds with variable phenolic structures [34]. The basic flavonoid structures are based upon a 15-carbon skeleton. Flavonoids skeleton consisting of two phenyl rings (A and B rings), that connected by a linear chain of 3-carbon atoms. A and B benzene rings linked via a heterocyclic pyrane ring (C). Although, within a flavonoids class differs in the pattern of substitution of the A and B rings [24]. Flavonoids are often hydroxylated in positions 3, 5, 7, 2, 3', 4', and 5'. Flavonoids typically on the basis of the structural features of the C ring can be divided into a variety of classes such as flavones, flavonols and flavanones. Main flavones are CH, apigenin, flavone, luteolin, baicalein and baicalin. They have a double bond between positions 2 and 3 and a ketone in position 4 of the C ring. Hence, flavonols such as quercetin, kaempferol and myricetin have a hydroxyl group (—OH) in position 3 of the C ring. Flavanones are another group that the C ring is saturated (Fig. 1) [12].

3. A summary on immune system

Defense against invaders is mediated by the activities of innate immunity and adaptive immunity system. The innate immune system consists of many cell types such as polymorphonuclears (PMNs), and soluble factors such as complement system, pro-inflammatory cytokines and vasoactive mediators which inducing inflammatory reactions [35]. The major way by which the innate immune system defends against infections and tissue injury is to stimulate acute inflammation. However, the chronic inflammation is a sophisticated process that takes over from acute inflammation if the tissue injury is not repaired or prolonged.

In adaptive immune system lymphocyte subpopulations have pivotal roles for inducing appropriate immune responses [36]. The T helper (Th) cells have the central role in all aspects of immune responses, for example, they are important in B cell biology including antibody class switching, macrophage activation and activation of cytotoxic T cells. Cytokines are the main network for Th communications, thus inappropriate activities play an

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