European Journal of Medicinal Chemistry 131 (2017) 68–80

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders

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ARTICLE INFO

Article history:
Received 22 December 2016
Received in revised form
20 February 2017
Accepted 3 March 2017
Available online 6 March 2017

Keywords:
Baicalin
Baicalein
Flavonoids
Chemoprevention
Inflammatory diseases

ABSTRACT

The flavonoids, baicalin (5,6-dihydroxy-2-phenyl-4H-1-benzopyran-4-one-7-*O*-D-β-glucuronic acid) **1** and its aglycone, baicalein **2** are found in edible medicinal plants, *Scutellaria baicalensis* Georgi and *Oroxylum indicum* (L.) Kurz in abundant quantities. The antioxidant and anti-inflammatory effects of these flavonoids have been demonstrated in various disease models, including diabetes, cardiovascular diseases, inflammatory bowel diseases, gout and rheumatoid arthritis, asthma, neurodegenerative-, liver- and kidney diseases, encephalomyelitis, and carcinogenesis. These flavonoids have almost no toxicity to human normal epithelial, peripheral and myeloid cells. Their antioxidant and anti-inflammatory activities are largely due to their abilities to scavenge the reactive oxygen species (ROS) and improvement of antioxidant status by attenuating the activity of NF-κB and suppressing the expression of several inflammatory cytokines and chemokines including monocyte chemotactic protein-1 (MCP-1), nitric oxide synthase, cyclooxygenases, lipoxygenases, cellular adhesion molecules, tumor necrosis factor and interleukins. In this review, we summarize the antioxidant and anti-inflammatory effects of baicalin and baicalein with molecular mechanisms for their chemopreventive and chemotherapeutic applications in the treatment of inflammatory-related diseases.

Abbreviations: 6-OHDA, 6-hydroxydopamine; 12-LOX, 12-lipoxygenase; AIDS, acquired immunodeficiency disorder syndrome; AhR, aryl hydrocarbon receptor; AIH, autoimmune hepatitis; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; ALT, alanine aminotranferase; ANA, antinuclear antibiotics; AST, aspartate transaminase; AUC, area under time concentration curve; bax, bel-2 associated X protein; bel-2, B-cell lymphoma-2; BNP, brain natriuretic peptide; CAT, catalase; $CD3^+$ cells, cluster of differentiation 3 + T cells; CDK, cyclin-dependent kinase; CL, clearance; CKD, chronic kidney disease; Con A, concanavalin A; DA, dopamine; EAE, experimental autoimmune encephalomyelitis; ECs, cardiovascular endothelial cells; ECM, extracellular matrix; ERK 1/2, extracellular signal regulated kinase 1/2; FAS, fatty acid synthase; FGFR, fibroblast growth factor receptor; G- CSF, granulocyte-colony stimulating factor; GFAP, glial fibrillary acidic protein; g.g., gastric gavage; GSH-P_x, glutathione peroxidase; GSK-3β, glycogen synthase kinase-3 beta; GSIS, glucose-stimulated insulin secretion; 12-HETE, 12-hydroxyeicosatetraenoic acid; HFD, high-fat diet; HIF-1α, hypoxia-inducible factor-1 alpha; HMC-1, human must cell line-1; HSCs, hepatic stellate cells; HO-1, heme oxygenase-1; HUVECs, human umbilical vein endothelial cells; IBD, inflammatory bowel disease; ICAM-1, intercellular adhesion molecule-1; IκBα, inhibitor kappa B-alpha; IFNγ, interferon-gamma; i.g., intragastric; IgE, immunoglobulin E; IgG, γ-globulins; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal; i.v., intravenous; LBs, lewy bodies; LDL, low density lipoprotein; LKM-1, liver-kidney microsomal autoantibodies-1; 12-LOX, 12-lipoxygenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic factor-1; M-CSF, macrophage colony stimulating factor; MDA, malondialdehyde; MIP-1β, macrophage inflammatory protein-1 beta; miR 10a, micro RNA-10a; MMP, matrix metalloproteinase; MNCs, mononuclear cells; MOG, myelin oligodendrocyte glycoprotein; MPO, myeloperoxidase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor kappa B; NO, nitric oxide; oxLDL, oxidized low-density lipoprotein; ORP-9, oxysterol binding protein −related protein 9; OVA, ovalbumin; PAH, pulmonary artery hypertension; P_{app}, apparent permeability; PASMCs, pulmonary artery smooth muscle cells; PCNA, proliferating cell nuclear antigen; PD, parkinson's disease; PDGF, platelet-derived growth factor; PDGF-Rβ, platelet-derived growth factor-receptor beta; P-gp, permeability-glycoprotein; PKA, protein kinase A; PLP, proteolipid protein; PPAR, peroxisome proliferator-activated receptor; pRB, phosphorylated retinoblastoma; PVSR, pulmonary vascular structure remodeling; RORγt, retinoic acid receptor-related orphan receptor gamma t, a central factor of IL-17 transcription; ROS, reactive oxygen species; RVSP, right ventricular systolic pressure; SCID-mice, severe combined immunodeficiency-mice; α- SMA, alpha-smooth muscle actin; SOCS-3, suppressor of cytokine signaling-3; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein-1c; STAT, signal transducer and activator of transcription; STZ, streptozotocin; TIMP-2, tissue inhibitor of metalloproteinase-2; TGF-β, transforming growth factor-beta; Th-1 cells, T(thymus)- helper −1 cells; TNF-α, tumor necrosis factor-alpha; TrxR, thioredoxin reductase; Treg cells, regulatory T cells; UUO, unilateral ureteral obstruction; VCAM-1, vascular cell adhesion molecule-1; V_d, volume of distribution; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells.

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http://dx.doi.org/10.1016/j.ejmech.2017.03.004
0223-5234/

Contents

1. Introduction

Flavonoids are one of the largest classes of naturally occurring polyphenolic compounds, found in high concentrations in dietary fruits and vegetables. The human consumption of flavonoid-rich fruits and vegetables reduces the risk of several inflammatory diseases including cancers [1]. Some natural flavonoids have been developed as efficient drugs. For example, silymarin, a mixture of isomeric flavonolignans, isolated from *Silybum marianum* (milk thistle) fruits, has been used in different countries for the treatment of cirrhosis, chronic hepatitis and other liver disorders [2]. Naringin and naringenin, isolated from *Citrus paradisi* fruit juice have been used for treatment of hepatic fibrosis [3].

Baicalin (**1**) and its aglycone, baicalein (**2**) (Fig. 1) are the major flavonoid constituents in the plants of genus *Scutellaria* (Lamiaceae) namely *Scutellaria baicalensis* Georgi (SBG), *S. lateflora* L., *S. galericulata*, and *S. rivularia* Wall as well as in *Oroxylum indicum* (L.) Kurz (OI, Bignoniaceae) [4–8]. The *Scutellaria* plant species are grown in Asian countries including China, eastern Russia, Mongolia, Japan, Korea, and Siberia [9]. Whereas *Oroxylum indicum* is grown in India, Sri Lanka, Bangladesh, Pakistan, Nepal, Bhutan, Cambodia, Malaysia, Indonesia, Vietnam, Thailand, China, and other south Asian countries [10]. The roots of *Scutellaria baicalensis* (commonly known as *Scutellaria* radix) are widely used in traditional Chinese medicines for clinical treatment of hepatitis, hyperlipidemia, atherosclerosis, hypertension, dysentery, common cold and other respiratory disorders [11]. The stem-bark, roots and seeds of *Oroxylum indicum* have been used in traditional medicines of India, China and other Asian countries for the treatment of jaundice, diabetes, diarrhea and dysentery, rheumatic pain, coughs, pharyngitis, bronchitis and other respiratory disorders [12,13]. In SBG roots, baicalin and baicalein are found in 10.11% and 5.41%, respectively [11]. In OI, baicalein is the major flavonoid constituent of fruit, root bark and leaf, while baicalin is found in abundant quantity in leaf and stem bark [14]. Both baicalin and baicalein have been found to exhibit several pharmacological activities including antioxidant, anti-inflammatory, anticancer, anticardiovascular, antidiabetic, hepatoprotective, antiviral, anti-ulcerative colitis, antithrombotic, eye protective and neuroprotective activities [15–26]. Previous review articles on baicalin and baicalein have high-lighted their anticancer, cardioprotective, anti-ocular disorder, and antitumor activities [23,27–31]. Most of these pharmacological activities of baicalin and baicalein are associated with their antioxidant and anti-inflammatory efficacies. This review summarizes the molecular mechanisms of baicalin and baicalein in the prevention and treatment of inflammatory-related diseases.

Inflammation is a localized protective reaction of the injured tissue in the body. The tissue injury is caused by several factors including microbial infections, allergic irritations of xenobiotics, excessive stress, nutritional imbalance, genetic factor, etc. The symptoms of inflammation in injured tissue are characterized by pain, heat, redness, swelling and loss of function. As a preventive measure, the injured tissue dilates its blood vessels to increase the supply of more blood along with infiltration of leukocytes (basophils, neutrophils, eosinophils), lymphocytes (T cells, B cells, NK cells, monocytes, macrophages), mast cells and platelets and induce their activation for up-regulation of protective cytokines, chemokines and adhesion molecules. The protective immune cells are activated by the activation of kinases, IKKα and IKKβ via phosphorylation of IκB and release of inactivated NF-κB from IκB and its translocation from cytoplasm to nucleus, followed by attachment of NF-κB to the receptors of DNA genes for expression of pro-inflammatory cytokines, chemokines and CAM molecules as per need to defend the trauma or shock [32]. The prolonged inflammation process, known as chronic inflammation are caused from incorrect regulation of NF-κB by the injured tissue and invaded microbes, leads to fibrosis and apoptosis of tissue cells and develops several degenerative and vascular diseases including rheumatoid-arthritis, asthma, atherosclerosis, cancer, acquired immunodeficiency disorder syndrome (AIDS), diabetes, inflammatory bowel disease (IBD), gastritis, multiple sclerosis (MS), cardiovascular diseases, sepsis, CNS depression, psoriasis, etc [33–35]. In most cases, cytokines, TNF-α and IL-1β and toll-like (microbial pattern recognition) receptors (TLRs) serve as effective activators of NF-κB [36]. Therefore, the understanding of the over-expression of pro-inflammatory mediators that aggravate a particular inflammatory disorder and down-regulation of their expressions to inactivate NF-κB will be useful for treatment of the disorder [37]. For example, in atherosclerosis, the cytokines, vascular cell adhesion molecule 1 (VCAM-1), monocyte chemoattractant protein –1(MCP-1), P- and E-selectins are expressed from vascular endothelium and arterial surface cells, whereas in cardiovascular disease, ICAM-1 expression occurs in endothelial cells and in