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Review

The main bioactive compounds of *Scutellaria baicalensis* Georgi. for alleviation of inflammatory cytokines: A comprehensive review

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ABSTRACT

Scutellaria baicalensis Georgi., a plant used in traditional Chinese medicine, has multiple biological activities, including anti-inflammatory, antiviral, antitumor, antioxidant, and antibacterial effects, and can be used to treat respiratory tract infections, pneumonia, colitis, hepatitis, and allergic diseases. The main active substances of *S. baicalensis*, baicalein, baicalin, wogonin, wogonoside, and oroxylin A, can act directly on immune cells such as lymphocytes, macrophages, mast cells, dendritic cells, monocytes, and neutrophils, and inhibit the production of the inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α, and other inflammatory mediators such as nitric oxide, prostaglandins, leukotrienes, and reactive oxygen species. The molecular mechanisms underlying the immunomodulatory and anti-inflammatory effects of the active compounds of *S. baicalensis* include downregulation of toll-like receptors, activation of the Nrf2 and PPAR signaling pathways, and inhibition of the nuclear thioredoxin system and inflammation-associated pathways such as those of MAPK, Akt, NFκB, and JAK-STAT. Given that in addition to the downregulation of cytokine production, the active constituents of *S. baicalensis* also have antiviral and antibacterial effects, they may be more promising candidate therapeutics for the prevention of infection-related cytokine storms than are drugs having only antimicrobial or anti-inflammatory activities.

1. Introduction

1.1. Cytokine storms

Inflammation is the body's first line of defense against infection or injury, which activates innate and acquired immune responses. Although microorganisms have evolved a series of different strategies that are designed to prevent the triggering of inflammatory reactions, some pathogens, such as the influenza virus and *Francisella tularensis*, can provoke life-threatening cytokine storms in the host [1]. The term cytokine storm is used to describe an overactive immune response to external stimuli, which is characterized by the rapid uncontrollable secretion of a multitude of harmful molecules, including pro-inflammatory cytokines, prostaglandins (PGs), and leukotrienes (LTs). Additional events include an excessive proliferation of T cells and macrophages; accumulation of well-differentiated phagocytic macrophages; tissue infiltration by T lymphocytes, monocytes, macrophages, and neutrophils; and upregulation of inflammatory mediators, including reactive oxygen species (ROS) and nitric oxide (NO). Cumulatively, these processes can eventually lead to organ failure and death.

Cytokine storms are associated with numerous infectious and non-infectious diseases, including influenza, COVID-19 [2,3], Middle East respiratory syndrome (MERS-CoV), atypical pneumonia (SARS) [4], familial hemophagocytic syndrome, septicemia [5], systemic juvenile idiopathic arthritis, and lupus erythematosus, and can also be caused by certain immunological treatments such as chimeric antigen receptor (CAR)-T cell therapy. Indeed, clinical studies have found that most infectious diseases are not directly caused by pathogens but rather by cytokine storms associated with an overactivated immune response [6,7], which can lead to multiple organ dysfunction syndrome, thus defining disease severity [8]. Huang et al. [9] have reported that the levels of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-1RA, IL-7, IL-8, and IL-9, fibroblast growth factor (FGF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage

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colony-stimulating factor (GM-CSF), interferon (IFN)-γ, IFN-γ-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory proteins (MIP)1α and MIP1β, platelet-derived growth factor (PDGF), tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF) are significantly higher in the plasma of patients with COVID-19 than in healthy individuals. Furthermore, plasma concentrations of IL-2, IL-7, GS-CF, IP-10, MCP-1, MIP1α, and TNF-α in critically ill patients admitted to intensive care units were significantly higher than those in non-critical patients. Cytokine storms are a characteristic feature of sepsis, a severe clinical syndrome associated with acute infection, and it has been reported that plasma levels of TNF-α, IL-6, IL-1β, IL-1α, IL-12, IL-17, CXCL1, CXCL2, MCP-1, IL-8, CXCL10, GM-CSF, M-CSF, and G-CSF are markedly elevated in patients with sepsis [10]. A significant increase in IL-6, TNF-α, IL-8, and MCP-1 levels has also been observed in the plasma of patients with H1N1 influenza virus infection [11] and it has been shown that the use of immunomodulators to suppress the cytokine storm could effectively reduce mortality and organ damage in cases of acute influenza [12]. Therefore, targeting the cytokine storm can potentially prevent organ and system failure and suppress disease progression, particularly in critically ill patients (Fig. 1).

1.2. Characteristic cytokines and therapy of cytokine storms

Cytokines, the main players in the cytokine storm, are a group of small proteins secreted by cells for intercellular communication, which can act as immunomodulators regulating inflammatory responses after binding to their respective receptors. They can be divided into five categories: IFNs, ILs, chemokines, CSFs, and TNFs [13]. There are three types of IFNs, namely, type I (IFN-α and IFN-β), type II (IFN-γ), and type III (IFN-λ), which have antiviral and anticancer effects, inhibit cell proliferation, and regulate immunity [14,15]. Among these, IFN-λ is produced primarily by CD4 and CD8 T cells and promotes inflammatory reactions. ILs, which can be are divided into pro-inflammatory (IL-1β, IL-6, IL-12, and IL-17) and anti-inflammatory (IL-10) mediators [10], are the most important group of cytokines released during infection, which play roles in regulating the survival, activation, proliferation, differentiation, and migration of immune cells, thereby controlling inflammatory responses [16,17]. TNF-α and TNF-β, produced by macrophages and activated T cells, respectively, are key cytokines involved in response to acute viral infections, including influenza, dengue fever, and Ebola. However, the overexpression of these TNFs is also associated with the development of inflammation, fever, arthritis, and septicemia [18, 19]. Chemokines are a family of small cytokines divided into four categories (CXC, CC, C, and CX3C) [20] that can promote the migration of immune cells, such as neutrophils, monocytes, macrophages, and lymphocytes, from blood vessels to inflammatory sites [21,22]. CSFs stimulate the proliferation and differentiation of hematopoietic stem cells, which, according to their target, can be divided into various subtypes, such as macrophage CSF (M-CSF), granulocyte CSF (G-CSF), and granulocyte-macrophage (GM-CSF) that form part of the pro-inflammatory cytokine network and promote inflammation [23]. Cytokine storms caused by infectious agents such as influenza A virus are characterized by a significant increase in the secretion of pro-inflammatory cytokines, including IFN-λ, TNF-α, IL-1β, IL-2, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-18, IL-33, G-CSF, GM-CSF, VEGF-A, MCP-1 (CCL2), IP-10 (CXCL10), CXCL11, and MIP-1. It has been shown that when the innate immune system is activated by pathogens, IL-6 can be rapidly upregulated by up to 1000-fold compared with resting levels [1, 24–28]. TNFs, along with IL-1 family members such as IL-1β, are the first cytokines released during the cytokine storm, which can subsequently induce the secretion of other cytokines. IL-1β, for example, can upregulate the secretion of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IFN-γ, TNF, MCP-1, and PDGF. Consequently, high levels of TNF and IL-1 in circulation are considered to be initial markers of the occurrence of a cytokine storm [6,29] (Fig. 2).

At present, the treatment strategies for cytokine storms include glucocorticoids, peroxisome proliferation-activated receptor (PPAR) agonists, COX and TNF inhibitors, antioxidants, IL-1 and IL-6 antagonists, and suppressors of monocyte–macrophage recruitment and T cell activation [4,12]. In addition, there is convincing evidence to suggest that some Chinese herbal medicines also have strong immunosuppressive effects. For example, Shen Fu Injection, Re Du Ning Injection, and tetrandrine have been shown to significantly reduce the levels of IL-1β, IL-6, TNF-α, and IL-8 [30]. A further traditional Chinese medicine, Qiangzhi Decoction, has been reported to significantly reduce virus titers and attenuate the severity of cytokine storms associated with influenza A pneumonia by inhibiting the production of IFN-γ, IL-6, TNF-α, and intercellular adhesion molecule-1 (ICAM-1) [31]. Consequently, the use of certain traditional Chinese medicines has been considered beneficial in the treatment of critically ill patients suffering from cytokine storms, such as those observed in COVID-19 [30].

1.3. Scutellaria baicalensis and its active components

Scutellaria baicalensis Georgi., commonly referred to as Chinese

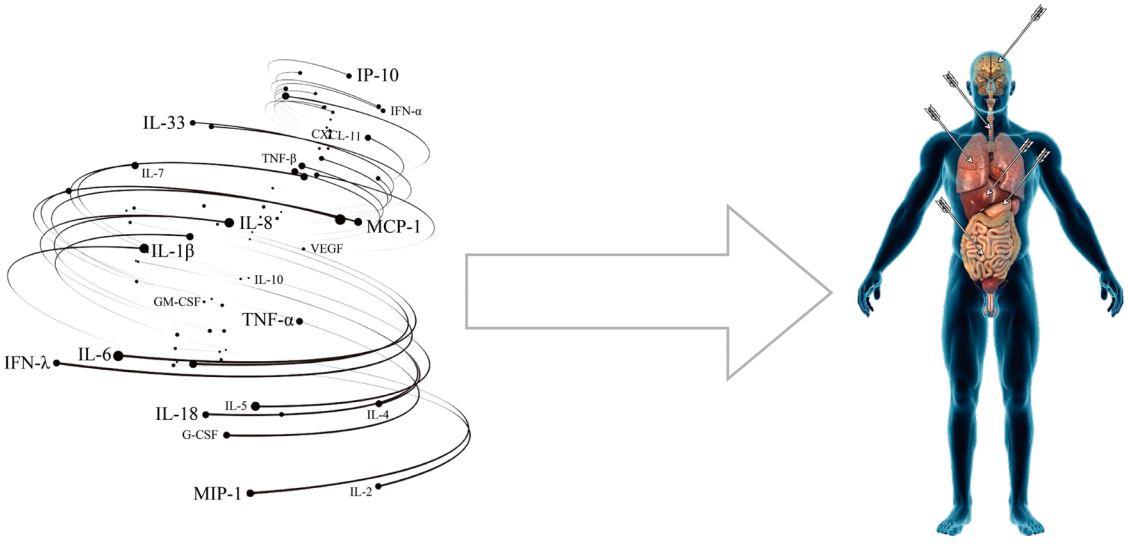

Fig. 1. The cytokine storm can lead to inflammatory damage to organ tissues, including those of the bronchi, lungs, kidneys, and intestines. The cytokine storm is also implicated in the occurrence of multiple organ dysfunction syndrome.

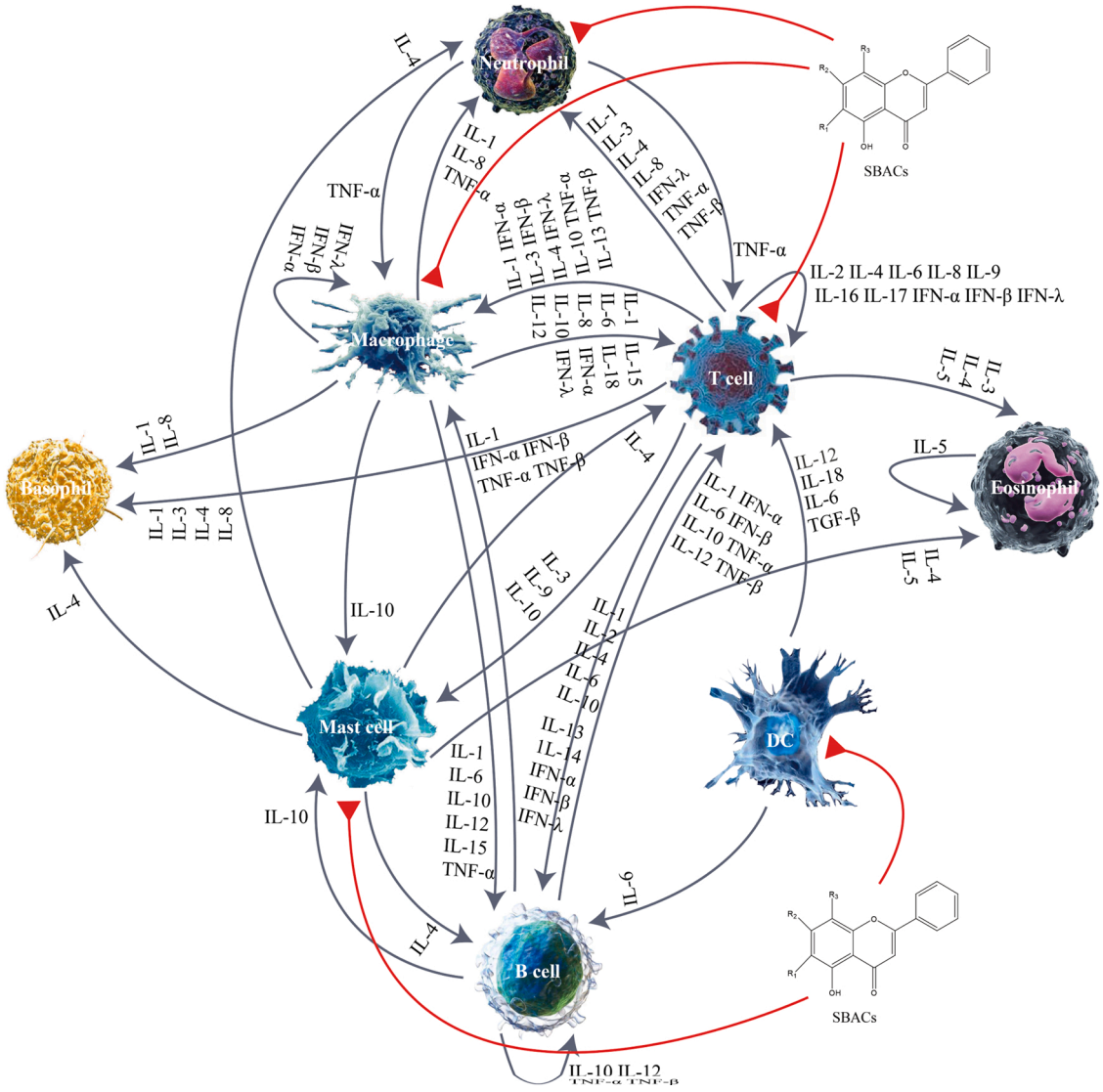

Fig. 2. Cytokines, the main players in the cytokine storm, are a group of small proteins mainly secreted by immune cells, which can act as immunomodulators that regulate inflammatory responses. *Scutellaria baicalensis* active components (SBACs) can act directly on immune cells such as lymphocytes, macrophages, mast cells, dendritic cells, monocytes, and neutrophils, and thereby inhibit the production of inflammatory cytokines. "→", promotion; "⟞", inhibition.

skullcap, which has been used as a medicinal plant in China for thousands of years, can promote a significant immunosuppressive effect by inhibiting the production of pro-inflammatory IL-1β, IL-18, and TNF-α, and is widely applied in the treatment of hepatitis, pneumonia, enteritis, allergic reactions, dysentery, colds, and respiratory infections. For example, Jung et al. have reported that an extract of *S. baicalensis* can significantly inhibit the passive cutaneous anaphylaxis reaction and histamine release [32]. In addition, the clinical application of baicalein aluminum capsules containing *S. baicalensis* as the main component has been found to be effective in the treatment of enteritis and dysentery since it was placed on the market in 1976, with effective rates of up to 97.27 % for acute and chronic enteritis and 93 % for bacillary dysentery.

Flavonoids such as baicalin (10.11 %), baicalein (5.41 %), wogonoside (3.55 %), wogonin (1.3 %), and oroxylin A are the main bioactive components extracted from the roots of *S. baicalensis* [33–36] (Fig. 3), and it has been reported that these compounds can promote immunosuppressive effects and be used to treat inflammatory diseases by regulating the levels of TNFs, ILs, chemokines, and other inflammatory mediators in vivo [37,38]. For example, baicalin has proved effective in the treatment of enteritis induced by deoxynivalenol by attenuating release of the cytokines IL-1β, IL-6, IL-8, IFN-γ, and TNF-α [39]. In combination with ribavirin, baicalein has also been shown to reduce pulmonary inflammation and significantly improve the survival rate of mice infected with H1N1 influenza virus [40]. Furthermore, wogonoside has been shown to improve lipopolysaccharide (LPS)-induced acute lung injury in mice by reducing lung infiltration of macrophages and neutrophils [41].

Although numerous previous studies have examined the effects of *S. baicalensis* active components (SBACs) on immune cells and cytokine secretion, the related reviews published to date have tended to focus on the anticancer [42,43], anti-inflammatory [44], antiviral, antibacterial, hepatoprotective [37], and neuroprotective [45] activities of these component, along with the relevant extraction and isolation methods [36]. There have, however, been no reviews that have sought to summarize the effects of SBACs on the cytokines that are typically associated with the cytokine storm. Accordingly, in this review, we present recent experimental data on SBAC activity in inhibiting the production of cytokines and other pro-inflammatory mediators characteristic of the cytokine storm and evaluate the underlying molecular mechanisms. Although to date there have been no reports describing the direct use of SBACs in the treatment of cytokine storms, we believe that the information presented in this review can provide a theoretical foundation for

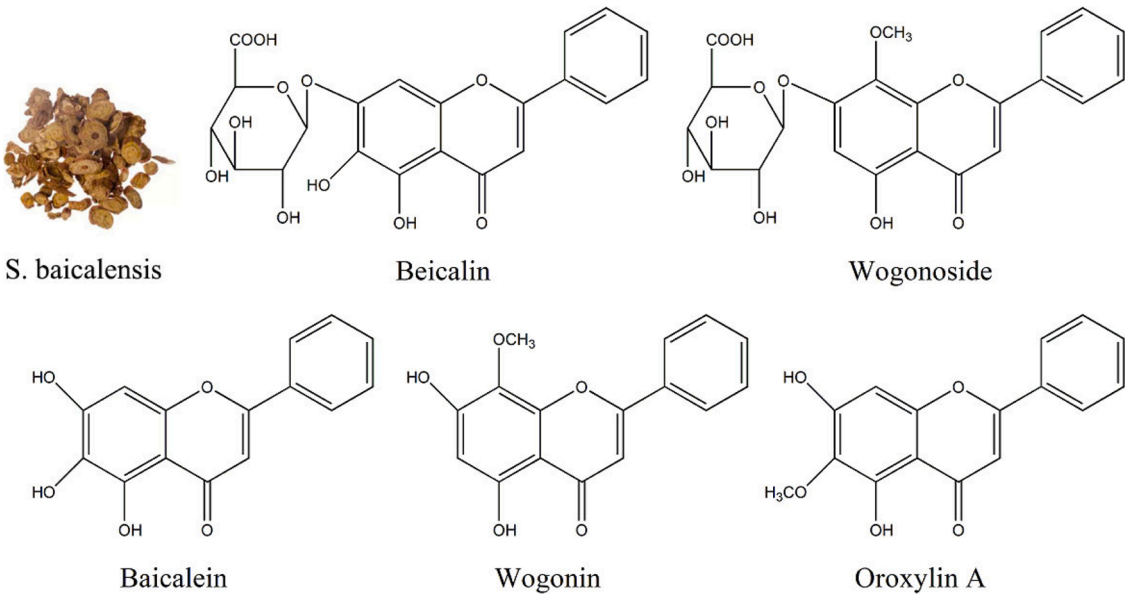

Fig. 3. The chemical structures of baicalein, baicalin, wogonin, wogonoside, and oroxylin A.

the future application of SBACs in treating cytokine storms and its destructive consequences, as well as providing directions for further research on the immunomodulatory properties of SBACs.

2. Effects of SBACs on immune cells

2.1. Macrophages

Macrophages are integral components of the innate immune system that reside in almost all human tissues, wherein they phagocytize pathogenic bacteria, aging and apoptotic cells, cell fragments, and tumor cells [46,47]. Macrophages also play important roles as antigen-presenting and cytokine-secreting cells that release a series of regulatory mediators with cytotoxic, pro-inflammatory, angiogenic, or fibrogenic effects. However, an imbalance in the expression or release of inflammatory mediators by these is known to cause cytokine storms, with subsequent tissue damage and the development of chronic diseases [48]. Depending on phenotype and function, macrophages can be divided into classical activated pro-inflammatory M1 macrophages and alternatively activated anti-inflammatory/wound repair M2 macrophages [48,49]. M1 macrophages produce a large number of pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, IL-18, IL-23, TNF-α, and IFN-γ, and chemokines, including CXCL1, CXCL3, CXCL5, CXCL8, CXCL9, CXCL10, CXCL11, CXCL13, CXCL16, CCL2, CCL3, CCL4, CCL5, CCL8, CCL15, CCL11, CCL19, CCL20, and CX3CL1 [50], as well as ROS and NO [51]. M2 macrophages produce the anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor (TGF)-β, and also secrete IL-13, IL-8, IL-1R, MCP-1β, IP-10, and MIP-1β, as well as the chemokines CCL1, CCL2, CCL13, CCL14, CCL17, CCL18, CCL22, CCL23, CCL24, and CCL26 [52–54]. Thus, macrophages secrete a diverse array of pro-inflammatory cytokines and chemokines that can potentially contribute to the development of cytokine storms (Fig. 4).

It has been shown that water extracts of *S. baicalensis* can significantly inhibit the production of IL-1β, IL-3, IL-6, IL-10, IL-12, IL-17, TNF-α, IP-10, keratinocyte-derived chemokine (KC), hypoxia-inducible factor-1α (HIF-1α), and VEGF, and reduce the expression of Cox-2 and iNOS in LPS-induced macrophages. Moreover, these extracts have been found to reduce the infiltration of macrophages into tissues [55,56]. Studies have also shown that baicalein not only inhibits the release of pro-inflammatory IL-1β, IL-6, and TNF-α by LPS-induced macrophages

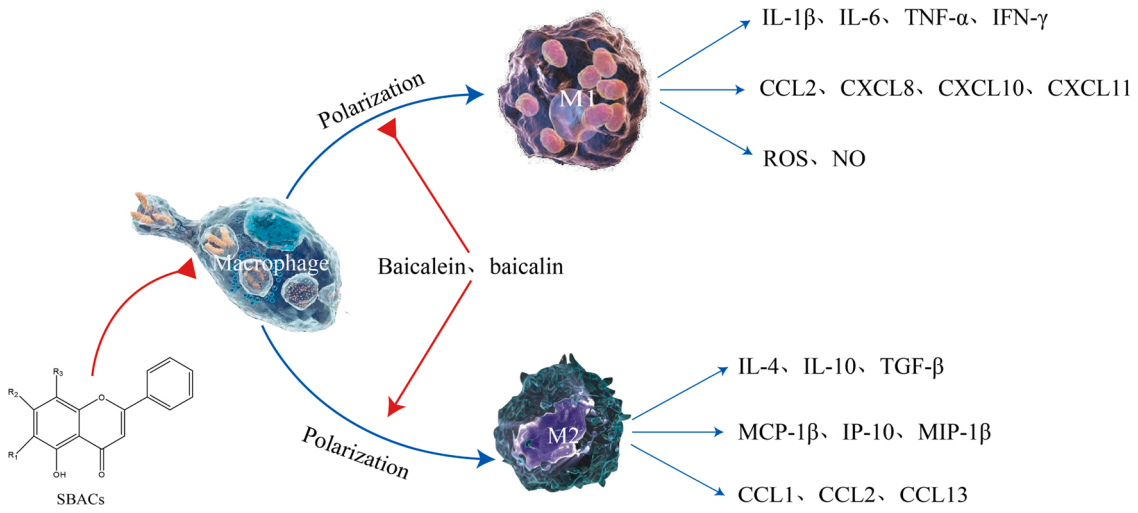

Fig. 4. The active components of *Scutellaria baicalensis* can inhibit the tissue infiltration of macrophages and the production of cytokines such as IL-1β, IL-6, IL-12, IL-17, TNF-α and IP-10 in macrophages. In addition, baicalein and baicalin can regulate the M1/M2 polarization of macrophages. "→", promotion; "⟞", inhibition.

[57] but also prevents macrophage infiltration into the kidneys [58], liver [59], brain, and other organs. Furthermore, it has been demonstrated that baicalein can dose-dependently inhibit the LPS-induced expression of iNOS and COX-2 in macrophages [60,61] and also reduce the production of NO and PGE_2 [89]. Baicalein can also downregulate IL-12 [62] and other pro-inflammatory mediators such as ROS, endothelin (ET)-1, and thromboxane A2 (TXA2), and increase the level of superoxide dismutase (SOD) in macrophages [63], and directly affects the polarization of macrophages by increasing the rate of M2/M1 polarization [64].

Similar to baicalein, baicalin can reduce NO release by downregulating the expression of iNOS in macrophages [65,66], and at a concentration of 50 μM inhibits the LPS-induced polarization of macrophages to the M1 phenotype, whilst inducing that to the M2 phenotype. It can also downregulate TNF-α, IL-23, and IFN regulatory factor (IRF5) and upregulate IL-10, arginase 1, and IRF4 [67]. A further study has reported that baicalin inhibits the production of ROS, ET-1, and TXA2, increases the expression of SOD, and inhibits macrophage activation, thereby alleviating endotoxic shock in mice [68]. Moreover, baicalin can downregulate the expression of macrophage migration inhibitor (MIF), MCP-1, and MIP-3α (CCL20) [69].

A further SBAC, wogonin, has been shown to inhibit the production of PGE_2 by LPS-induced macrophages via a dose-dependent downregulation of the expression and activity of COX-2 [70], and also reduces the production of NO by downregulating the expression of iNOS [71,72]. Wogonin has also been found to inhibit the production of NO and expression of IL-1α, IL-1β, IL-6, IL-10, IP-10, G-CSF, GM-CSF, LIF (IL-6 class cytokine), CXCL5, MCP-1, M-CSF, MIP-1α, MIP-1β, MIP-2, CCL5, TNF-α, and VEGF in macrophages activated by virus-mimicking double-stranded RNA [73,74]. Wogonoside has been demonstrated to inhibit the infiltration of macrophages and neutrophils in an LPS-induced model of acute lung injury [75] and also to reduce the production of NO and PGE_2 and expression of TNF-α, IL-6, iNOS, and COX-2 in RAW264.7 macrophages [76].

In polyinosinic-polycytidylic acid-induced RAW 264.7 macrophages, oroxylin A has been observed to significantly inhibit the production of the pro-inflammatory factors NO, IL-1α, IL-1β, IL-6, IL-10, IP-10, G-CSF, GM-CSF, LPS-induced CXC chemokine (LIX), MCP-1, MIP-1α, MIP-1β, MIP-2, TNF-α, and VEGF [77], and can also downregulate COX-2 and iNOS and enhance the expression of antioxidant enzymes such as HO-1 and NAD(P)H quinone oxidoreductase 1 (NQO1) [78,79]. Moreover, in LPS-treated macrophages, it has been reported that oroxylin A inhibits the expression of TNF-α, IL-1β, IL-6, iNOS, and COX-2 in an ER-dependent manner [80].

Collectively, the aforementioned observations clearly indicate that SBACs can effectively inhibit production of the initial markers (IL-1β, IL-6, and TNF-α) of the cytokine storm, which are secreted primarily by macrophages, and thus have the potential to reduce the severity this destructive immune response. In contrast to wogonin, wogonoside, and oroxylin A, baicalein and baicalin not only directly inhibit the production of cytokines in macrophages but also regulate the M1/M2 polarization of macrophages, and consequently have a stronger immunosuppressive effect.

2.2. Dendritic cells

Dendritic cells (DCs) are the most prominent and highly specific antigen-presenting immune cells distributed in multiple lymphoid and non-lymphoid tissues. Mature DCs secrete pro-inflammatory cytokines and costimulatory molecules, although have a comparatively limited ability to capture and present antigens [81]. Activated DCs of the cDC1 subtype produce large amounts of IL-12 and activate the Th1 cell-mediated inflammatory response, whereas cDC2 cells secrete substantial amounts of chemokines such as CCL5, CCL3 (MIP-1α), and CCL4 (MIP-1β) [82,83].

It has been shown that in LPS-activated DCs, baicalin can significantly downregulate the production of IL-12 and surface costimulatory molecules such as CD80 and CD86, along with major histocompatibility complex (MHC)-I and MHC-II, and can also upregulate the antigen uptake ability of DCs, thereby indicating the inhibition of DC maturation, which results in a reduction in DC-dependent $CD4^+$ T cell activation and differentiation into Th1 lymphocytes [84]. Baicalin has also been reported to induce the apoptosis of immature DCs in dose- and time-dependent manners [85], reduce DC numbers, and inhibit their maturation in the bone marrow [86]. Although unlike macrophages, DCs do not directly secrete the different cytokines that contribute to the development of cytokine storms, they do play an important role in the activation of lymphocytes, particularly with respect to the Th1 immune response, and the production of related cytokines. Accordingly, we speculate that baicalin can indirectly reduce T lymphocyte activation and inhibit the production of cytokine storm-specific cytokines related to Th1, such as IFN-λ, IL-2, and TNF-α, by inhibiting the maturation of DCs. Apart from baicalin, however, there have been no reports on the effects of other SBACs on DCs.

2.3. Mast cells

Mast cells (MCs) are immune cells that differentiate from hematopoietic stem cells [87] in response to IL-9 and stem cell factor (SCF), which promote the proliferation and differentiation of MC progenitors [88]. MCs can be found in most tissues, including those of the stomach, colon, lymph nodes, brain, heart, and lungs [89,90], and have different phenotypes depending on their tissue location, with mucosal and connective tissue MCs being the two main types [91,92]. MCs express MHC-I and MHC-II, process bacterial antigens and present these to T lymphocytes [93,94], and secrete histamine, 5-hydroxytryptamine, kinin, MCP protease, LTs, PGs, platelet-activating factor, VEGF, chemokines, helper stimulating molecule OX40 L, GM-CSF, TNF-α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-13, and other cytokines [95–97].

It has been shown that an extract of *S. baicalensis* and its main constituent flavonoids baicalein, wogonin, baicalin, and oroxylin A, can inhibit the degranulation of MCs and their production of histamine and pro-inflammatory cytokines [98–101]. Baicalein has been found to significantly inhibit the release of LTs, PGD_2, and GM-CSF in MCs [102], and to dose-dependently reduce the expression of IL-6, IL-8, and MCP-1 in the HMC-1 human MC line activated by IL-1β or TNF-α [103,104]. Baicalin can also inhibit the release of histamine, trypsin, and hexosaminase from MCs, as well as MC production of the pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α [105,106]. It can accordingly be speculated that baicalein and baicalin inhibit development of the cytokine storm and attenuate the allergic reactions caused by such storms by reducing the production of characteristic cytokines and inflammatory mediators in MCs. To date, however, the effects of wogonin, wogonoside, and oroxylin A on MCs have yet to be studied in vitro.

2.4. Monocytes and neutrophils

Similar to macrophages, DCs, and MCs, monocytes and neutrophils are derived from myeloid progenitor cells in the bone marrow and perform phagocytic and antigen-presenting functions. Upon infection, monocytes not only directly participate in the immune response but also invade the affected tissues and differentiate into macrophages and DCs [107,1–109]. Activated monocytes release pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α and the chemokine CCL2 [110], as well as the anti-inflammatory cytokine IL-10 and ROS [111,112]. Neutrophils, also known as polymorphonuclear leukocytes, are terminally differentiated cells representing the largest group of leukocytes that can directly target pathogens [113,114]. They have chemotactic, phagocytic, and bactericidal properties and can attack pathogens via degranulation, release of antimicrobial peptides (such as centrocyte elastase NE), MPO, matrix metalloproteinases, and ROS [115], as well as by secreting cytokines such as IL-1α, IL-1β, TNF-α, IL-8, and IL-12β [116,

117].

Baicalein has been found to inhibit the respiratory burst activity of neutrophils and their production of ROS [118], and can also suppress the accumulation of ROS in monocytes [119]. In both neutrophils and monocytes activated by *N* -formyl-methionyl-leucyl-phenylalanine (FMLP) or phorbol 12-myristate 13-acetate (PMA), baicalein and baicalin have been shown to effectively prevent the assembly of NADPH oxidase and inhibit the activity of MPO, and can also downregulate the expression of cell surface adhesion factor Mac-1 (CD11b/CD18), thereby reducing neutrophil adhesion. Compared with baicalin, however, the inhibitory effects of baicalein on neutrophils and monocytes have been found to be considerably stronger [120].

Wogonin and wogonoside have also been shown to be effective in suppressing the inflammatory activity of neutrophils via inhibition of their infiltration into the respiratory tract [121], lungs [41,122], and other organs [123], whereas oroxylin A can significantly downregulate IL-6 secretion in LPS-induced THP-1 human monocytes [124]. In addition, given that in response to infection, monocytes and neutrophils can migrate to the site of infection, thereby promoting the occurrence of local cytokine storms, we speculate that SBACs can attenuate the severity of these storms by inhibiting the chemotaxis of monocytes and neutrophils and their production of cytokines.

2.5. Microglia

Microglia are resident macrophages in the brain and the most important immune cells in the central nervous system [125]. These cells play protective roles, safeguarding the integrity of cerebral neurons via immune surveillance, phagocytosis, antigen presentation, and secretion of cytokines. However, when overactivated, microglia secrete excessive amounts of pro-inflammatory mediators such as NO, ROS, IL-6, TNF-α, and CCL-2 [126].

In microglia activated by LPS or hypoxia, baicalein has been shown to significantly downregulate the levels of pro-inflammatory factors such as NO, ROS, IL-6, TNF-α, and COX-2, thereby protecting cerebral neurons from inflammation-related damage [126–129]. Baicalein has been demonstrated to inhibit the activation of nuclear factor IL-6 (NF-IL6), which has the effects of reducing the expression of iNOS and release of NO in microglia induced by endotoxin/cytokines, and thus attenuating microglial activation [130]. It has also been reported that baicalein selectively downregulates the activity of 12/15-lipoxygenase (12/15-LOX) and production of inflammatory mediators, such as 12-hydroxyeicosatetraenoic acid (12-HETE), 15-HETE, and 13-hydroxyoctadecadienoic acid (13-HODE), and reduces the expression of pro-inflammatory IL-1β, IL-12p40, CCL3, CXCL10, and CCL20 in microglia [131]. Similarly to baicalein, oroxylin A can dose-dependently downregulate the expression of iNOS and release of NO and prevent the upregulation of IL-1β and IL-6 in LPS-induced microglia [132], and has also been found to inhibit the activation and infiltration of microglia in a rat optic nerve comminution model [133].

Baicalin can reduce the activation and proliferation of BV-2 microglia induced by β-amyloid peptide, and also reduces the secretion of the pro-inflammatory mediators IL-6, TNF-α, and NO [134]. Furthermore, in LPS-activated microglia, baicalin has been observed to significantly reduce the secretion of IL-1β, IL-6, and IL-18 and the expression of iNOS [135,136]. Similar effects have been reported for wogonin, which has been shown to downregulate the expression of iNOS and COX-2 and production of the pro-inflammatory mediators IL-1β, IL-6, TNF-α, MCP-1, PGE_2, and NO, and inhibits the migration of LPS-activated microglia [125,137–140]. However, it has yet to be established whether wogonoside has similar inhibitory effects on the activation of microglia.

Accumulating evidence indicates that SBACs can attenuate local cytokine storms in the brain by inhibiting the production of characteristic cytokines, and protecting cerebral neurons from inflammatory injury caused by activated microglia, thereby indicating their potential in the treatment of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.

2.6. T lymphocytes

The immune system consists of both innate and acquired immune mechanisms, the latter of which is dependent on the activity of T and B lymphocytes, which express antigen receptors that recognize pathogen-associated molecules. However, deregulation of adaptive immune mechanisms can lead to self-antigen recognition and autoimmunity. CD4 T lymphocytes play a key role in autoimmune inflammation by promoting the secretion of antibodies by B cells, enhancing and maintaining the immune response of CD8 T lymphocytes, and regulating the function of macrophages. Upon stimulation by antigens and cytokines (such as IL-12), naive CD4 T cells differentiate into T helper (Th) cells (Th1, Th2, Th9, and Th17) and regulatory (Treg) cells [141]. Th cells and the cytokines they secrete play an important role in the development of cytokine storms.

IL-12-stimulated CD4 T cells differentiate into Th1 cells, which secrete large amounts of IFN-λ, IL-2, and TNF-α [142]. Th1 cells play an important role in immune defense against intracellular pathogens and are also implicated in the development of autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis [143]. Th2 cells, which mainly secrete IL-4, IL-5, IL-13, and TNF-α and, to a lesser extent, IL-2 and IL-9, define the immunity developed against extracellular organisms [144]. Th9 cells, activated by TGF-β and IL-4, produce large amounts of IL-9 and IL-10 [145] and play an important role in allergic inflammation of the respiratory tract [146], whereas Th17 cells, which differentiate from naïve CD4 cells stimulated by TGF-β and IL-9, mainly secrete IL-9, IL-17A, IL-17 F, IL-21, and IL-22 [147]. Studies have shown that Th1 and Th17 are involved in the development of autoimmune encephalomyelitis [148] and myocardial fibrosis [149]. Treg cells can inhibit the functions of other immune cells, including CD4 and CD8 T cells, natural killer cells, and B cells, and perform a range of regulatory functions involving cell–cell contact, release of cytokines (TGF-β or IL-10), and the production of inhibitory metabolites (such as adenosine) [150] (Fig. 5).

2.6.1. Apoptosis of activated T lymphocytes

It has been shown that baicalein can selectively promote the apoptosis of concanavalin (ConA)-activated $CD3^+$ splenocytes, LPS-activated $CD19^+$ splenocytes, and phorbol/ionomycin-activated Jurkat T cells, which correspond to the loss of mitochondrial membrane potential, cytochrome *C* release from mitochondria, an increase of the Bcl-2/Bax ratio, and activation of caspase-9 and caspase-3. Following intraperitoneal injection of baicalein (100 mg/kg), mice with ConA-induced autoimmune hepatitis showed a significant reduction in lymphocyte infiltration in the liver, reductions in serum ALT, IFN-λ, and TNF-α, and improved liver status [151]. Similar results have been reported in a further study, in which baicalin was observed to induce the apoptosis of Jurkat T cells via the mitochondrial pathway, involving caspase-3 activation, ROS production, cytochrome *C* release, and the disturbance of mitochondrial membrane potential [152]. Apoptosis-promoting activity in T cells has also been observed in response to treatment with wogonin, which was found to inhibit the growth of human T cells in an in vivo model of xenotransplantation leukemia [153]. Similarly, wogonoside has been found to suppress the growth of T lymphoblastic leukemia MOLT-3 cells and Jurkat cells by promoting apoptosis [154].

2.6.2. T cell proliferation and infiltration

It has been shown that baicalein can inhibit the ConA-induced activation and proliferation of T lymphocytes and their secretion of IL-2, IL-4, IL-6, and IFN-λ [155]. Baicalin has been found to promote the proliferation of $CD4^+CD29^+$ T cells in patients with ulcerative colitis [156], although inhibits that of T cells induced by staphylococcal exotoxin

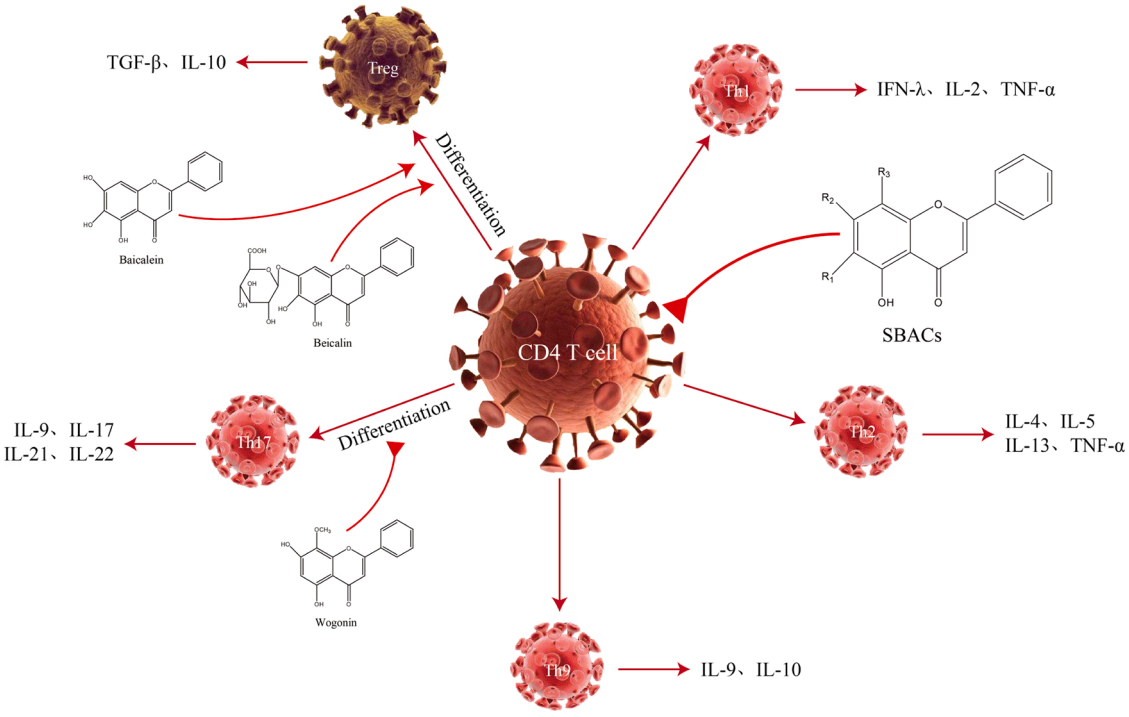

Fig. 5. Naïve CD4 T cells can differentiate into various effector and regulatory subsets. The active components of *Scutellaria baicalensis* can inhibit the production of T cell-related cytokines such as IL-2, IL-4, IL-5, IL-6, IL-12, IL-13, IL-17, TNF-α, and IFN- λ. In addition, baicalein and baicalin can inhibit the tissue infiltration of T lymphocytes and induce the differentiation of initial CD4 + T cells into Treg cells. Furthermore, wogonin can inhibit the differentiation of initial T cells into Th17 cells. "→", promotion; "⟞", inhibition.

[157] and attenuates the infiltration of CD4 and CD8 T lymphocytes in the lungs caused by respiratory syncytial virus infection [158].

2.6.3. T lymphocyte differentiation and cytokine secretion

In a mouse model of food allergy, oral administration of baicalein (20 mg/kg) was shown to reduce serum levels of effector T cells and IgE, and the production of Th2 (IL-4, IL-5, IL-10, IL-13), Th1 (IFN-γ, IL-12), and Th17 (IL-17) cytokines in mesenteric lymph node lymphocytes, whilst increasing the levels of Treg-related TGF-β [159]. In the same study, the findings of in vitro experiments showed that baicalein induced the differentiation of CD4 T cells into Treg cells via an aromatic hydrocarbon receptor and promoted the expression of granzyme B (inducer of effector T cell death), CTLA-4/TGF-β (blocker of T cell activation), and Foxp3, while inhibiting the proliferation of effector T cells. Similar results were obtained in a further study, in which baicalin was shown to promote the differentiation and regulatory activity of Treg cells and induce the surface expression of Foxp3 [160].

Wogonin has been reported to inhibit T cell differentiation into Th17 cells [121] and the activity of TGF-β1-induced Treg cells and their secretion of IL-10 [161]. Similarly, oroxylin A has been found to inhibit the proliferation and activity of Treg cells by reducing T cell sensitivity to TGF-β1 [162].

Although the studies conducted to date have indicated that baicalein, baicalin, wogonin, and wogonoside can all promote T cell apoptosis, the in vitro experiments conducted with baicalin, wogonin, and wogonoside were performed using tumor cell line T cells, and accordingly, the results obtained may not reflect the effects of these compounds on normal T cells. In contrast, the studies conducted to date on baicalein have tended to be more comprehensive, and have indicated that whereas baicalein can selectively promote the apoptosis of activated T cells, it has no effect on the initial T cells, thus indicating the safety of its immunosuppressive effects and that it would not have excessively detrimental effects on the immune system. In addition, unlike wogonin and oroxylin A, which have been found to significantly inhibit the proliferation and immune activity of Treg cells, baicalein and baicalin not only promote a significant differentiation of CD4 T cells into Treg cells, but also promote the production of TGF-β. Therefore, we believe that compared with wogonin, wogonoside, and oroxylin A, baicalein and baicalin have stronger inhibitory effects on the immune activity of Th cells and production of inflammatory cytokines, and accordingly have a greater potential to inhibit the development of cytokine storms.

3. Other cells involved in inflammation

In addition to professional immune cells, some types of epithelial cells (e.g., respiratory, pulmonary, intestinal, breast, and retinal pigment) can also participate in local cytokine storms and inflammatory reactions by releasing immunomodulatory factors. For example, pulmonary epithelial cells secrete cytokines and chemokines, such as CCL20, GM-CSF, TGF-β1, IL-33, and CXCL5, which promote the recruitment and activation of multiple immune cells, causing allergic and inflammatory reactions [163], whereas intestinal epithelial cells can be induced by TNF-α or bacteria to secrete the pro-inflammatory cytokines IL-8 and IL-1β [164].

Among SBACs, baicalin and wogonin have been shown to inhibit pro-inflammatory cytokine production in different types of epithelial cells. Baicalin can significantly downregulate the expression and secretion of IL-6, IL-8, and TNF-α in HBE16 respiratory epithelial cells induced by LPS [165]. Similarly, baicalin has been reported to reduce the production of TNF-α and IL-1 in bovine mammary epithelial cells stimulated by LPS [166], whereas wogonin has been shown to downregulate PMA-induced COX-2 expression in pulmonary epithelial cells, thereby inhibiting the production of PGs and other inflammatory mediators [167]. It has also been shown that Wogonin can attenuate downregulation of the tight junction proteins claudin-1 and ZO-1 and the upregulation of IL-1β, IL-6, IL-8, COX-2, and iNOS induced by LPS in Caco-2 intestinal epithelial cells [168].

4. Molecular mechanisms of SBAC immunomodulatory activity

4.1. Inhibition of arachidonic acid metabolism

Arachidonic acid is an omega-6 polyunsaturated fatty acid that is incorporated into the structural membrane phospholipids or fat particles of immune cells [169]. The arachidonic acid released from phospholipids by the activity of phospholipases PLA2, PLC, and PLD [170,171] can be metabolized by COX, LOX, cytochrome P450, and cannabinoids to yield biologically active molecules that can regulate inflammation and immunity. COX-1 and COX-2 can convert arachidonic acid into PGG2 and PGH2, which are subsequently metabolized to bioactive PGs and thromboxanes via the activity of PG synthases. Various LOX enzymes can metabolize arachidonic acid to produce LTs, lipoxygenin, and 12/15-HPETE [172–174]. SBACs have been shown to reduce the production of arachidonic acid-derived inflammatory mediators by inhibiting the activity and expression of COX-2 and LOX.

Baicalein has been reported to inhibit the expression of COX-2 in BV-2 microglia, RAW 264.7 macrophages, and lung tissue [66,126,175], as well as the synthesis of LTC_4 in lymphocytes [176] and that of LTB_4 and LTC_4 in polymorphonuclear leukocytes [177]. Wogonin inhibits the expression and activity of COX-2 and the production of PGE_2 in macrophages [178–181], and in the treatment of radiation-induced injuries of the stomach and skin, wogonin has also been observed to downregulate the expression of COX-2 and 5S-HETE production [182,183]. Similarly, oroxylin A has been shown to inhibit COX-2 expression and reduce the synthesis of PGE_2 in LPS-induced macrophages [78,79]. Furthermore, baicalin can selectively inhibit the activity of platelet LOX [184] and 5-LOX and reduce production of the 5-LOX metabolite LT [185,186]. Baicalin has also been shown to inhibit the expression of COX-2 in rats with brain injury [187,188], and found to have significant anti-depressant activity in mice with mild chronic stress by inhibiting COX-2 expression and activity and reducing PGE_2 levels in the frontal cortex and hippocampus [189]. Similarly, the downregulation of COX-2 by wogonoside was observed to be associated with a reduction in the production of PGE_2 in LPS-activated macrophages [76].

4.2. Inhibition of TLR signaling

The TLR family comprises 10 transmembrane receptors (TLR1–10) that are located on the surface of immune and epithelial cells. TLRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), such as bacterial diacylated lipopeptide/lipoteichoic acid, bacterial lipopeptides, LPS, and bacterial flagellin, ssRNA, dsRNA, and dsDNA [190]. Upon ligand binding, TLRs recruit intracellular myeloid differentiation factor (MyD88), which in turn recruits IL-1 receptor-related kinase (IRAK) and TNF receptor-related kinase (TRAF6), thereby activating NF-κB and MAPK signaling and enhancing the expression of pro-inflammatory cytokines and chemokines [191–193]. Accumulating evidence indicates that the anti-inflammatory effects of SBACs are mediated via the regulation of TLR-dependent signaling mechanisms.

In LPS-induced models of inflammation, baicalein has been shown to bind directly to MD2, thereby effectively suppressing the activation of TLR4-MD2 and TLR4/MyD88 signaling, and thus reducing serum levels of IL-6 and TNF-α. Baicalein has also been found to inhibit the expression of TLR4 in an LPS-induced model of mastitis, which resulted in a reduction in TNF-α and IL-1β expression [194]. Furthermore, in a mouse model of allergy, baicalein was found to reduce TLR2 expression and the levels of IL-4 and IL-13, and suppressed the infiltration of eosinophils into the respiratory tract [195]. Baicalein can also inhibit the expression of TLR3, TLR6, and TLR9 in mice with monocrotaline-induced sinusoid obstruction syndrome [196].

Baicalin has been shown to alleviate experimental colitis, hepatitis, and ischemia-reperfusion liver injury by downregulating the expression of TLR4 and MyD88, which had the effect of reducing levels of the pro-inflammatory mediators iNOS, COX-2, IL-1β, and IL-18 [136,197–200]. Orally administered baicalin has also been found to significantly reduce lung inflammatory responses in mice infected with H1N1 influenza virus by downregulating the expression of TLR7 and activating protein 1 (AP-1) [201], whereas in a mouse model of periodontitis, baicalin was observed to reduce the levels of TNF-α, IL-1β, and MPO by inhibiting the expression of TLR2 and TLR4 [202].

Wogonin has been found to inhibit the expression of TLR4, MyD88, and TAK1 in LPS-induced Caco-2 cells, thereby downregulating the production of inflammatory mediators [203]. A further study using a model of traumatic brain injury reported similar results, indicating that wogonin can inhibit the expression of IL-1β, IL-6, MIP-2, and COX-2 via regulation of the TLR4/NF-kB pathway, which reduces the infiltration of leukocytes and activation of microglia [204]. Furthermore, studies using models of acute liver and lung injury have revealed that wogonoside can significantly downregulate TLR4 expression, MPO activity, and the secretion of pro-inflammatory cytokines [205,206], whereas oroxylin A was found to promote similar effects in a model of acute liver injury induced by LPS/D-galactosamine; i.e., downregulation of TLR4 expression and activation of downstream NF-kB signaling, which inhibited TNF-α production [207].

4.3. Activation of the transcription factor Nrf2

Oxidative phosphorylation is the main source of ATP in aerobic organisms, which is inevitably accompanied by ROS production. However, excessive ROS accumulation induced by different stressors can result in oxidative damage to DNA, lipids, and proteins, and trigger inflammation, which can be prevented by the activity of the antioxidant defense system [208]. Nrf2, a member of the Cap'n'Collar (CNC) family of basic leucine zipper transcription factors, plays a key role in maintaining an intracellular redox balance. Although normally localized in the cytoplasm where it complexes with Keap1, in response to oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, wherein it binds to specific ARE promoters and induces the expression of genes encoding the antioxidant enzymes SOD, GST, HO-1, GPX-1, glutathione reductase (GR), and NQO1. Thus, Nrf2 is assumed to play an essential role in protecting cells against oxidative stress, inflammation, and apoptosis [209]. SBACs have been shown to induce the activation of Nrf2, thereby promoting the induction of antioxidant defense mechanisms (Fig. 6).

It has been found that baicalein induces the expression of Nrf2, NQO1, and HO-1 in HepG2 cells and inhibits Nrf2 ubiquitination and proteasomal turnover, whilst stimulating the ubiquitination and modification of Keap1, which results in the enhanced nuclear translocation of Nrf2 and its binding to ARE promoters [210]. A further study similarly showed that baicalein inhibits the binding of Nrf2 to Keap1 [211]. By enhancing Nrf2 activation, baicalein triggers multiple anti-inflammatory mechanisms, including upregulation of the expression of GPX, NQO-1, SOD, CAT, and HO-1, and a reduction in levels of intracellular superoxide anion (the main ROS), which have the effects of reducing IL-1β and IL18 secretion [212,213].

Similarly to baicalein, baicalin has been found to activate Nrf2 by inducing its phosphorylation and inhibiting binding to Keap1, which enhances the expression of antioxidant enzymes and reduces ROS accumulation [214]. Moreover, baicalin can promote Nrf2 expression, reduce ROS, and alleviate cell injury induced by H_2O_2 [215]. Similar effects have been observed in LPS-induced acute lung injury, under which conditions, baicalin was found to enhance the expression of HO-1, SOD, and CAT, and reduce the levels of malondialdehyde (MDA), ROS, and other oxidation products via regulation of the Nrf2 pathway [216].

Wogonin has likewise been shown to enhance the nuclear translocation of Nrf2 by downregulating Keap1 expression and inhibiting the binding between Nrf2 and Keap1, thereby inducing Nrf2 transcriptional activity and enhancing the expression of HO-1, SOD2, NQO-1, and GCLC in HCT116 and THP-1 cells [217], rat nucleus pulposus cells [218], and

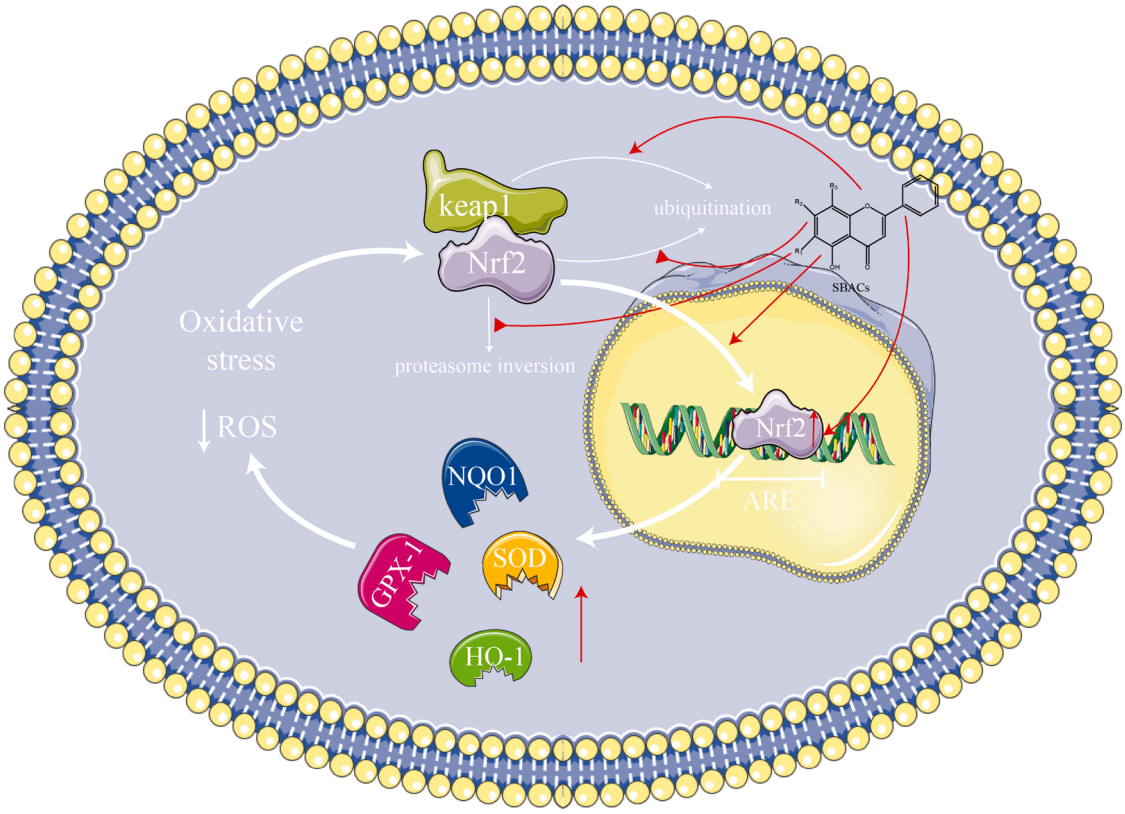

Fig. 6. The Nrf2 signal pathway plays a key role in maintaining intracellular redox balance. The active components of *Scutellaria baicalensis* can enhance activation of the Nrf2 antioxidant signal pathway by inhibiting the ubiquitination of Nrf2, inhibiting the proteasome inversion of Nrf2, increasing the expression of Nrf2, blocking the binding between Nrf2 and Keap1, stimulating the ubiquitination and modification of Keap1, down-regulating the expression of Keap1, enhancing the nuclear transfer of Nrf2, and enhancing the sequence binding activity of Nrf2 and ARE. Collectively, these activities contribute to enhancing the expression of downstream antioxidant genes, such as those encoding the proteins GPX, NQO-1, SOD, CAT, and HO-1. "→", promotion; "⟝", inhibition.

human chondrocytes [219]. In contrast, however, other studies have reported that wogonin inhibits the Nrf2 pathway by downregulating Nrf2 transcription and its binding to ARE promoters in human myeloid leukemia K562/A02 cells [220] and breast cancer MCF-7 cells [221], which reversed the resistance of cancer cells to chemotherapeutic drugs. Given these contrasting observations, we speculate that the opposite effects of wogonin on the Nrf2 signaling pathway in different cell types may be related to the unique physiological state of tumor cells. We hope that future studies will be able to shed light on the mechanisms underlying these differences.

Oroxylin A has been shown to significantly increase the expression and nuclear transfer of Nrf2 and its binding to ARE, resulting in the induction of target genes encoding HO-1 and NQO1 [78], and also inhibits Nrf2 ubiquitination and proteasomal degradation, thereby enhancing Nrf2/ARE transcriptional activity.

4.4. Inhibition of the thioredoxin (Trx) system

The Trx system, which consists of Trx reductase (TrxR), Trx, and NADPH, provides antioxidant defense against intracellular oxidative stress and plays an important role in DNA replication, transcription, and repair [222,223]. Moreover, the system is also implicated in the regulation of NF-κB expression and transactivation [155].

Baicalein has been shown to bind to the active site of TrxR and inhibit TrxR activity and Trx nuclear accumulation in mitogen-induced T lymphocytes, thereby reducing the secretion of IL-2, IL-4, IL-6, and IFN-λ, upregulating apoptotic signal-regulated kinase (ASK)-1, and inducing caspase-3 activity, which collectively contribute to promoting cell death in murine T cell lymphoma [224]. To date, however, there have been no studies that have examined whether baicalin, wogonin, wogonoside, or oroxylin A can also inhibit the thioredoxin system.

4.5. Inhibition of the MAPK, Akt, NF-κB, and JAK-STAT signaling pathways

The NF-κB transcription factor family consists of c-Rel, RelA, RelB, p50/p105, and p52/p100 proteins. In its inactive state, NF-κB is bound to the inhibitor IκB. However, in response to activation by external stimuli (stress, pathogens, and cytokines) via multiple pathways (TLRs, IL-1 receptor, TNF receptor, IL-1/TLR, and IL-17 receptor), IκB is degraded and NF-κB is released and translocated to the nucleus, wherein it regulates the transcription of target genes, including those encoding pro-inflammatory cytokines, chemokines, immune receptors, and cell surface adhesion molecules [225,226]. NF-κB is highly expressed in activated lymphocytes and tumor cells, in which it controls cell survival, proliferation, and apoptosis [227]. NF-κB is accordingly considered to be a key regulator of immune activity and inflammation.

The MAPK family members extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 regulate multiple cellular processes, including gene expression, mitosis, and cell survival, apoptosis, metabolism, and differentiation [228,229]. MAPK signaling pathways are known to activate the transcriptional activity of NF-κB [230,231]. The transcriptional activator STAT is phosphorylated by Janus kinase (JAK) and after dimerization is translocated to the nucleus, wherein it regulates the expression of target genes. The JAK/STAT signaling pathway is activated by multiple cytokines and growth factors, including IL-2~7, GM-CSF, growth hormone (GH), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and IFNs [232], and is involved in the control of cell proliferation, apoptosis, immune responses, and inflammation [233].

SBACs have been shown to regulate these key signaling mechanisms in immune cells, which may account for their anti-inflammatory effects (Fig. 7).

It has been reported that in an LPS-induced mouse mastitis model, oral administration of 20 mg/kg baicalein significantly inhibited NF-κB–p65 phosphorylation and IκBα degradation, and reduced the phosphorylation-dependent activation of p38, ERK, and JNK, thereby resulting in a suppression of inflammation [234]. By inhibiting NF-κB and MAPK signaling, baicalein reduces the expression of TNF-α, IL-1β, IL-6, IL-8, MCP-1, iNOS, COX-2, PGE2, MMP-9, and VEGF [103, 235–241]. It has also been reported that in LPS-induced RAW264.7 macrophages, baicalein significantly reduces the phosphorylation of STAT1, STAT3, JAK1, and JAK2 and inhibits STAT1 and STAT3 nuclear transfer, which has the effect of downregulating iNOS expression, NO and ROS production, and secretion of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 [242].

Furthermore, in a cigarette smoke-induced model of chronic obstructive pulmonary disease, baicalin was shown to block NF-κB signaling by inhibiting NF-κB–p65 phosphorylation, IκB-α degradation, and the binding of NF-κB to DNA, which resulted in the reduced expression of IL-8, IL-6, and TNF-α [243]. Baicalin has also been found to reduce the phosphorylation of p38, JNK, and ERK in mice with *Staphylococcus aureus*-induced mastitis, thereby reducing the expression of TNF-α, IL-1β, and IL-6 [244], whereas in BV2 microglia induced by β-amyloid peptide, baicalin was shown to regulate JAK2/STAT3 signaling by inhibiting JAK2 and STAT3 phosphorylation, which promoted a reduction in the secretion of IL-6, TNF-α, and NO [134].

In a model of traumatic brain injury, wogonin was found to reduce

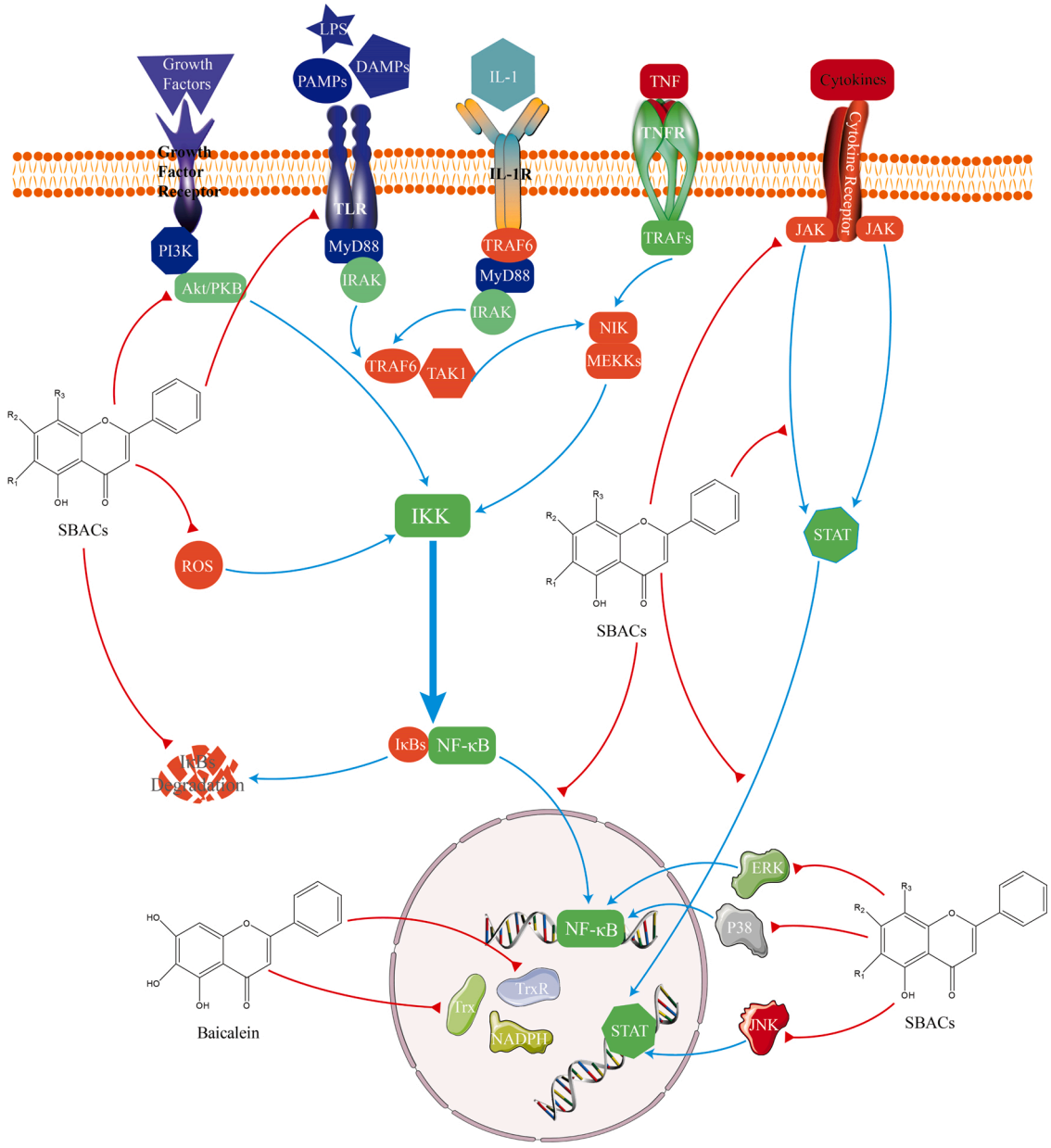

Fig. 7. The active components of *Scutellaria baicalensis* (SBACs) can inhibit activation of the NF-κB signal pathway by reducing the degradation of IκB and the nuclear translocation of NF-κB protein. These active components can also bind directly to TLR4-MD2, inhibit the expression of TLR, and reduce oxidative stress, thereby inhibiting the activation of NF-κB and the expression of downstream pro-inflammatory cytokines. Moreover, baicalein can attenuate the transcriptional activity of NF-κB by inhibiting the thioredoxin system. In addition, SBACs can block the MAPK signal pathway by inhibiting the phosphorylation of MAPK proteins such as ERK, JNK, and p38. Similarly SBACs can block the JAK-STAT signal pathway by inhibiting the phosphorylation of JAK and STAT and the nuclear transfer of STAT, thereby inhibiting the production of downstream inflammatory mediators such as iNOS, COX-2, TNF-α, IL-1β, and IL-6. "→", promotion; "⟞", inhibition.

the levels of IL-1β, IL-6, MIP-2, and COX-2 by inhibiting TLR4 expression, NF-kB nuclear translocation, and NF-kB binding to DNA, thereby alleviating the inflammatory response mediated by the TLR4/NF-kB pathway [245]. It has also been observed that wogonin can inhibit the phosphorylation of the MAPK members p38, ERK, and JNK in acute lung injury, which had the effect of downregulating iNOS and COX-2 [246]. In LPS/INF-λ-activated BV2 microglia, wogonin was similarly found to inhibit the phosphorylation of JAK-1, JAK-2, JAK-3, tyrosine kinase 2 (Tyk-2), STAT1, and STAT3, and thus block JAK-STAT signaling and reduce the production of pro-inflammatory IL-6 and TNF-α [247].

In rats with spinal injury and mice with inflammatory bowel disease, treatment with wogonoside has been found to reduce the levels of IL-1β, TNF-α, and IL-6 by inhibiting activation of the NF-κB pathway, thereby reducing inflammation [248,249]. Wogonoside has also been demonstrated to downregulate the phosphorylation of JNK, ERK, and p38, and activation of the MAPK pathway, and inhibit angiogenesis induced by LPS [250], and can reduce the expression of IL-1β, IL-6, and TNF-α by inhibiting MAPK-mediated signaling [251].

In LPS-stimulated THP-1 human mononuclear cells, oroxylin A has been shown to inhibit the phosphorylation of IκBα and IKKα/β and the nuclear translocation of NF-κB p65, thereby reducing the production of IL-6 [124]. Furthermore, by inhibiting the activation of NF-kB activation, oroxylin A reduced the levels of IL-4, IL-5, IL-13, TNF-α, iNOS, COX-2, PGE_2, and NO in RAW264.7 macrophages [79] and mice with acute lung injury [252]. It has also been shown that oroxylin A can inhibit JNK, p38, and ERK phosphorylation, and in so doing, suppress activation of the MAPK pathway [253].

4.6. Inflammasome

Inflammasomes are large multimolecular complexes that control the activation of caspase-1, which in turn regulates the maturation of IL-1β and IL-18. IL-1β is a pro-inflammatory cytokine that can cause local and systemic inflammation, as well as a febrile response to infection or injury, whereas IL-18 induces the production of other cytokines, including IFN-γ, IL-13, IL-4, and IL-8, and the lymphokines Th1 and Th2. Four types of inflammasome have been identified according to their Nod (nucleotide oligomerization domain)-like receptors (NLRs), namely, NLRP1, NLRC4, NLRP3, and AIM, and these function as key mediators of inflammasome activation via the recognition of PAMPs and DAMPs. NLRP3-type inflammasomes are activated by microbial derivatives, bacterial porotoxins, influenza virus RNA, extracellular ATP, and other PAMPs, and are also sensitive to ROS, autophagy, endoplasmic reticulum stress, virions, and the flow rates of K^+, H^+, and Ca^{2+} [29,254,255] (Fig. 8).

Baicalein has been shown to inhibit NLRP3 inflammasome activation and IL-1β maturation by downregulating the expression of NLRP3, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), and caspase-1 in LPS-stimulated and ATP-activated THP-1 human macrophages [256], microglia [257], and rat brains with acrolein-induced neurodegeneration [258]. Similarly, baicalin can suppress the activation of NLRP3 inflammasome-mediated signaling by inhibiting the expression of NLRP3, caspase-1, and NOD2, which reduces the secretion of IL-1β and IL-18 in LPS-stimulated porcine mononuclear phagocytes [259,260], palmitic acid-induced AML-12 hepatocytes [261] and LPS/Aβ-stimulated BV2 microglia [262].

Wogonoside has also been found to downregulate the expression of cleaved caspase-1, cleaved IL-1β, NLRP3, and ASC, inhibit the activation of NLRP3 inflammasomes, and reduce the production of IL-1β and IL-18 in the colon of mice with DSS-induced colitis [249]. Similar activity has been reported for oroxylin A, which has been observed to significantly reduce the expression of NLRP3 and caspase-1 in intestinal mucosa and inhibit the activation of NLRP3 inflammasomes, thereby reducing IL-1β secretion and alleviating experimental colitis in mice [263]. It has also been found that oroxylin A can inhibit NLRP3 inflammasome activation by reducing ROS accumulation, which has the effect of diminishing the inflammatory necrosis of stem cells [264].

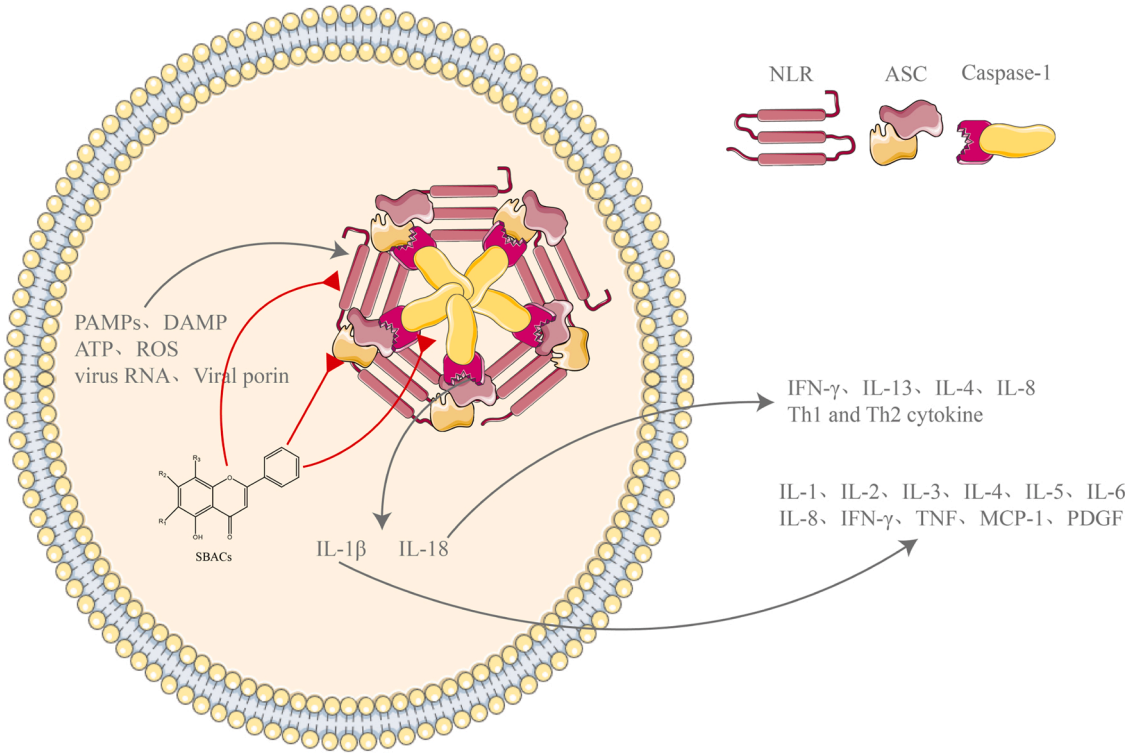

Fig. 8. Inflammasomes regulate the maturation of IL-1β and IL-18. The active components of *Scutellaria baicalensis* can inhibit the activation of NLRP3-type inflammasomes by down-regulating the protein levels of NLRP3, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and caspase-1, thereby inhibiting the maturation of IL-1β and IL-18 and reducing the production of secondary cytokines. "→", promotion; "⟞", inhibition.

4.7. PPARs

PPARs are ligand-activated transcription factors of the nuclear hormone receptor superfamily, which are ubiquitously expressed in the body. Upon activation by endogenous PGs and fatty acids, PPARs modulate the transcription of genes related to energy homeostasis. They can be divided into three subfamilies, namely, PPAR-α, PPAR-β/δ, and PPAR-γ, of which PPAR-α and PPAR-γ play important roles in lipid and glucose metabolism, respectively, whereas PPAR-β is implicated in the regulation of glucose metabolism and fatty acid oxidation [265]. It has been established that PPARs can repress the transcription of numerous inflammation-related genes, including NF-κB, AP-1, activated T nuclear factor (NFAT), and STAT. Furthermore, PPAR-α and PPAR-β/δ not only inhibit the NF-κB pathway by upregulating the expression of IκB, but also reduce the levels of pro-inflammatory mediators such as LTB_4 by upregulating the expression of cytochrome P450 and β-oxidase [266].

It has been found that baicalein can enhance the expression of PPAR-β/δ in the central nervous system of mice with experimental autoimmune encephalomyelitis, thereby inhibiting the functional activity of NF-κB and MAPK and the activation of microglia [267]. However, given that 12-HETE, the main metabolite of 12/15-LOX, was observed to reverse the upregulation of PPAR-β/δ expression induced by baicalein, the authors speculate that baicalein regulates the expression of PPAR-β/δ in microglia by inhibiting 12/15-LOX. Conversely, as 12/15-LOX metabolites can function as PPAR-γ ligands, inhibition of the 12/15-LOX pathway by baicalein can reverse the upregulation of PPAR-γ induced by cerebral ischemia/reperfusion, and thereby reduce PPAR-γ translocation from the cytoplasm to the nucleus [268].

In contrast to baicalein, baicalin has been shown to reduce the levels of phospho-PPAR-γ but enhance those of PPAR-γ and its binding to DNA in young rats with pulmonary hypertension, thereby activating the PPAR-γ pathway and inhibiting high-mobility group box1(HMGB1)/receptor-advanced glycation end product (RAGE) inflammatory signaling, which has the effect of reducing IL6 and CTGF levels in lung tissue and attenuates respiratory inflammation [269]. Moreover, baicalin has been reported to inhibit NF-κB activation and the expression of target genes encoding VCAM-1, IL-1β, and IL-6 by upregulating PPAR-γ expression and PPAR-γ–DNA binding in mouse kidneys and LPS-activated cells [270].

Similarly to baicalin, wogonin has been shown to induce the expression of PPAR-γ, thereby promoting the inhibition of NF-κB-p65 activation and significantly reducing the expression of TNF-α and IL-6, culminating in the attenuation of inflammation in alcoholic liver disease [271]. Wogonin can also reverse the reduction in PPAR-γ expression induced by cisplatin [272], enhance the expression of PPAR-γ and PPAR-α in the liver and 3T3-L1 adipocytes, and functions as a PPAR-α agonist enhancing PPAR-α transactivation in HEK-293T cells [273].

Thus, wogonin and baicalein respectively represent PPAR-α and PPAR-β/δ agonists, and similarly to baicalin, wogonin can activate PPAR-γ, whereas baicalein inhibits it.

5. Conclusions and future perspectives

In this review, we summarize our current knowledge regarding the anti-cytokine effects of the *Scutellaria baicalensis* active components baicalein, baicalin, wogonin, wogonoside, and oroxylin A. SBACs can act directly on different immune cells, including lymphocytes, macrophages, MCs, DCs, monocytes, and neutrophils, wherein they inhibit the production of multiple pro-inflammatory cytokines and chemokines, and inflammatory mediators, whilst promoting the production of certain anti-inflammatory cytokines. The molecular mechanisms underlying the immunomodulatory activities of SBACs include the inhibition of arachidonic acid metabolism, TLR expression and binding to the MD2 coreceptor, and nuclear Trx system; a reduction in inflammasome function; downregulation of key molecular pathways (MAPK, Akt, NFκB, and JAK-STAT); and induction of Nrf2/ARE- and PPAR-mediated signaling.

Although SBACs have effects on a diverse range of immune cell types, most studies have tended to focus on macrophages and microglia, and have accordingly shown that all the SBACs assessed can significantly inhibit production of the cytokine storm markers IL-1β, IL-6, and TNF-α in these cells, whereas baicalein and baicalin have also been found to inhibit M1 (pro-inflammatory) and induce M2 (anti-inflammatory) polarization of macrophages. In neutrophils and monocytes, the inhibitory activity of baicalein appears to be considerably stronger than that of baicalin. Studies on the effects of SBACs on cells of the acquired immune system have primarily investigated baicalein and baicalein, and there is currently comparatively less data on the activities of wogonin, wogonoside, and oroxylin A. Baicalein, baicalin, wogonin, wogonoside, and oroxylin A are not only characterized by significant immunomodulatory activity but also show antiviral and antibacterial effects against a variety of human pathogens. For example, it has been reported that an ethanol extract of *S. baicalensis* administered at low concentrations significantly inhibited the replication of SARS-CoV-2 and the activity of SARS-CoV-2 3C-like protease [274], similar effects of which have been reported for baicalein and baicalin [275]. Baicalin, baicalein, wogonin, and oroxylin A have also been found to inhibit the activity of H1N1 influenza virus at doses lower than that of oseltamivir phosphate [276]. Furthermore, baicalin effectively suppresses *S. aureus* growth and biofilm formation and reduces the expression of *S. aureus* toxic factors [277], and baicalein has similarly been shown to inhibit *S. aureus* growth and alleviate symptoms of the associated pneumonia [278].

The term “cytokine storm” is used to describe the massive uncontrolled release of pro-inflammatory mediators and the associated severe inflammation, which can cause irreversible organ failure and death. Inflammation associated with the cytokine storm is initiated locally and spreads throughout the body via the systemic circulation. For example, after acute pulmonary infection caused by viruses and bacteria, large amounts of acute reactive cytokines, including TNF, IL-1β, and IL-8, and the chemokine MCP-1 are secreted into the circulation, and TNF and IL-1β stimulate the continuous release of IL-6 and other cytokines. In addition to pulmonary infections, acute infections of the gastrointestinal and urinary tracts, central nervous system, skin, joints, and other organs may also induce the development cytokine storms [13]. It has reported that high viral titers and massive release of inflammatory cytokines are associated with the high morbidity and mortality observed in COVID-19 patients [279]. Accordingly, to prevent the development of cytokine storms induced by viral and bacterial infections, we should adopt two therapeutic strategies, namely, targeting pathogens and controlling inflammation. In this regard, it has been reported that immunomodulatory therapy can significantly improve the prognosis of individuals with infectious diseases, irrespective of the use of antiviral or antimicrobial agents. At present, a diverse array of immunomodulatory substances are applied in the treatment of cytokine storms, including glucocorticoids, PPAR agonists, PG and COX inhibitors, antioxidants, platelet-activating factor inhibitors, IL-1 and IL-6 antagonists, tumor necrosis factor inhibitors, statins, arbidol, and herbs [1,24].

In addition to significantly inhibiting the production of cytokines that are characteristic of cytokine storms induced by infection (IFN-λ, TNF-α, IL-1β, IL-2, IL-5, IL-6, IL-8, G-CSF, GM-CSF, VEGF, MCP-1, IP-10, and MIP-1), SBACs also have antiviral and antibacterial activities, targeting multiple pathogens such as influenza virus [280], respiratory syncytial virus [281], coronavirus [274,275,282], and bacteria [283, 284]. Consequently, compared with drugs showing only antiviral or anti-inflammatory activity, SBACs may have more promising therapeutic potential with respect to the treatment of cytokine storms caused by infection. To date, however, studies on SBACs have focused predominantly on their antiviral activity, whereas comparatively little attention has been devoted to their ability to prevent the cytokine storms that develop in response to infection. Accordingly, these properties should be examined in future pre-clinical and clinical studies, with particular emphasis on the following aspects. Firstly, the therapeutic

activity of SBACs in suppressing cytokine storms and preventing tissue damage induced by infection should be systematically examined in animal models of influenza virus, respiratory syncytial virus, and other viral and bacterial infections. Secondly, the properties of *S. baicalensis* extracts, which may have more pronounced effects on cytokine production compared with those of individual SBACs, should be investigated more comprehensive with regards to their effect on cytokine storms. Thirdly, the anti-viral activity of SBACs, which to date has primarily been investigated in vitro, needs to be systematically examined in vivo. Fourthly, to meet the requirements of clinical application, the oral bioavailability of SBACs needs to be enhanced, given that baicalein, baicalin, wogonin, wogonoside, and oroxylin A are all insoluble in water, and accordingly their oral absorption and bioavailability are poor.

We hope that this review will stimulate interest and serve as reference for future research on SBACs as potential therapeutics for the treatment of cytokine storms.

Declaration of Competing Interest

The authors report no declarations of interest.

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