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Traditional Chinese Medicines Regulate Inflammation Through Signals Mediated by cAMP−phosphodiesterases*

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Abstract Inflammation is a defense mechanism that protects human body from harmful stimuli. However, uncontrolled inflammation can lead to damage to tissues locally or systemically. Studies, including ours, have shown that traditional Chinese medicines (TCM) exert significant anti-inflammatory effects through the inhibition of cAMP-PDEs activity. We aimed to provide an overview of cAMP-mediated modulatory effects of cAMP-PDEs-selective TCM on key proteins of inflammatory signaling pathways, mainly involving inhibition of NF-κB, MAPKs (p38, ERK, or JNK), TLR, MyD88, and STAT3, and activation of Nrf2, HO-1, AMPK, and PPARγ. Among them, inhibition of NF-κB is the most important way to play anti-inflammatory roles for all cAMP-PDEs-selective TCM.

Key words traditional Chinese medicine, inflammatory signaling pathway, cAMP-phosphodiesterases
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In general, inflammation progression contains alteration, exudation, and proliferation phases[1-2]. Cyclic adenosine monophosphate (cAMP) has been observed to involve in inflammatory response, exudation, and fibrosis, and thus gained significant attention recently. It is believed that an increase in cAMP levels can inhibit and regulate inflammation[3-4]. Homeostasis of intracellular cAMP levels is mainly dependent upon the synthesis of adenylate cyclase (AC) and the hydrolysis of cAMP-phosphodiesterases (PDEs). Therefore, cAMP-PDEs have been recognized as new targets for therapy of inflammation[5]. The screening of anti-inflammatory drugs, based on these targets, has become an important way to develop new drugs.

Anti-inflammatory drugs are the second largest class of drugs in clinical application after anti-infective drugs. Traditional Chinese medicines (TCM) are widely used in anti-inflammation besides steroidal and non-steroidal anti-inflammatory drugs. The development of new anti-inflammatory TCM, at the cellular and molecular levels, is imperative for many diseases. Our 20-year work demonstrates the anti-inflammation of TCM-mediated effect through inhibiting cAMP-PDEs activity. The other ways involve inhibition of p-extracellular regulated protein kinases (ERK) and p-p65 nuclear factor-kappaB (NF-κB) of inflammatory signaling pathways downstream of cAMP, which further inhibit the expression of adhesion molecules and the release of proinflammatory factors. The role of inflammatory signaling pathways has been highlighted in the pathogenesis of many diseases and signaling molecules involved in these pathways are considered valuable targets for new treatment approaches.

In this review, we elaborate on how cAMP-PDEs-selective TCM can effectively inhibit various inflammatory reactions or multiple signaling

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molecules involved in inflammation, mainly including NF-κB, mitogen activated protein kinases (MAPKs), Toll-likereceptors (TLRs), myeloiddifferentiationfactor88 (MyD88), signal transducer and activator of transcription (STAT) 3, nuclear factor erythroid-2-related factor 2 (Nrf2), heme oxygenase (HO) -1, AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor (PPAR) γ, phosphatidylinositol-3-kinase (PI3K), and protein kinase B (PKB/Akt).

1 Anti-inflammatory effect of cAMP-PDEs-selective TCM

According to the "Handbook for Quick Search of Nature and Flavour Functions of Commonly Used TCM"[6] and the principle of "strengthening body resistance and eliminating evil" of Traditional Chinese Medicine, 21 "anti-inflammatory" TCM and 54 "body resistance strengthening and evil eliminating" TCM (12 TCM are common to both groups) are selected, and the inhibitory effect of the TCM extracts, on the activity of cAMP-PDEs, is tested in neutrophils. Results show that 19 TCM out of 21 (accounting for 90%) and 38 TCM out of 54 (accounting for 70%) have an inhibitory effect on cAMP-PDEs activity[7-8], suggesting that inhibiting the activity of cAMP-PDEs is an important mechanism for most therapeutic roles played by TCM. Among them, extracts of *Radix paeoniae alba* (*baishao*), *Perilla frutescens* (*zisuye*), *Cyperus rotundus* (*xiangfu*), *Coptis chinensis* (*huanglian*), *Astragalus membranaceus* (*huangqi*), *Mentha haplocalyx* (*bohe*), *Rhizoma anemarrhenae* (*zhimu*), *Isatidis folium* (*daqingye*), *Lonicera japonica flos* (*jinyinhua*), *Cuscutae semen* (*tusizi*), *Epimedii folium* (*yinyanghuo*), *Forsythia suspensa* (*lianqiao*), *Schisandra chinensis* (*wuweizi*), *Foeniculum vulgare mill* (*xiaohuixiang*), *Radix bupleuri* (*chaihu*), *Pueraria lobata* (*gegen*), *Caulis sinomenii* (*qingfengteng*), *Angelica sinensis* (*danggui*), *Mori folium* (*sangye*), and *Ligusticum chuanxiong* (*chuanxiong*) inhibit cAMP-PDEs activity to a large extent. The inhibitory effect of some TCM, such as *jinyinhua* and *lianqiao*[9], *yinyanghuo*[10], *wuweizi*[11], and *Scutellaria baicalensis* (*huangqin*)[12] on cAMP-PDEs, is consistent with previous reports.

Studies have shown that the cAMP-PDEs-selective TCM have a robust anti-inflammatory effect. Researches including ours indicate that *baishao* extract has inhibitory effects on xylene-induced ear swelling in mice, carrageenan-induced foot swelling in rats, complete Freund's adjuvant (CFA) -induced arthritis in rats, carrageenan-induced pleural inflammation in mice, or acetic acid-induced capillary permeability in mice[13-16]. Gallic acid, an active ingredient of *baishao*, can inhibit the activity of cAMP-PDEs and the degree of swelling in rats with CFA-induced arthritis[17]. Capsules of white paeony are already on the market for the treatment of rheumatoid arthritis (RA), and contain total glucosides of paeony, as the main ingredient. Research shows that the inhibitory effect of total glucosides of paeony on inflammation in rats suffering with RA may be related to the down-regulation of the expression of p65 NF-κB and the inhibition of the production of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β [18].

Jinyinhua has an immunosuppressive effect and controls inflammation by inhibiting proinflammatory factors. Its extract reduces inflammatory factors in subcutaneous inflammatory exudates from carrageenan-induced foot swelling in rats and plays an anti-inflammatory role similar to non-steroidal anti-inflammatory drugs. The extract of *Jinyinhua* also alleviates myocardial degeneration, necrosis or inflammatory cell infiltration in mice with viral myocarditis and inhibits the expression of caspase-3 and NF-κB[19]. Chlorogenic acid, an effective component of *jinyinhua*, has an anti-inflammatory effect in vitro, which is mediated by inhibiting the activation of proinflammatory factors.

Lianqiao is widely used in TCM to treat pneumonia, typhoid, dysentery, ulcers, or oedema. The shell decoction, macroporous adsorbent resin or polyphenols of *lianqiao* have anti-inflammatory and antipyretic effects on xylene- or croton oil-induced ear swelling in mice and endotoxin-induced fever in rabbits, which are the main effective parts of *lianqiao*[20]. *Lianqiao* extract and monomers such as forsythiaside A, forsythiasin, and forsythiaside mainly affect the synthesis of inflammatory mediators to play an anti-inflammatory role[21]. Pretreatment with *lianqiao* can reduce the expression of TLR4 and NF-κB and the secretion of IL-6 and IL-10 in rat splenic lymphocytes under the effects of an endotoxin. Thus, *lianqiao* shows anti-inflammatory and immunomodulatory effects[22].

Chaihu has anti-inflammatory and analgesic effects on ear swelling induced by xylene in mice and pain induced by a hot plate[23]. *Chaihu* saponin has a remarkable anti-inflammatory effect and it inhibits many inflammatory processes, including inflammatory exudation, increased capillary permeability, inflammatory mediator release, leukocyte migration, and so on. A combination of *Chaihu* and *Huangqin* has a definite anti-fibrosis effect in the liver, by inhibiting TLR4/NF-κB signaling pathway and alleviating inflammation[24].

Danggui decoction inhibits the inflammatory response of ear edema in mice induced by xylene, painful writhing in mice induced by acetic acid, abdominal inflammation in rats induced by lipopolysaccharide (LPS), or the damage of rat vascular smooth muscle cells (VSMCs) induced by H_2O_2[25-27]. The effective fraction (organic acids) of *danggui* can down-regulate the expression of TLR4 induced by LPS, inhibit the activation of NF-κB, and decrease the expression of lectin-like oxidized low density lipoprotein receptor-1, vascular cell adhesion molecule (VCAM)-1, monocyte chemotactic protein (MCP)-1, and IL-6. Therefore, it can prevent inflammation and lipid-mediated pathological processes of atherosclerosis. Ferulic acid, the main component of organic acids in *danggui*, plays a major role in this process[28].

Gegen extract alleviates the swelling of joints in rats with acute gouty arthritis, induced by microcrystalline sodium urate. In addition, its extract improves the inflammation of ulcerative colitis (UC) in rats induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) and ethanol, and its mechanism may be related to down-regulating expression of p38 MAPK and p65 NF-κB, and up-regulating expression of PPARγ[29]. Total flavones of *gegen* have a significant effect on chronic alcoholic hepatic injury in rats induced by the Lieber-Decarli diet, which is known to inhibit TLR4 and TLR2, thereby inhibiting Kupffer cell activation[30].

2 Anti−inflammatory signaling pathways of cAMP−PDEs−selective TCM ingredients

Nucleotide signaling molecules contribute significantly to the regulation of cellular signal pathways. In the immune system, cAMP is well established as a potent regulator of innate and adaptive immune cell function. Therapeutic strategies to interrupt or enhance cAMP generation or its effects have immunoregulatory potential in autoimmune and inflammatory disorders[31]. Cyclic-AMP-PDEs are key enzymes in the cAMP signaling cascade. Their inhibition increases cAMP levels inside the immune or inflammatory cells. Thus, pharmacological modulation of the activity of cAMP-PDEs, by the ingredients present in TCM, can play a profound role in the function of the immune cells. Cyclic-AMP is an important second messenger not only due to its involvement in a vast number of physiological processes but also because of its activation of protein kinase A (PKA), exchange protein activated by cAMP (EPAC), cAMP response element-binding (CREB), or cAMP-gated channels, etc.

In addition, studies have shown that cAMP is involved in the regulation of several important inflammatory signaling pathways, such as the MAPKs, NF-κB/IκB, PI3K/Akt, and janus kinase (JAK)/STAT pathways[32-39]. However, the specific signaling pathway that is used by cAMP is based on the stimulating factors and specificity of the cells. Luteolin and gallic acid, found in *zisuye* and *baishao*, respectively, are reported to have anti-inflammatory properties and are efficient inhibitors of cAMP-PDEs[17,40], and we decided to study their anti-inflammatory signal mechanism further. Moreover, we studied 14 representative ingredients from TCM, which can inhibit the activity of cAMP-PDEs[41-52], and analyzed the roles they play in anti-inflammatory signaling pathways.

2.1 Luteolin

Luteolin can alleviate inflammation in a variety of ways, which include inhibiting key inflammatory signaling pathways such as NF-κB and MAPKs (p38, ERK, and JNK), finally inhibiting the expression of proinflammatory cytokines and inflammatory mediators. Our studies show that the anti-inflammatory mechanisms of luteolin involve: a. Inhibiting the activity of cAMP-PDEs in microvascular endothelial cells (MECs), blocking N-formylmethionyl-leucyl-phenyl-alanine (fMLP)-induced p65 NF-κB phosphorylation, and decreasing the expression of VCAM-1 (*in vitro*) on MECs and soluble intercellular cell adhesion molecule (sICAM)-1 (*in vivo*) in the serum[53]; b. Inhibiting cAMP-PDE4 activity of neutrophils, increasing cAMP levels and suppressing fMLP-induced ERK phosphorylation[54],

blocking lymphocyte function associated antigen-1 expression on neutrophils, and eventually suppressing the adhesion of neutrophils and MECs to each other[40]. Luteolin reduces fAβ1-40-induced inflammatory response and cytokine production. Luteolin protects the blood-brain barrier against fAβ1-40-induced injury by inhibiting p38 MAPK activation, downregulating phosphorylated IκB kinase levels, inhibiting IκBα degradation, blocking p65 NF-κB nuclear translocation, and inhibiting the release of inflammatory cytokines[55]. IL-1β -induced JNK and p38 activation in SW982 cells is inhibited by luteolin. Moreover, IL-1β -induced activator protein (AP)-1 and NF-κB activation is inhibited by luteolin. Thus, luteolin reduces the production of MMPs and cytokines by inhibiting MAPKs (JNK and p38) and transcription factors (AP-1 and NF-κB)[56].

2.2 Gallic acid

Studies show that the NF-κB pathway plays a leading role in the anti-inflammatory signaling pathway induced by gallic acid (GA). GA efficiently suppresses the NF-κB signaling pathway in TNBS-induced UC in mice[57]. *Toona sinensis* (leaf extracts, TS) and its compound GA inhibit LPS-induced NF-κB in the abdominal region of transgenic mice. Thus, the anti-inflammatory potential of TS and GA is mediated by the downregulation of the NF-κB pathway[58]. GA inhibits MyD88 expression and downregulates NF-κB signaling in mice with IL-33-induced asthma, which shows GA can reduce the severity of asthma via downregulation of the MyD88/NF-κB signaling pathway[59]. GA reduces the activation and nuclear accumulation of p-STAT3, prevents the degradation of IκB and inhibits the nuclear translocation of p65 NF-κB, in the colonic mucosa of an experimental murine model of UC, which suggests that GA exerts anti-inflammatory effects mediated through the suppression of p65 NF-κB and IL-6/p-STAT3 activation[60]. *Terminalia bellirica (Gaertn.) Roxb.* extract (TBE) and its compound GA attenuate LPS-induced activation of MAPK and NF-κB in RAW 264 macrophages. Furthermore, TBE and GA increase Nrf2, Akt, and AMPK levels. Therefore, TBE and GA exert protective effects against inflammation by suppressing MAPK/NF-κB pathway and by activating the Akt/AMPK/Nrf2 pathway[61].

2.3 Ginsenoside Rg1

Ginsenoside Rg1 (G-Rg1), one of the most notable active components of *Panax ginseng* (*renshen*), has been widely reported to exert anti-inflammatory effects. The anti-inflammatory signaling pathways of G-Rg1 are complex. G-Rg1 inhibits LPS-induced microglial activation and production of TNF-α, IL-1β and nitric oxide (NO). In addition, G-Rg1 treatment inhibits the LPS-induced phosphorylation of IκB, ERK1/2, JNK and p38 MAPK in the lesioned side of substantial nigra[62]. G-Rg1 alleviates palmitic acid-induced hepatic steatosis and inflammation and activates the AMPK pathway in HepG2 cells, which is correlated with the inactivation of the NF-κB pathway and translocation of p65 from the cytoplasm to the nucleus[63]. G-Rg1 treatment reduces the symptoms of cardiac hypertrophy and hypertension, decreases oxidative stress, inflammatory response, NF-κB expression, and NACHT, LRR and PYD domains-containing protein (NLRP) 3 inflammasome activation in streptozotocin (STZ) -induced diabetic rats. In addition, G-Rg1 treatment increases the expression of AMPK, Nrf2 and HO-1 in cardiac tissues[64-65]. G-Rg1 protects HK-2 cells from LPS-induced inflammation and apoptosis. Furthermore, the down-regulations of p-PI3K and p-AKT and the up-regulations of phosphatase and tensin homolog deleted on chromosome ten (PTEN), p-IκBα, p-p65, and Bcl-3 induced by LPS, are recovered after G-Rg1 treatment[66]. G-Rg1 treatment suppresses apoptosis rate of LPS-induced A549 cells and reduces the severity of hepatic steatosis in rats that have been fed a diet of high-fat and high-sugar, to induce insulin resistance. Moreover, G-Rg1 suppresses the expression of IL-1β, IL-6, TNF-α, NF-κB and G6Pase; however, p-Akt is seen to be up-regulated[67]. G-Rg1 treatment suppresses apoptosis rate of LPS-induced A549 cells and relieves mouse lung tissue damage. In both A549 cells and mouse lung tissues, studies show that G-Rg1 perfusion suppresses the secretion of inflammatory cytokines and relieves cells from endoplasmic reticulum stress(ERS), as seen by the decreased expression of marker proteins, by upregulating sirtuin 1 (SIRT1). PPARγ activation by its agonist rosiglitazone attenuates neurological deficits, apoptosis and inflammation in the hippocampus of cerebral ischemia-reperfusion (I/R) rats. G-Rg1 shows a similar effect to rosiglitazone in

activating PPARγ/HO-1, in protecting against apoptosis and inflammation[68].

2.4 Puerarin

Puerarin is the most abundant isoflavone-C-glucoside extracted from *gegen* and possesses many biological activities[69]. Puerarin can not only directly regulate the expression of inflammatory factors, but also block the activation of NF-κB signaling pathways induced by inflammatory factors, thus indirectly regulating the secretion of inflammatory factors and alleviating inflammation. The activation of NF-κB and TNF-α pathway in peripheral blood mononuclear cells may play an important role in the pathogenesis of asthma. Genistein and puerarin can inhibit the NF-κB and TNF-α pathway in patients with asthma[70]. Puerarin inhibits the expression of TNF-α, ICAM-1, VCAM-1, and E-selectin proteins and mRNAs in human umbilical vein endothelial cells (HUVECs). The inhibition is attributed to suppress NF-κB activation at the transcriptional level[71]. Puerarin can reduce ICAM-1 expression and decrease nuclear translocation of p65 NF-κB to suppress the inflammatory reaction in ischemic brain tissue of rats[72]. Treatment with puerarin decreases clinical scoring of collagen antibody-induced arthritis and suppresses oxidative stress and inflammatory response in mice. Puerarin also inhibits mRNA expression of matrix metallpproteinase-9 and protein expression of TLR4 following collagen antibody-induced arthritis in mice. Furthermore, up-regulation of p-JAK2 and p-STAT3 protein expression is suppressed by puerarin. The results indicate the effect of puerarin in attenuating inflammation and oxidation in mice with collagen antibody-induced arthritis *via* TLR4/NF-κB or JAK/STAT signaling[73].

2.5 Quercetin

Quercetin possesses anti-inflammatory and anti-carcinogenic properties and protects against oxidative stress and inflammation-related metabolic complications of psoriasis, RA, cardiovascular disease, and so on. Quercetin plays an anti-inflammatory role mainly through TLR/MyD88/MAPKs/NF-κB or PI3K/Akt pathways. Quercetin is able to down-regulate the inflammatory response of bone marrow-derived macrophages in vitro and inhibits cytokine and inducible nitric oxide synthase (iNOS) expression through inhibition of the NF-κB pathway, without modification of JNK activity[74]. Quercetin ameliorates all markers of inflammation and oxidative stress measured in a rat model of adjuvant arthritis. In addition, quercetin increases the expression of HO-1 and decreases NF-κB activity in the joints and lungs of arthritic rats[75]. Quercetin can ameliorate the deteriorating histopathology and proinflammatory factors in skin tissue in imiquimod (IMQ) -induced mice, and the mechanism may be associated with the down-regulation of NF-κB, IKKα, NIK and RelB expression and up-regulation of TNF receptor-associated factor (TRAF) 3, which plays a critical role in the non-canonical NF-κB pathway[76]. Intense exercise-induced ERS and inflammation are attenuated by quercetin in BALB/C mice. PI3K/Akt activation and JNK, activating transcription factor 6 (ATF6), and NF-κB suppression are involved in the protective role of quercetin[77]. Quercetin intervention attenuates pancreatic and ileal damage in acute necrotizing pancreatitis (ANP) in rats and ameliorates intestinal barrier disruption and inflammation. Meantime, quercetin suppresses intestinal TLR4/MyD88/p38 MAPK pathway and ERS activation[78]. Quercetin decreases atherosclerotic inflammation *via* three signaling pathways: a. Inhibiting the expression of VCAM-1 and ICAM-1 enhanced by oxidized low density lipoprotein (oxLDL) in HUVECs by downregulating the expression of MCP-1, TLR2, and TLR4 and the nuclear translocation of p65 NF-κB[79]; b. Suppressing the activities of TLRs, p38, ERK1/2, and JNK in oxLDL-stimulated human peripheral blood mononuclear cells (hPBMCs) using specific inhibitors and subsequently inhibiting NF-κB activation and TNF-α release[80]; and c. Reducing reactive oxygen species (ROS) levels, caspase-3 activation, and inflammatory cytokines release by promoting PI3K/Akt and Bcl-2 expression and reducing caspase-3 and NF-κB activation, in high fructose-induced atherosclerosis[81]. Quercetin can also protect the liver from damage *via* three pathways: a. Protecting human hepatoma cells (HepG2) against activation of the NF-κB pathway induced by TNF-α, which is mediated partly by ERK, JNK, and ROS[82]; b. Decreasing proinflammatory markers, TLR2/4 activation, and MAPK phosphorylation, which in turn inactivates NF-κB and the inflammatory cytokines in CCl_4-induced mice[83]; and c. Inducing Nrf2 nuclear translocation and HO-1 activity in nickel-induced mice and inhibiting p38 and STAT1 activation, which in turn inactivate NF-κB in the liver[84].

2.6 Osthole

Osthole is a compound that is extracted from fruits of *Cnidium monnieri* (*shechuangzi*), which has multiple bioactive functions, including antioxidant, anti-inflammatory, anticancer, antiplatelet, and estrogenic effects and confers resistance to pain. NFκB pathway plays a key role in the anti-inflammatory process of osthole. Osthole can improve neurological function and increase the number of neurons at the site of injury. Additionally, osthole treatment reduces microglia activation and glial scar formation, lowers the level of the proinflammatory cytokines, and blocks the activation of NF-κB in a mouse model of cortical stab wound injury in the brain. Treatment of osthole can suppress cellular apoptosis and release of inflammatory factors by blocking injury-induced IκB-α phosphorylation and NF-κB translocation and upregulating IκB-α, in SH-SY5Y cells[85]. Treatment with osthole inhibits IL-1β-stimulated proliferation and migration, inhibits the expression of matrix metalloproteinases, blocks the generation of IL-6 and TNF-α, and inhibits NF-κB and MAPK pathways, in IL-1β-stimulated SW982 cells[86]. Treatment with osthole inhibits chronic kidney failure (CRF) induced TNF-α, IL-8, and IL-6 expression and suppresses NF-κB protein expression in rats. Osthole treatment also attenuates the protein expression of transforming growth factor (TGF)-β1, reduces MCP-1 activity, and increases the PI3K/Akt ratio in CRF rats[87]. The secretion of TNF-α, IL-6, and IL-1β by LPSstimulated BV2 cells is reduced by osthole treatment. Moreover, osthole treatment inhibits LPS-induced activation of the NF-κB signaling pathway and upregulates the expression of Nrf2 and HO-1[88].

2.7 Genistein

Genistein is extracted from soybean and has anti-inflammatory, anti-oxidative, and anti-cancer effects. Genistein mediates complex anti-inflammatory pathways. Genistein inhibits high glucose (HG)-induced adhesion of monocytes to human aortic endothelial cells (HAEC) and suppresses endothelial production of MCP-1 and IL-8. Inhibition of AC or PKA significantly attenuates the antiadhesion effect of genistein. Consistently, genistein improves HG-impaired intracellular cAMP production and PKA activity in HAEC[89]. Similarily, genistein protects against TNF-α-induced vascular endothelial inflammation *via* the PKA signaling pathway[90]. Genistein can improve IMQ-induced pathological scores of cutaneous skin lesions in mice. Furthermore, genistein inhibits phosphorylated STAT3 expression in IMQ mice dorsal skin and in TNF-α-induced HaCaT cells. Genistein also inhibits TNF-α induced nuclear translocation of NF-κB and the phosphorylation of I-κBα[91]. Genistein can counteract oxLDL-induced expressions of adhesion molecules and chemokines in HUVECs. Furthemore, genistein reduces miR-155, elevates SOCS1, and inhibits the NF-κB signaling pathway[92]. Genistein decreases the secretion of IL-1β, IL-6, and IL-8 from TNF-α-stimulated MH7A cells. Genistein also prevents TNF-α-induced NF-κB translocation and phosphorylation of IκB kinase-α/β and IκBα and suppresses TNF-α-induced AMPK inhibition. The production of IL-1β, IL-6, and IL-8 induced by TNF-α is decreased by the PI3K inhibitor, suggesting that the inhibition of Akt activation might inhibit IL-1β, IL-6, and IL-8 production induced by TNF-α. These findings indicate that genistein suppresses TNF-α-induced inflammation by inhibiting the ROS/Akt/NF-κB pathway and promoting AMPK activation in MH7A cells[93]. Genistein inhibits IL-1β-induced expression of catabolic factors NOS2, COX-2, and matrix metalloproteinases (MMPs) and stimulates HO-1 expression, which has been associated with Nrf2 pathway activation in human chondrocytes. In a rat model, genistein is also shown to attenuate the progression of traumatic osteoarthritis[94]. Genistein attenuates ovalbumin (OVA)-induced airway inflammation and modulates the Th1/Th2 reaction by inhibiting GATA-binding protein (GATA)-3 and STAT-6 production while increasing T-bet production[95]. One of the earliest neuropathological changes in Alzheimer's disease is the accumulation of astrocytes at sites of A-beta deposition. A beta induces inflammatory mediators and these effects are prevented when cells are pretreated with estradiol or genistein. The A beta-stimulated expression of proinflammatory genes is antagonized by the action of the PPARγ[96].

2.8 Paeoniflorin

Paeoniflorin, a bioactive compound from *baishao*, is known for its antioxidative, antiinflammatory, antiallergic, and antiapoptotic activity. It protects against vascular inflammation. Moreover, the NF-κB pathway plays a leading role in

the pharmacological action of paeoniflorin. Pretreatment with paeoniflorin attenuates phorbol-12-myristate 13-acetate plus calcium ionophore (PMACI)-induced production of TNF-α, IL-1β, histamine release, and caspase-1 activation in HMC-1 cells. Furthermore, paeoniflorin is showed to prevent activation of NF-κB and MAPK signaling pathways in activated HMC-1 cells[97]. Paeoniflorin pretreatment inhibits Aβ1-42-induced production of TNF-α, IL-1β, and IL-6 in rodent microglia. Moreover, the nuclear translocation of p65 NF-κB and phosphorylation of IκBα, in Aβ1-42-stimulated microglial cells, are suppressed by paeoniflorin administration[98]. Paeoniflorin promotes cell survival rate and decreases over-production of inflammatory cytokines, ERS markers, and the ultrastructural abnormalities in LPS-stimulated HUVECs. Specific inhibitors or activators are used to confirm the role of the IRE1α/NF-κB pathway in paeoniflorin-mediated protection against LPS-induced HUVEC injury[99]. In vitro treatment of paeoniflorin inhibits LPS-induced expression of COX-2, iNOS, TNF-α, IL-6, and MMP-9. In addition, paeoniflorin suppresses NF-κB signaling *via* activating the Nrf2/HO-1 signaling pathway in LPS-stimulated Caco-2 cells[100]. Paeoniflorin decreases the levels of uric acid and creatinine in the urine, serum and kidney levels of cytokine, and attenuates the histological changes seen in kidney tissues, caused in cyclophosphamide-induced mice. Moreover, paeoniflorin increases AMPK levels and inhibits NF-κB signaling pathway and apoptosis, in cyclophosphamide-stimulated kidney tissues[101].

2.9 Catechin

Catechin is one of the main polyphenol compounds found in green tea and possesses a range of health benefits in periodontitis, allergic disease, coronary heart disease, gout, and adipose inflammation. Thymic stromal lymphopoietin (TSLP), found in epithelial cells, plays a significant role in the development of allergic disease and the production of TSLP is related to activation of the NF-κB signaling pathway. As an upstream regulator of TSLP, the NF-κB signaling pathway is suppressed after catechin treatment, which is demonstrated by a decrease in p-p65 NF-κB and p65 NF-κB levels, reduction of IκBα degradation, and p65 NF-κB nuclear translocation[102]. Catechin can attenuate the production of IL-1β by inhibiting pro-IL-1β expression *via* the downregulation of TLC, p38 MAPK, and NF-κB signaling in THP-1-derived macrophages, infected with *P. gingivalis* in a mouse model[103]. In 3T3-L1 adipocytes, catechin, and quercetin attenuate TNF-α-induced elevated protein carbonyls, increase proinflammatory cytokine expression, and decrease adiponectin. The protective effects of catechin and quercetin on adipose inflammation are in part associated with their capacity to decrease the activation of JNK and p38, or prevent the downregulation of PPARγ[104].

2.10 Ferulic acid

Ferulic acid (FA) is an important therapeutic agent that is extracted from TCM such as *chuanxiong* and *danggui*. FA displays a wide range of therapeutic effects and can be used for the prevention and treatment of endometritis, depression, and acute respiratory distress syndrome. MAPK and NF-κB pathways play an important role in the anti-inflammatory effect of FA. FA pretreatment alleviates LPS-induced pulmonary histological changes, improves LPS-induced inflammation, reduces oxidative stress, and inactivates multiple MAPK signaling pathways in the lungs[105]. Bovine endometrial epithelial cells were pretreated with FA followed by LPS treatment. The results show that mRNA expression of LPS-induced proinflammatory cytokines is decreased with FA pretreatment. Moreover, FA inhibits the degradation of IκB and phosphorylation of p65 NF-κB and suppresses the phosphorylation of MAPKs, including p38 and JNK. FA inhibits H_2O_2-induced injury and increases cell viability in rat VSMCs. The level of ROS generation is reduced by pretreatment with FA by inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression and down-regulation of MAPK and Akt pathways. H_2O_2 stimulates the production of IL-6, IL-1β, TNF-α, and NO, which can be reduced by pretreatment with FA through the inhibition of p-NF-κB and iNOS expression[106]. Chronic unpredictable mild stress (CUMS) shows decreased sucrose preference and increased immobility time in mice. It also causes up-regulation of IL-1β, IL-6, and TNF-α and activation of microglia, NF-κB signaling, and NLRP3 inflammasome in the prefrontal cortex of mice. The activation of inflammatory response, induced by CUMS, is reversed by FA[107].

2.11 Emodin

Emodin, an anthraquinone derivative from *Radix rhizoma Rhei* (*dahuang*), has been reported to possess anti-tumor, anti-inflammatory, and anti-diabetic activity. NF-κB and MAPKs pathways play an important role in the anti-inflammatory effect of emodin. Due to the interventionary effect of emodin lipid nano-microbubbles, the protein expressions of p-p38, p-ERK, and p-JNK and levels of inflammatory cytokines, like TNF-α, IL-1β, and IL-6, are decreased in mechanical stretch induced AT-II cells[108]. Treatment with emodin can improve corneal structure and reduce corneal injury by reducing the corneal inflammatory response, induced by LPS. Emodin can inhibit the decreasing level of IκBα expression and mRNA expression of TNF-α and ICAM-1, in corneal tissues[109]. Emodin inhibits LPS-induced TLR2, NF-κB, TNF-α, IL-1β and IL-6 mRNA and protein expression in cultured NRK-52E cells. Emodin attenuates inflammation by inhibiting TLR2-mediated NF-κB signaling pathway[110]. Emodin can ameliorate LPS-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) in mice. LPS-induced up-regulation of ICAM-1, MCP-1, and TNF-α, LPS-induced down-regulation of PPARγ, and LPS-enhanced p65 NF-κB activation and DNA binding activity, are substantially suppressed by emodin in RAW264.7 cells[111]. Emodin treatment of cough variant asthma (CVA), in mice, increases the levels of immunoglobulin E (IgE) and IgG1/IgG2a, inhibits the infiltration of inflammatory cells, and reduces the levels of inflammatory cytokines in bronchoalveolar lavage fluid (BALF) and serum. Furthermore, the expressions of Notch 1, 2, 3, and DLL4, in lung tissue, are inhibited by emodin treatment. The results show that emodin alleviates inflammation in CVA mice by the suppression of the Notch pathway[112].

2.12 Chlorogenic acid

Chlorogenic acid (CA) is one of the most abundant polyphenols in *jinyinhua*, and has known immunoprotective, antioxidant, and anti-inflammatory properties. The NF-κB pathway plays a key role in mediating the anti-inflammatory effect of CA. CA suppresses IL-1β-induced mRNA expression of VCAM-1, ICAM-1, and endothelial cell selectin. In addition, CA attenuates or blocks IL-1β-induced nuclear translocation of p50 and p65 NF-κB. CA also reduces the adhesion of human monocyte cells to IL-1β-treated HUVECs[113]. CA can inhibit ICAM-1, VCAM-1, and MCP-1 expression in HUVECs, induced by AGEs-BSA, and decreases the expression of related kinases in the ROS/p38 MAPK/NF-κB pathway, thereby inhibiting advanced glycation end products of bovine serum albumin (AGEs-BSA)-induced inflammation in HUVECs[114]. Treatment of CA attenuates CCl_4-induced liver damage and symptoms of liver fibrosis. CA also reduces the expression levels of TLR4, MyD88, iNOS, and COX-2. Furthermore, CA suppresses CCl_4-induced NF-κB activation. CA can efficiently inhibit CCl_4-induced liver fibrosis in rats through TLR4/MyD88/NF-κB signaling pathway[115] and attenuate diabetic renal damage. Pre-treatment with CA increases the nuclear translocation of Nrf2 and the expression of HO-1 and reduces the phosphorylation of IκB and the subsequent nuclear translocation of NF-κB[116].

2.13 Ligustrazine

Ligustrazine, isolated from *chuanxiong*, has been proven to have significant anti-inflammatory and anti-oxidative stress effects and has been widely used for asthma treatment. Ligustrazine suppresses airway and lung inflammation in the OVA-induced mouse asthma model. Ligustrazine also induces inhibition of inflammatory cells and reduces IL-4, IL-5, IL-17A, chemokine C-C motif ligand (CCL) 3, CCL19, and CCL21 level in the BALF of mice with asthma. Furthermore, ligustrazine induces down-regulation of CCL19 receptor chemokine C-C receptor (CCR) 7, STAT3, and p38 MAPK protein expression. Collectively, ligustrazine is effective in attenuation of allergic airway inflammatory changes probably via the STAT3 and p38 MAPK pathways[117]. Treatment with ligustrazine can decrease hind-paw volume change and alleviate the histopathological changes in sections of rat paws, in FCA-induced arthritis. Ligustrazine also reduces the serum levels of proinflammatory cytokines. Moreover, ligustrazine inhibits the SIRT1/NF-κB pathway and activates the Nrf2/HO-1 pathway[118]. Ligustrazine relieves the inflammatory changes of airway, reduces the infiltration of inflammatory cells in tracheal wall, and decreases the thickening of airway wall in OVA + aluminum hydroxide-induced asthma model of mice. Ligustrazine also reduces serum IgE, IL-5, GATA-3, and TGF-β1 levels. Furthermore, ligustrazine decreases the expressions of TGF-β1 and Smad2 in lung tissues of mice, but it increases the expression of

Smad7. Thus, ligustrazine can improve airway remodeling in asthma by regulating the TGF-β/Smad signaling pathway[119].

2.14 Astilbin

Astilbin is a flavonoid compound derived from the *rhizome of Smilax china L.* (*baqia*) and has been used to treat inflammatory kidney injury because of its anti-inflammatory activity. Astilbin can inhibit HG-induced cell proliferation and the expression and secretion of inflammatory cytokines. The HG-mediated induction of the inflammatory response and extracellular matrix (ECM) accumulation is inhibited by astilbin treatment. The TLR4/MyD88/NF-κB pathway is activated by HG and the inhibitor of TLR4 exhibits the same effect as astilbin, in reversing the effects of HG[120]. Kidney function parameters are restored in astilbin-treated hyperuricemic rats. Astilbin prevents renal damage induced by the expression of thioredoxin-interacting protein (TXNIP) and its related inflammation signaling pathway, like NLRP3/NF-κB. Moreover, astilbin inhibits activation of the JAK2/STAT3 cascade and over-expression of SOCS3 in the kidney of potassium oxonate-induced mice[121]. Astilbin can inhibit cisplatin-induced cellular apoptosis and recover cell growth. Astilbin decreases ROS accumulation and alleviates ROS-induced activation of p53, MAPKs, and Akt signaling cascades. Astilbin effectively enhances Nrf2 activation and transcription of its target antioxidant genes, to reduce ROS accumulation in cisplatin-induced HEK-293 cells. Furthermore, astilbin suppresses TNF-α expression, NF-κB activation, and iNOS and COX-2 expression[122].

3 Conclusion

Cyclic-AMP-PDEs-selective TCM screened in our laboratory have definite anti-inflammatory effects. In summary, our results establish that, as shown in Table 1 and Figure 1, the anti-inflammatory signals of cAMP-PDEs-selective TCM mediated by cAMP mainly involve inhibiting the activity or protein expression of NF-κB, MAPKs (p38, ERK, or JNK), TLR, MyD88, and STAT3 and promoting the activity or protein expression of Nrf2, HO-1, AMPK, and PPARγ. Among them, inhibition of NF-κB is the most important way to play anti-inflammatory roles for all cAMP-PDEs-selective TCM. In addition, the regulatory signaling mechanisms of anti-inflammatory drugs seem to be complex or have multiple-targets. Gallic acid, G-Rg1, quercetin, or catechin play an anti-inflammatory role by promoting the activity or expression of Akt, while genistein, ferulic acid, or astilbin exert the same effect by inhibiting the activity or expression of Akt. This complex adjustment of TCM also exists in individual reports of PI3K in this review.

Table 1 Regulation of cAMP−PDEs−selective TCM on key proteins of inflammatory signaling pathways

TCM	NF-κB	MAPKs	TLR	MyD88	STAT3	JAK	Akt	PI3K	Nrf2	HO-1	AMPK	PPARγ
Luteolin	↓	↓										
Gallic acid	↓	↓		↓	↓		↑		↑		↑	
Ginsenoside Rg1	↓	↓					↑	↑	↑	↑	↑	↑
Puerarin	↓		↓		↓	↓						
Quercetin	↓	↓	↓	↓			↑	↑	↑	↑		
Osthole	↓	↓					↑	↑	↑	↑		
Genistein	↓				↓		↓	↓	↑	↑	↑	↑
Paeoniflorin	↓	↓							↑	↑	↑	
Catechin	↓	↓										↑
Ferulic acid	↓	↓					↓					
Emodin	↓	↓	↓									↑
Chlorogenic acid	↓	↓	↓	↓								
Ligustrazine	↓	↓			↓				↑	↑		
Astilbin	↓	↓	↓	↓	↓	↓	↓		↑			

“↓”, inhibition; “↑”, activation.

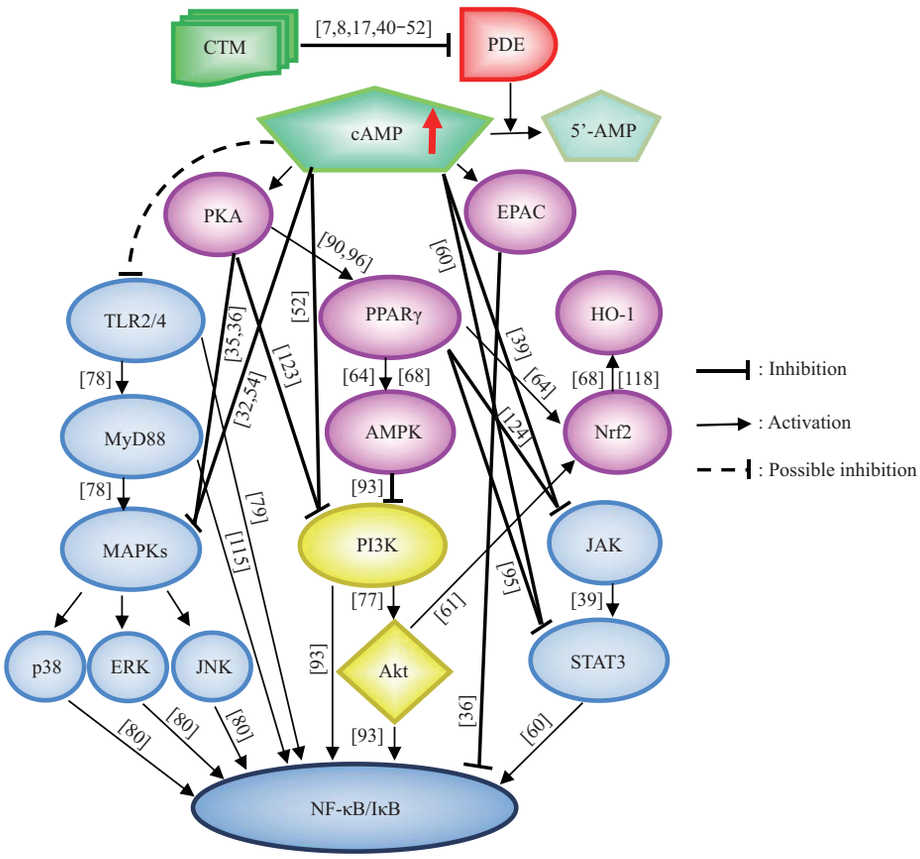

Fig. 1　TCM regulate inflammation through possible signaling pathways mediated by cAMP−phosphodiesterases

PDE(cAMP-phosphodiesterases). Signal proteins in pink, or blue mean activation, or inhibition of TCM on them, respectively.

Notably, cAMP-PDEs are not the only targets of anti-inflammatory drugs. There are other targets, such as phospholipase A2, COX, or lipoxygenase, in immune or inflammatory cells. For example, genistein and catechin are both selective inhibitors of cAMP-PDEs that have anti-inflammatory effect mediated *via* cAMP and phospholipase A2 inhibitor, which play the same role mediated by arachidonic acid. Therefore, drugs can inhibit inflammation through a variety of signaling pathways. Which anti-inflammatory pathway of drug the body or cell specifically activate, is related to its state and key stimulating factor. In short, the anti-inflammatory effect or anti-inflammatory signaling mechanism of TCM is at least partially related to cAMP, mediated by their inhibition of cAMP-PDEs.

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中药通过cAMP–磷酸二酯酶介导的信号调节炎症*

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摘要　炎症是保护人体免受有害刺激的一种防御机制. 然而，失控的炎症可导致局部或系统性组织损伤. 研究表明，中药可以通过抑制cAMP-磷酸二酯酶（PDEs）活性发挥抗炎作用. 本文综述了cAMP-PDEs选择性中药介导的cAMP对多种炎症信号通路中关键蛋白的调节作用，主要包括对NF-κB、MAPKs（p38、ERK或JNK）、TLR、MyD88和STAT3的抑制作用以及对Nrf2、HO-1、AMPK和PPARγ的激活作用. 其中，对NF-κB的抑制作用是cAMP-PDEs选择性中药最重要的信号转导通路.

关键词　中药，炎症信号通路，cAMP-磷酸二酯酶

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