Targeting P2 receptors in purinergic signaling: a new strategy of active ingredients in traditional Chinese herbals for diseases treatment

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Abstract

Adenosine triphosphate (ATP) and its metabolites adenosine diphosphate, adenosine monophosphate, and adenosine in purinergic signaling pathway play important roles in many diseases. Activation of P2 receptors (P2R) channels and subsequent membrane depolarization can induce accumulation of extracellular ATP, and furtherly cause kinds of diseases, such as pain- and immune-related diseases, cardiac dysfunction, and tumorigenesis. Active ingredients of traditional Chinese herbals which exhibit superior pharmacological activities on diversified P2R channels have been considered as an alternative strategy of disease treatment. Experimental evidence of potential ingredients in Chinese herbs targeting P2R and their pharmacological activities were outlined in the study.

Keywords P2 receptors · Purinergic signaling pathway · Active ingredients of Chinese herbs

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Introduction

Purine substances, being responsible for information transmission, define metabolic adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and adenosine by nucleotides [1]. Purinergic signaling pathway refers to the system of purinergic signal transduction consisting of endogenous nucleosides, nucleotides, and their receptors [2]. Sensitized purinergic receptors may perform different functions in the manner of neurotransmitter, autocrine or paracrine, and cause pain, inflammation, ischemic stroke, diabetes mellitus, and cancer [3, 4]. In the family of purinergic receptors, adenosine-activated P1 receptors (P1R) are comprised of four

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subtypes, A1R, A2AR, A2BR, and A3R [5]. ATP- and ADP-activated P2R are subdivided into two subtypes, P2XR and P2YR [6, 7]. The hydrolyzed ATP starts working after binding to P2R and then ecto-ATPases on the surface of most cells extract one and two phosphorus atoms of ATP, turning them into ADP and AMP, respectively, or even adenosine alone [8, 9]. In addition, ectonucleoside triphosphate phosphohydrolases (ENTPDases), ecto-5'-nucleotidase (5'-NT), ecto-nucleotide pyrophosphatase/phosphodiesterases (ENPPs), and alkaline phosphatases (APs) are involved in the degradation of ATP [10–12]. ATP signaling can be classified into short term and long term [13]. In the purinergic signaling pathway, extracellular ATP

is hydrolyzed to different ATP analogs via several enzymes [14]. ATP has been shown to function on purinergic receptors and then activate or inhibit the effector enzymes coupled with G proteins, thereby activating the amplification of the downstream signal cascade [15, 16]. ATP may also directly target the gated ion channels by ligands, allowing signal transduction to be accomplished by ion flow across the membrane [17]. Meanwhile, in both neurons and non-neurons, extracellular ATP plays a very vital biological role [18]. In the central and peripheral nervous systems, short-term ATP signaling could serve as a co-transmitter and neuromodulator to participate in platelet aggregation, endocrine and exocrine secretion, and blood vessel

Table 1 Chinese herbals derived-compounds targeting purinergic P2 receptors and involved mechanisms.

Active ingredients	MF	MW	Chemical formula	Dose (mg·kg ⁻¹)	Pharmacological actions	Targets	Ref
Tetramethylpyrazine	C ₈ H ₁₂ N ₂	136.198		100, i.p., 2 w	Anti-inflammation, strengthening heart, lowering blood pressure, inhibiting platelet aggregation and relieving pain	P2X3R	[45-52]
Sodium Ferulate	C ₁₀ H ₉ NaO ₄	216.168		100, i.p., 2 w	Alleviating hyperalgesia and neuropathic pain	P2X3R	[53-54, 160]
Lappaconitine	C ₃₂ H ₄₄ N ₂ O ₈	584.71		4, i.p., 2 w	Anti-inflammation, anti-nociception, anti-arrhythm, anti-rheumatism, anti-cancer, inhibiting the activity of hippocampal neurons and immunoregulatory activities	P2X3R	[55, 56]
Hesperidin	C ₂₈ H ₃₄ O ₁₅	610.561		50, i.p., 2 w	Inhibiting the nociceptive transmission	P2X3R	[57]
Sinomenine	C ₁₉ H ₂₃ NO ₄	329.390		40, i.p., 2 w	Anti-inflammation and relieving the hyperalgesia	P2X3R	[60]
1,8-Cineole	C ₁₀ H ₁₈ O	154.249		100, i.p., 2 w	Anti-inflammation, anti-oxidant and alleviating pathological pain	P2X3R	[61, 62]
Emodin	C ₁₅ H ₁₀ O ₅	270.24		50, i.p. 2 w	Anti-inflammation, inhibiting liver and kidney fibrosis, inhibiting cell proliferation, relieving peripheral neuralgia and inhibiting breast and lung cancer	P2X2R, P2X3R, P2X7R, ADA	[68] [104-106], [145]
Curcumin	C ₂₁ H ₂₀ O ₆	368.385		4 mg/mL, sublingual vein, 2 w	Desensitizing the primary afferents of DRG, relieving mechanical and thermal hyperalgesia	P2X3R P2X7R P2Y12R	[70] [127] [71]
Gardenoside	C ₁₇ H ₂₄ O ₁₁	404.368		60 μmol/mL, i.g., 2 w	Protecting neural cells and treating neuropathic pain	P2X3R P2X7R	[72]
Puerarin	C ₂₁ H ₂₀ O ₉	270.24		100, i.p., 2 w	Improving the cardiac function by relieving the inflammation and associated pain	P2X3R P2X7R	[76-78, 133] [79]

Table 1 (continued)

Resveratrol	C ₁₄ H ₁₂ O ₃	228.24		100 and 200, i.p., 4 w	Anti-oxidant, anti-free radical, anti-tumor, anti-microbial and anti-platelet aggregation	P2X3R P2X7R	[81–82] [83, 84]
Astragaloside	C ₂₁ H ₂₀ O ₁₁	448.38		50, i.g., 2 w	Suppressing neuropathic pain	P2X4R	[85]
Artemisinin	C ₁₅ H ₂₂ O ₅	282.336		5, i.p. 2 w	Anti-inflammation, anti-tumor and anti-malaria	P2X4R	[86–88]
Osthole	C ₁₅ H ₁₆ O ₅	244.285		20, i.p. 2 w	Suppressing neuropathic pain and nociceptive responses and alleviating hyperglycaemia	P2X4R	[89, 90]
Mangiferin	C ₁₉ H ₁₈ O ₁₁	422.342		100, i.g. 1 w	Anti-inflammation and anti-apoptotic effects	CD73R	[103]
Rhein	C ₁₅ H ₈ O ₆	284.220		10 µM/L	Anti-inflammation, anti-tumor and anti-angiogenesis	P2X4R P2X7R	[110] [111]
Naringin	C ₂₇ H ₃₂ O ₁₄	580.535		80 µM	Anti-inflammatory, anti-oxidative and anti-apoptotic properties	P2X7R	[112–113]
Geniposide	C ₁₇ H ₂₄ O ₁₀	388.366		33.2 µg/mL	Anti-inflammation	P2Y14R	[114–116]
Evodiamine	C ₁₉ H ₁₇ N ₃ O	303.365		0.25 µM	Anti-inflammation, anti-rheumatic and anti-nociceptive effects	P2X4R P2X7R	[120] [121]
Bullatine A	C ₂₂ H ₃₃ NO ₂	343.503		50 µM	Anti-inflammation	P2X7R	[123]
Oxymatrine	C ₁₅ H ₂₄ O ₂	264.363		5, i.p., 2 w	Anti-inflammation, anti-ulcer, anti-arrhythmic and anti-tumor	P2X3R	[134–135]
Baicalin	C ₂₁ H ₁₈ O ₁₁	446.364		100, i.p., 2 w	Anti-inflammation, anti-oxidative and anti-apoptotic activities	P2Y12R	[136, 137]
Isorhapontigenin	C ₁₅ H ₁₄ O ₄	258.27		60 µM	Anti-inflammation, anti-cancer and anti-oxidant activities	P2Y12R	[152–155]

MF, molecular formula; MW, molecular weight

regulation [19]. However, cell proliferation, differentiation, and apoptosis are affected by long-term ATP signaling. It is also involved in the healing of wounds, atherosclerosis, and renovation of epithelial cells, inflammation, and also tumorigenesis [20–22]. The development of distinct effects depends on the concentration of extracellular ATP, state of the target cell, and subtype of purinergic receptor [23] (Table 1).

Numerous studies have shown that a significant number of diseases are involved in purinergic signaling pathways [24, 25]. Nevertheless, most of the medications used for clinical treatment of the above-mentioned diseases have weak therapeutic effects and some obvious side effects, compromising patients' quality of life and further raising the burden of society's health care [26, 27]. Therefore, it is urgently needed to develop

alternatives with better therapeutic effect and little impact on other normal physiological functions. In the clinical prevention and treatment of purine disorders with less side effects, conventional Chinese medicines (TCMs) such as acupuncture medicinal plants and their herbal extracts prospectively have specific advantages [28–30]. In addition, several studies have shown that novel unique molecular entities derived from TCMs are capable of upgrading these diseases via P2R modulation [31, 32]. Thus, the purpose of this review was to summarize the active ingredients of TCMs that have potential cure effects by regulating P2 purinergic signaling pathways.

Active ingredients of TCMs for painful diseases management via P2X3R and P2X7R

As an uncomfortable feeling caused by tissue injury, depending on the time or period, pain can be divided into acute pain (physiological pain) and chronic pain (pathological pain) [33–35]. Although acute pain evoked by trauma or surgery has self-healing properties, if left unchecked, it can be converted into chronic pain [36]. It can be further categorized into neuropathic pain, cancer pain, and inflammatory pain [37]. However, a growing number of animal experiments have shown that intradermal injection of ATP and its analogs can induce in vivo pain-defending behaviors [38–40]. Neurons may be stimulated by activated nociceptors with ATP to generate extreme inward currents leading to neuropathic pain and abnormal behavioral manifestations [41, 42]. In detail, in acute isolation and culture of dorsal root ganglia (DRG) neurons, ATP or its agonists released by post-synaptic or impaired nerves can induce inward depolarizing currents and elicit pain mediated by P2XR [43]. Therefore, there is a close connection, particularly in neuropathic pain, between pain and purinergic signaling pathways. Researchers have recently found that some of the established TCM compounds had an effect on pain through purinergic P2R [44].

Tetramethylpyrazine (TMP) pain relief was closely linked to its robust anti-inflammatory effects as an active component of the amide alkaloid derived from *Ligusticum walliichi* [45–47]. Nociceptive reactions caused by ATP or β -meATP have been shown to be inhibited by intrathecal application of TMP [48]. Meanwhile, intracellular records have shown that TMP can reduce the depolarization potential of ATP or β -meATP induced by the DRG nerve cell membrane [49]. By blocking the expression of P2X3R in trigeminal neuralgia, TMP may also inhibit P2X3R-mediated pain transmission in neuropathic primary sensory neurons in burned rats [50, 51]. Moreover, in HEK293 cells transfected with a P2X3R plasmid, TMP retained ATP-activated currents [52]. *Ligusticum walliichi* sodium ferulate (SF) could restrain hyperalgesia in DRG neurons and initiate pain and primary afferent sensitization in chronic constriction injury (CCI) rats by reducing pain transmission mediated by P2X3R [53, 54]. Similarly, decreased P2X3R expression and sensitization by

lappaconitin reduced the analgesic effect of CCI rat DRG neurons [55, 56]. Hesperidin inhibited P2X3R mediated nociceptive transmission in the DRG of CCI rats [57]. Sinomenine's suppressed expression of P2X3R can explain its anti-inflammatory pain effects [58–60], while 1.8-cineole anti-inflammatory effects have contributed to the relief of pathological pain triggered by P2X3R stimulation [61, 62]. Robust anti-inflammatory, anti-cell proliferation, and anti-liver and kidney fibrosis is exerted by Emodin primarily isolated from rhubarb, polygonum, and buckthorn [63–67]. More specifically, emodin blocked the thermal and mechanical allodynia transmission of neuropathic pain by reducing P2X2R and P2X3R expression [68]. Amusingly, curcumin nanoparticles with improved bioavailability can inhibit activation of P2X3R and P2Y12R, resulting in mechanical hyperalgesia and thermal hyperalgesia in gp120-treated rats by desensitizing the primary afferents of DRG [69–71]. The natural *Gardenia jasminoides* Ellis fruit glycoside ligand gardenoside can be a possible medication for the treatment of sciatica by decreasing P2X3R and P2X7R [72]. Puerarin has been predominantly used clinically for pain-related cardiovascular disorders such as angina pectoris, myocardial infarction, and coronary heart disease as a flavonoid glycoside identified from radix puerariae [73–75]. The mechanisms involved may be linked to the reduction of P2X3R and P2X7R mRNA and protein levels in peripheral mononuclear cells [76–79]. In *Polygonum cuspidatum*, resveratrol (RES) relieves pain in peripheral and central inflammatory diseases by decreasing arachidonic acid metabolism [80]. In addition, RES suppressed neuropathic pain transmission in DRG satellite glial cells and relieved mechanical hyperalgesia in rats treated with gp120 by inhibiting P2X3R and P2X7R [81–84]. Astragalin therapy has been reported to be able to reduce neuropathic pain by blocking P2X4-mediated signaling in rat DRG [85]. Artemisinin could inhibit the upregulation of P2X4R in satellite glial cells as a form of sesquiterpene lactone in *Artemisia annua* leaves, thereby alleviating abnormal mechanical and thermal pain in rats with neuropathic pain [86–88]. Similarly, the anti-inflammatory and anti-oxidant properties of osthole may be impaired by downregulation of P2X4R and relief of mechanical and thermal hyperalgesia in DM rats [89, 90], as well as by neuropathic pain and nociceptive reactions [91]. Accumulated evidence indicates that purines contribute to the initiation and development of pain as a key component. To relieve pain-related diseases, the majority of active ingredients in TCMs will mainly target P2X3R and P2X7R.

Active ingredients of TCMs for inflammation-related diseases management via P2X4R and P2X7R

As a normal and essential reaction to infection, cell stress, and tissue damage, immoderate inflammation involves a complex

process that helps the body to recognize and battle foreign antigens, causing rheumatoid arthritis, atherosclerosis, and cancer [92–94]. The ATP purinergic signaling mediator has been shown to contribute to the fine tuning of inflammation and immune responses, effectively eliminating minimal damage to healthy tissues [95, 96]. Evidence has shown that the upregulated P2XR of immunocytes can trigger an inflammatory cascade [97]. Predominantly expressed P2X7R in various types of macrophages participated in immune responses and inflammatory diseases [98]. Predominantly expressed P2X7R in various types of macrophages participated in immune responses and inflammatory diseases [99].

By decreasing ATP hydrolysis, curcuminoids from ginger and turmeric exerted anti-inflammatory properties in hypertensive rats [100–102]. The anti-inflammatory properties of mangiferin were correlated with the activation of adenosine-CD73 signaling pathway, attenuating renal ischemia reperfusion injury [103]. The P2X7R-related inflammation responses induced by ATP could be repressed by emodin as a potential P2X7R antagonist [104–106]. Rhein is a natural bioactive derivative of anthraquinone extensively found widely in TCMs such as rhubarb, polygonum multiflorum, and aloe. They have anti-inflammation, anti-tumor, and anti-angiogenesis activities [107–109]. Rhein has been reported to inhibit ATP-induced inflammatory responses through inhibition of P2X4R and P2X7R, as evidenced by depressed development of Ca^{2+} and ROS, as well as by suppressed expression of MMP-9, COX-2, IL-6, and IL-1 β [110, 111]. Naringin inflammatory inhibition has also been confirmed in relation to the reduction of P2X7 expression in gp120-induced inflammation [112, 113]. Gardenia is a widely used TCMs in clinic in the treatment of inflammation and fever [114, 115]. Its bioactive compound geniposide is related to interfering with P2Y14R expression and inhibition of ERK1/2-mediated inflammatory events [116]. Interestingly, it was announced that low adenosine expression may intensify the inflammatory injury of renal ischemia reperfusion insults in rats, which was reversed by administration of ferulic acid [117, 118]. In extremely glucose-challenged human umbilical vein endothelial cells, evodiamine-suppressed P2X4R and P2X7R lead to inflammation recurrence [119–121]. Bullatin A selectively antagonizing P2X7R was closely linked to ATP-induced BV-2 cell inflammatory injury inhibition [122, 123]. Reduced P2X7R expression was correlated with the anti-inflammatory effect of cis-RES, leading to suppression of ROS production and activation of caspase-1/4 [124, 125]. Existing inflammatory suppression of curcumin stopped post-stroke depression development by inhibiting the activity of P2X7R [126, 127]. According to the above literature, the active ingredient of TCMs can explicitly inhibit P2X4R and P2X7R activity, thereby restricting the expression of inflammatory factors such as IL-6 and IL-1 β .

Active ingredients of TCMs for myocardial ischemia diseases management via P2X3R

Ischemic cardiomyopathy mainly manifested as metabolic disorders of cardiomyocytes, heart enlargement, arrhythmia, and heart failure, becoming the leading cause of death in the world [128–130]. Adenine nucleotides and nucleosides can function on purinergic P2XR of cardiovascular system and improve the performance of ischemic myocardium by enhancing contractility and relaxation [131, 132]. Puerarin therapy reduced ATP-activated currents in DRG neurons and upregulated P2X3R in the superior cervical ganglia (SCG) and cardiac sympathetic nerves after myocardial ischemia [55, 133]. Oxymatrine withstood the exacerbated sympathoexcitatory reflex by decreasing the activation effect of P2X3R in SCG and DRG neurons, which blocked nociceptive transmission triggered by myocardial ischemia in rats [134, 135]. In diabetic cardiac autonomic neuropathy, treatment with baicalin reduced elevated expression and activation of P2Y12R and repressed phosphorylation of p38-induced inflammatory injury [136, 137]. In conclusion, TCMs active ingredients are potential drugs to confine myocardial ischemia diseases by ameliorating ATP metabolic disorders and reducing P2X3R in purinergic signaling.

Active ingredients of TCMs for cancer management via P2X7R

Cancer has become one of the major diseases affecting the health and longevity of people, given the increasing morbidity and mortality [138, 139]. It has been established that there are relatively high levels of ATP in the tumor microenvironment, raising the amount of purinoreceptors [140–142]. Natural products actually play an important role in the treatment of cancer, with a large number of anti-cancer agents used in clinical therapies coming from a range of natural sources, including plants, animals, and microorganisms [143]. Zhang et al. showed that emodin exhibited strong cytotoxic activity against leukemia cells of K562 by inhibiting adenosine deaminase (ADA) activity [144]. Simultaneously, emodin could reduce the invasiveness of human breast and lung cancer cells as a P2X7R antagonist [145]. *Uncaria tomentosa* (Willd.) DC. (Rubiaceae). Rubiaceae have excellent anti-oxidant efficiency and are used for a number of therapeutic purposes, including cancer, arthritis and inflammatory diseases [146]. Its hydroalcoholic extract can decrease P2X7R expression in MDA-MB-231 cells; tumor invasion and metastasis may be restrained [147]. The above studies indicated that the active ingredients of TCMs could be a possible tool for cancer treatment by reducing ATP concentration and P2X7R activity in the microenvironment of the tumor.

Active ingredients of TCMs for platelet-related diseases management via inhibiting adenine nucleotides and nucleosides

Platelets activation can result in the expression and/or activation of surface receptors, secretion of vasoactive substances, adhesion, aggregation, and finally thrombus formation [148, 149]. In addition, thromboxane A2 and ADP secreted agonists in turn generate subsequent transmembrane signaling [150]. Adenine nucleotides and nucleosides such as ATP, ADP, and adenosine modulate platelet aggregation [151]. Isorhapontigenin (ISO) isolated from *Gnetum cleistostachyum* has been shown to exhibit effects of anti-cancer, anti-oxidant, and anti-inflammatory [152–154]. It has also been stated that ISO has selective inhibitory effects on platelet activation induced by ADP, likely by binding to P2Y₁₂R [155]. The activity of platelets with ectonucleotidase was shown to exert a hypotensive effect by increasing circulating ATP concentrations [156]. Similarly, by suppressing the hydrolysis of ATP, ADP, and AMP, ginger and turmeric rhizomes may effectively decrease platelet ectonucleotidase and adenosine deaminase activity in hypertensive rats [157]. *Scutia buxifolia* Reissek extracts led to the depression of NTPDase and CD73 function, defending against platelet aggregation caused by ADP in rats [158, 159]. Similarly, the therapeutic effects of activation of cAMP and cGMP on thrombosis were also observed in SF [160]. The above evidence suggests that by inhibiting the concentration of adenine nucleotides and nucleosides, the active ingredients of TCMs could minimize platelet aggregation. By systematically and deliberately reviewing the literature of active ingredients for purinergic signaling.

Conclusion and future prospects

Growing studies have reported that P2R is closely linked to pain-, inflammation-, cardiovascular disease-, cancer-, and platelet-related diseases in the purinergic signaling pathway [43, 97, 132, 142, 151]. According to the review of the above literature, we found that these above diseases could be notably alleviated by inhibiting the behaviors of P2X₃, P2X₄, and P2X₇. TCMs exert curative effects and lower prices with their own special mechanism, as well as more plentiful natural resources [161–163]. However, there are still many concerns about using of TCMs to treat diseases that are related with purinergic signaling. First, we found that toxic reactions caused by purine receptors targeting were rarely investigated. For example, evidence has shown that long-term usage of rhein can cause liver and kidney toxicity [164]. In addition, testing the in vivo metabolic process and tissue distribution of active ingredients is crucial. A strong forum for systematic elucidation of drug absorption, delivery, metabolism,

excretion, and toxicity may be the combined metabonomics, serum pharmacochimistry, and tissue-targeted and microfluidic-dependent mass spectrometry imaging [165–167]. Meanwhile, studies have shown that some of the active compounds, such as palmatine, are not readily absorbed in the body and have lower bioavailability [168]. To improve the solubility and concentration of drugs in the tissue, biocompatible molecular nanotechnology, and targeted drug technology can be executed. It is surprising that the CRISPR-edited P2XR approach can be used to investigate the in-depth mechanisms of purine disorders in diseases and drug efficacy [169].

Authors' contribution Sanyin Zhang and Xiaobo Wang conceived the study; Xing Dong, Xiaopeng Ai, Ying Guo, Peng Yang, Ya Hou, and Jinrong Bai collected, analyzed, and interpreted the relevant literatures; Xing Dong and Ya Hou drew all the figures; Xiaopeng Ai, Xing Dong, and Xiaobo Wang wrote the manuscript; Sanyin Zhang and Xiaobo Wang supervised the study and revised the manuscript. The final version of the manuscript was read and approved by all authors.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable

Conflict of interest All authors declare no competing interests.

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