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REVIEW ARTICLE

Purinergic receptor ligands: the cytokine storm attenuators, potential therapeutic agents for the treatment of COVID-19

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ABSTRACT

The coronavirus disease-19 (COVID-19), at first, was reported in Wuhan, China, and then rapidly became pandemic throughout the world. Cytokine storm syndrome (CSS) in COVID-19 patients is associated with high levels of cytokines and chemokines that cause multiple organ failure, systemic inflammation, and hemodynamic instabilities. Acute respiratory distress syndrome (ARDS), a common complication of COVID-19, is a consequence of cytokine storm. In this regard, several drugs have been being investigated to suppress this inflammatory condition. Purinergic signaling receptors comprising of P1 adenosine and P2 purinoceptors play a critical role in inflammation. Therefore, activation or inhibition of some subtypes of these kinds of receptors is most likely to be beneficial to attenuate cytokine storm. This article summarizes suggested therapeutic drugs with potential anti-inflammatory effects through purinergic receptors.

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Introduction

In December 2019, the initial reports about the patients with pneumonia probably associated with seafood products in Wuhan were recorded [1]. Promptly severe acute respiratory syndrome coronavirus (SARS-CoV-2) was identified as the cause of coronavirus disease-2019 (COVID-19) which became a pandemic rapidly. Although it is less known about the SARS-CoV-2 pathogenesis, it is well known that the interaction between the patients' immune system and SARS-CoV-2 determines the diversity of symptoms of the disease [2]. Cytokine storm syndrome (CSS) is a subject linked to COVID-19 which has been investigating during coronavirus pandemic [3–6]. In CSS, a group of disorders results in systemic inflammation, multiple organ failure, and hemodynamic fluctuations [7]. Various experiments have indicated high plasma levels of cytokines and chemokines in patients with COVID-19-associated CSS. Lung infection caused by the coronavirus initially increases chemokines secretion, which is a stimulating factor for the migration of innate immune cells to the site [8–10]. IFN-γ has been demonstrated as a critical mediator of inflammation in CSS. Interleukin-1β (IL-1β), IL-18, and IL-33, with a crucial role in inflammation *via* natural killer (NK) and T cells, stimulate the secretion of IFN-γ. Besides, IL-1β and IL-18 are the hosts' responses to infection and inflammatory conditions [11,12].

Moreover, it has been supposed that IL-6 has a significant role in CSS so that a high level of IL-6 causes cardiovascular dysfunctions [13]. Serious attempts have been carried out to control these cascades; however, they have not been fully successful so far. High levels of IL-10 have also been unable to alleviate inflammation storm [3]. Using tocilizumab (an anti-IL-6 receptor antibody) has had promising results in 21 COVID-19 patients with critical conditions in China [14]. Canakinumab has also been used for selective inhibition of IL-1β which has given encouraging results [15]. Many therapeutic agents administered in COVID-19 have been aimed to regulate the storm of inflammation. Tocilizumab (an immunomodulator) is the most administered drug in the therapy of COVID-19. Anakinra, baricitinib, corticosteroids, chloroquine, hydroxychloroquine, etc., have been used chiefly as immunomodulatory drugs to treat COVID-19 so far [16]. The significant role of purinoceptors, located on immune cells (neutrophils, eosinophils, monocytes, macrophages, mast cells, and lymphocytes), has been documented in inflammatory cytokines release [17,18]. These receptors, classified as P1 and P2, respond to adenosine and ATP, respectively [19,20]. Extracellular ATP and its derivatives act on purinoceptors that are involved in inflammatory conditions [20]. It seems that the role of purinergic receptor inhibition has not been considered thoroughly in the therapy of COVID-19 [21]. In the current literature, we aimed to review and suggest some synthetic and natural blockers of purinergic receptors which may have beneficial effects on the treatment of COVID-19 through CSS inhibition (Figure 1).

Purinoceptors role in inflammatory conditions

Purinergic signaling receptors comprise P1 adenosine and P2 purinoceptors. The first group is divided into subfamilies (A1, A2A, A2B, and A3). The P2 purinoceptors are classified into

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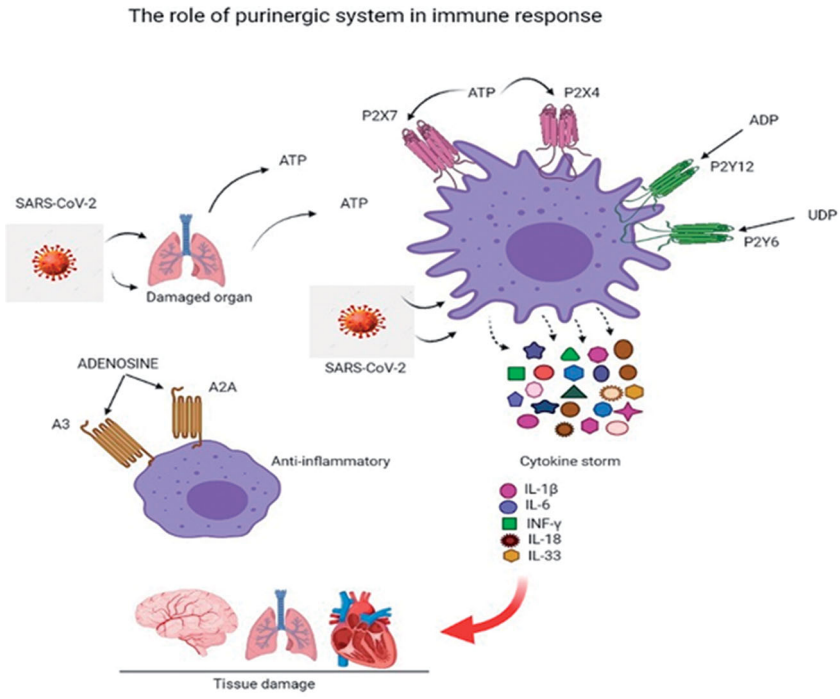

Figure 1. The role of purinergic signaling on immune system activation. The nucleotide adenosine triphosphate (ATP) and its derivatives released from injured tissues act on various purinoceptor subtypes of P1 and P2. When activated, P2 receptor subtypes (P2X, P2Y) expressed on various immune cells participate in the release of several inflammatory cytokines. P1 receptors (A1, A2, A3) however have an anti-inflammatory effect.

P2X ionotropic nucleotide receptors (P2X1-7) and P2Y (P2Y1-2, P2Y4, P2Y6, and P2Y11-14) metabotropic nucleotide receptors [18,22].

Although various studies indicated the crucial role of P2X receptors (P2XR) in inflammation [23–25], the inhibitory role of A2A receptor (A2AR) in proinflammatory cytokines production [26–29] and cardioprotective role of A1and A3 receptors have been revealed. Therefore, upregulation of them (A2A, A1, A3) may have a beneficial effect on lung, heart, and kidney injury caused by CSS in COVID-19 [30–34]. Adenosine A2AR expressed in macrophages, neutrophils, lymphocytes, platelets, and endothelial cells and the A2A signaling are engaged in the development of regulatory T cells that negatively affect T cells activation [35]. Thus, it possesses a significant anti-inflammatory and antithrombotic effects in this regard [36–38]. Although anti-inflammatory and proresolution effects of A2B have been reported by some studies [39–44], other experiments have shown that A_{2B} receptor not only plays a significant role in the triggering of inflammatory response by mast cells, but also has proinflammatory effects in various human lung cell types [45–48]. It seems that that anti-inflammatory or pro-inflammatory role of A2B receptors varies based on the different types of inflammation and tissues [49]. A3 signaling suppresses neutrophil degranulation in injured tissue, activation of TNF-α and platelets, and chemotaxis of eosinophils [50]. Moreover, A3 receptors play an anti-inflammatory role [51–53]. However, it must be emphasized that, although suppressing some inflammatory cytokines may be helpful, attenuating cellular and humoral immunity may adversely affect virus clearance. In this regard, while A2A receptors have potent anti-inflammatory (e.g. by suppressing monocyte cytokine production) roles, they are also potent immunosuppressive receptors [54,55].

Among P2XR subtypes (P2X1-7), the critical role of P2X1, P2X4, and P2X7 receptors (P2X1R, P2X4R, and P2X7R) in inflammatory conditions has been well identified [21,56]. T lymphocyte activation is linked to P2X1R due to its role in the entrance of calcium into the cell [57]. Data have shown the wide distribution of P2X4R in the brain, spinal cord, ganglia, liver, kidney, and lung [58,59]. Furthermore, P2X4R is expressed at high levels of mRNA in immune cells [57]. Besides, P2X4R fast trafficking to the macrophages in response to inflammatory provocations [60] and augmentation of bacterial killing ability of these cells have been indicated [61].

P2X7R, well known in different inflammatory conditions, is also expressed on immune cells (macrophages and monocytes). It has an essential role in CSS by releasing inflammatory cytokines and chemokines, such as IL-1, IL-2, IL-6, IL-18, IL-1β, and IL-1α, suggesting the vital role of P2X7R inhibitors in patients with intensified immune responses in COVID-19 [23,62]. Moreover, in response to viral infections, P2X4R, P2X2 receptors (P2X2R), and P2X7R expressed in microglia, astrocytes, and neurons, stimulate the release of inflammatory cytokines and chemokines, including reactive oxygen species (ROS), nitric oxide (NO), IL-1β, and tumor necrosis factor α (TNF-α) [63–68].

P2Y1R and P2Y2R expressing strongly in macrophages have also a significant part in CSS *via* the release of inflammatory mediators, such as TNF-α, IL-1β, IL-6, and NO [69]. In addition, P2Y1-2 receptor blockade can inhibit platelet function in acute coronary syndrome [70,71]. The P2Y2R receptor has a regulatory impact on production of mucus by airway epithelia [72].

Purinergic signaling in SARS-CoV-2 infections

Acute respiratory distress syndrome (ARDS) is a common complication of COVID-19. Similar to other coronaviruses, SARS-CoV-2 involved the central nervous system; thus, clinical manifestations, such as acute cerebrovascular problems, headache, and disturbed consciousness have been recorded [73,74]. Cytokine storm which is by SARS-CoV-2 can result in severe lung disease and eventually ARDS [75,76]. Furthermore, ATP-P2X7 receptor footprint is similarly visible in this acute lung injury [77,78]. In addition to the lungs, capability of SARS-CoV-2 to enter macrophages has been verified. Therefore, here a logical idea might be the inhibition of macrophages to prevent coronavirus damages [79]. Myocardial damage associated with COVID-19 infection has been reported as a substantial manifestation of the disease. The host immune responses are the prominent reason for cardiovascular diseases caused by SARS-CoV-2 infection. The severity of lesions depends on the intensity of inflammatory cytokine and chemokine release [18]. There are convincing reasons that inhibition of P2XR may lead to inhibition of macrophages and hence, attenuate the cytokines storm and coronavirus injuries. P2X receptors (especially P2X7R) highly expressed in macrophages stimulate IL-1β, IL-18, and IL-6 releases. Besides, the critical role of these cells firstly in the cytokine storm in COVID-19 and secondly in the expression of angiotensin-converting enzyme 2 (ACE2; a receptor used by the virus to get into human cells) have been documented [80,81].

Purinergic system inhibitors, encouraging agents for attenuating the cytokine storm

Regarding the immunomodulatory effect of the purinergic system, it seems that P2X1R, P2X4R P2X7R, P2Y1R, and P2Y2R inhibition and A2A and A3 receptors upregulation could be an inspiring mechanism for attenuating CSS in COVID-19. The following synthetic and natural products with potential inhibitory effects on purinergic receptors are supposed to be useful for controlling the cytokine storm COVID-19.

Adenosine

Adenosine, as previously described, exerts anti-inflammatory effects through adenosine receptors. It has been suggested that increasing the adenosine levels by targeting the enzymatic regulators (adenosine deaminase, adenosine kinase, equilibrative nucleoside transporter 1) might have a therapeutic role against COVID-19 [82].

Adenosine has indicated the ability of diminishing inflammation, regulating endothelial integrity as well as lung fluids in animal models of ALI and ARDS [83–85]. In the case of lung inflammation, it fosters cellular response to hypoxia [86] and reduces the extravasation of cytokines and proteins on the alveolus [87]. To investigate the therapeutic effect of adenosine in COVID-19, for a patient suffering from SARS-CoV-2-related ARDS on routine therapies who did not show clinical improvements, inhaled adenosine in a mixture of 21% oxygen was applied. After 5 days, the SARS-CoV-2 test was negative and a rapid improvement in clinical condition as well as radiological pictures was shown [88]. Therefore, it seems that adenosine can act as a therapeutic option for COVID-19 ARDS.

Methylxanthines

It seems that cytokine storm, inflammation, and suppressed immune system, peculiarly lymphopenia, neutropenia, and a diminished level of Cluster of Differentiation 8+ (CD8+) T cells, are the main features in most patients with COVID-19 which ultimately result in COVID-19 induced lung diseases [89–91]. On the other hand, methylxanthines have been being used to treat bronchial asthma due to their impact on lowering airway inflammation and hypersensitivity. The role of purinergic receptors (P_1) inhibition by methylxanthines for reducing inflammation has been identified [92]. These drugs have shown immune-modulatory effects in low therapeutic concentration [93].

Caffeine and theophylline (more potent) are nonselective adenosine receptor antagonists [94,95]. ATP liberated from injured cells is broken down to adenosine in an enzymatic reaction [96]. Except for the A3 receptor, theophylline and caffeine inhibit A_1, A_{2A}, and A_{2B} receptors at therapeutic concentrations [95]. While caffeine exerts an anti-inflammatory effect in high plasma concentration (100 μM or more) through phosphodiesterase inhibition, it may exacerbate the immune response in normal plasma concentration (50–60 μM) [92]. It has been supposed that decreasing inflammation by theophylline in asthma and chronic obstructive pulmonary disease (COPD) is a beneficial privilege of theophylline administration. Regarding the importance of A_{2B} receptors on mast cells in the initiation of the lung inflammatory response, a relatively potent blockade of the A_{2B} receptor by theophylline at pharmacological concentrations could be significant [36,45,97]. Therefore, theophylline shows pro-and anti-inflammatory effects by antagonizing A_1, A_{2A}, and A_{2B} receptors [98]. Recently, it has been suggested that the co-administration of theophylline and corticosteroids during the therapy of patients with COVID-19 may amplify the anti-inflammatory effect of corticosteroids and reduce corticosteroid resistance [99]. Pentoxifylline (another methylxanthine) as a potential anti-inflammatory and the immunomodulatory drug has been recommended to treat COVID-19 [91]. Pentoxifylline (PTX) activates A2AR response to adenosine which stimulates the production of IL-10, an anti-inflammatory molecule [100,101]. Besides, in a randomized clinical control trial (RCT), pentoxifylline reduced IL-6 serum concentration [102], a risen cytokine during cytokine storm in the patients with COVID-19 [103]. Since the significant role of pentoxifylline in the suppression of IL-1β and IL-6 has been approved, its probable role as a potential therapeutic agent for the treatment of COVID-19 can be considered [104].

Dipyridamole

Dipyridamole (DIP) as an antiplatelet drug prevents intracellular uptake of adenosine that is released intracellularly [105]. Adenosine, a potent immunoregulatory nucleoside, acts on A2AR during inflammatory states to limit tissue damage and inhibit platelet activation [106,107]. DIP which is an adenosinergic pathway activator can be considered as a probable treatment for the COVID-19. Recently, an RCT showed that DIP decreased chronic inflammation associated with human immunodeficiency virus (HIV) through extracellular adenosine increase and T-cell activation decrease [108]. Moreover, in a controlled pilot study, patients with respiratory complications associated with COVID-19 were treated with DIP. All patients but one were recovered significantly compared to the control group in which death occurred in 23.5% of patients [109]. Considering DIP and pentoxifylline work in complementary ways to up-regulate A2AR signaling, co-administration of them for the early-stage treatment of COVID-19 has been proposed [105]. Apart from anticoagulant and anti-inflammatory effects, DIP blunts various viruses, including SARS-CoV-2 replication based on the various documents [105,109]. Regarding the SARS-CoV-2 complications, such as ARDS, hypercoagulability, and cytokine storm, DIP with the mentioned clinical profile may be useful in this regard.

Colchicine (P2X7 inhibitor)

Colchicine, a tricyclic lipid-soluble alkaloid extracted from Colchicum autumnalle and gloriosa superba, has been utilizing for several diseases, such as gout, pseudogout, scleroderma, amyloidosis, liver cirrhosis, recurrent idiopathic pericarditis, and even coronary artery disease [110,111]. Moreover, colchicine prevents superoxide production by leukocytes and the release of several cytokines and chemokines [112,113]. Colchicine also lessens TNF-α, IL-6, and IL-8 production [111,114]. It has also been documented that P2X7R activation releases inflammatory cytokines, like IL-1β, which finally leads to the inflammatory response [62,115]. In this regard, an *in vitro* study has shown that colchicine blocks P2X7 and P2X2 signaling pathways which consequently cause a significant decline in IL-1β, ROS, nitrites, and IFN-γ production [116].

Although anti-inflammatory effects of colchicine seem to be attributed to inhibition of microtubule polymerization and infiltration of leukocytes, the inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome is considered as the main mechanism [111,117]. Inhibition of inflammasome occurs as a consequence of P2X7R suppression [118]. In acute coronary syndrome, colchicine limits the production of interleukin IL-1b, IL-18, and IL-6 *via* NLRP3 inflammasome inhibition [119,120]. One of the primary pathogenic mechanisms of COVID-19 is thought to be *via* NLRP3 inflammasome [121]. When the SARS-CoV2 virus enters the cell through ACE2, immunological mechanisms stimulate NLRP3 activation [122]. According to experimental surveys inflammasome NLRP3 plays a vital role in developing ARDS/ALI [123–126].

Because of this anti-inflammatory potential of colchicine, several clinical trials have been investigating its therapeutic effects in COVID-19. The probable role of colchicine in preventing and managing COVID-19 complications associated with cytokine storm has been suggested [127]. A meta-analysis demonstrated the efficacy of colchicine in COVID-19 management [128]. Accordingly, a better survival rate of patients with severe COVID-19 on colchicine therapy at the day of 8 compared to standard therapy has been reported, which is attributed to inhibition of central pro-inflammatory cytokines responsible for ARDS [129]. Furthermore, colchicine administration in COVID-19 patients on the fifth day of fever or after the 8th day of influenza-like symptoms initiation was recommended by Della-Torre et al. to decrease ALI and multi-organ damage caused by cytokine storm as early treatment alters the immune response to SARS-CoV-2 [130]. Also, pretreatment of rats with colchicine in the study of Yue et al. illustrated improvement in lung oxygenation with a significant decline in pulmonary edema and neutrophil recruitment, which probably prevents ARDS development [131]. Thus, colchicine inhibits P2X7R, P2X2R, and consequently NLRP3 inflammasome which ultimately attenuates cytokine storm.

Antidepressants (paroxetine, duloxetine, fluoxetine) (P2X4 inhibitor)

Anti-inflammatory impacts of some antidepressant groups, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), are a portion of their therapeutic application [132–134]. Various antidepressants prevent numerous inflammatory mediators' secretion associated with blockade of purinergic signaling or different signaling pathway [135–139]. It has been shown that some antidepressants, including paroxetine, fluoxetine, maprotiline, or clomipramine block the human P2X4 receptors that paroxetine exerts the strongest inhibitory effect [135,136]. Likewise, paroxetine directly blocks human P2X7 [137] which mainly regulates the secretion of IL-1β from monocytes, macrophages, and microglia [62]. It has also been indicated that duloxetine inhibits rodent and human P2X4R but not P2X7R [140]. The effect of antidepressants on the secretion of various pro-inflammatory markers, including IL-10, IL-4, IL-1β, and TNF-α has been studied [139]. An investigation about the inflammatory responses of some antidepressants, such as fluoxetine, sertraline, paroxetine, citalopram, mirtazapine, fluvoxamine, and venlafaxine showed that all investigated antidepressants suppressed the IL-6 production so that the most and the least efficient drugs were fluvoxamine and venlafaxine respectively [141,142]. In this regard, except for citalopram, the other drugs prevented IL-1β secretion which the best efficacy was associated with venlafaxine. [141]. Furthermore, paroxetine downregulates IL-1β, TNF-α, and IL-17, and upregulates IL-10 [143]. In addition, venlafaxine prevents the production of TNF-α [132], and duloxetine enhances IL-10 levels [144].

A meta-analysis [145] conducted on patients with major depressive disorder on antidepressant therapy, importantly

SSRIs, showed low plasma level of inflammatory mediators, such as IL-10, TNF-α, and CCL-2 that are related to COVID-19 severity [146] and IL-6, which highly correlates with the disease mortality [146,147]. Moreover, associated with COVID-19 severity, TNF-α, IL-6, IL-10, and CCL-2 have been decreased in patients receiving antidepressants [145,146]. Similarly, in a retrospective observational study, COVID-19 patients on antidepressants, especially escitalopram, fluoxetine, paroxetine, and venlafaxine had a significantly lower risk of intubation or death [148]. The assumed mechanism consists of inhibition of acid sphingomyelinase activity [149], prevention of epithelial cell infection [150], controlling cytokine storm *via* acting as S1R agonist [151,152], lowering inflammatory mediators [145,146], and some antiviral effects [153]. However, as previously described anti-inflammatory effects of various antidepressants whether or not mediated by purinergic signaling might be beneficial in the therapy of COVID-19. They decrease inflammatory cytokines and chemokines by suppressing several pathways like the purinergic signaling pathway.

Gefapixan (P2X3 inhibitor)

P2X3 receptor (P2X3R), the ATP-gated ion channel, is expressed predominantly on peripheral sensory nerves and fibers that innervate the airways [154]. Histamine and ATP stimulate cough reflex through P2X3Rs [155]. The role of ATP and P2X3R in pain and inflammation has been reported previously [156,157]. In a mouse model of inflammatory bowel disease (IBD), the knockout of P2X3R lowered inflammatory symptoms [158]. Activation of P2X3R through inflammation of peripheral tissue contributes to the release of pro-inflammatory cytokines, including TNF-α and IL-8 that causes inflammatory hyperalgesia [159]. It has been proposed that bradykinin in inflamed peripheral tissue increases the release of ATP which activates P2X3R and results in inflammatory hyperalgesia [159]. Furthermore, P2X3R antagonists may alleviate inflammatory hyperalgesia by a mechanism other than affecting prostaglandin-E2 (PGE2) or released sympathetic amines at the site of inflammation [160]. However, P2X3R blockade does not affect IL-1β release [159]. Several human studies have demonstrated the increase of P2X3 expression in the urothelium of the bladder in interstitial cystitis [161], endometriosis endometrium, and endometriosis lesions [162]. It has been shown that in knee joint inflammation the rise of P2X3R expression in chondrocytes occurs that contributes to the inflammation process. Moreover, antagonizing P2X3R may help inflammatory joint disease [163]. Gefapixant, a P2X3R antagonist, has been investigated to control osteoarthritis of the knee and interstitial cystitis/bladder pain [164]

Gefapixant is shown to be effective for controlling chronic cough by regulating upper and lower respiratory tract sensitivity [165] which diminished cough frequency by 75% in a first trial [166]. Patients with chronic cough experience prolonged inflammation in the esophagus and lungs that stimulate afferent nerves causing reduced cough threshold and sensation of throat scratchiness [167].

A meta-analysis by Abu-Zaid et al. revealed the effectiveness of gefapixant in ameliorating frequency and severity of cough and quality of life [155]. Two weeks high-dose (600 mg/BID) gefapixant trial diminished cough by 75% [154]. Moreover, similar results achieved from another 2 weeks' treatment of patients with refractory cough with four different doses of gefapixant were significant with all doses [166].

It has been documented that although the initial cause of ARDS contributing to morbidity and mortality is the infection by SARS-CoV-2, the innate immune response is responsible for its development [168]. Based on a meta-analysis, the cough was reported in 57% of cases which is the most common primary symptom of these patients [169]. However, it can persist for months after recovery of the disease, named post-COVID syndrome [170]. Moreover, the infection of sensory nerves of the cough reflex by SARS-CoV-2 causes neuroinflammation which is considered as the mechanism of cough hypersensitivity [171].

As mentioned above, gefapixant, a P2X3R antagonist, regulates upper and lower respiratory tract sensitivity and improves chronic cough due to hypersensitivity. Therefore, co-administration of gefapixant with other agents for improving some respiratory complications of Covid-19 may be useful.

Clopidogrel, prasugrel, cangrelor, ticagrelor (P2Y12 inhibitor)

P2Y12R antagonists have been widely used as antithrombotic agents. Clopidogrel which is a prodrug blocks P2Y12R irreversibly. The other P2Y12R antagonists have been improved clinically and pharmacologically relative to clopidogrel [172]. Compared to clopidogrel, prasugrel, ticagrelor, and cangrelor are faster and more potent with stronger anticipated platelet inhibitory effects [173,174]. In addition to antithrombotic activity, the undeniable role of P2Y12 antagonists in preventing inflammation has been documented [175]. In this regard, it has been indicated that platelet activation has a significant part in inflammation. Moreover, P2Y12 receptors expressed in immune cells may participate in the inflammatory response [176]. Data have shown that P2Y12R which is expressed in microglial cells, activates them [177]. Various studies demonstrated that activation of P2Y12R in human eosinophils, macrophages, and T lymphocytes induced the release of eosinophil peroxidase, macrophage chemotaxis, and biological responses of T-cells, respectively [178–180]. When activated, platelets secretes a variety of proinflammatory mediators, such as IL-1β and IL-8 that have the main role in the activation, proliferation, and chemotaxis of immune cells [181–183]. Accordingly, some mediators released from platelets induce secretion of IL-6 from monocytes [184]. Moreover, several experiments indicated that P2Y12 inhibitors, such as clopidogrel and ticagrelor reduced the plasma levels of IL-6, IL-1β, and TNF-α in the human or rat model of lipopolysaccharide (LPS)-induced inflammation [185–188]. To date, several clinical studies investigating the anti-inflammatory effects of P2Y12 antagonists have been performed. In these experiments, P2Y12R is considered as a

potential target in different inflammatory diseases such as chronic asthma, pneumonia, and sepsis [186,189,190]. Similarly, inflammatory responses and thrombotic events are two crucial agents contributing to the morbidity and mortality of patients with COVID-19. As described above, the P2Y12 blockers reduce platelet–leukocyte aggregation and pro-inflammatory cytokines associated and non-associated with platelets. Thus, the beneficial effects of P2Y12R inhibition therapy should be further examined in thrombo-inflammatory disease.

Plant natural products

Identification of natural products, already been used as anti-inflammatory agents clinically, is more laborious compared to synthetic products. However, the anti-inflammatory effects of some plant natural products with the inhibitory effect on purinoceptors have been documented [191–193]. Nevertheless, most natural products acting on purinergic receptors have not been approved yet for clinical use.

The flavonoid amentoflavone extracted from the Rheedia longifolia leaves exerted anti-inflammatory activity and an inhibitory effect on P2X7R in Rat [194,195]. The flavones Baicalein and Resveratrol have shown anti-inflammatory effects associated with P2XR. These phenolic compounds significantly inhibited Ca2+ influx induced by P2X7R activation [196]. Interestingly, they have presented an exemplary safety and tolerance profile in clinical trials [197–199].

Puerarin is another flavonoid derived from the Chinese herb Pueraria lobate root which exerts its inflammatory effect by intervention in the P2X4 function and expression [200]. This compound has been used in China population for the therapy of ischemic stroke. Based on a meta-analysis, among the 35 randomized controlled clinical trials administered Puerarin for the stroke treatment, 11 trials slight adverse effects reported [201]. Then, considering its logical safety profile in humans, it can be considered for the attenuation of inflammatory responses in COVID-19.

Anthraquinones are other compounds with the anti-inflammatory effect which are available in several medicinal Chinese herbs, such as Cassia occidentalis, Rheum palmatum L., Aloe vera, and Polygonum multiflorum Thunb [202]. Emodin and rhein have shown anti-inflammatory and immunosuppressive effects. Recently it has been documented that emodin inhibits the P2X7R signaling pathway leading to a decrease in the release of pro-inflammatory cytokines [203,204]. Another anthraquinone, rhein is the major active metabolite of the commercial drug diacerein, approved to treat inflammatory osteoarthritis in many countries has exerted anti-inflammatory and immunosuppressive activity by interference in P2X7R-mediated responses [205,206]. However, human administration of these compounds has not been approved.

Conclusion

Cytokine storm results in multiple organ failure, peculiarly ARDS, which deteriorates the condition of patients with COVID-19 requiring prompt initiation of anti-inflammatory medications. Targeting purinergic receptors has been indicated to be a promising treatment to suppress inflammation. Medications with inhibitory effects on P2 purinoceptors or stimulating P1 adenosine receptors are recommended to be used as monotherapy or in combination with other drugs, efficient in COVID-19, to control inflammation and prevent complications.

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