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Natural phytochemicals as P2X7 receptor inhibitors for the treatment of inflammation-related diseases

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REVIEW

Abstract

P2X7 receptor (P2X7R) inhibition is critical for reducing the overactivation of its downstream signaling pathway in autoimmune diseases. Phytochemicals are a source of medicinal compounds for various diseases and contribute to the development of effective and safe P2X7R-targeted drugs. This review is aimed at identifying and screening novel safe, effective, and economically feasible inhibitors of P2X7R from phytochemicals extracted from food and plants. The results of the docking study revealed that the VINA scores of dihydrotanshinone, baicalin, berberine, genistin, dioscin, resveratrol, apigenin, cannabidiol, esculin, and luteolin were lower than or equal to that of A740003 (P2X7R inhibitor). The VINA scores of dihydrotanshinone and baicalin were lower than or equal to JNJ47965567 (P2X7R inhibitor). Dihydrotanshinone and baicalin can be used as lead compounds for P2X7R inhibition. These active ingredients will contribute to the discovery of lead compounds and the development of innovative P2X7R agents for the treatment of autoimmune diseases.

Keywords: autoimmune diseases; baicalin; dihydrotanshinone; molecular docking; P2X7 receptor; phytochemicals

Introduction

Currently, the P2X7 receptor (P2X7R) is being investigated as a potential therapeutic target for anti-inflammatory drugs (Di Virgilio *et al*., 2017). The potential of P2X7R has been highlighted in various inflammatory pathologies, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, rheumatoid arthritis (RA), and cardiovascular diseases (CVDs) (Adinolfi *et al*., 2018; Shi *et al*., 2021; Thawkar and Kaur, 2019).

The P2X family participates in purinergic signaling networks in which ATP (adenosine 5'-triphosphate), other nucleotides, and nucleosides are extracellular signaling molecules. The P2X receptor is a trimer-coordinated cation channel, and its family consists of seven receptors (P2X1-7), among which P2X7R is the highest content in the P2X family members (Illes *et al*., 2021). P2X7R is a unique member of the P2X receptor subclass, composed of the same three P2X7 subunits containing 595 amino acids. The gene is located on human chromosome 12q24.31 with 53kb spanning (Roman *et al*., 2009). P2X7R is widely expressed in monocytes or macrophages, T cells, mast cells, fibroblasts, epithelial cells, microglia, endocrine and exocrine pancreas in cells, and tissues (He *et al*., 2021). P2X7R can activate proinflammatory cascade reactions and play a key role in immunity and autoimmunity, which means that inhibiting

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P2X7R overexpression may be a novel trend for anti-inflammatory drug therapy (Xu *et al*., 2020).

Due to the chemical diversity of dietary phytochemicals, they have received increasing attention in the prevention and treatment of inflammation-related diseases (Zhu *et al*., 2018). In short, inhibition of P2X7R activity can be achieved by inhibiting inflammatory responses and inflammation-related diseases. Phytochemicals are a source of therapeutic substances for many diseases and contribute to the development of effective and safe drugs targeting P2X7R. Therefore, it is important to identify natural compounds that inhibit P2X7R activity. The purpose of this study is to search for and virtually screen novel safe, effective, and economically feasible P2X7R inhibitors from phytochemicals extracted from food and plants.

ATP and P2X7R

P2X7R is a ligand-gated ion channel, belonging to the purinergic type 2 receptor family (P2), which is activated by interaction with extracellular ATP molecules (Campagno *et al*., 2021). ATP can be considered the prototype of DAMPs. The molecular complex P2X7R/ATP induces conformational changes in protein subunits, opens a pore in the macromolecular structure of ion channels, and is released from damaged cells (Faria *et al*., 2019). Once in the extracellular space, ATP initiates and amplifies inflammatory processes by activating many different purinergic receptors in target cells (Huang *et al*., 2021). Specifically, most mammalian cells contain up to 5–10 mM of ATP in the cytoplasm, with concentrations in the extracellular space in the high nanomole or low micromole range (Nevoral *et al*., 2018). ATP, once released from the cytoplasm of damaged or dead cells or during its active release, can reach high concentrations in the extracellular space, activating micromole ATP concentrations leading to the opening of channels for Na^+, K^+, or Ca^{2+} (Na^+ and Ca^{2+} influx and K^+ efflux) through the plasma membrane (Haanes *et al.*, 2012; Zhao *et al*., 2021a). When P2X7R is stimulated by high ATP concentration (mM range), after a long time or repeated stimulation, P2X7R reaches a large permeability state, forming or inducing large conductivity ion channels. Molecules of more than 900 Da can penetrate the membrane through these large pores, thus making possible the liberation of inflammatory cytokines (Skaper *et al*., 2010).

P2X7R and NLRP3

Long-term stimulation of P2X7 by ATP leads to inflammatory cell death program termed "pyroptosis." The key role of P2X7R in the innate immune response is to rapidly activate the assembly of NLRP3 (nuclear oligomeric domain-like receptor family Pyrin domain contains 3) inflammasome (Pelegrin, 2021), and then the cleavage of NLRP3 inflammasome activates Caspase-1. Pro-IL-1β (Pro-interleukin-1β) and Pro-IL-18 are then cleaved to mature IL-1β and IL-18 (Sharma and Kanneganti, 2021). IL-1β and IL-18 are major mediators of P2X7-induced inflammatory response, promoting immune cell recruitment and inflammatory response (Ahn *et al*., 2020) (Figure 1). Activation of the NLRP3 inflammasome by P2X7R may be due to decreased cytoplasmic K^+ and increased cytoplasmic Ca^{2+}, which may be caused by channel opening or pore formation due to P2X7R activation. Danger-associated molecular patterns (DAMPs) and ATP-induced activation of P2X7R lead to NLRP3 inflammasome formation and entry of hydrophilic solutes into the cytoplasm, which is thought to result in cell death (Hao *et al*., 2017). Therefore, the development of P2X7R inhibitors may be a relevant strategy for the discovery of new drugs for the treatment of inflammatory conditions.

Phytochemicals

Apigenin

Apigenin is a natural flavonoid formed by glycosylation, widely distributed in plants such as celery, parsley, and chamomile, with anti-inflammatory, anticancer, and antioxidant activities (Ginwala *et al*., 2019; Kashyap *et al*., 2022; Tang *et al*., 2017). Apigenin relieved pain, reduced paw swelling, and decreased potential inflammation. Apigenin could decrease the levels of the phosphorylation of P2X7, nuclear factor kappa B (NF-κB) p65, IKKα, IKKβ and IκBα, suggesting that apigenin treatment of arthritis is related to its inhibitory P2X7/NF-κB signaling pathway (Chang *et al*., 2015).

Baicalin

Baicalin, one of the main active components of Scutellaria radix, which can effectively improve chronic inflammation, immune disorders, lipid metabolism disorders, and oxidative stress in the initiation and progression of CVDs, such as atherosclerosis, myocardial infarction, and heart failure (Huang *et al*., 2019; Xin *et al*., 2020). Baicalin plays an important role in diabetes with depression by inhibiting the P2X7/NLRP3/IL-1β signaling pathway (Wang *et al*., 2020a).

Berberine

Berberine is a natural alkaloid extracted from Rhizoma coptidis and Cortex phellodendri, has potent anti-inflammatory and antioxidant activities, and can be

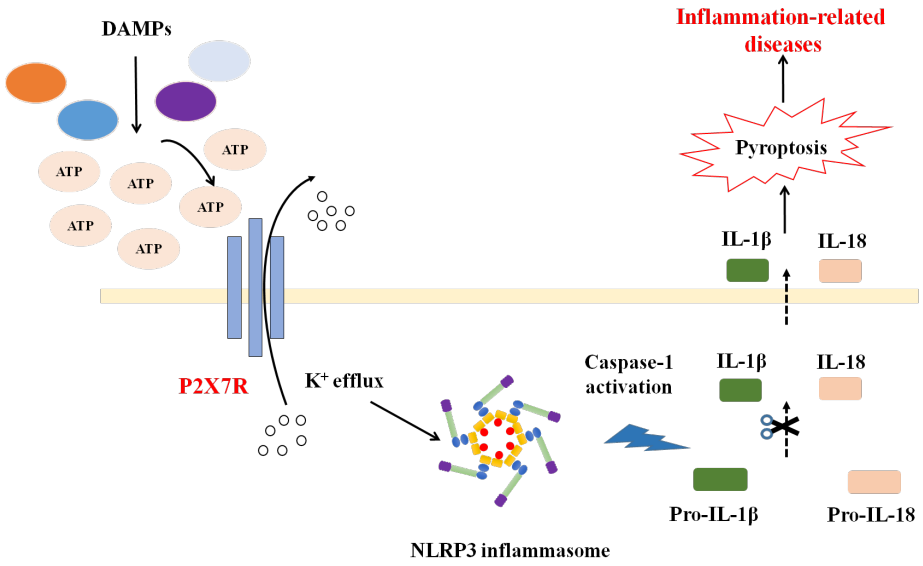

Figure 1. Diagram of P2X7R and its downstream NLRP3 signaling pathway.

used for neuroprotection and cardiovascular protection (Cicero and Baggioni, 2016; Tew *et al*., 2020). Berberine significantly upregulated miR150-5p in ox-LDL-induced macrophages, decreased the expression of P2X7R, downregulated the level of MMP-9, and led to AMPK-α/MAPK inactivation, indicating that berberine inhibited P2X7R-mediated MMP-9 expression by suppressing the AMPK-α and MAPK signaling (Lu *et al*., 2021a). Berberine significantly inhibited the activation of P2X7R, inhibited the involvement of P2X7 in NLRP3 inflammasome activation, and reduced IL-1β level, which showed that berberine had an inhibitory effect on LPS-induced NLRP3 inflammasome activation in RAW264.7 murine macrophages. The mechanism of berberine is related to its interference with the activation of P2X7R, which is involved in the activation of the NLRP3 inflammasome (Vivoli *et al*., 2016).

Betulin

Betulin, a naturally occurring pentacyclic triterpenoid, is mainly isolated from the bark of *Betula pubescens*, which has a variety of pharmacological effects, including antimalarial, anti-inflammatory, anticancer, and other activities (Alakurtti *et al*., 2006; Tuli *et al*., 2021). Betulin significantly alleviated histopathological changes, reduced serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), triglyceride (TG) levels, and inhibited the secretion of inflammatory factors and blocked the P2X7R-NLRP3 signaling pathway (Dou *et al*., 2022).

Cannabidiol

Cannabidiol is one of the main pharmacologically active phytocannabinoids of *Cannabis sativa* L., which has anti-inflammatory and antioxidant effects and can be used to improve diabetes and diabetic complications, hypertension, ischemia-reperfusion injury, and neurodegenerative diseases (Atalay *et al*., 2019; Burstein, 2015). Cannabidiol suppressed the overexpression of NLRP3 inflammasome in THP-1 monocytes and was associated with decreased potassium efflux, and inhibitory effects on the P2X7R, suggesting that the anti-NLRP3 inflammasome effect was linked to the modulation of the P2X7R in THP-1 monocytes (Liu *et al*., 2020a).

Chrysophanol

Chrysophanol belongs to the anthraquinone family from *Senna tora* and rhubarb and is effective in cancer treatment, has an hepatoprotective, anti-microbial, and anti-inflammatory properties (Prateeksha *et al*., 2019; Ye *et al*., 2020). Chrysophanol remarkably reduced the elevations of IL-6, IL-1β, and TNF-α caused by LPS stimulation, and inhibited the expressions of P2X7, p-IKKα, p-IKKβ, p-IκBα, and p-NF-κB p65, which might exert an antidepressant effect through inhibiting P2X7/NF-κB signaling pathway (Zhang *et al*., 2016).

Curcumin

Curcumin is a major effect component of turmeric (*Curcuma longa* Linn), which has anticancer, antibiotic, anti-inflammatory, and antiaging activities, and has therapeutic efficacy on various human diseases, including cancer, cardiovascular diseases, diabetes, and arthritis (Kotha and Luthria, 2019). Curcumin could block the Ca^{2+} accumulation and the inflammatory responses

associated with post-stroke depression (PSD), and reduce the P2X7R expression, which deactivated Ca^{2+} channel-mediated inflammatory response (Wang *et al*., 2020). Curcumin could correct the depressive-like behaviors, decrease mRNA expression of IL-1β, IL-6, and TNF-α, and suppress NF-κB activation, which also inhibited the stressed-induced activation of P2X7R/NLRP3 inflammasome axis (Zhang *et al*., 2019).

Dihydromyricetin

Dihydromyricetin is a dihydro-flavonoid that is isolated from *Ampelopsis grossedentata*, and has various biological effects including anti-inflammatory, antioxidant, and neuroprotective effects (Hou *et al*., 2021; Zhang *et al*., 2018). Dihydromyricetin could restore the spinal cord, and hippocampus of rats with comorbid diabetic neuropathic pain (DNP) and major depressive disorder (MDD) by reducing the expression of P2X7R (Guan *et al*., 2019). Dihydromyricetin could decrease P2X7R expression in primary hippocampal astrocytes, and inhibit the elevated TNF-α, IL-1β, free Ca^{2+}, and ERK1/2 phosphorylation levels, suggesting that dihydromyricetin can protect primary hippocampal astrocytes from P2X7 receptor-mediated damage (Ge *et al*., 2020).

Dihydrotanshinone

Dihydrotanshinone is extracted from *Salvia miltiorrhiza* Bunge, which has anticancer, anti-inflammatory, anti-Alzheimer's disease, and other pharmacological effects, and helps in cardiovascular protection (Allegri *et al*., 2021; Chen *et al*., 2019). Dihydrotanshinone could preserve the blood retinal barrier (BRB) integrity from high glucose (HG)/2'(3')-O-(4-Benzoylbenzoyl) adenosine-5'-triphosphate (BzATP), which might decrease expression of TLR-4, IL-1β, IL-6, TNF-α, and IL-8, and inhibit the levels of P2X7R, VEGF-A, and ICAM-1 (Fresta *et al*., 2020).

Dioscin

Dioscin which is isolated from some medicinal plants, presents diverse pharmacological actions such as anti-inflammation, immunoregulation, antitumor, antifungal, and antihyperlipidemic activities, and can be used in the treatment of diabetes, osteoporosis, obesity, and hyperuricemia (Tao *et al*., 2018; Yang *et al*., 2019). Dioscin could suppress the protein expressions of P2X7R and NLRP3 inflammasome in diabetes cognitive dysfunction, which indicates that dioscin alleviated diabetes cognitive dysfunction via regulating the P2X7R/NLRP3 axis (Lu *et al*., 2021).

Emodin

Emodin is one of the natural anthraquinones isolated from the root and rhizome of *Rheum palmatum* and *Polygonum cuspidatum*, which exerts effects on several biological activities including anti-inflammatory, antivirus, antitumor, antioxidant, and antimicrobial activities (Dong *et al*., 2016; Semwal *et al*., 2021). Emodin could inhibit the elevated level of Ca^{2+}, reduce the IL-1β release, and suppress the ROS production and phagocytosis attenuation in rat peritoneal macrophages by inhibiting the activation of P2X7R (Zhu *et al*., 2014).

Esculin

Esculin is a coumarin derivative, present in the genus Fraxinus, *Artemisia capillaries*, or *Citrus limonia*, which has vasoprotective, antiallergic, anti-inflammatory, and antioxidant effects (Parsons *et al*., 2019; Song *et al*., 2018). Esculin alleviated hyperglycemia-induced kidney damage, prevented the development of P2X7R-mediated proinflammatory and oxidative mechanisms, and alleviate kidney damage by improving mitochondrial function in diabetic animals (Serralha *et al*., 2020).

Gallic acid

Gallic acid is a natural secondary metabolite and is widely isolated from various fruits, plants, and nuts, and has antioxidant, antimicrobial, antiallergic, and anti-inflammatory properties (Bai *et al*., 2021; Liu *et al*., 2020). Gallic acid decreased the coexpression of P2X7 and glial fibrillary acidic protein in the dorsal root ganglia, suggesting that gallic acid may alleviate neuropathic pain by inhibiting the P2X7 receptor and suppressing the activation of the TNF-α/STAT3 signaling pathway (Yang *et al*., 2021).

Genistin

Genistin, a type of isoflavone glycoside that is abundant in the soybean, kudzu (Japanese arrowroot), and other plant-based products, has been reported to possess various therapeutic effects, including antioxidative, anti-inflammatory, anticancer, cardioprotective, neuroprotective, and hepatoprotective activities (Choi *et al*., 2020; Islam *et al*., 2020). Genistin enhanced the protective effect on the rats with myocardial ischemia-reperfusion injury, which may rely on its antioxidant and anti-inflammatory activities via suppression of the P2X7/NF-κB pathways (Gu *et al*. 2016).

Ginsenoside Rg1

Ginsenoside Rg1 is the active extract of ginseng, which can be used to relieve sepsis lung injury and protect myocardial cell injury (He and Yao, 2021; Shen *et al*., 2017). Ginsenoside Rg1 could suppress LPS-mediated induction of proapoptotic Bax, activate Akt, and balance mitochondrial Ca^{2+} levels, increase MMP and reduce ROS levels and superoxide production, which activated the Akt/GSK-3β pathway through P2X7 receptors to inhibit sepsis-induced cardiac dysfunction and mitochondrial dysfunction (Liu *et al*., 2022).

Luteolin

Luteolin is a kind of natural secondary metabolite, which belongs to flavones, found in fruits, vegetables, and plants. Luteolin exhibited excellent antioxidant, anticancer, antimicrobial, neuroprotective, cardioprotective, antiviral, and anti-inflammatory effects (Aziz *et al*., 2018; Taheri *et al*., 2021). Luteolin could attenuate the increased ALT and AST in the serum and infiltration of immune cells, suppress the production and release of HMGB1 and the activation of caspase-1, which reversed LPS-induced hepatic injury by regulating the release of HMGB1 through the P2X7R-RAGE-TLR4 axis (Zhang *et al*., 2021a).

Paeoniflorin

Paeoniflorin, a water-soluble monoterpene glycoside extracted from *Paeonia lactiflora* Pall., has a wide range of medicinal properties including anti-inflammatory, antioxidant, antithrombotic, anticonvulsive, analgesic, cardioprotective, neuroprotective, hepatoprotective, antitumoral, and immune-regulatory activities (Xin *et al*., 2019; Zhou *et al*., 2020). Paeoniflorin could reduce the levels of IL-1β and IL-6, and decrease the expression and activation of the ATP sensor P2X7R, indicating that paeoniflorin might be useful for the management of primary Sjögren's syndrome via downregulating P2X7R expression (Yu *et al*., 2015).

Phillygenin

Phillygenin, isolated from Forsythiae Fructus, has shown good antioxidant, anti-inflammatory, and anticancer activities (Ding *et al*., 2021; Zhou *et al*., 2021). Phillygenin could decrease the gene expressions of IL-1β, IL-18, P2X7R, NLRP3, Caspase-1, NF-κB, and IκBα, which suppressed the expression of the NLRP3/NF-κB signaling pathway by downregulating P2X7R to alleviate the LPS or ATP-induced inflammation of L02 cells (Deng *et al*., 2022).

Quercetin

Quercetin is one of the major flavonoids found in vegetables and fruits, and has several pharmacological effects including anti-inflammatory, antioxidant, and platelet antiaggregant effects (Babaei *et al*., 2018; Patel *et al*., 2018). Quercetin could improve the liver function, attenuate hepatic TG, TC accumulation, reduce the MDA content and suppress the hepatic oxidative stress biomarkers, down-regulate the expression of P2X7R, and up-regulate the expression of phosphatidylinositol 3-kinase (PI3K), Kelch-like ECH associated protein1 (Keap1), Nuclear Factor E2 related factor 2 (Nrf2) (Zhao *et al*., 2021).

Resveratrol

Resveratrol, is an active polyphenolic compound in peanuts, grapes, and red wines, and has been used to cure diseases such as diabetes, neuroinflammation, and neurodegenerative, and cardiovascular disease based on the health benefits including antiobesity, cardioprotective, neuroprotective, antidiabetic, antioxidants, and antiaging effects (Yu *et al*., 2021; Zhang *et al*., 2021). Resveratrol could significantly reduce the p38 MAPK activation, mainly by inhibiting p38 MAPK signaling pathway to reduce FFA-induced P2X7 receptor-mediated inflammatory IL-6 overexpression (Xu *et al*., 2015).

Rhein

Rhein is one of the anthraquinones from the rhizome of rhubarb, which can be used as a laxative and stomach-strengthening medicine for clinical use, has anticancer, antioxidative, anti-inflammation, immunosuppressive, cardioprotective, hepatoprotective, and nephroprotective effects (Cheng *et al*., 2021; Li *et al*., 2021). Rhein could inhibit ATP/BzATP-induced Ca^{2+} increase, pore formation, ROS production, phagocytosis attenuation, IL-1β release and cell apoptosis by inhibiting the P2X7R in rats' peritoneal macrophages (Hu *et al*., 2015).

Salidroside

Salidroside, an important phenylpropanoid glycoside found in the herb *Rhodiola rosea* L., has various pharmacological effects, including anti-inflammatory and antioxidant, and can be used in the treatment of Alzheimer's disease, depression, epilepsy stroke, and cardiovascular diseases (Sun *et al*., 2020; Zhao *et al*., 2021). Salidroside

could ameliorate depression via suppression of the P2X7/NF-κB/NLRP3 mediated pyroptosis, and rescue nigericin-induced pyroptosis in the PC12 cells (Chai *et al.*, 2022).

Molecular docking

P2X7 (PDB Code: 5U1X) in PDB format (Karasawa and Kawate, 2016) and phytochemicals in SDF format were input to CB-Dock for molecular docking (Liu *et al.*, 2020). The lower the VINA score, stronger is the binding affinity. Molecular docking showed that the VINA scores of dihydrotanshinone, baicalin, berberine, genistin, dioscin, resveratrol, apigenin, cannabidiol, esculin, and luteolin were lower than or equal to that of the P2X7 receptor inhibitor (A740003). VINA scores of dihydrotanshinone and baicalin were lower than or equal to that of the P2X7 receptor inhibitor (JNJ47965567). Hence, dihydrotanshinone and baicalin were the most active and could be used as lead compounds for inhibiting P2X7R in the prevention and treatment of various inflammatory diseases (Table 1 and Figure 2).

Table 1. Docking of phytochemicals with P2X7.

Chemicals	Vina score	Cavity score	Center (x, y, z)	Size (x, y, z)
JNJ47965567	–9.1	797	–12, –4, –21	24, 24, 35
A740003	–8.0	797	–12, –4, –21	24, 24, 35
Dihydrotanshinone	–9.2	797	–12, –4, –21	20, 20, 35
Baicalin	–9.1	797	–12, –4, –21	23, 23, 35
Berberine	–8.9	797	–12, –4, –21	22, 22, 35
Genistin	–8.7	797	–12, –4, –21	25, 25, 35
Dioscin	–8.4	797	–12, –4, –21	31, 31, 31
Resveratrol	–8.1	797	–12, –4, –21	21, 21, 35
Apigenin	–8.0	797	–12, –4, –21	21, 21, 35
Cannabidiol	–8.0	797	–12, –4, –21	22, 22, 35
Esculin	–8.0	797	–12, –4, –21	22, 22, 35
Luteolin	–8.0	797	–12, –4, –21	21, 21, 35
Betulin	–7.6	797	–12, –4, –21	22, 22, 35
Curcumin	–7.6	797	–12, –4, –21	25, 25, 35
Emodin	–7.6	797	–12, –4, –21	19, 19, 35
Paeoniflorin	–7.6	797	–12, –4, –21	23, 23, 35
Phillygenin	–7.6	797	–12, –4, –21	23, 23, 35
Quercetin	–7.6	797	–12, –4, –21	21, 21, 35
Rhein	–7.4	797	–12, –4, –21	20, 20, 35
Chrysophanol	–7.3	797	–12, –4, –21	19, 19, 35
Salidroside	–7.3	797	–12, –4, –21	21, 21, 35
Ginsenoside Rg1	–6.8	797	–12, –4, –21	26, 26, 35
Dihydromyricetin	–6.3	797	–12, –4, –21	20, 20, 35
Gallic acid	–5.3	797	–12, –4, –21	24, 17, 35

Conclusion

Phytochemicals have a broad application prospect in the prevention and treatment of various inflammatory diseases by targeting the P2X7R and exerting strong inhibitory effects. The CB-DOCK docking platform can be used to determine which chemicals effectively inhibit P2X7 receptor activity. Molecular docking showed that dihydrotanshinone and baicalin were the lead compounds. In this study, the P2X7 receptor and its mechanism in the development of inflammatory diseases were described in detail, and the virtual screening of phytochemicals as inhibitors of P2X7R. We will conduct experimental studies on the relevant targets of the phytochemicals described in this study, further elucidate their protective effects on reducing P2X7R activity, and provide effective compounds for the prevention and treatment of inflammatory diseases in the future.

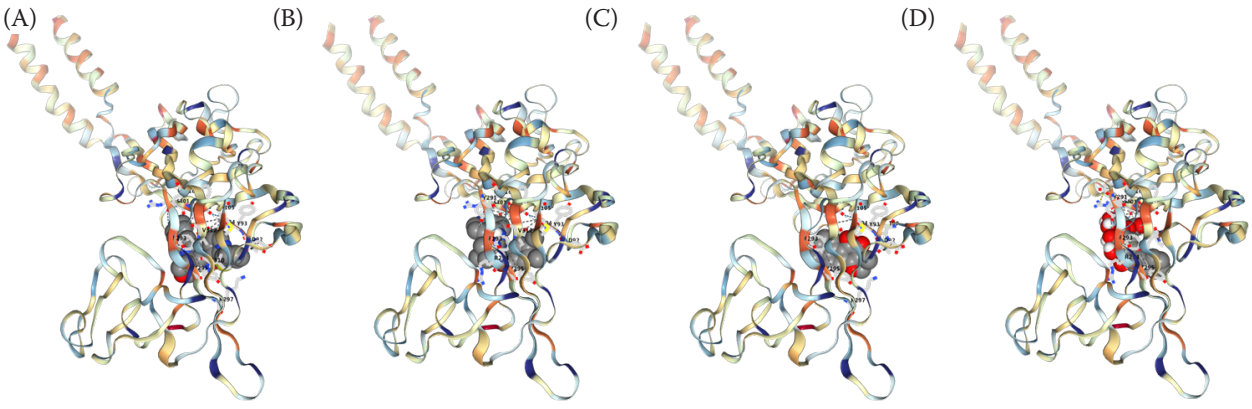

Figure 2. The 3D pictures of phytochemicals with P2X7R. (A) JNJ47965567, (B) A740003, (C) Dihydrotanshinone, (D) Baicalin, (E) Berberine, (F) Genistin, (G) Dioscin, (H) Resveratrol, (I) Apigenin, (J) Cannabidiol, (K) Esculin, (L) Luteolin.

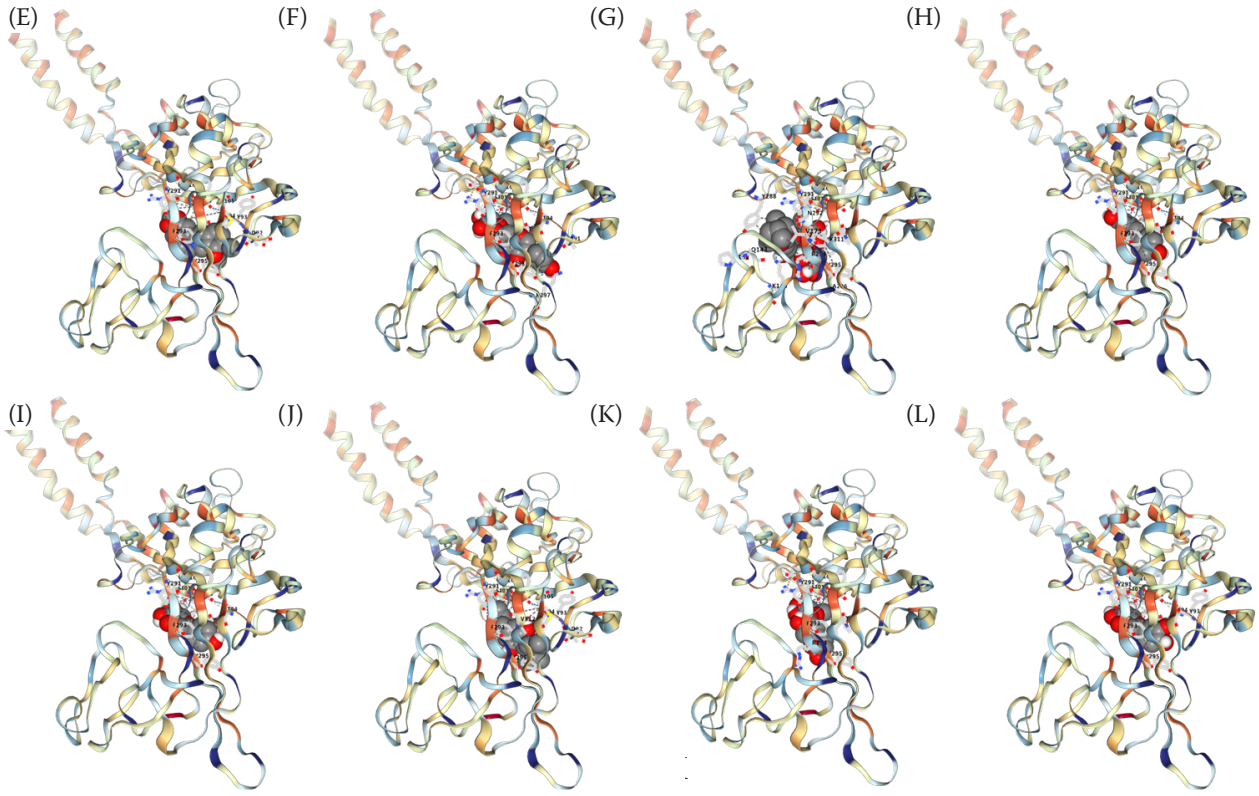

Figure 2. (Continued)

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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