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Review article

The promising therapeutic potentials of ginsenosides mediated through p38 MAPK signaling inhibition

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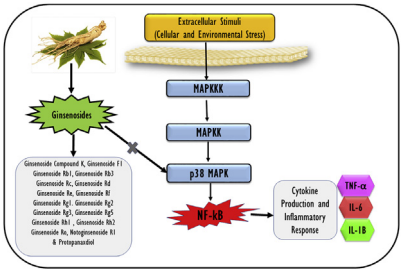
HIGHLIGHTS

- p38 MAPK plays many roles in human disease pathophysiology. Therefore, great therapeutic benefits can be attained from p38 MAPK inhibitors.
- Several ginsenosides showed to possess great therapeutic potentials mediated by its ability to downregulate p38 MAPK signaling.
- *in silico* studies were conducted to explore the binding of these ginsenosides to p38 MAPK and evidenced the promising their inhibitory effect.

GRAPHICAL ABSTRACT



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ABSTRACT

The p38 mitogen-activated protein kinases (p38 MAPK) is a 38kD polypeptide recognized as the target for many potential anti-inflammatory agents. Accumulating evidence indicates that p38 MAPK could perform many roles in human disease pathophysiology. Therefore, great therapeutic benefits can be attained from p38 MAPK inhibitors. Ginseng is an exceptionally valued medicinal plant of the family *Araliaceae* (*Panax* genus). Recently, several studies targeted the therapeutic effects of purified individual ginsenoside, the most significant active ingredient of ginseng, and studied its particular molecular mechanism(s) of action rather than whole-plant extracts. Interestingly, several ginsenosides: ginsenosides compound K, F1, Rb1, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rg5, Rh1, Rh2, Ro, notoginsenoside R1, and protopanaxadiol have shown to possess great therapeutic potentials mediated by their ability to downregulate p38 MAPK signaling in different cell lines and experimental animal models. Our review compiles the research findings of various ginsenosides as potent anti-inflammatory agents, highlighting the crucial role of p38 MAPK suppression in their pharmacological actions. In addition, *in silico* studies were conducted to explore the probable binding of these ginsenosides to p38 MAPK. The results obtained proposed p38 MAPK involvement in the beneficial pharmacological activities of ginsenosides in different ailments.

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1. Introduction

1.1. Ginseng and ginsenosides

Ginseng is an exceptionally esteemed medicinal plant of the family *Araliaceae* (*Panax* genus) [1, 2]. The *Panax* genus consists of at least nine species [3]. *P. ginseng,* the most generally utilized, is indigenous to the far-eastern nations. *P. quinquefolium* is native to America and Canada [3]. *P. ginseng* has been substantially investigated because of its potential therapeutic effects on the human body. The name "ginseng" refers to the Chinese words Jen Sheng, signifying "man-herb" and *Panax*, meaning "all healing," which communicate the conventional belief of ginseng to fix all human diseases. Ginsenosides represent the main constituents of ginseng obtained from different parts of the plant [4]. It is interesting to know that over 40 structurally differing ginsenosides from the root of *P.* ginseng were isolated and recognized [5]. Ginsenosides compose a diverse group of triterpene saponins [6], having a four-ring structure and a steroidal frame with sugar components [7]. The fundamental structure of ginsenosides is comparative in light of the fact that practically all ginsenosides comprise 30 carbon molecules organized in four rings of steroid cores [8]. No less than two (carbon-3 and -20) or three (carbon-3, -6, and -20) hydroxyl (OH) groups are free or attached to ginsenoside's sugars. Based on the location of the OH group on carbon-20, ginsenosides similarly occur as stereoisomers. As indicated by the distinction of position and amount of sugar, ginsenosides are subdivided into four groups: A-Protopanaxadiol (A-PPD), B-Protopanaxatriol, C-Oleanolic acid, and D-Ocotillol [9, 10, 11].

It is worthy to note that plant part, species, age, growing techniques, gathering term and storage affects the nature of ginsenosides in ginseng [12, 13]. Ginsenoside Rf, for example, is distinctive to Far East ginseng, whereas F11 is found only in American ginseng. Therefore, the Rf/F11 proportion is utilized as a phytoconstituent marker to discriminate between different ginseng [14, 15]. Ginseng's saponin amounts are legitimately relative to its growing stage, attaining the highest growth by the age of six years [12, 16]. Almost all ginseng roots are either air-dried or vaporized for 2–4 h followed by drying at 100 °C, giving the ginseng known as red ginseng a dimmer appearance. The heat conversion and deglycosylation of ginsenosides, which occur naturally, grant the red ginseng a distinctive saponin profile [17, 18]. The existence of these compounds confirms red ginseng's popular awareness of better therapeutic values over white ginseng [19, 20].

1.2. p38 MAPK signaling pathway

Mitogen-activated protein kinases (MAPKs) are intracellular enzymes that play a key role in cell response to various stimuli, such as inflammatory cytokines, which will induce GTPase-stimulation of numerous upward kinases, the mitogen-activated protein kinase kinase kinases (MAPKKKs). These serine/threonine kinases phosphorylate and activate MAPK kinases, which consequently phosphorylate p38 mitogen-activated protein kinases (p38 MAPK) [21, 22, 23]. The MAPK superfamily p38 comprises four isoforms. p38α (named simply as "p38") was initially described as being a MAPK aimed against toxin and increased osmotic pressure in the cells, it binds to pyridinyl imidazole enzymes inhibiting the inflammatory cytokine in monocytes, such as interleukin1 (IL-1), tumor necrosis factor-α (TNF-α), and the lipopolysaccharide (LPS) stimulant [24, 25]. Gene database and the specified sequence tag reported having an identification of >70 percent to p38β and 60 percent to p38α [26]. P38α is thought to mainly regulate the inflammatory process; whereas the inflammatory roles of the others remain indefinable [27].

1.2.1. p38 MAPK and inflammation

p38 MAPK represents a fundamental part in producing inflammatory mediators through both transcription-dependent and post-transcription control mechanisms. Many inflammatory response proteins rely for their development on the p38 MAPK signaling and the degree of this dependence differs based on the cell type. The inflammatory cytokines: TNF-α, IL-1β, and cyclooxygenase (COX)-2 were reported to significantly regulate p38 [28]. Suppression of the p38 MAPK signaling resulted in reduced inflammatory mediator release and consequently blockage of the inflammatory response [29]. In addition to mediating inflammatory molecular growth, p38 MAPK is activated significantly by cytokines; TNF-α and IL-1β show important cell retorts to these cytokines [30] (Figure 1). The p38 MAPK also played a crucial part in immune cells' differentiation [31]. All these mechanisms contribute to inflammation production. Therefore, p38 MAPK was presented as a therapeutic option for potential medicines to treat inflammatory diseases because of its essential role in inflammation [30, 32].

In endothelial cells, the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is involved in TNF-α-induced upregulation of E-selectin via p38 MAPK and JNK [33].The pro-inflammatory cytokine TNF-α is regulated by LPS stimulation in neutrophils via the p38 pathway [34]. NF-κB regulates the transcription of adhesion molecules, enzymes, and cytokines involved in inflammatory diseases [35]. The activation of NF-κB has been linked to p38 MAPK. Several studies have shown that the p38 MAPK inhibitor SB203580 effectively inhibits NF-κB -dependent transcription. p38 MAPK has been implicated in the activation of NF-κB [34, 35, 36]. Therefore, the activation of protein kinases like MAPK is critical for the production and action of many pro-inflammatory cytokines in inflammation. As a result, protein kinases have become important drug targets.

Importantly, ginsenosides possess anti-inflammatory effects. The anti-inflammatory mechanism of ginsenosides was discovered to be the negative regulation of pro-inflammatory cytokine expressions (TNF-α, IL-1β, and IL-6) and enzyme expressions (iNOS and COX-2) [11,37]. Kim *et al.* (2019) reviewed the anti-inflammatory effects of ginsenosides in different diseases associated with inflammation [11].

1.2.2. p38 MAPK and oxidative stress

Mitochondria are a major source of reactive oxygen species (ROS) induced by oxidative stress, the mitochondrial respiration chain is the main site of ROS production [38]. Alterations in the respiratory chain and metabolic state typically increase ROS production. Disrupting the balance between ROS production and utilization can cause oxidative stress to develop [39]. When ROS is present in low concentrations in mitochondria, it acts as a protective agent. Increased ROS concentrations weaken this function, resulting in mitochondrial dysfunction. The greater the accumulation of ROS, the greater the oxidative damage to mitochondria, which produces more ROS, creating a vicious cycle [40].

In addition, p38 MAPK is considered to be a ROS sensor and may be induced by oxidative stress. The p38 MAPK activation's downstream effects depend on the actual assembly of the Nox subunits into the NAPDH oxidase complex responsible to deliver ROS [41]. Previously, ROS was reported to activate p38 MAPK in different models [42, 43, 44, 45]. Suppressing LPS-induced mitochondrial ROS inhibited cytokines release by preventing MAPK and NF-κB activation [46].

Ginsenosides effectively regulate mitochondrial function in response to oxidative stress by inhibiting ROS production and maintaining mitochondrial membrane potential stability [47].

1.2.3. p38 MAPK inhibition

The inhibitor class pyridinyl imidazole targets p38σ and p38β but does not target p38δ or p38 γ. These compounds effectively inhibit neutrophil, monocyte, and macrophage responses [48]. As certain cells express p38α, yet not p38β, p38α was reported to be the affected p38-isoform [49]. Activation of p38 MAPK is based on the activation of Thr180 and Tyr182 in the Thr-Gly-Tyr pattern [50]. p38 MAPK binds to adenosine triphosphate (ATP) until activated. Many target proteins in p38 pathway are significant kinases and gene expression regulators, which have fundamental functions in controlling various cell progressions, such as protein transcription, cell cycle progression, and apoptotic death [51, 52].

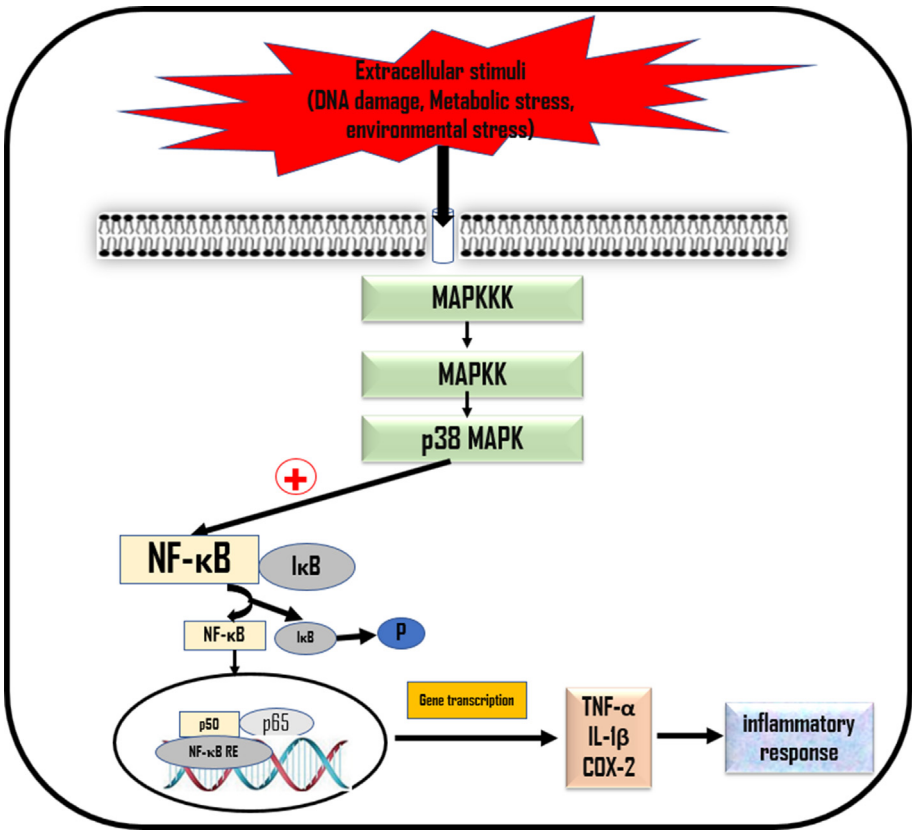


Figure 1. p38 MAPK signaling and mediated inflammatory response.

The majority of p38 MAPK inhibitors are tailored to the ATP-binding site with high specificity to p38 MAPK and its various isoforms. Several compounds have shown to be effective in preclinical models and to have good biological activities. Despite the fact that a large number of people have enrolled in clinical trials, many of them have been stopped [53, 54]. Some studies were halted because of the absence of the inhibitor's efficacy, while in other cases, it was discontinued due to the heart, GIT, brain and other adverse effects [55].

In view of that and based on the aforementioned explanation, targeting p38 MAPK signaling pathway as a potent mediator for inflammation, propose a powerful therapeutic hope for many inflammatory diseases.

2. The modulatory effect of ginsenosides on p38 MAPK signaling

In this part, we reviewed studies displaying the role of p38 MPAK inhibition in mediating the pharmacological activities of ginsenosides. Only ginsenosides (compound K, F1, Rb1, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rg5, Rh1, Rh2, Ro, notoginsenoside R1, and PPD) reported to inhibit p38 MPAK were included in this section and their chemical structure was shown in Table 1. In addition, their promising effects and therapeutic potentials regarding p38 MAPK inhibition were summarized in Table 2.

2.1. Ginsenoside compound K (ginsenoside CK)

Ginsenoside CK is the principal by-product of PPD, the constituent of *Panax ginseng* [56]. Many researches evaluated the pharmacotherapeutic actions of ginsenoside CK such as anticancer in both *in vitro* cancer cells [57] and experimental animal models [58]. Ginsenoside CK has antioxidant [59], antidepressant [60], and anti-epileptic [61] effects.

Traditionally, it has been claimed that ginsenoside CK's anti-inflammatory effects may rely on many mechanisms. Reducing the inducible nitric oxide synthase (iNOS), COX-2, and inflammatory mediators was the most common mechanism [62, 63, 64]. Joh *et al.* (2011) reported its ability to suppress the expression of proinflammatory cytokines by downregulating interleukin-1 receptor-associated kinase 1 (IRAK-1), MAPK, *I kappa* B kinase (IKK)-α, and NF-κB activities in peritoneal murine macrophages treated with LPS [65]. Furthermore, ginsenoside CK inhibited inflammatory responses in zymosan-treated cells by adversely controlling proinflammatory cytokine secretion, MAPK activation, and ROS generation [66].

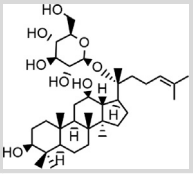
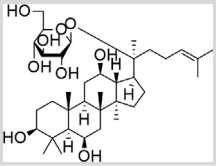
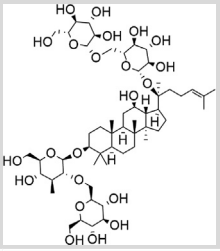
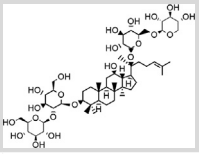
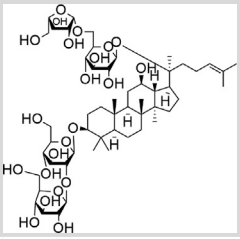
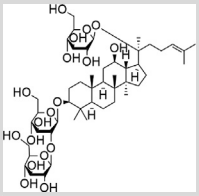
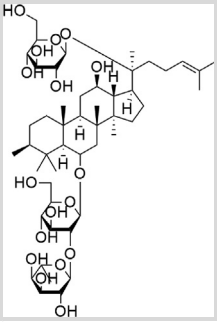
Ginsenoside CK's anti-inflammatory action was observed in microglial cells activated by LPS, where ginsenoside CK hindered inflammatory responses by monitoring both ROS production and MAPKs, NF-κB, and activator protein 1 (AP-1) activities [67]. In addition, ginsenoside CK suppressed iNOS and COX2 expressions through the downregulation of NF-κB in LPS-activated inflammation in RAW264.7 cells [68]. Furthermore, ginsenoside CK downregulated intestinal inflammation by curbing NF-κB signaling in colitis instigated by 2,4,6-Trinitrobenzenesulfonic acid (TNBS) or sodium dextran sulfate [62, 66] in rodents.

Jung *et al.* (2006) concluded that ginsenoside CK has the ability to control brain cancers' progression through repressing PMA-induced p38 MAPK, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) activation [69].

Hong *et al.* (2018) reported that BIOGF1K, ginsenoside CK-rich fraction obtained from *Panax* ginseng, has an antiphotoaging effect and can be used topically. This action is mediated by decreasing the activity of MAPKs [70]. Likewise, BIOGF1K decreased MAPKs activation in RBL-2H3 and HMC-1 cells, thereby supporting its promising potential for treating atopic dermatitis [71].

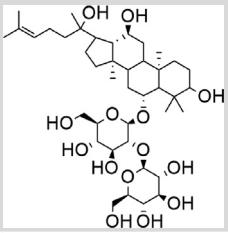
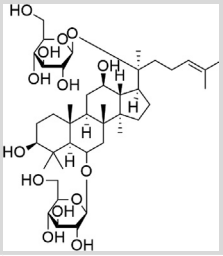
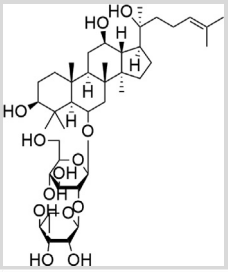
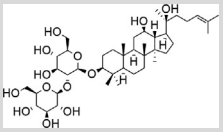
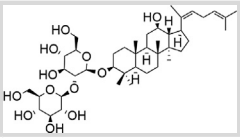
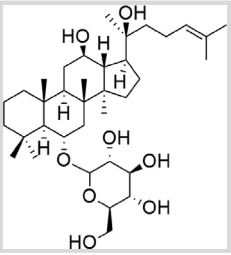
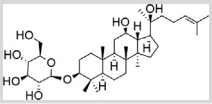
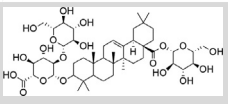
The correlation between the anti-inflammatory activities of ginsenoside CK and p38 MAPK suppression was postulated. An early study done by Cuong *et al.* (2009) reported that pretreatment with ginsenoside CK attenuated zymosan-instigated inflammatory cytokines through decreased TNF-α, IL-6, and IL-12 p40, while it suppressed p38 MAPK and

Table 1. Structure of selected ginsenosides.

Compound name	CID	IUPAC name	Structure
Ginsenoside Compound K	9852086	(2S,3R,4S,5S,6R)-2-[(2S)-2-[(3S,5R,8R,9R,10R, 12R,13R,14R,17S)-3,12-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta [a]phenanthren-17-yl]-6-methylhept-5-en-2-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside F1	9809542	(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-[(2*S*)-6-methyl-2-[(3*S*,5*R*,6*S*,8*R*,9*R*,10*R*,12*R*,13*R*,14*R*, 17*S*)-3,6,12-trihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1*H*-cyclopenta[a] phenanthren-17-yl]hept-5-en-2-yl]oxyoxane-3,4,5-triol	
Ginsenoside Rb1	9898279	(2R,3R,4S,5S,6R)-2-[[(2R,3S,4S,5R,6S)-6-[(2S)-2-[(3S,5R,8R,9R, 10R,12R,13R,14R, 17S)-3-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxy- methyl)-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-2-yl]oxy-12-hydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11, 12,13,15,16,17-dodecahydro-1H-cyclopenta [a] phenanthren-17-yl]-6-methylhept-5-en-2-yl]oxy-3,4,5-trihydroxyoxan-2-yl] methoxy]-6-(hydroxy-methyl)oxane-3,4,5-triol	
Ginsenoside Rb3	12912363	(2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxyl methyl)-2-[[(3S,5R,8R, 9R,10R,12R,13R,14R,17S)-12-hydroxy-4,4,8,10,14-pentamethyl-17-[(2S)-6-methyl-2-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2S,3R,4S,5R)-3,4,5-trihydroxyoxan-2-yl]oxymethyl]oxan-2-yl]oxyhept-5-en-2-yl]-2,3,5,6,7,9,11,12, 13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Rc	12855889	(2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-2-[[(3S,5R,8R,9R,10R, 12R,13R,14R,17S)-17-[(2S)-2-[(2S,3R,4S,5S,6R)-6-[[(2R,3R,4R,5S)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]oxymethyl]-3,4,5-trihydroxyoxan-2-yl]oxy-6-methylhept-5-en-2-yl]-12-hydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11, 12,13,15,16,17-dodeca-hydro-1H-cyclopenta [a]phenanthren-3-yl]oxy]-4,5-dihydroxy-6-(hydroxyl methyl)oxan-3-yl] oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Rd	24721561	(2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-2-[[(3S, 5R,6S,8R,9R,10R,12R, 13R,14R,17S)-3,12-dihydroxy-4,4,8,10,14-pentamethyl-17-[(2S)-6-methyl-2-[(2S,3R, 4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyhept-5-en-2-yl]-2,3,5,6, 7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-4,5 dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxy- methyl)oxane-3,4,5-triol	
Ginsenoside Re	441921	2S,3R,4R,5R,6S)-2-[(2R,3R,4S,5S,6R)-2-[[(3S,5R,6S,8R,9R,10R,12R,13R,14R,17S)-3,12-dihydroxy-4,4,8,10,14-pentamethyl-17-[(2S)-6-methyl-2-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyhept-5-en-2-yl]-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-methyloxane-3,4,5-triol	

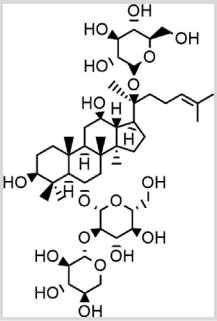
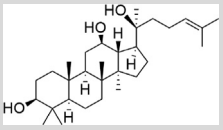
(*continued on next page*)

Table 1 (*continued*)

Compound name	CID	IUPAC name	Structure
Ginsenoside Rf	441922	(2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-2-[[(3S,5R, 6S,8R,9R,10R,12R, 13R,14R,17S)-3,12-dihydroxy-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13, 15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Rg1	441923	2-[[3,12-dihydroxy-4,4,8,10,14-pentamethyl-17-[6-methyl-2-[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyhept-5-en-2-yl]-2,3,5,6,7,9,11,12,13,15, 16,17-dodecahydro-1H-cyclopenta[a]phenanthren-6-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Rg2	21599924	(2S,3R,4R,5R,6S)-2-[(2R,3R,4S,5S,6R)-2-[[(6R,10R,12S,14R)-3,12-dihydroxy-17-[(E,2S)-2-hydroxy-6-methyloct-5-en-2-yl]-4,4,10,14-tetramethyl-1,2,3,5,6,7,8,9,11,12,13,15,16,17-tetradecahydrocyclopenta[a]phenanthren-6-yl] oxy]-4,5-dihydroxy-6-(hydroxymethyl)oxan-3-yl]oxy-6-methyloxane-3,4,5-triol	
Ginsenoside Rg3	9918693	2-[4,5-dihydroxy-2-[[12-hydroxy-17-(2-hydroxy-6-methylhept-5-en-2-yl)-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta [a]phenanthren-3-yl]oxy]-6-(hydroxy-methyl)oxan-3-yl]oxy-6-(hydroxymethyl) oxane-3,4,5-triol	
Ginsenoside Rg5	11550001	(2S,3R,4S,5S,6R)-2-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-2-[[(3S,5R,8R,9R, 10R,12R,13R,14R,17S)-12-hydroxy-4,4,8,10,14-pentamethyl-17-[(2E)-6-methylhepta-2,5-dien-2-yl]-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Rh1	12855920	2-[[3,12-dihydroxy-17-(2-hydroxy-6-methylhept-5-en-2-yl)-4,4,8,10, 14-pentamethyl-2,3,5,6,7,9,11, 12,13,15,16,17-dodecahydro-1H-cyclopenta [a]phenan-thren-6-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Rh2	119307	(2R,3R,4S,5S,6R)-2-[[(3S,5R,8R,9R,10R,12R, 13R,14R,17S)-12-hydroxy-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3, 5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol	
Ginsenoside Ro	11815492	(2S,3S,4S,5R,6R)-6-[[(3S,4aR,6aR,6bS,8aS, 12aS,14aR,14bR)-4,4,6a, 6b,11,11,14b-heptamethyl-8a-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxylmethyl) oxan-2-yl] oxycarbonyl-1,2,3,4a, 5,6,7,8,9,10,12,12a,14,14a-tetradecahydropicen-3yl] oxy]-3,4-dihydroxy-5-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxyoxane-2-carboxylic acid	

(*continued on next page*)

Table 1 (*continued*)

Compound name	CID	IUPAC name	Structure
Notoginsenoside R_1	441934	(2S,3R,4S,5S,6R)-2-[(2S)-2-[(3S,5R,6S,8R,9R,10R, 12R,13R, 14R,17S)-6-[(2R,3R,4S,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-3-[(2S,3R,4S,5R)-3,4,5-trihydroxyoxan-2-yl]oxyoxan-2-yl]oxy-3,12-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-en-2-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	
Protopanaxadiol	11213350	((3S,5R,8R,9R,10R,12R,13R,14R,17S)-17-[(2S)-2-hydroxy-6-methylhept-5-en-2-yl]-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3,12-diol)	

ERK1/2 activation. Moreover, ginsenoside CK inhibited zymosan-mediated superoxide generation, nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) actions, and macrophages Ser345-p47phox phosphorylation [63].

Jeong *et al.* (2010) evaluated the ability of ginsenoside CK to regulate the expression of matrix metalloproteinases (MMPs) to inhibit the migration of human umbilical vein endothelial cells (HUVEC) by the modulation of p38 MAPK; hence, concluded that ginsenoside CK has an antiangiogenesis effect mediated by the suppression of p38 MAPK and protein kinase B (Akt) in HUVECs [72]. Another study done by Lu *et al.* (2019) reported that ginsenoside CK counteracts oxidized low-density lipoprotein (ox-LDL)- instigated damage through the suppression of NF-κB, p38 MAPK, and JNK signals in HUVECs [73].

Joh *et al.* (2011) reported that ginsenoside CK strongly curbed TNF-α, IL-1β, and IL-6 though it significantly augmented IL-10 levels. Additionally, ginsenoside CK effectively decreased both COX-2 and iNOS levels while it suppressed NF-κB activation. Interestingly, ginsenoside CK inactivated IRAK-1, IKK-β, and MAPKs (p38 MAPK, ERK, and JNK) and concluded that ginsenoside CK could be used effectively to treat inflammatory conditions like colitis [62].

Song *et al.* (2018) reported that ginsenoside CK effectively protects against diabetic nephropathy through controlling p38 MAPK/NF-κB signaling. In this study, ginsenoside CK downregulated NLRP3 inflammasome components and cytokines: IL-1β and IL-18 in-vivo and in-vitro. Significantly, ginsenoside CK inhibited kidney p38 MAPK phosphorylation. In addition, ginsenoside CK decreased NADPH oxidase level and ROS [74]. Furthermore, a recent study was done by Lu *et al.* (2020) concluded that ginsenoside CK potently suppressed NF-κB, p38MAPK, and JNK signals; thereby alleviating macrophage inflammation and foam cell and showing therapeutic potential for the treatment of atherosclerosis [75].

On the other side, the apoptotic effect of ginsenoside CK has been examined in different cancer cell lines through p38 MAPK activation [76, 77, 78].

2.2. Ginsenoside F1

Ginsenoside F1 is a protopanaxatriol, obtained from the Korean Red Ginseng [79]. Ginsenoside F1 has various pharmacological properties and is reported to protect against cerebral ischemia [80], Alzheimer's disease [81], and ultraviolet-B-induced apoptosis [82]. Ginsenoside F1 was also reported to increase NK cell function suggesting its chemotherapeutic potential in NK cell-based immunotherapy [83].

With regard to the anti-inflammatory activity of ginsenoside F1, Qin *et al.* (2017) reported that ginsenoside F1 attenuated endothelial cell inflammation in the mice model through the effective inhibition of cytokine production through the suppression of NF-κB; thereby, it can be used in the treatment of atherosclerosis [84].

An in-silico study proved that ginsenoside F1 can act as a nontoxic drug-like molecule and clearly defines its inhibitory action on p38 MAPK at the molecular level of interaction. Besides, molecular dynamics supported p38 MAPK and ginsenoside F1 structural stability [85]. Few studies have targeted the role of ginsenoside F1 against the p38 MAPK signaling pathway. However, Hou *et al.* (2018) proposed ginsenoside F1 as a potential therapeutic approach to alleviate senescent astrocytes' harmful influence in the aged brain and related diseases. This action is mediated through suppressing the senescence-associated secretory phenotype from astrocytes induced by d-galactose through the inhibition of p38 MAPK-dependent NF-κB activity [86].

2.3. Ginsenoside Rb1

Ginsenoside Rb1 was obtained from the classical Chinese medicine *Panax ginseng* C. A. [87]. Ginsenoside Rb_1 showed a significant role in the management of several ailments such as diabetes [88], CKD-associated vascular calcification [89], myocardial infarction [90], diabetic retinopathy [91], cognitive impairment [92], heart arrythmia [93], acetaminophen-induced hepatotoxicity [94], cisplatin-induced memory impairment [95] and others.

The anti-inflammatory activity of ginsenoside Rb1 was previously evidenced, where it was revealed that ginsenoside Rb1 repressed TNF-α development of RAW264.7 macrophages stimulated by LPS [96, 97]. Likewise, ginsenoside Rb1 suppressed the stimulation of NF-κB and TNF-α in LPS-activated macrophages, decreased stimulation of IRAK-1, IKK-α, NF-κB, and MAPKs, and inhibited the IRAK activation-mediated inflammatory responses induced by TNBS in a rat model of colitis [62].

Robust evidence demonstrated the ability of ginsenoside Rb1 to exert antiosteoporotic action through preventing the distinction between RANKL-activated osteoclast and macrophages and inhibiting RANKL-provoked p38 MAPK/NF-κB pathway, and thus potently suppressing c-Fos and NF of activated T cells (NFAT) C1 [98]. Hashimoto *et al.* (2012) revealed that ginsenoside Rb1 prevented the programmed cell death provoked by 1-methyl-4-phenylpyridinium ion (MPP (+)) in PC12 cells by inhibiting p38 MAPK and stress-activated protein kinase (SAPK)/JNK signals. In this study, treatment of the MPP(+)-treated PC12 cells with ginsenoside Rb1 resulted in an increase in ERK1/2 or Akt phosphorylation, while the p-p38 MAPK significantly decreased [99]. Zhou *et al.* (2017) similarly illustrated the ability of ginsenoside Rb1 to protect against TNF-α-instigated oxidative injury and inflammation through the suppression of p38 MAPK and JNK and signaling in HUVECs [100].

Table 2. Summary of ginsenosides' effects on p38 MAPK in different models.

Compound	Disease/Model	Effects	Reference
Ginsenoside compound K	Development and invasion of brain tumors using U87MG and U373MG cells	- Blocked the PMA-induced p38 MAPK, ERK, and JNK activation. - Downregulated MMP-9-induced by PMA. - Suppressed AP-1 binding.	[69]
	Zymosan-induced inflammatory cytokine production using RAW264.7 macrophage	- Decreased TNF-α and Interleukins - Suppressed p38 MAPK and ERK1/2 activation. - Decreased superoxide production - Decreased NADPH oxidase enzymatic activities - Suppressed Ser345-p47phox phosphorylation.	[63]
	Angiogenesis-provoked by bFGF using HUVECs	- Has an antiangiogenesis effect mediated by the suppression of p38 MAPK and Akt in HUVECs.	[72]
	ox-LDL-induced injury in HUVECs	- Prevented ox-LDL-induced injury through the inhibition of NF-κB, p38 MAPK, and JNK signals.	[73]
	Colitis induced by TNBS in mice and *in vitro* murine peritoneal macrophages induced by LPS	- Strongly inhibited TNF-α and interleukins expression. - Significantly augmented IL-10 level. - Effectively decreased both COX-2 and iNOS levels - Suppressed NF-κB activation. - Inactivated IRAK-1, IKK-β, and MAPKs and concluded that ginsenoside CK could be used effectively to treat inflammatory conditions like colitis.	[62]
	Renal inflammation in diabetic nephropathy induced by HFD/STZ and rat glomerular mesangial cell line HBZY-1 exposed to high glucose.	- Downregulated NLRP3 inflammasome components and cytokines; IL-1β and IL-18 *in vivo* and *in vitro*. - Inhibited kidney p38 MAPK phosphorylation. - Decreased NADHP oxidase level and ROS.	[74]
	Atherosclerosis-induced by Ox-LDL in RAW264.7	- Potently suppressed NF-κB, p38MAPK, and JNK signals.	[75]
Ginsenoside F1	Age-related brain inflammation – SASP induced by d-galactose in Astrocytic CRT and U373-MG cells	- Suppressed SASP induced by d-galactose through the inhibition of p38 MAPK-dependent NF-κB activity. - Downregulated IL-8 effectively.	[86]
Ginsenoside Rb1	Osteoporosis – RANKL-induced osteoclast differentiation using RAW264.7 cells	- Exerted anti-osteoporotic action through preventing the distinction between RANKL-activated osteoclast and RAW264.7 macrophages. - Inhibited RANKL-induced p38 MAPK/NF-κB pathway. - Blocked the expression of c-Fos and NFAT C1, the important factors for osteoclasts distinction.	[98]
	MPP(+)-induced apoptosis in PC12 cells	- Increased phosphorylation levels of ERK1/2 or Akt in MPP(+)-treated PC12 cells, while it reduced the activation of p38 MAPK.	[99]
	TNF-α-induced inflammation in HUVECs	- Inhibits inflammatory response and decreases VCAM-1, ICAM-1, IL-6, IL-1β, VEGF, MMP-2, and MMP-9 levels. - Downregulated p38 MAPK and JNK signaling. - Suppressed ROS and MDA production, while it elevated SOD, CAT, and GSH-Px enzymatic activities.	[100]
	Balloon injury-induced vascular neointimal hyperplasia in rats	- Suppressed p-ERK1/2 and the mRNA expression of c-myc and downregulated the p38 MAPK gene.	[101]
	Abdominal aortic aneurysm induced by angiotensin II in ApoE(−/−) mice	- Protected against abdominal aortic aneurysm agent through inhibiting the JNK and p38 MAPK signaling pathways. - Attenuated Ang II-induced diameter enlargement, MMP production, and VSMC dysfunction.	[102]
	Myocardial I/R in rats	- Decreased caspase-3 activity and lowered TNF-α level in the myocardium. - Downregulated phospho-p38α MAPK.	[103]
	In vivo using zymosan A in rat. *In vitro* using HUVECs and THP-1 cells from H_2O_2-mediated cytotoxicity	- Protected endothelial cells cytotoxicity through the curbing of oxLDL-provoked p38 MAPK and VCAM-1 protein expression in addition to decreased TNF-α level. - Exhibited antioxidant activity mediated by PI3K/Akt/Nrf2 activation.	[104]
	renal proximal tubular apoptosis induced by tacrolimus-induced apoptosis using LLC-PK1 cells	- Decreased KIM-1 and cleaved-caspase-3 levels - Suppressed p38 MAPK phosphorylation.	[105]
	Renal fibrosis and CKD using *in vivo* unilateral ureter obstruction in mice and *in vitro* HBSS-induced HK-2 cells.	- Attenuated autophagy through the AMPK/mTOR pathway in HK-2 cells and *in vivo* mice model. - Effectively inhibited p38 and ERK activation in HK-2 cells exposed to HBSS.	[106]
Ginsenoside Rb3	Cigarette smoke-induced cell injury in WI-38 and 16HBE cells	- Prevented the inflammatory response and oxidative stress caused by cigarette smoke extract as well as excessive accumulation of extracellular matrix. - Inhibited the p38 MAPK/NF-κB and TGF-β1/VEGF pathways.	[110]
	Periodontitis-induced LPS in rats.	- Effectively decreased p38 MAPK phosphorylation and NF-κB and decreased interleukins levels. - Decreased the expression of total Akt.	[111]

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Table 2 (*continued*)

Compound	Disease/Model	Effects	Reference
Ginsenoside Rc	LPS-induced inflammation in RAW264.7 and HEK293 cells transfected with various inducers of inflammation.	- Blocked the production of cytokines derived from macrophages for tumor necrosis. - Suppressed TANK-binding kinase 1/IκB kinase ε/IRF3, and p38 MAPK/ATF-2 signaling activation.	[113]
Ginsenoside Rd	Cancer metastasis using HepG2 cells	- Blocked MMP activation and MAPK signaling.	[122]
	TNBS-induced colitis in rats	- Potently inhibited the inflammatory perturbing evidenced by decreasing the MPO activity mediated by lowering cytokine production and suppressing of p38 MAPK and JNK phosphorylation.	[123]
	Cartilage degradation of OA-induced by IL-1β using S12 cells	- Suppressed cartilage degradation of OA by suppressing MMP3 through the inhibition of p-p38 MAPK activation.	[121]
Ginsenoside Re	Neuroinflammation by LPS-induced inflammation in microglial cells	- Delayed the progression of neuroinflammatory through the attenuation of LPS-induced MAPK phosphorylation.	[128]
	Heart dysfunction induced by LPS in mice.	- Significantly prevented cardiac dysfunction induced by LPS through the effective inhibition of phosphorylated MAPKs.	[129]
	Ox-LDL-induced endothelial apoptosis using HUVECs	- Restored the balanced redox state of the cells. - Inhibited the activation of NF-κB and the caspase cascade by activating the PI3K/Akt pathway and inhibiting the phosphorylation of p38 MAPK. - Downregulated lectin-like Ox-LDL receptor-1 and NADPH oxidase. - Upregulated the expression of estrogen receptor-alpha.	[130]
	Angiotensin II-induced gap-junction remodeling in isolated beating rat atria.	- Suppressed p38 MAPK, NF-κB, and AP-1 - Effectively upregulated PPARγ level.	[131]
Ginsenoside Rf	TNF-α-stimulated HT-29 and RAW264.7 cells.	- Reduced cytokines, TNF-α, IL-1β, IL-6, NO release, and suppressed ROS production that linked to p38 MAPK/NF-κB activation.	[137]
Ginsenoside Rg1	MPTP-induced Parkinson disease in mice	- Reduced p-p38 MAPK, COX-2-, and PGE2-positive cells noticeably 6 h after the third injection of MPTP.	[142]
	CSDS-induced depressive-like behaviors in rats	- Inhibited p-p38 MAPK and NF-κB p65 subunit activation. - Inhibited neuronal apoptosis induced by CUMS exposure. - Upregulated Nrf2 expression.	[143]
	CSDS-induced depressive-like behaviors in mice	- Effectively decreased IL-6, TNF-α, and IL-1β production and both iNOS and COX2 enzymes. - Decreased caspase-9 and -3 level and inhibited hippocampal microglial activation. - Inactivated both p-p38 MAPK and p-JNK1/2 and inhibited NF-κB phosphorylation, thereby regulated SIRT1 and reduced acetylated p65 level.	[144]
	LPS-induced microglial activation in mice	- Suppressed microglial activation induced by LPS through suppressing Iba-1 and iNOS. - Suppressed IκB and nuclear translocation of p65 subunit of NF-κB phosphorylation through the effective suppression of p38 MAPK, ERK1/2, and JNK phosphorylation.	[145]
	Neuroinflammation by LPS – in BV2 microglial cells	- Significantly attenuated the LPS-induced expression of NF-κB and reduced cytokines TNF-α, IL-1β, iNOS, and COX-2 through the effective inhibition of p38 MAPK, IκB-α, CREB, ERK1/2, and JNK phosphorylation.	[138]
	LPS-induced neuronal degeneration in rat	- Protected against LPS-induced microglial inflammation in mesencephalic dopaminergic neurons through the inhibition of p38 MAPK signaling pathway.	[139]
	Oxygen-glucose-deprivation in NSCs.	- Downregulated p-p38 and p-JNK expression. - Suppressed apoptosis - Decreased oxidative stress	[146]
	Ventricular remodeling model of myocardial infarction in rats	- Activated PI3K/Akt signaling. - Inhibited p38 MAPK.	[147]
	Insulin resistance induced by insulin – in HepG2 cells.	- Raised glucose uptake through a decrease in ROS. - Suppressed p38 MAPK phosphorylation and GSK3β expression. - Effectively elevated Akt phosphorylation.	[148]
	Left ventricular hypertrophy and cardiac dysfunction-induced by transverse aortic constriction in rats	- Upregulated p-Akt level. - Potently inhibited p38 MAPK signaling.	[149]
	RPE cells from CoCl2 and hypoxia assaults	- Potently inhibited ROS production through effective suppression of p38 MAPK and JNK activation.	[150]
	Podocytes from sMAC-induced injury	- Attenuated F-actin damage. - Restored the antioxidant status mediated by the suppression of p38 MAPK activation.	[151]
	Shear-induced inflammation	- Suppressed p38 MAPK, ERK, and JNK phosphorylation is similar to that of specific chemical inhibitors for MAPK signal.	[152]

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Table 2 (*continued*)

Compound	Disease/Model	Effects	Reference
Ginsenoside Rg2	LPS-induced leukocyte adhesion into the vascular wall using HUVECs	- Suppressed LPS-mediated p38 MAPK monocyte adhesion. - Downregulated VCAM-1 and ICAM-1 and NF-κB.	[154]
Ginsenoside Rg3	RANKL-induced osteoclasts differentiation in RAW264.7 cells	- Showed the effective inhibition of Cat-K through p38 MAPK downregulation.	[162]
	Hepatitis B virus replication	- Decreased IL-8 and TNF-α levels. - Inhibited p38 MAPK. - Inhibited c-Jun N-terminal kinase phosphorylation and downregulated AP-1.	[163]
	LLC cancer cell lines	- Induce cell apoptosis mediated through the deactivation of the p38 MAPK pathway.	[164]
Ginsenoside Rg5	Diabetic nephropathy induced by high-fat diet/STZ-in mice	- Suppressed the expression of NF-κB and the phosphorylation of p38 MAPK. - Effectively decreased IL-1β and IL-18 production and inflammatory response. - Restored oxidant/antioxidant balance.	[220]
Ginsenoside Rh1	Invasion and migration of THP-1 acute monocytic leukemia cells	- Suppressed the phosphorylation of MAPKs.	[183]
	Hepatocellular carcinoma using HepG2 cell lines	- Suppressed ERK, JNK, and p38 MAPK activation. - Downregulated c-Jun and c-Fos.	[185]
	Colon *in vitro* and tumor growth *in vivo*	- Downregulated MMP1 and MMP3, promoted TIMP3 expression, and effectively decreased the ratios of p-pp38 MAPK/p38 MAPK, p-ERK1/2/ERK1/2, and p-JNK/JNK.	[186]
Ginsenoside Rh2	Allergic airway inflammation animal model	- Suppressed phosphorylation of p38 MAPK and activation of NF-κB.	[192]
	Human astroglioma cells	- Repressed the expression of MMP-9 through the inhibition of p38 MAPK.	[193]
	HepG2 cells	- Ginsenoside Rh2 treatment alone, cotreatment with ginsenoside Rh2 and SB203580 (p38 MAPK inhibitor) resulted in cell death, which increased from 20% to 50%, suggesting that p38 MAPK inhibition can increase ginsenoside Rh2 apoptosis induction.	[187]
Ginsenoside Ro	TXA2-associated thrombosis	- Holds a significant antiplatelet potential and attenuated thromboxane-A2 production through suppressing p38-MAPK-mediated cPLA2a phosphorylation and AA release.	[202]
Notoginsenoside R1	I/R-induced myocardial injury in rabbits	- Possessed a cardioprotective effect through p38 MAPK inhibition and suppressed apoptosis. - Inhibited TGF-β1-TAK1 signaling pathway-related proteins.	[208]
	PASMCs exposed to hypoxia and hypercapnia	- Alleviated hypoxia and HHPV and inhibiting the activation of ERK and p38 MAPK pathways.	[209]
Protopanaxadiol	Triple-negative breast cancer metastasis *in vivo* and TNBC *in vitro* MDA-MB-231 and SUM159 cells	- Inhibited EGFR phosphorylation and inactivated ERK1/2, p38, and JNK signaling.	[216]

Several researchers reported the cardiovascular protective properties of ginsenoside Rb1 through p38 MAPK inhibition. Zhang *et al.* (2012) investigated its ability to suppress balloon injury-induced vascular neointimal hyperplasia in rats through the suppression of p-ERK1/2 and the mRNA expression of c-myc and downregulated the p38 MAPK gene [101]. Zhang *et al.* (2015) explained the beneficial role of ginsenoside Rb1 in abdominal aortic aneurysm through the suppression of the JNK and p38 MAPK signals [102]. Furthermore, the ability of ginsenoside Rb1 to ameliorate myocardial ischemia/perfusion (I/R) injury through the suppression of p38α MAPK phosphorylation was demonstrated by Li *et al.* (2016). In this study, caspase-3 activity and TNF-α levels were suppressed in the heart muscle. Phospho-p38α MAPK and not the total 38α MAPK levels were markedly upregulated in the I/R model, and these elevated levels were decreased by ginsenoside Rb1 [103]. Moreover, Fan *et al.* (2016) reported the ginsenoside Rb1 ability to protect endothelial cells (ECs) against cytotoxicity-induced by H_2O_2 through the mitigation of oxLDL-induced p38 and vascular cell adhesion molecule 1(VCAM-1) expression, in addition to decreased TNF-α. It also exhibited antioxidant activity mediated by Nrf2 activation [104].

With regard to the renoprotective potential of ginsenoside Rb1 mediated by p38 MAPK signal inhibition, Lee *et al.* (2018) reported that ginsenoside Rb1 protects against tacrolimus-instigated cell death in kidney proximal tubular LLC-PK1 cells through the suppression of p38 MAPK phosphorylation [105]. Furthermore, Liu *et al.* (2020) reported that ginsenoside Rb1 attenuates autophagy through the MAPK/mammalian target of rapamycin (mTOR) signal in kidney tubular epithelial cells. In this study, ginsenoside Rb1 treatment successfully decreased p38 MAPK and ERK activation in HK-2 cells exposed to Hank's balanced salt solution (HBSS) and suggested that ginsenoside Rb1 can be used for the treatment of chronic kidney diseases (CKD) [106].

On the other hand, Xin *et al.* (2019) concluded the ability of ginsenoside Rb1 to increase macrophage phagocytosis mediated by p38 MAPK/Akt pathway, while curbing p38 MAPK phosphorylation by using SB203580, the specific p38 MAPK inhibitor, thus reducing phagocytosis [107].

2.4. Ginsenoside Rb3

Ginsenoside Rb3 was obtained from *Panax ginseng* C. A. Meyer [87]. The pharmacological role of ginsenoside Rb3 as an anti-inflammatory agent was studied by Ma *et al.* (2014), who stated that the ameliorative effect of ginsenoside Rb3 against oxygen-glucose deprivation-reperfusion damage was due to curbing JNK-instigated NF-κB stimulation, indicating that it might protect against myocardial I/R damage [108]. Liu *et al.* (2020) reported that treatment with ginsenoside Rb3/ginsenoside Rb2 attenuated myocardial I/R, as evidenced by improved cardiac function, decreased IL-6, and TNF-α serum levels as well as restoring antioxidant balance in myocardial tissues [109].

Ginsenoside Rb3 prevented the inflammatory response and ROS caused by cigarette smoke extract as well as the buildup of extracellular matrix in WI-38 and 16HBE cells to defend against cell damage through curbing p38 MAPK/NF-κB and transforming growth factor

(TGF)-β1/vascular endothelial growth factor pathways [110]. Another recent study conducted by Sun *et al.* (2020) investigated that ginsenoside Rb3 potently suppressed LPS-induced cytokine production through MAPK/Akt/NF-κB signal and alleviated bone resorption. Ginsenoside Rb3 effectively decreased p38 MAPK and NF-κB phosphorylation and curbed IL-1β, IL-6, and IL-8 levels [111].

2.5. Ginsenoside Rc

Ginsenoside Rc was isolated from Korean *Panax ginseng* [112]. It was found to block cytokines' production derived from macrophages such as TNF-α and IL-1β. In activated HEK293 cells, RAW264.7 macrophages, and human synovial cells, ginsenoside Rc similarly showed a marked suppression in the activation of TANK-binding kinase 1/IκB kinaseε/interferon regulatory factor-3 and p38/activating transcription factor 2(ATF-2) pathway [113]. In contrast, ginsenoside Rc was reported to not prevent fibronectin expression induced by high glucose in mesangial cells mediated by p38 MAPK activation [114].

2.6. Ginsenoside Rd

Ginsenoside Rd was obtained from *Panax ginseng* C. A. Meyer [87]. Ginsenoside Rd therapy has been investigated as anti-inflammatory in many studies, such as autoimmune encephalomyelitis [115], cardiac hypertrophy [116], acute ischemic stroke [117], ulcerative colitis [118], and others.

Ginsenoside Rd showed an anti-inflammatory activity through a potent decrease in in the synthesis of NO and prostaglandin E2 (PGE2). Therefore, ginsenoside Rd's protective mechanisms might include interference with the expression iNOS and COX-2 [119]. Another study concluded the effectiveness of ginsenoside Rd to suppress poly(ADP-ribose) polymerase-1 and subsequently decreased apoptosis and NF-κB subunit nuclear accumulation in rats with arterial occlusion of the right middle brain [120].

Shin *et al.* (2009) demonstrated the suppressive effect of ginsenoside Rd on the main elements contributed in the cartilage degradation of osteoarthritis by suppressing MMP3 through the inhibition of p-p38 MAPK activation [121]. In addition, Yoon *et al.* (2012) showed the ability of ginsenoside Rd to mitigate metastasis mediated by blocking MMP activation and MAPK signal in HepG2 cells [122]. Furthermore, Yang *et al.* (2012) revealed that ginsenoside Rd potently inhibited colitis instigated by TNBS, evidenced by decreasing the MPO activity mediated through lowering cytokine production and suppressing p38 MAPK and JNK phosphorylation [123].

2.7. Ginsenoside Re

Ginsenoside Re was isolated from *Panax ginseng* [124]. Ginsenoside Re has a potent anti-inflammatory effect in different disease models such as amyotrophic lateral sclerosis [125], Parkinson's disease [126], and LPS-induced inflammation [127].

Lee *et al.* (2012) suggested that ginsenoside Re may display a possible therapeutic drug to delay the development of neuroinflammation through the attenuation of LPS-induced MAPK phosphorylation, which mediates microglial toxicity and inflammatory responses [128].

The cardioprotective activity of ginsenoside Re against LPS-induced heart dysfunction and inflammatory response was reported by Chen *et al.* (2016) who reported that ginsenoside Re significantly prevented cardiac dysfunction induced by LPS through the effective inhibition of p-ERK1/2, p-JNK, and p-p38 MAPK [129]. Additionally, ginsenoside Re has the ability to counteract Ox-LDL-instigated endothelial cell death through reinforcing the antioxidant status of the cells and inhibiting NF-κB provocation and apoptosis through the stimulation of the phosphatidylinositol-3-kinase (PI3K)/Akt signal and suppressing the p38 MAPK phosphorylation. These effects are mediated by mitigating the enzymatic activity of NADPH oxidase and lectin-like Ox-LDL receptor-1 expression, while boosting estrogen receptor-α expression. Therefore, ginsenoside Re successfully attenuates the endothelial apoptosis-induced by Ox-LDL through antioxidative and anti-inflammatory actions [130]. In addition, it halted angiotensin II-induced gap-junction remodeling. In this study, atrial activities of p38 MAPK, NF-κB, and AP-1 were markedly elevated by Ang II, while the level of peroxisome proliferator-activated receptor gamma (PPARγ) significantly decreased. These effects were attenuated by ginsenoside Re. Also, in this study, rosiglitazone, a PPARγ agonist, blocked these effects [131].

On the other side Shi *et al.* (2016) reported the antiangiopathy activities of ginsenoside Re in diabetes mediated by MAPKs activation [132].

2.8. Ginsenoside Rf

Ginsenoside Rf was isolated from *Panax ginseng* [133]. Ginsenoside Rf has a promising neuroprotective effect in different models of neuronal injury [134, 135]. In a rodent model of endometriosis, ginsenoside Rf relieved dysmenorrhea and inflammation through the brain-derived neurotrophic factor – tropomyosin receptor kinase – cyclic adenosine monophosphate (cAMP) response element-binding protein pathway [136]. In addition, in a rat model of incisional pain, ginsenoside Rf has potent antinociceptive/anti-inflammatory effects [133].

Ginsenoside Rf downregulated p38 MAPK signaling and has been supported by few studies. Ahn *et al.* (2016) assessed its suppressing actions on the inflammation cytokines downstream of p38 MAPK/NF-kB activation in colon and macrophage cells, which indicated a possible role of ginsenoside F1 for the management of ailments such as Irritable Bowel Diseases (IBD) [137].

2.9. Ginsenoside Rg1

Ginsenoside Rg1 was isolated from Korean *Panax ginseng* [112]. Many therapeutic benefits for ginsenoside Rg1 have been documented.

Ginsenoside Rg1 downregulated NF-κB and curbed the amounts of TNF-α, iNOS, COX-2, and IL-1β in microglial cells, which were stimulated by LPS [138, 139]. Ginsenoside Rg1's inhibitory effect on inflammation had been studied previously, through NF-κB curbing in LPS-instigated macrophages cells and mice peritoneal macrophages. Likewise, ginsenoside Rg1 downregulated IL-6 by regulating the NF-κB or Akt/mTOR signals. Another recent study demonstrated that ginsenoside Rg1 protected diverse tissues from I/R injury through the regulation of inflammation and apoptosis. Ginsenoside Rg1 was protected against hepatic I/R in rats through the suppression of NF-κB signaling and ROS-inducing factor [140, 141].

It is worthy to note that the therapeutic use of ginsenoside Rg1, which relied on modulating p38 MAPK is the neuroprotective therapeutic potential which was studied by several researchers in experimental animal models and in *in vitro* cell lines.

Wang *et al.* (2008) reported decreased COX-2 expression by ginsenoside Rg1 in Parkinson's animals provoked by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) through the inhibition of p38 MAPK. In this study, the number of phosphorylated p38 MAPK, COX-2, and PGE2 positive cells was markedly decreased by ginsenoside Rg1 6 h after the third injection of MPTP. [142]. Fan *et al.* (2018) reported the ability of ginsenoside Rg1 to prevent depression in rats, ginsenoside Rg1-inhibited neuronal programmed cell death provoked by chronic unpredictable mild stress exposure, and upregulated Nrf2 expression while it inhibited p-p38 MAPK and NF-κB p65 subunit activation [143]. Likewise, a recent study conducted by Jiang *et al.* (2020) investigated that ginsenoside Rg1 effectively treated depression caused by 4-week chronic social defeat stress exposure. Ginsenoside Rg1 treatment decreased IL-6, TNF-α, and IL-1β production and both iNOS and COX2 enzymes. Ginsenoside Rg1 decreased hippocampal caspase levels and inhibited microglial activation. Importantly, ginsenoside Rg1 inactivated both p-p38 MAPK and p-JNK1/2, and inhibited NF-κB

phosphorylation, thereby regulated SIRT1, and reduced acetylated p65 expression [144].

In *in vitro* studies, an early study conducted by Hu *et al.* (2011) revealed that ginsenoside Rg1 suppressed microglial activation induced by LPS through the suppression of Iba-1 and iNOS. Ginsenoside Rg1 suppressed IκB and p65 subunit of NF-κB nuclear translocation through the effective inhibition of MAPKs phosphorylation [145]. Likewise, Zong *et al.* (2012) revealed the ability of ginsenoside Rg1 to significantly attenuate the LPS-provoked expression of NF-κB and reduced cytokines, iNOS, and COX-2 in BV-2 cells through the effective inhibition of p38 MAPK, IκB-α, cAMP response element-binding protein, JNK, and ERK1/2 phosphorylation [138]. Furthermore, Sun *et al.* (2016) highlighted that ginsenoside Rg1 has the ability to protect mesencephalic dopaminergic neurons from LPS-induced microglial inflammation and p38 MAPK signal suppression, which might contribute in ginsenoside Rg's anti-inflammatory effect [139]. Additionally, ginsenoside Rg1 not only protects against LPS-provoked injury in microglial cells but also protects against oxygen-glucose-deprivation in neural stem cells as reported by Li *et al.* (2017). In this study, ginsenoside Rg1 markedly suppressed the apoptosis in neural stem cells, decreased ROS, and downregulated p-p38 and p-JNK expressions [146].

Cross talk between p38 MAPK and Akt signaling has been studied in several literatures. In promoting angiogenesis and alleviating heart muscle fibrosis, ginsenoside Rg1 improved left ventricular function and the potential mechanisms include p38 MAPK inhibition and PI3K/Akt activation. [147]. Fan *et al.* (2019) reported that ginsenoside Rg1 alleviated insulin resistance in HepG2 cells. In this study, ginsenoside Rg1 increased glucose uptake through a decrease in ROS and the suppression of p38 MAPK phosphorylation and glycogen synthase kinase 3 beta expression while it effectively elevated Akt phosphorylation [148]. Zhang *et al.* (2013) reported ginsenoside Rg1's ability to treat left ventricular hypertrophy and heart failure provoked by transverse aortic constriction through p-Akt activation and p38 MAPK suppression [149].

Other models were also reported. Li *et al.* (2013) reported that ginsenoside Rg1 preserved the retinal pigment epithelium cells induced by cobalt chloride or hypoxia. In this study, ginsenoside Rg1 potently inhibited ROS production through the effective suppression of p38 MAPK and JNK activation [150]. Zhang *et al.* (2011) investigated the ability of ginsenoside Rg1 to protect podocytes from supramolecular activation cluster-induced injury through the suppression of F-actin damage and restoring the antioxidant status mediated by the suppression of p38 MAPK activation [151]. He and Li, (2015) reported that ginsenoside Rg1 prevents the shear-provoked inflammatory response by curbing the MAPK pathway, similar to the specific MAPK inhibitors [152].

2.10. Ginsenoside Rg2

Ginsenoside Rg2 was obtained from the root of *Panax ginseng* C. A. [153]. The anti-inflammatory and antioxidative effects of ginsenosides Rg2 through suppressing p38 MAPK signaling have been studied. Ginsenoside Rg2 has provided direct vascular benefits with the suppression of leukocyte adhesion into the vascular wall by the reduction of reduced LPS-mediated p38 MAPK monocyte adhesion to HUVEC [154].

2.11. Ginsenoside Rg3

Ginsenoside Rg_3 was isolated from Korean *Panax ginseng* [112]. Ginsenoside Rg3 had the effect of enhancing cardiac dysfunction caused by myocardial I/R and the ginsenoside Rg3 ′s pharmacological action mechanism was linked to its antiapoptotic and anti-inflammatory properties [155]. Guo *et al.* demonstrated the immunomodulatory function of ginsenoside Rg3 in promoting M2-type macrophages through PPARγ-dependent mechanism. They established its potentials in the management of atherosclerosis associated with diabetes [156].

Several studies reported the anticancer-related anti-inflammatory effects of ginsenoside Rg3. It induced apoptosis in breast cancer cells, by hindering NF-κB signals through inactivating ERK and Akt as well as by destabilizing the mutant p53 [157]. Ginsenoside Rg3 inhibited the development of colorectal tumors by the downregulation of NF-κB signal [158]. Furthermore, the anti-inflammatory properties of ginsenoside Rg3 were shown to be a potential candidate for the treatment of the aging process induced by chemotherapy and its inflammatory or paracrine side effects, which may show how ginsenoside Rg3 can suppress aging and its associated problems [159].

Additionally, Ginsenoside Rg3 prevented inflammatory neurotoxicity and microglial activation, it has exerted suppressive effects in neurodegenerative conditions. Ginsenoside Rg3 suppressed the expression of TNF-α and of NF-κB in microglial cells that were activated in the 42 amino acid form of beta amyloid (Abeta42). Pretreatment with ginsenoside Rg3 improved TNF-α-treated Neuro-2α-cell survival [160]. Also, through suppression of the hippocampal inflammatory mediators, production is induced by LPS in rat brains and memory impairments are alleviated [161].

Considerable studies were published on the anti-inflammatory effect of ginsenoside Rg3 in relation to p38 MAPK suppression. Ginsenoside Rg3 was shown to effectively decrease the receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclasts differentiation. This action involved a high-binding interaction with Cathepsin K (Cat-K) as well as the effective ability to decrease the RANKL-induced osteoclastogenesis differentiation through the suppression of Cat-K mediated by downregulating p38 MAPK signal [162]. Similarly, treatment with Rg3 showed anti-hepatitis B activity through the degradation of TNF receptor-associated factor 6/transforming growth factor activated kinase-1(TAK1) and the curbing of p38 MAPK activity [163]. Additionally, the anticancer activity of ginsenoside Rg3 mediated through the deactivation of the p38 MAPK pathway, explained its ability to provoke programmed cell death in many cancer cells including lung cancer [164].

On the other hand, some literatures demonstrated the ability of ginsenoside Rg3 to promote cell survival and insulin secretion through the activation of p38 MAPK and ERK phosphorylation against intermittent high glucose [165]. Similarly, Xin *et al.* (2019) reported that ginsenoside Rg3 enhances phagocytosis through ERK1/2 and p38 MAPK activation [166].

2.12. Ginsenoside Rg5

Ginsenoside Rg5 was isolated from red *Panax ginseng* [167]. Various studies have assessed the pharmacological effects of ginsenoside Rg5. Ginsenoside Rg5 induced apoptosis and autophagy in the mouse model against breast cancer by suppressing the PI3K/Akt [168].

Many studies investigated the ginsenoside Rg5 anti-inflammatory activities. Ginsenoside Rg5 decreased the IL-1β, TNFα, COX-2, iNOS expression and IRAK-1, IKK-α and NF-κB phosphorylation, and decrease IRAK-1 and IRAK4 degradation in the alveolar macrophages induced by LPS [169]. In addition, ginsenoside Rg5's anti-inflammatory activity was noted in TNF-α activated hepatic cells and in hepatocarcinoma through the suppression of NF-κB, COX2, and iNOS. Ginsenoside Rg5 suppressed streptozotocin (STZ)- induced COX-2 and iNOS expression, the essential neuroinflammatory enzymes [170]. Ginsenoside Rg5 dramatically inhibited thymus- and activation-regulated chemokine (TARC/CCL17) expression in HaCaT cells that were stimulated by TNF-α/IFN-γ. In RAW264.7 cells, the production of NO and ROS induced by LPS was likewise reduced by ginsenoside Rg5. Furthermore, ginsenoside Rg5 inhibited NF-κB/p38 MAPK/signal transducer and activator of transcription (STAT)-1 signal, which are involved in the expression of chemokine and NO production [171].

A very recent study illustrated that ginsenoside Rg5 could attenuate kidney damage in diabetic mice induced by oxidative stress through curbing NF-κB and p-p38 MAPK and effectively decreasing cytokines IL-1β and IL-18 production. Additionally, ginsenoside Rg5 restored oxidant/antioxidant balance, thereby protecting against diabetic nephropathy [172].

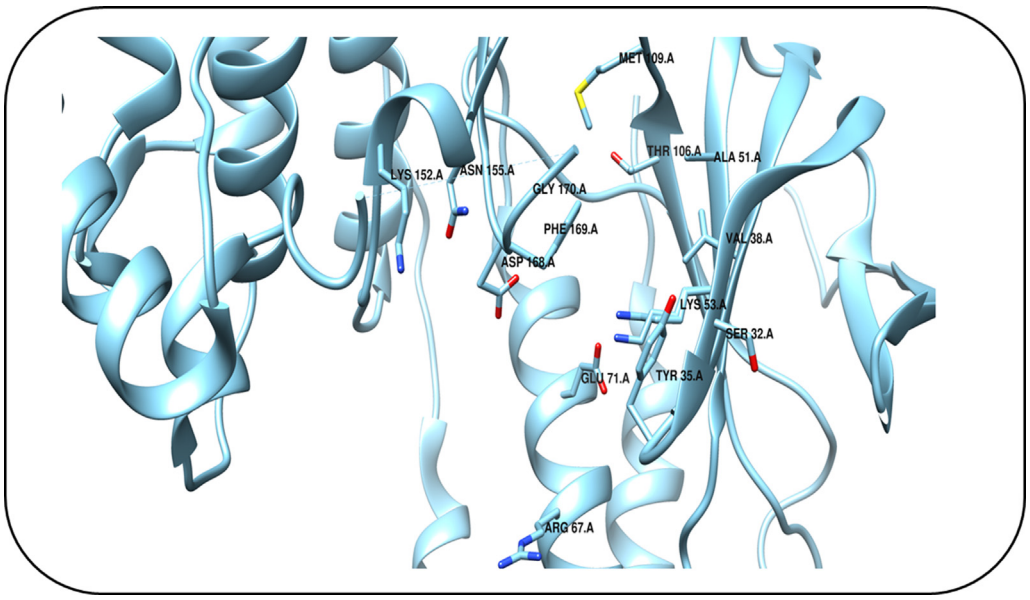

Figure 2. The binding pocket of p38 MAPK. The following residues represent the binding site of p38 MAPK and were used for site-specific docking study: S32, Y35, V38, A51, K53, R67, E71, T106, M109, K152, N155, D168, F169, and G170 residues.

On the other hand, Liu and Fan (2019) revealed the potential use of ginsenoside Rg5 to treat gastric cancer, which was mediated by p38 MAPK activation and the p38 inhibitor SB203580, while the knockdown of p38 MAPK by siRNA reversed the apoptotic induction by ginsenoside Rg5 [173].

2.13. Ginsenoside Rh1

Ginsenoside Rh1 was isolated from *Panax ginseng* [174]. Numerous studies have attempted to explain the therapeutic role of ginsenoside Rh1. Administration of ginsenoside Rh1 for long-term improved learning and memory by promoting cell viability in the mouse's hippocampus [175]. Ginsenoside Rh1 has antifibrotic and hepatoprotective activities [176]. It ameliorated high-fat dietary obesity in mice through the suppression of the differentiation of adipocytes [177]. Ginsenoside Rh1 has potentiated dexamethasone's anti-inflammatory actions in chronic inflammatory disease by antagonizing the resistance induced by dexamethasone [178].

Ginsenoside Rh1 inhibited the high mobility group box 1 (HMGB1)-mediated hyperpermeability and leukocyte migration in mice as revealed by Lee *et al.* (2019). In addition, ginsenoside Rh1 treatment decreased the *in vivo* cecal ligation and puncture-induced release of HMGB1, sepsis-related mortality, and tissue injury [179]. Ginsenoside Rh1 exerted anti-inflammatory action through curbing COX-2 and iNOS expression by inhibiting the activation and downstream transcription of JAK/STAT and ERK signals, including NF-κB, interferon regulatory factor 1, and STAT1 in interferon gamma (IFN-γ)-stimulated microglial cells [180, 181]. Ginsenoside Rh1 decreased immunoglobulin E and IL-6 levels in atopic dermatitis rodents, thereby significantly reducing inflammatory cell infiltration and mast cell granulation. In addition, ginsenoside Rh1 alleviated atopic dermatitis and ear-swelling symptoms [182].

Previous studies have explored the relationships between ginsenoside Rh1's anti-inflammatory activity and p38 MAPK downregulation. The suppressive effects of ginsenoside Rh1 on monocyte function was considered as a potent anti-inflammatory action through the attenuation of the phosphorylation of MAPKs [183]. In addition, it was found to prevent the invasion and migration of phorbol myristate acetate-simulated U87MG cells through the inhibition of MAPKs and DNA-binding activities: NF-κB and AP-1 [184].

Furthermore, ginsenoside Rh1 has been reported as a potential novel chemotherapy to treat malignant cancers through the inactivation of p38 MAPK signaling [185]. Likewise, Lyu *et al.* (2019) reported the ginsenoside Rh1 to inhibit colorectal carcinoma invasiveness both *in vitro* and in animal models. Rh1 downregulated MMP1 and MMP3 and promoted the tissue inhibitor of metalloproteinase 3 expression and effectively decreased the phosphorylation of MAPKs *in vitro* and *in vivo*, concluding that ginsenoside Rh1 mediated its action through MAPK-signaling inactivation [186].

2.14. Ginsenoside Rh2

Ginsenoside Rh2 was obtained from the root of *Panax ginseng* [187]. Ginsenoside Rh2 represented different pharmacological roles, including: antiproliferative and apoptotic role by regulating the TNF-α signaling pathway in human leukemia cells [188] and increasing mitochondrial ROS in human Jurkat leukemia cells [189]; Anti-allergic and

Table 3. Molecular docking of ginsenosides as potential inhibitors of p38 MAPK.

Compounds	Lowest energy of docking (kcal/mol)
Ginsenoside Compound K	**-8.84 ± 0.28**
Ginsenoside F1	**-8.88 ± 0.40**
Ginsenoside Rb1	-7.88 ± 0.38
Ginsenoside Rb3	**-8.79 ± 0.27**
Ginsenoside Rc	-7.95 ± 0.36
Ginsenoside Rd	**-8.94 ± 0.33**
Ginsenoside Re	-8.56 ± 0.34
Ginsenoside Rf	-8.31 ± 0.36
Ginsenoside Rg1	-8.20 ± 0.38
Ginsenoside Rg2	-8.50 ± 0.27
Ginsenoside Rg3	-8.30 ± 0.10
Ginsenoside Rg5	-8.83 ± 0.25
Ginsenoside Rh1	-7.15 ± 0.26
Ginsenoside Rh_2	-8.52 ± 0.20
Ginsenoside Ro	**-9.34 ± 0.39**
Notoginsenoside R1	-8.47 ± 0.31
Protopanaxadiol	-7.84 ± 0.33
SB2 (standard)	**-9.16 ± 0.64**

Most promising ginsenosides regarding energy binding were written in bold and their docking models were presented in Figure 3.

anti-inflammatory activities by hindering the development of NO and PGE2 [190]; and anti-inflammatory actions in neuronal cells by the inhibition of LPS/IFN-γ-induced NO generation in murine BV-2 cells. Also, decreased TNF-α, iNOS, COX-2, and IL-1β, while curbing intercellular adhesion molecule 1 in astroglial cells mediated by curbing NF-κB and JNK/AP-1 signaling [191]. The anti-inflammatory properties of ginsenoside Rh2 in murine asthma model had been studied. Li *et al.* (2015) revealed that ginsenoside Rh2 inhibited peribronchiolar inflammation, cytokine production, airway inflammatory cell recruitment, in addition to the expression of IgE, and aryl hydrocarbon receptors in a murine asthma model by curbing of p38 MAPK and NF-κB activation. Therefore, ginsenoside Rh2 may be convenient for treating inflammatory disorders in the airways, such as asthma [192].

Kim *et al.* (2007) demonstrated that ginsenoside Rh2, acquired from PPD by gut flora, curbed the expression of MMP-9 by mitigating p38 MAPK [193]. Kim *et al.* (2014) also documented p38 MAPK as a survival factor in cancer cells. In this study, compared to ginsenoside Rh2 treatment alone, cotreatment with ginsenoside Rh2 and SB203580 resulted in cell death, which increased from 20% to 50%, suggesting that p38 MAPK inhibition can increase ginsenoside Rh2-provoked programmed cell death in hepatocellular carcinoma. Nevertheless, the effect of ERK or JNK mitigation on cytotoxicity has not been observed. [187].

In contrast, several researchers investigated that ginsenoside Rh2 exhibited anticancer activity mediated by p38 MAPK activation [187, 194, 195, 196].

2.15. Ginsenoside Ro

Ginsenoside Ro was isolated from the root of *Panax ginseng* [197]. Ginsenoside Ro exhibits various pharmacological activities, particularly antioxidant and anti-inflammatory activities. Ginsenoside Ro had a possible anti-photoaging skin property in fibroblasts against UV-B radiation [198]. Ginsenoside Ro prevented dose-dependent thrombin-provoked platelet aggregation and diminished fibrinogen attachment to αIIb/β3 by phosphorylated cAMP-dependent vasodilator-stimulated phosphoprotein (VASP; Ser157). Additionally, ginsenoside Ro mitigated the of the clot that represented thrombi intensification [199]. Ginsenoside Ro has inhibited in vivo tumor development of B16F10-transplanted tumors, and its anti-tumor effects are depending on its metabolites' biological action. Those metabolites' anti-tumor effectiveness was due to their antiangiogenic activity [200].

Ginsenoside Ro downregulated p-ERK/2 to mitigate thrombin-elevation [Ca2 +], which helped inhibiting ATP, 5-HT release, and p-selectin expression while positively regulating cAMP-dependent IP3RI

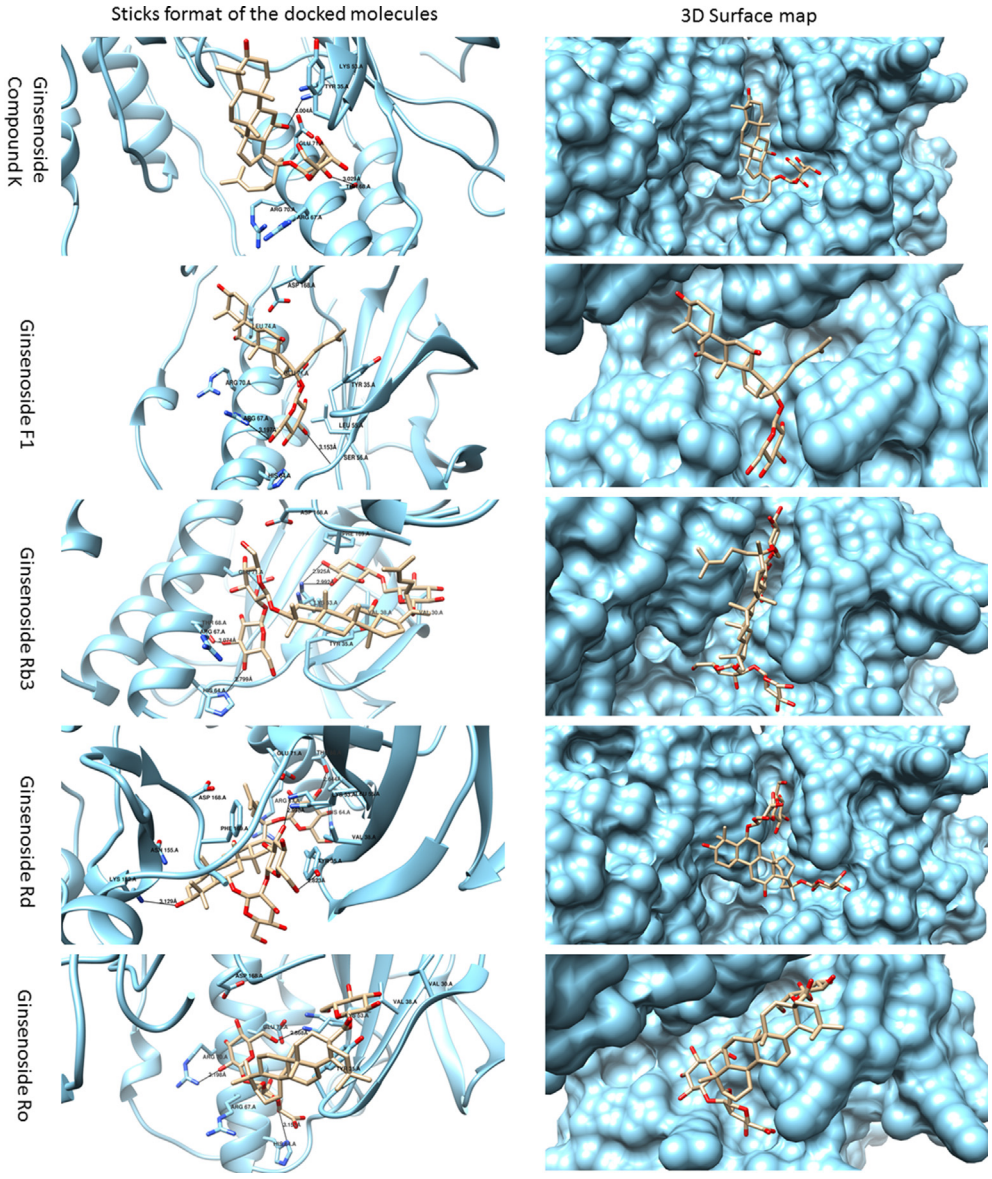

Figure 3. Docking models of Ginsenoside Compound K (CK), Ginsenoside F1, Ginsenoside-Rb3, Ginsenoside-Rd, and Ginsenoside RO with p38 MAPK. Steroidal-like structure with multiple bounded OH groups of ginsenoside derivatives allowed them to form multiple hydrogen bonds with the polar amino acids and hydrophobic interaction with the hydrophobic residues in the active site. These different noncovalent interactions enable the derivatives to fit well in the binding pocket of p38 MAPK as shown in the surface map of the predicted complexes.

(Ser1756) phosphorylation [201]. Up to now, no more studies highlighted the direct link between the ginsenoside subtype Ro's anti-inflammatory action and p38 MAPK signaling suppression. Only Shin *et al.* (2019) evidenced that ginsenoside Ro holds a significant antiplatelet potential and attenuates thromboxane-A2 production by suppressing p38-MAPK-mediated cytosolic phospholipase A2a (cPLA2a) phosphorylation and arachidonic acid release [202].

2.16. Notoginsenoside R_1

Notoginsenoside R1 was obtained from the root of *Panax notoginseng* [203]. Several studies reported that notoginsenoside R1 exhibited a strong anti-inflammatory [203] anticancer [204] and antioxidant [205] activities.

Sun *et al.* (2019) demonstrated that notoginsenoside R1 relieved PC-12 cells from inflammatory damage caused by LPS through the elevation of miR-132 and subsequently suppression of the JNK pathway [206]. In another study, notoginsenoside R1 prevented acrylamide-induced mitochondrial apoptosis by upregulating thioredoxin-1 in rat adrenal chromaffin cell tumor (PC12) cells. Notoginsenoside R1 ameliorated I/R-provoked damage in different systems primarily by stimulating α-dependent 3-kinase phosphoinositide estrogen receptor [207].

The inhibitory effect of notoginsenoside R1 on p38 MAPK signaling has been well-studied by different researchers. The activation of TAK1 in mice might additionally activate p38 MAPK, therefore, upregulating inflammation and inducing myocardial programmed cell death. Notoginsenoside R1 possesses a cardioprotective effect through the modulation of this pathway [208]. Another study conducted by Qiu *et al.* (2016) reported the role of notoginsenoside R1 in the management of chronic obstructive pulmonary disease by alleviating hypoxia and hypercapnia-induced pulmonary vasoconstriction and suppression of ERK and p38 MAPK activation [209].

2.17. Protopanaxadiol

PPD is a major active metabolite from *Panax ginseng* [210]. It possesses a wide range of biological activities such as anti-inflammatory [211, 212], antiapoptotic [212], anticancer [213], and antioxidant [214, 215] activities. Peng *et al.* (2019) reported that PPD suppressed breast carcinoma metastasis in vivo through Epidermal Growth Factor Receptor (EGFR)-mediated MAPK pathway. This demonstrated that 20(S)-PPD treatment curbed EGFR phosphorylation and inactivated MAPK signaling [216]. Another study conducted by Jang *et al.* (2012) reported that PPD modulated the expression of COX-2, IκB-α, p-ERK 1/2, and p-SAPK/JNK levels and blocked apoptotic markers; caspases and cleaved poly (ADP-ribose) polymerase (PARP), such as in hepatic inflammation and apoptosis in hyperlipemic mice [217].

3. *In silico* evidence

The molecular docking approach has been used widely to elucidate the binding modes of drug candidates to the active site of the target protein. We have utilized docking to obtain the potential binding energies of different ginsenosides with p38 MAPK. Molecular docking was performed by using Autodock vina 1.5.6 [218]. The complex crystal structure of p38 MAPK with its inhibitor was retrieved from a protein data bank with PDB ID: 3ZS5. The water molecules and ligands were removed, and the PDBQT file was prepared accordingly. The binding residues of p38 MAPK with its inhibitor were identified and visualized (Figure 2) [219]. Chimera 1.12 software was used to visualize the best-scored conformation of the different ginsenosides with the active site of p38 MAPK. To predict the binding affinity for the selected ginsenosides with p38 MAPK, the average of the lowest docking energy was utilized to predict the binding affinity for the selected ginsenosides. All the compounds' binding affinities with p38 MAPK were compared with SB2, the standard inhibitor for p38 MAPK, and cocrystallize with it. Interestingly, most of the compounds have shown promising binding affinities with p38 MAPK, and all the binding energies of docking were shown in Table 3. The compounds of the highest binding affinities were further used to clarify their binding mechanism with p38 MAPK.

All studied ginsenosides composed a well-fitted structure inside the binding cavity of p38 MAPK (Figure 3). This promising inhibitory effect might be attributed to its unique structural features that combine the steroidal-like structure allowing ginsenosides to exhibit hydrophobic interaction with the hydrophobic residues in the active site, and the multiple bounded OH groups enabling them to form hydrogen bonds with the polar amino acids. These different noncovalent interactions could be the main reason for such promising binding between ginsenosides and p38 MAPK.

As illustrated in Figure 3, **Ginsenoside Compound K (CK)** forms two hydrogen bonds (H-bonds) with the side chains of K53 and T68. **Ginsenoside F1** forms two hydrogen bonds with S56 and R67 and exhibit hydrophobic interface with L55 and L74. **Ginsenoside Rb3** forms four H-bonds with K53, H64, and T68 and exhibit hydrophobic interaction with V30, V38, Y35, and F169 in the active site's vicinity. **Ginsenoside Rd** forms four hydrogen bonds with the side chains of Y35, K53, T68, and K152 and exhibited hydrophobic interaction with V38, L54, and F169. **Ginsenoside Ro** forms three hydrogen bonds with the side chain of K53, H64, and R70. It also exhibits hydrophobic interaction with V30, V38, and Y35.

4. Conclusion

Accumulating evidence indicates that p38 MAPK could play many roles in human disease pathophysiology. Therefore, great therapeutic benefits can be attained from p38 MAPK inhibitors. Ginseng is an exceptionally valued medicinal plant of the family *Araliaceae* (*Panax* genus). Several studies and efforts have recently targeted the therapeutic effects on purified individual ginsenoside, ginseng's most active ingredient, and have investigated its molecular mechanism(s) rather than whole-plant extracts. Interestingly, several ginsenosides: ginsenosides compound K, F1, Rb1, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rg5, Rh1, Rh2, Ro, notoginsenoside R1, and PPD, have shown to possess great therapeutic potentials mediated by its ability to downregulate p38 MAPK signaling in different cells and experimental animal models. Our review compiles the research findings of different ginsenosides as potent anti-inflammatory drugs, highlighting the key role of suppressing p38 MAPK in their pharmacological actions (Table 2). In addition, *in silico* studies were conducted to explore the likely binding of these ginsenosides to p38 MAPK and evidenced the promising inhibitory effect of ginsenosides. This effect could be attributed to its unique structural features that combine the steroidal-like structure, which allowed ginsenosides to exhibit hydrophobic interaction with the hydrophobic residues in the active site and the multiple-bounded OH groups that enable them to form H-bonds with the polar amino acids. These different noncovalent interactions could be the main reason for such promising binding between ginsenosides and p38 MAPK. Notably, ginsenoside compound K, ginsenoside F1, ginsenoside Rb3, Ginsenoside Rd, and ginsenoside Ro produced energy of binding comparable with that of the standard p38 MAPK inhibitor SB2.

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Author contribution statement

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] J.M. Ellis, P. Reddy, Effects of Panax ginseng on quality of life, Ann. Pharmacother. 36 (3) (2002) 375–379.
[2] S.Y. Hu, A contribution to our knowledge of ginseng, Am. J. Chin. Med. 5 (1) (1977) 1–23.
[3] L. Jia, Y. Zhao, Current evaluation of the millennium phytomedicine–ginseng (I): etymology, pharmacognosy, phytochemistry, market and regulations, Curr. Med. Chem. 16 (19) (2009) 2475–2484.
[4] N. Fuzzati, Analysis methods of ginsenosides, J. Chromatogr. B, Analyt. Technol. Biomed. Life Sci. 812 (1-2) (2004) 119–133.
[5] O. Shehzad, I.J. Ha, Y. Park, Y.W. Ha, Y.S. Kim, Development of a rapid and convenient method to separate eight ginsenosides from Panax ginseng by high-speed counter-current chromatography coupled with evaporative light scattering detection, J. Separ. Sci. 34 (10) (2011) 1116–1122.
[6] O. Shehzad, H.P. Kim, Y.S. Kim, State-of-the-art separation of ginsenosides from Korean white and red ginseng by countercurrent chromatography, Anal. Bioanal. Chem. 405 (13) (2013) 4523–4530.
[7] S. Khan, A. Tosun, Y.S. Kim, Ginsenosides as Food Supplements and Their Potential Role in Immunological and Neurodegenerative Disorders, Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease, Elsevier, 2015, pp. 303–309.
[8] C. Guo, X. Cui, X. Yang, S. Wu, Advances in studies on biotransformation of ginsensides, Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China J. Chin. Mat. Med. 39 (20) (2014) 3899–3904.
[9] K.C. Shin, D.K. Oh, Characterization of a novel recombinant β-glucosidase from Sphingopyxis alaskensis that specifically hydrolyzes the outer glucose at the C-3 position in protopanaxadiol-type ginsenosides, J. Biotechnol. 172 (2014) 30–37.
[10] L. Wang, S.J. Zhao, Y.L. Liang, Y. Sun, H.J. Cao, Y. Han, Identification of the protopanaxatriol synthase gene CYP6H for ginsenoside biosynthesis in Panax quinquefolius, Funct. Integr. Genom. 14 (3) (2014) 559–570.
[11] J.H. Kim, Y.S. Yi, M.Y. Kim, J.Y. Cho, Role of ginsenosides, the main active components of Panax ginseng, in inflammatory responses and diseases, J. Ginseng Res. 41 (4) (2017) 435–443.
[12] W. Lim, K.W. Mudge, F. Vermeylen, Effects of population, age, and cultivation methods on ginsenoside content of wild American ginseng (Panax quinquefolium), J. Agric. Food Chem. 53 (22) (2005) 8498–8505.
[13] E.M. Schlag, M.S. McIntosh, Ginsenoside content and variation among and within American ginseng (Panax quinquefolius L.) populations, Phytochemistry 67 (14) (2006) 1510–1519.
[14] W. Li, C. Gu, H. Zhang, D.V. Awang, J.F. Fitzloff, H.H. Fong, R.B. van Breemen, Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish Panax ginseng C. A. Meyer (Asian ginseng) and Panax quinquefolius L. (North American ginseng), Anal. Chem. 72 (21) (2000) 5417–5422.
[15] V.A. Assinewe, B.R. Baum, D. Gagnon, J.T. Arnason, Phytochemistry of wild populations of Panax quinquefolius L. (North American ginseng), J. Agric. Food Chem. 51 (16) (2003) 4549–4553.
[16] F. Soldati, O. Tanaka, Panax ginseng: relation between age of plant and content of ginsenosides, Planta Med. 50 (4) (1984) 351–352.
[17] J.-H. Ryu, J.-H. Park, J.-H. Eun, J.-H. Jung, D.H.J.P. Sohn, A dammarane glycoside from Korean red ginseng, Phytochemistry 44 (5) (1997) 931–933.
[18] S.W. Kwon, S.B. Han, I.H. Park, J.M. Kim, M.K. Park, J.H. Park, Liquid chromatographic determination of less polar ginsenosides in processed ginseng, J. Chromatogr. A 921 (2) (2001) 335–339.
[19] C.Z. Wang, S. Anderson, W. Du, T.C. He, C.S. Yuan, Red ginseng and cancer treatment, Chin. J. Nat. Med. 14 (1) (2016) 7–16.
[20] S.K. Park, S.H. Hyun, G. In, C.K. Park, Y.S. Kwak, Y.J. Jang, B. Kim, J.H. Kim, C.K. Han, The antioxidant activities of Korean Red Ginseng (Panax ginseng) and ginsenosides: a systemic review through in vivo and clinical trials, J. Ginseng Res. 45 (1) (2021) 41–47.
[21] G.L. Johnson, R. Lapadat, Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases, Science (New York, N.Y.) 298 (5600) (2002) 1911–1912.
[22] Y.J. Guo, W.W. Pan, S.B. Liu, Z.F. Shen, Y. Xu, L.L. Hu, ERK/MAPK signalling pathway and tumorigenesis, Exp. Therap. Med. 19 (3) (2020) 1997–2007.
[23] C. Braicu, M. Buse, C. Busuioc, R. Drula, D. Gulei, L. Raduly, A. Rusu, A. Irimie, A.G. Atanasov, O. Slaby, C. Ionescu, I. Berindan-Neagoe, A comprehensive review on MAPK: a promising therapeutic target in cancer, Cancers 11 (10) (2019).
[24] G.L. Johnson, R.J.S. Lapadat, Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases, Science 298 (5600) (2002) 1911–1912.
[25] A. Cuadrado, A.R. Nebreda, Mechanisms and functions of p38 MAPK signalling, Biochem. J. 429 (3) (2010) 403–417.
[26] J.X. Yu, A.J. Craig, M.E. Duffy, C. Villacorta-Martin, V. Miguela, M. Ruiz de Galarreta, A.P. Scopton, L. Silber, A.Y. Maldonado, A. Rialdi, E. Guccione, A. Lujambio, A. Villanueva, A.C. Dar, Phenotype-based screens with conformation-specific inhibitors reveal p38 gamma and delta as targets for HCC polypharmacology, Mol. Cancer Therapeut. 18 (9) (2019) 1506–1519.
[27] S. Hwang, X. Wang, R.M. Rodrigues, J. Ma, Y. He, W. Seo, S.H. Park, S.J. Kim, D. Feng, B. Gao, Protective and detrimental roles of p38alpha MAPK in different stages of nonalcoholic fatty liver disease, Hepatology (2020).
[28] S. Banerjee, D. Bose, N. Chatterjee, S. Das, S. Chakraborty, T. Das, K.D. Saha, Attenuated Leishmania induce pro-inflammatory mediators and influence leishmanicidal activity by p38 MAPK dependent phagosome maturation in Leishmania donovani co-infected macrophages, Sci. Rep. 6 (2016) 22335.
[29] Y. Chen, K. Shou, C. Gong, H. Yang, Y. Yang, T. Bao, Anti-inflammatory effect of geniposide on osteoarthritis by suppressing the activation of p38 MAPK signaling pathway, BioMed Res. Int. 2018 (2018) 8384576.
[30] E. Herlaar, Z. Brown, p38 MAPK signalling cascades in inflammatory disease, Mol. Med. Today 5 (10) (1999) 439–447.
[31] D. Cui, Y. Zhao, J. Xu, Activation of CXCL5-CXCR2 axis promotes proliferation and accelerates G1 to S phase transition of papillary thyroid carcinoma cells and activates JNK and p38 pathways, Cancer Biol. Ther. 20 (5) (2019) 608–616.
[32] R.P.H. De Maeyer, R.C. van de Merwe, R. Louie, O.V. Bracken, O.P. Devine, D.R. Goldstein, M. Uddin, A.N. Akbar, D.W. Gilroy, Blocking elevated p38 MAPK restores efferocytosis and inflammatory resolution in the elderly, Nat. Immunol. 21 (6) (2020) 615–625.
[33] M.A. Read, M.Z. Whitley, S. Gupta, J.W. Pierce, J. Best, R.J. Davis, T. Collins, Tumor necrosis factor alpha-induced E-selectin expression is activated by the nuclear factor-kappaB and c-JUN N-terminal kinase/p38 mitogen-activated protein kinase pathways, J. Biol. Chem. 272 (5) (1997) 2753–2761.
[34] J.A. Nick, N.J. Avdi, S.K. Young, L.A. Lehman, P.P. McDonald, S.C. Frasch, M.A. Billstrom, P.M. Henson, G.L. Johnson, G.S. Worthen, Selective activation and functional significance of p38alpha mitogen-activated protein kinase in lipopolysaccharide-stimulated neutrophils, J. Clin. Invest. 103 (6) (1999) 851–858.
[35] M. Bergmann, L. Hart, M. Lindsay, P.J. Barnes, R. Newton, IkappaBalpha degradation and nuclear factor-kappaB DNA binding are insufficient for interleukin-1beta and tumor necrosis factor-alpha-induced kappaB-dependent transcription. Requirement for an additional activation pathway, J. Biol. Chem. 273 (12) (1998) 6607–6610.
[36] S. Wesselborg, M.K. Bauer, M. Vogt, M.L. Schmitz, K. Schulze-Osthoff, Activation of transcription factor NF-kappaB and p38 mitogen-activated protein kinase is mediated by distinct and separate stress effector pathways, J. Biol. Chem. 272 (19) (1997) 12422–12429.
[37] J.M. Lü, Q. Yao, C. Chen, Ginseng compounds: an update on their molecular mechanisms and medical applications, Curr. Vasc. Pharmacol. 7 (3) (2009) 293–302.
[38] J. Xu, Z. Hao, X. Gou, W. Tian, Y. Jin, S. Cui, J. Guo, Y. Sun, Y. Wang, Z. Xu, Imaging of reactive oxygen species burst from mitochondria using laser scanning confocal microscopy, Microsc. Res. Tech. 76 (6) (2013) 612–617.
[39] N.I. Venediktova, O.V. Mashchenko, E.Y. Talanov, N.V. Belosludtseva, G.D. Mironova, Energy metabolism and oxidative status of rat liver mitochondria in conditions of experimentally induced hyperthyroidism, Mitochondrion 52 (2020) 190–196.
[40] C.H. Yeh, J.J. Yang, M.L. Yang, Y.C. Li, Y.H. Kuan, Rutin decreases lipopolysaccharide-induced acute lung injury via inhibition of oxidative stress and the MAPK-NF-κB pathway, Free Rad. Biol. Med. 69 (2014) 249–257.
[41] A.M. Tormos, R. Taléns-Visconti, A.R. Nebreda, J. Sastre, p38 MAPK: a dual role in hepatocyte proliferation through reactive oxygen species, Free Radic. Res. 47 (11) (2013) 905–916.
[42] A. Van Laethem, K. Nys, S. Van Kelst, S. Claerhout, H. Ichijo, J.R. Vandenheede, M. Garmyn, P. Agostinis, Apoptosis signal regulating kinase-1 connects reactive oxygen species to p38 MAPK-induced mitochondrial apoptosis in UVB-irradiated human keratinocytes, Free Rad. Biol. Med. 41 (9) (2006) 1361–1371.
[43] J. Pan, Q. Chang, X. Wang, Y. Son, Z. Zhang, G. Chen, J. Luo, Y. Bi, F. Chen, X. Shi, Reactive oxygen species-activated Akt/ASK1/p38 signaling pathway in nickel compound-induced apoptosis in BEAS 2B cells, Chem. Res. Toxicol. 23 (3) (2010) 568–577.
[44] X. Wang, J.Z. Liu, J.X. Hu, H. Wu, Y.L. Li, H.L. Chen, H. Bai, C.X. Hai, ROS-activated p38 MAPK/ERK-Akt cascade plays a central role in palmitic acid-stimulated hepatocyte proliferation, Free Rad. Biol. Med. 51 (2) (2011) 539–551.
[45] J.Y. Choi, H.J. Cho, S.G. Hwang, W.J. Kim, J.I. Kim, H.D. Um, J.K. Park, Podophyllotoxin acetate enhances γ-ionizing radiation-induced apoptotic cell death by stimulating the ROS/p38/caspase pathway, Biomed. Pharmacother. = Biomedecine & pharmacotherapie 70 (2015) 111–118.
[46] J. Park, J.S. Min, B. Kim, U.B. Chae, J.W. Yun, M.S. Choi, I.K. Kong, K.T. Chang, D.S. Lee, Mitochondrial ROS govern the LPS-induced pro-inflammatory response in microglia cells by regulating MAPK and NF-κB pathways, Neurosci. Lett. 584 (2015) 191–196.
[47] F. Wang, Y.S. Roh, Mitochondrial connection to ginsenosides, Arch Pharm. Res. 43 (10) (2020) 1031–1045.
[48] J. Branger, B. van den Blink, S. Weijer, J. Madwed, C.L. Bos, A. Gupta, C.L. Yong, S.H. Polmar, D.P. Olszyna, C.E. Hack, S.J. van Deventer, M.P. Peppelenbosch,

T. van der Poll, Anti-inflammatory effects of a p38 mitogen-activated protein kinase inhibitor during human endotoxemia, J. Immunol. 168 (8) (2002) 4070–4077.
[49] X. Luo, B. Fitzsimmons, A. Mohan, L. Zhang, N. Terrando, H. Kordasiewicz, R.R. Ji, Intrathecal administration of antisense oligonucleotide against p38alpha but not p38beta MAP kinase isoform reduces neuropathic and postoperative pain and TLR4-induced pain in male mice, Brain Behav. Immun. 72 (2018) 34–44.
[50] J.D. Ashwell, The many paths to p38 mitogen-activated protein kinase activation in the immune system, Nat. Rev. Immunol. 6 (7) (2006) 532–540.
[51] P.P. Roux, J. Blenis, ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions, Microbiol. Mol. Biol. Rev. : MMBR 68 (2) (2004) 320–344.
[52] E.F. Wagner, A.R. Nebreda, Signal integration by JNK and p38 MAPK pathways in cancer development, Nat. Rev. Cancer 9 (8) (2009) 537–549.
[53] J.F. Schindler, J.B. Monahan, W.G. Smith, p38 pathway kinases as anti-inflammatory drug targets, J. Dent. Res. 86 (9) (2007) 800–811.
[54] P. Cohen, Targeting protein kinases for the development of anti-inflammatory drugs, Curr. Opin. Cell Biol. 21 (2) (2009) 317–324.
[55] J.K. Noel, S. Crean, J.E. Claflin, G. Ranganathan, H. Linz, M. Lahn, Systematic review to establish the safety profiles for direct and indirect inhibitors of p38 Mitogen-activated protein kinases for treatment of cancer. A systematic review of the literature, Med. Oncol. (Northwood, Lond., Engl.) 25 (3) (2008) 323–330.
[56] Y. Chen, Y. Lu, Y. Yang, X. Chen, L. Zhu, D. Zhong, Determination of ginsenoside compound K in human plasma by liquid chromatography-tandem mass spectrometry of lithium adducts, Acta Pharm. Sin. B 5 (5) (2015) 461–466.
[57] C. Wakabayashi, K. Murakami, H. Hasegawa, J. Murata, I. Saiki, An intestinal bacterial metabolite of ginseng protopanaxadiol saponins has the ability to induce apoptosis in tumor cells, Biochem. Biophys. Res. Commun. 246 (3) (1998) 725–730.
[58] C.K. Law, H.H. Kwok, P.Y. Poon, C.C. Lau, Z.H. Jiang, W.C. Tai, W.W. Hsiao, N.K. Mak, P.Y. Yue, R.N. Wong, Ginsenoside compound K induces apoptosis in nasopharyngeal carcinoma cells via activation of apoptosis-inducing factor, Chin. Med. 9 (1) (2014) 11.
[59] L. Zhou, L. Chen, X. Zeng, J. Liao, D. Ouyang, Ginsenoside compound K alleviates sodium valproate-induced hepatotoxicity in rats via antioxidant effect, regulation of peroxisome pathway and iron homeostasis, Toxicol. Appl. Pharmacol. 386 (2020) 114829.
[60] W. Song, Y. Guo, S. Jiang, L. Wei, Z. Liu, X. Wang, Y. Su, Antidepressant effects of the ginsenoside metabolite compound K, assessed by behavioral despair test and chronic unpredictable mild stress model, Neurochem. Res. 43 (7) (2018) 1371–1382.
[61] X. Zeng, K. Hu, L. Chen, L. Zhou, W. Luo, C. Li, W. Zong, S. Chen, Q. Gao, G. Zeng, D. Jiang, X. Li, H. Zhou, D.S. Ouyang, The effects of ginsenoside compound K against epilepsy by enhancing the γ-aminobutyric acid signaling pathway, Front. Pharmacol. 9 (2018) 1020.
[62] E.H. Joh, I.A. Lee, I.H. Jung, D.H. Kim, Ginsenoside Rb1 and its metabolite compound K inhibit IRAK-1 activation–the key step of inflammation, Biochem. Pharmacol. 82 (3) (2011) 278–286.
[63] T.T. Cuong, C.S. Yang, J.M. Yuk, H.M. Lee, S.R. Ko, B.G. Cho, E.K. Jo, Glucocorticoid receptor agonist compound K regulates Dectin-1-dependent inflammatory signaling through inhibition of reactive oxygen species, Life Sci. 85 (17-18) (2009) 625–633.
[64] J.S. Park, J.A. Shin, J.S. Jung, J.W. Hyun, T.K. Van Le, D.H. Kim, E.M. Park, H.S. Kim, Anti-inflammatory mechanism of compound K in activated microglia and its neuroprotective effect on experimental stroke in mice, J. Pharmacol. Exp. Therapeut. 341 (1) (2012) 59–67.
[65] E.K. Park, Y.W. Shin, H.U. Lee, S.S. Kim, Y.C. Lee, B.Y. Lee, D.H. Kim, Inhibitory effect of ginsenoside Rb1 and compound K on NO and prostaglandin E2 biosyntheses of RAW264.7 cells induced by lipopolysaccharide, Biol. Pharmaceut. Bull. 28 (4) (2005) 652–656.
[66] J. Li, W. Zhong, W. Wang, S. Hu, J. Yuan, B. Zhang, T. Hu, G. Song, Ginsenoside metabolite compound K promotes recovery of dextran sulfate sodium-induced colitis and inhibits inflammatory responses by suppressing NF-κB activation, PLoS One 9 (2) (2014), e87810.
[67] J.-S. Park, J.A. Shin, J.-S. Jung, J.-W. Hyun, T.K. Van Le, D.-H. Kim, E.-M. Park, H.-S. Kim, Anti-inflammatory mechanism of compound K in activated microglia and its neuroprotective effect on experimental stroke in mice, J. Pharmacol. Exp. Therapeut. 341 (1) (2012) 59–67.
[68] E.-K. Park, Y.-W. Shin, H.-U. Lee, S.-S. Kim, Y.-C. Lee, B.-Y. Lee, D.-H. Kim, Inhibitory effect of ginsenoside Rb1 and compound K on NO and prostaglandin E2 biosyntheses of RAW264. 7 cells induced by lipopolysaccharide, Biol. Pharm. Bull. 28 (4) (2005) 652–656.
[69] S.H. Jung, M.S. Woo, S.Y. Kim, W.K. Kim, J.W. Hyun, E.J. Kim, D.H. Kim, H.S. Kim, Ginseng saponin metabolite suppresses phorbol ester-induced matrix metalloproteinase-9 expression through inhibition of activator protein-1 and mitogen-activated protein kinase signaling pathways in human astroglioma cells, Int. J. Cancer 118 (2) (2006) 490–497.
[70] Y.H. Hong, D. Kim, G. Nam, S. Yoo, S.Y. Han, S.G. Jeong, E. Kim, D. Jeong, K. Yoon, S. Kim, J. Park, J.Y. Cho, Photoaging protective effects of BIOGF1K, a compound-K-rich fraction prepared from Panax ginseng, J. Ginseng Res. 42 (1) (2018) 81–89.
[71] L.R. Lorz, D. Kim, M.Y. Kim, J.Y. Cho, Panax ginseng-derived fraction BIOGF1K reduces atopic dermatitis responses via suppression of mitogen-activated protein kinase signaling pathway, J. Ginseng Res. 44 (3) (2020) 453–460.
[72] A. Jeong, H.J. Lee, S.J. Jeong, H.J. Lee, E.O. Lee, H. Bae, S.H. Kim, Compound K inhibits basic fibroblast growth factor-induced angiogenesis via regulation of p38 mitogen activated protein kinase and AKT in human umbilical vein endothelial cells, Biol. Pharmaceut. Bull. 33 (6) (2010) 945–950.
[73] S. Lu, Y. Luo, P. Zhou, K. Yang, G. Sun, X. Sun, Ginsenoside compound K protects human umbilical vein endothelial cells against oxidized low-density lipoprotein-induced injury via inhibition of nuclear factor-κB, p38, and JNK MAPK pathways, J. Ginseng Res. 43 (1) (2019) 95–104.
[74] W. Song, L. Wei, Y. Du, Y. Wang, S. Jiang, Protective effect of ginsenoside metabolite compound K against diabetic nephropathy by inhibiting NLRP3 inflammasome activation and NF-κB/p38 signaling pathway in high-fat diet/streptozotocin-induced diabetic mice, Int. Immunopharm. 63 (2018) 227–238.
[75] S. Lu, Y. Luo, G. Sun, X. Sun, Ginsenoside compound K attenuates ox-LDL-mediated macrophage inflammation and foam cell formation via autophagy induction and modulating NF-κB, p38, and JNK MAPK signaling, Front. Pharmacol. 11 (2020) 567238.
[76] I.K. Lee, K.A. Kang, C.M. Lim, K.C. Kim, H.S. Kim, D.H. Kim, B.J. Kim, W.Y. Chang, J.H. Choi, J.W. Hyun, Compound K, a metabolite of ginseng saponin, induces mitochondria-dependent and caspase-dependent apoptosis via the generation of reactive oxygen species in human colon cancer cells, Int. J. Mol. Sci. 11 (12) (2010) 4916–4931.
[77] K. Choi, C. Choi, Proapoptotic ginsenosides compound K and Rh enhance Fas-induced cell death of human astrocytoma cells through distinct apoptotic signaling pathways, Cancer Res. Treatm. : Offic. J. Korean Cancer Assoc. 41 (1) (2009) 36–44.
[78] H. Wang, D. Jiang, J. Liu, S. Ye, S. Xiao, W. Wang, Z. Sun, Y. Xie, J. Wang, Compound K induces apoptosis of bladder cancer T24 cells via reactive oxygen species-mediated p38 MAPK pathway, Cancer Biother. Rad. 28 (8) (2013) 607–614.
[79] S.R. Ko, K.J. Choi, K. Uchida, Y. Suzuki, Enzymatic preparation of ginsenosides Rg2, Rh1, and F1 from protopanaxatriol-type ginseng saponin mixture, Planta Med. 69 (3) (2003) 285–286.
[80] J. Zhang, M. Liu, M. Huang, M. Chen, D. Zhang, L. Luo, G. Ye, L. Deng, Y. Peng, X. Wu, G. Liu, W. Ye, D. Zhang, Ginsenoside F1 promotes angiogenesis by activating the IGF-1/IGF1R pathway, Pharmacol. Res. 144 (2019) 292–305.
[81] J. Han, J.P. Oh, M. Yoo, C.H. Cui, B.M. Jeon, S.C. Kim, J.H. Han, Minor ginsenoside F1 improves memory in APP/PS1 mice, Mol. Brain 12 (1) (2019) 77.
[82] E.H. Lee, S.Y. Cho, S.J. Kim, E.S. Shin, H.K. Chang, D.H. Kim, M.H. Yeom, K.S. Woe, J. Lee, Y.C. Sim, T.R. Lee, Ginsenoside F1 protects human HaCaT keratinocytes from ultraviolet-B-induced apoptosis by maintaining constant levels of Bcl-2, J. Invest. Dermatol. 121 (3) (2003) 607–613.
[83] H.J. Kwon, H. Lee, G.E. Choi, S.J. Kwon, A.Y. Song, S.J. Kim, W.S. Choi, S.H. Hwang, S.C. Kim, H.S. Kim, Ginsenoside F1 promotes cytotoxic activity of NK cells via insulin-like growth factor-1-dependent mechanism, Front. Immunol. 9 (2018) 2785.
[84] M. Qin, Y. Luo, S. Lu, J. Sun, K. Yang, G. Sun, X. Sun, Ginsenoside F1 ameliorates endothelial cell inflammatory injury and prevents atherosclerosis in mice through A20-mediated suppression of NF-kB signaling, Front. Pharmacol. 8 (2017) 953.
[85] H.Y. Noh, J. Lu, M. Hanif Siddiqi, S. Natatajan, S. Kang, S. Ahn, Y.J. Kim, D.C. Yang, Computational investigation of ginsenoside F1 from Panax ginseng meyer as p38 MAP kinase inhibitor: molecular docking and dynamics simulations, ADMET analysis, and drug likeness prediction, Iran. J. Pharm. Res. : IJPR 17 (4) (2018) 1318–1327.
[86] J. Hou, C. Cui, S. Kim, C. Sung, C. Choi, Ginsenoside F1 suppresses astrocytic senescence-associated secretory phenotype, Chem. Biol. Interact. 283 (2018) 75–83.
[87] J. Lei, X. Li, X.-j. Gong, Y.-n. Zheng, Isolation, synthesis and structures of cytotoxic ginsenoside derivatives, Molecules 12 (9) (2007) 2140–2150.
[88] P. Zhou, W. Xie, S. He, Y. Sun, X. Meng, G. Sun, X. Sun, Ginsenoside Rb1 as an anti-diabetic agent and its underlying mechanism analysis, Cells 8 (3) (2019).
[89] P. Zhou, X. Zhang, M. Guo, R. Guo, L. Wang, Z. Zhang, Z. Lin, M. Dong, H. Dai, X. Ji, H. Lu, Ginsenoside Rb1 ameliorates CKD-associated vascular calcification by inhibiting the Wnt/β-catenin pathway, J. Cell Mol. Med. 23 (10) (2019) 7088–7098.
[90] Q. Zheng, X.Y. Bao, P.C. Zhu, Q. Tong, G.Q. Zheng, Y. Wang, Ginsenoside Rb1 for myocardial ischemia/reperfusion injury: preclinical evidence and possible mechanisms, Oxid. Med. Cell. Long. 2017 (2017) 6313625.
[91] C. Dong, P. Liu, H. Wang, M. Dong, G. Li, Y. Li, Ginsenoside Rb1 attenuates diabetic retinopathy in streptozotocin-induced diabetic rats1, Acta Cir. Bras. 34 (2) (2019), e201900201.
[92] R. Yang, X. Jiang, X. He, D. Liang, S. Sun, G. Zhou, Ginsenoside Rb1 improves cognitive impairment induced by insulin resistance through cdk5/p35-NMDAR-IDE pathway, BioMed Res. Int. 2020 (2020) 3905719.
[93] Z. Liu, L. Song, P. Zhang, Z. Cao, J. Hao, Y. Tian, A. Luo, P. Zhang, J. Ma, Ginsenoside Rb1 exerts antiarrhythmic effects by inhibiting I(Na) and I(CaL) in rabbit ventricular myocytes, Sci. Rep. 9 (1) (2019) 20425.
[94] S. Ren, J. Leng, X.Y. Xu, S. Jiang, Y.P. Wang, X.T. Yan, Z. Liu, C. Chen, Z. Wang, W. Li, Ginsenoside Rb1, A major saponin from Panax ginseng, exerts protective effects against acetaminophen-induced hepatotoxicity in mice, Am. J. Chin. Med. 47 (8) (2019) 1815–1831.
[95] C. Chen, H. Zhang, H. Xu, Y. Zheng, T. Wu, Y. Lian, Ginsenoside Rb1 ameliorates cisplatin-induced learning and memory impairments, J. Ginseng Res. 43 (4) (2019) 499–507.
[96] A. Rhule, S. Navarro, J.R. Smith, D.M. Shepherd, Panax notoginseng attenuates LPS-induced pro-inflammatory mediators in RAW264.7 cells, J. Ethnopharmacol. 106 (1) (2006) 121–128.
[97] J.Y. Cho, E.S. Yoo, K.U. Baik, M.H. Park, B.H. Han, In vitro inhibitory effect of protopanaxadiol ginsenosides on tumor necrosis factor (TNF)-alpha production

and its modulation by known TNF-alpha antagonists, Planta Med. 67 (3) (2001) 213–218.
[98] B. Cheng, J. Li, J. Du, X. Lv, L. Weng, C. Ling, Ginsenoside Rb1 inhibits osteoclastogenesis by modulating NF-κB and MAPKs pathways, Food Chem. Toxicol. 50 (5) (2012) 1610–1615.
[99] R. Hashimoto, J. Yu, H. Koizumi, Y. Ouchi, T. Okabe, Ginsenoside Rb1 prevents MPP(+)-Induced apoptosis in PC12 cells by stimulating estrogen receptors with consequent activation of ERK1/2, Akt and inhibition of SAPK/JNK, p38 MAPK, Evid. Base Compl. Alternative Med.: eCAM 2012 (2012) 693717.
[100] P. Zhou, S. Lu, Y. Luo, S. Wang, K. Yang, Y. Zhai, G. Sun, X. Sun, Attenuation of TNF-alpha-induced inflammatory injury in endothelial cells by ginsenoside Rb1 via inhibiting NF-kappaB, JNK and p38 signaling pathways, Front. Pharmacol. 8 (2017) 464.
[101] S. Zhang, J. Deng, Y. Gao, D.L. Yang, Q.H. Gong, X.N. Huang, Ginsenoside Rb_1 inhibits the carotid neointimal hyperplasia induced by balloon injury in rats via suppressing the phenotype modulation of vascular smooth muscle cells, Eur. J. Pharmacol. 685 (1-3) (2012) 126–132.
[102] X.J. Zhang, C. He, K. Tian, P. Li, H. Su, J.B. Wan, Ginsenoside Rb1 attenuates angiotensin II-induced abdominal aortic aneurysm through inactivation of the JNK and p38 signaling pathways, Vasc. Pharmacol. 73 (2015) 86–95.
[103] G. Li, W. Qian, C. Zhao, Analyzing the anti-ischemia-reperfusion injury effects of ginsenoside Rb1 mediated through the inhibition of p38α MAPK, Can. J. Physiol. Pharmacol. 94 (1) (2016) 97–103.
[104] J. Fan, D. Liu, C. He, X. Li, F. He, Inhibiting adhesion events by Panax notoginseng saponins and Ginsenoside Rb1 protecting arteries via activation of Nrf2 and suppression of p38 - VCAM-1 signal pathway, J. Ethnopharmacol. 192 (2016) 423–430.
[105] D. Lee, D.S. Lee, K. Jung, G.S. Hwang, H.L. Lee, N. Yamabe, H.J. Lee, D.W. Eom, K.H. Kim, K.S. Kang, Protective effect of ginsenoside Rb1 against tacrolimus-induced apoptosis in renal proximal tubular LLC-PK1 cells, J. Ginseng Res. 42 (1) (2018) 75–80.
[106] X. Liu, J. Chen, N. Sun, N. Li, Z. Zhang, T. Zheng, Z. Li, Ginsenoside Rb1 ameliorates autophagy via the AMPK/mTOR pathway in renal tubular epithelial cells in vitro and in vivo, Int. J. Biol. Macromol. 163 (2020) 996–1009.
[107] C. Xin, H. Quan, J.M. Kim, Y.H. Hur, J.Y. Shin, H.B. Bae, J.I. Choi, Ginsenoside Rb1 increases macrophage phagocytosis through p38 mitogen-activated protein kinase/Akt pathway, J. Ginseng Res. 43 (3) (2019) 394–401.
[108] L. Ma, H. Liu, Z. Xie, S. Yang, W. Xu, J. Hou, B. Yu, Ginsenoside Rb3 protects cardiomyocytes against ischemia-reperfusion injury via the inhibition of JNK-mediated NF-κB pathway: a mouse cardiomyocyte model, PLoS One 9 (8) (2014).
[109] X. Liu, Y. Jiang, W. Fu, X. Yu, D. Sui, Combination of the ginsenosides Rb3 and Rb2 exerts protective effects against myocardial ischemia reperfusion injury in rats, Int. J. Mol. Med. 45 (2) (2020) 519–531.
[110] M. Wang, X. Chen, W. Jin, X. Xu, X. Li, L. Sun, Ginsenoside Rb3 exerts protective properties against cigarette smoke extract-induced cell injury by inhibiting the p38 MAPK/NF-kappaB and TGF-beta1/VEGF pathways in fibroblasts and epithelial cells, Biomed. Pharmacother. = Biomedecine & pharmacotherapie 108 (2018) 1751–1758.
[111] M. Sun, Y. Ji, Z. Li, R. Chen, S. Zhou, C. Liu, M. Du, Ginsenoside Rb3 inhibits pro-inflammatory cytokines via MAPK/AKT/NF-κB pathways and attenuates rat alveolar bone resorption in response to porphyromonas gingivalis LPS, Molecules 25 (20) (2020).
[112] J.S. Yu, H.S. Roh, K.H. Baek, S. Lee, S. Kim, H.M. So, E. Moon, C. Pang, T.S. Jang, K.H. Kim, Bioactivity-guided isolation of ginsenosides from Korean Red Ginseng with cytotoxic activity against human lung adenocarcinoma cells, J. Ginseng Res. 42 (4) (2018) 562–570.
[113] T. Yu, Y. Yang, Y.S. Kwak, G.G. Song, M.Y. Kim, M.H. Rhee, J.Y. Cho, Ginsenoside Rc from Panax ginseng exerts anti-inflammatory activity by targeting TANK-binding kinase 1/interferon regulatory factor-3 and p38/ATF-2, J. Ginseng Res. 41 (2) (2017) 127–133.
[114] M.J. Park, C.S. Bae, S.K. Lim, D.I. Kim, J.C. Lim, J.C. Kim, H.J. Han, J.H. Moon, K.Y. Kim, K.C. Yoon, S.H. Park, Effect of protopanaxadiol derivatives in high glucose-induced fibronectin expression in primary cultured rat mesangial cells: role of mitogen-activated protein kinases and Akt, Arch Pharm. Res. 33 (1) (2010) 151–157.
[115] B. Jin, C. Zhang, Y. Geng, M. Liu, Therapeutic effect of ginsenoside Rd on experimental autoimmune encephalomyelitis model mice: regulation of inflammation and treg/Th17 cell balance, Mediat. Inflamm. 2020 (2020) 8827527.
[116] N. Zhang, X. An, P. Lang, F. Wang, Y. Xie, Ginsenoside Rd contributes the attenuation of cardiac hypertrophy in vivo and in vitro, Biomed. Pharmacother. = Biomedecine & pharmacotherapie 109 (2019) 1016–1023.
[117] G. Zhang, F. Xia, Y. Zhang, X. Zhang, Y. Cao, L. Wang, X. Liu, G. Zhao, M. Shi, Ginsenoside Rd is efficacious against acute ischemic stroke by suppressing microglial proteasome-mediated inflammation, Mol. Neurobiol. 53 (4) (2016) 2529–2540.
[118] C. Liu, J. Wang, Y. Yang, X. Liu, Y. Zhu, J. Zou, S. Peng, T.H. Le, Y. Chen, S. Zhao, B. He, Q. Mi, X. Zhang, Q. Du, Ginsenoside Rd ameliorates colitis by inducing p62-driven mitophagy-mediated NLRP3 inflammasome inactivation in mice, Biochem. Pharmacol. 155 (2018) 366–379.
[119] W.-M. Lin, Y.-M. Zhang, R. Moldzio, W.-D. Rausch, Ginsenoside Rd Attenuates Neuroinflammation of Dopaminergic Cells in Culture, Neuropsychiatric Disorders an Integrative Approach, Springer, 2007, pp. 105–112.
[120] G. Hu, Z. Wu, F. Yang, H. Zhao, X. Liu, Y. Deng, M. Shi, G. Zhao, Ginsenoside Rd blocks AIF mitochondrio-nuclear translocation and NF-κB nuclear accumulation by inhibiting poly(ADP-ribose) polymerase-1 after focal cerebral ischemia in rats, Neurol. Sci.: Offic. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 34 (12) (2013) 2101–2106.
[121] J.S. Shin, N. Park, J. Ra, Y. Kim, M. Shin, M. Hong, S.H. Kim, H.J. Kwon, S.P. Hong, J. Kim, H. Bae, Panax ginseng C.A. Meyer modulates the levels of MMP3 in S12 murine articular cartilage cell line, J. Ethnopharmacol. 124 (3) (2009) 397–403.
[122] J.H. Yoon, Y.J. Choi, S.W. Cha, S.G. Lee, Anti-metastatic effects of ginsenoside Rd via inactivation of MAPK signaling and induction of focal adhesion formation, Phytomedicine 19 (3-4) (2012) 284–292.
[123] X.L. Yang, T.K. Guo, Y.H. Wang, Y.H. Huang, X. Liu, X.X. Wang, W. Li, X. Zhao, L.P. Wang, S. Yan, D. Wu, Y.J. Wu, Ginsenoside Rd attenuates the inflammatory response via modulating p38 and JNK signaling pathways in rats with TNBS-induced relapsing colitis, Int. Immunopharm. 12 (2) (2012) 408–414.
[124] Y.C. Huang, C.T. Chen, S.C. Chen, P.H. Lai, H.C. Liang, Y. Chang, L.C. Yu, H.W. Sung, A natural compound (ginsenoside Re) isolated from Panax ginseng as a novel angiogenic agent for tissue regeneration, Pharmaceut. Res. 22 (4) (2005) 636–646.
[125] M. Cai, E.J. Yang, Ginsenoside Re attenuates neuroinflammation in a symptomatic ALS animal model, Am. J. Chin. Med. 44 (2) (2016) 401–413.
[126] X. Zhang, Y. Wang, C. Ma, Y. Yan, Y. Yang, X. Wang, W.D. Rausch, Ginsenoside Rd and ginsenoside Re offer neuroprotection in a novel model of Parkinson's disease, Am. J. Neurodegen. Dis. 5 (1) (2016) 52–61.
[127] I.A. Lee, S.R. Hyam, S.E. Jang, M.J. Han, D.H. Kim, Ginsenoside Re ameliorates inflammation by inhibiting the binding of lipopolysaccharide to TLR4 on macrophages, J. Agric. Food Chem. 60 (38) (2012) 9595–9602.
[128] K.W. Lee, S.Y. Jung, S.M. Choi, E.J. Yang, Effects of ginsenoside Re on LPS-induced inflammatory mediators in BV2 microglial cells, BMC Compl. Alternative Med. 12 (2012) 196.
[129] R.C. Chen, J. Wang, L. Yang, G.B. Sun, X.B. Sun, Protective effects of ginsenoside Re on lipopolysaccharide-induced cardiac dysfunction in mice, Food Funct. 7 (5) (2016) 2278–2287.
[130] K. Yang, Y. Luo, S. Lu, R. Hu, Y. Du, P. Liao, G. Sun, X. Sun, Salvianolic acid B and ginsenoside Re synergistically protect against ox-LDL-induced endothelial apoptosis through the antioxidative and antiinflammatory mechanisms, Front. Pharmacol. 9 (2018) 662.
[131] B. Zhang, X. Cui, H.H. Jin, L. Hong, X. Liu, X. Li, Q.G. Zhang, L.P. Liu, Ginsenoside Re prevents angiotensin II-induced gap-junction remodeling by activation of PPARγ in isolated beating rat atria, Life Sci. 190 (2017) 36–45.
[132] Y. Shi, X. Wan, N. Shao, R. Ye, N. Zhang, Y. Zhang, Protective and anti-angiopathy effects of ginsenoside Re against diabetes mellitus via the activation of p38 MAPK, ERK1/2 and JNK signaling, Mol. Med. Rep. 14 (5) (2016) 4849–4856.
[133] M.K. Kim, H. Kang, C.W. Baek, Y.H. Jung, Y.C. Woo, G.J. Choi, H.Y. Shin, K.S. Kim, Antinociceptive and anti-inflammatory effects of ginsenoside Rf in a rat model of incisional pain, J. Ginseng Res. 42 (2) (2018) 183–191.
[134] Y. Li, C. Chen, S. Li, C. Jiang, Ginsenoside Rf relieves mechanical hypersensitivity, depression-like behavior, and inflammatory reactions in chronic constriction injury rats, Phytother Res. : PTR 33 (4) (2019) 1095–1103.
[135] Y. Kim, H.Y. Lee, Y.J. Choi, S.H. Cho, Antidepressant effects of ginsenoside Rf on behavioral change in the glial degeneration model of depression by reversing glial loss, J. Ginseng Res. 44 (4) (2020) 603–610.
[136] X. Qin, Y. Liu, Y. Feng, J. Jiang, Ginsenoside Rf alleviates dysmenorrhea and inflammation through the BDNF-TrkB-CREB pathway in a rat model of endometriosis, Food Funct. 10 (1) (2019) 244–249.
[137] S. Ahn, M.H. Siddiqi, V.C. Aceituno, S.Y. Simu, D.C. Yang, Suppression of MAPKs/NF-κB activation induces intestinal anti-inflammatory action of ginsenoside Rf in HT-29 and RAW264.7 cells, Immunol. Invest. 45 (5) (2016) 439–449.
[138] Y. Zong, Q.L. Ai, L.M. Zhong, J.N. Dai, P. Yang, Y. He, J. Sun, E.A. Ling, D. Lu, Ginsenoside Rg1 attenuates lipopolysaccharide-induced inflammatory responses via the phospholipase C-γ1 signaling pathway in murine BV-2 microglial cells, Curr. Med. Chem. 19 (5) (2012) 770–779.
[139] X.C. Sun, X.F. Ren, L. Chen, X.Q. Gao, J.X. Xie, W.F. Chen, Glucocorticoid receptor is involved in the neuroprotective effect of ginsenoside Rg1 against inflammation-induced dopaminergic neuronal degeneration in substantia nigra, J. Steroid Biochem. Mol. Biol. 155 (Pt A) (2016) 94–103.
[140] Y. Yang, X. Li, L. Zhang, L. Liu, G. Jing, H. Cai, Ginsenoside Rg1 suppressed inflammation and neuron apoptosis by activating PPARγ/HO-1 in hippocampus in rat model of cerebral ischemia-reperfusion injury, Int. J. Clin. Exp. Pathol. 8 (3) (2015) 2484–2494.
[141] C.L. Xie, J.H. Li, W.W. Wang, G.Q. Zheng, L.X. Wang, Neuroprotective effect of ginsenoside-Rg1 on cerebral ischemia/reperfusion injury in rats by downregulating protease-activated receptor-1 expression, Life Sci. 121 (2015) 145–151.
[142] Q. Wang, H. Zheng, Z.F. Zhang, Y.X. Zhang, Ginsenoside Rg1 modulates COX-2 expression in the substantia nigra of mice with MPTP-induced Parkinson disease through the P38 signaling pathway, Nan fang yi ke da xue xue bao = J. South. Med. Univ. 28 (9) (2008) 1594–1598.
[143] C. Fan, Q. Song, P. Wang, Y. Li, M. Yang, S.Y. Yu, Neuroprotective effects of ginsenoside-rg1 against depression-like behaviors via suppressing glial activation, synaptic deficits, and neuronal apoptosis in rats, Front. Immunol. 9 (2018) 2889.
[144] N. Jiang, J. Lv, H. Wang, H. Huang, Q. Wang, C. Lu, G. Zeng, X.M. Liu, Ginsenoside Rg1 ameliorates chronic social defeat stress-induced depressive-like behaviors and hippocampal neuroinflammation, Life Sci. 252 (2020) 117669.
[145] J.F. Hu, X.Y. Song, S.F. Chu, J. Chen, H.J. Ji, X.Y. Chen, Y.H. Yuan, N. Han, J.T. Zhang, N.H. Chen, Inhibitory effect of ginsenoside Rg1 on lipopolysaccharide-induced microglial activation in mice, Brain Res. 1374 (2011) 8–14.

[146] Y. Li, L. Suo, Y. Liu, H. Li, W. Xue, Protective effects of ginsenoside Rg1 against oxygen-glucose-deprivation-induced apoptosis in neural stem cells, J. Neurol. Sci. 373 (2017) 107–112.

[147] H. Yin, Z. Liu, F. Li, M. Ni, B. Wang, Y. Qiao, X. Xu, M. Zhang, J. Zhang, H. Lu, Y. Zhang, Ginsenoside-Rg1 enhances angiogenesis and ameliorates ventricular remodeling in a rat model of myocardial infarction, J. Mol. Med. (Berl.) 89 (4) (2011) 363–375.

[148] X. Fan, J. Tao, Y. Zhou, Y. Hou, Y. Wang, D. Gu, Y. Su, Y. Jang, S. Li, Investigations on the effects of ginsenoside-Rg1 on glucose uptake and metabolism in insulin resistant HepG2 cells, Eur. J. Pharmacol. 843 (2019) 277–284.

[149] Y.J. Zhang, X.L. Zhang, M.H. Li, J. Iqbal, C.V. Bourantas, J.J. Li, X.Y. Su, T. Muramatsu, N.L. Tian, S.L. Chen, The ginsenoside Rg1 prevents transverse aortic constriction-induced left ventricular hypertrophy and cardiac dysfunction by inhibiting fibrosis and enhancing angiogenesis, J. Cardiovasc. Pharmacol. 62 (1) (2013) 50–57.

[150] K.R. Li, Z.Q. Zhang, J. Yao, Y.X. Zhao, J. Duan, C. Cao, Q. Jiang, Ginsenoside Rg-1 protects retinal pigment epithelium (RPE) cells from cobalt chloride (CoCl2) and hypoxia assaults, PLoS One 8 (12) (2013), e84171.

[151] M.H. Zhang, J.M. Fan, X.S. Xie, Y.Y. Deng, Y.P. Chen, R. Zhen, J. Li, Y. Cheng, J. Wen, Ginsenoside-Rg1 protects podocytes from complement mediated injury, J. Ethnopharmacol. 137 (1) (2011) 99–107.

[152] J. He, Y.L. Li, Ginsenoside Rg1 downregulates the shear stress induced MCP-1 expression by inhibiting MAPK signaling pathway, Am. J. Chin. Med. 43 (2) (2015) 305–317.

[153] T. Kaku, Y. Kawashima, Isolation and characterization of ginsenoside-Rg2, 20R-prosapogenin, 20S-prosapogenin and delta 20-prosapogenin. Chemical studies on saponins of Panax ginseng CA Meyer, Third report, Arzneim. Forsch. 30 (6) (1980) 936–943.

[154] Y.S. Cho, C.H. Kim, T.S. Ha, S.J. Lee, H.Y. Ahn, Ginsenoside rg2 inhibits lipopolysaccharide-induced adhesion molecule expression in human umbilical vein endothelial cell, Korean J. Physiol. Pharmacol. 17 (2) (2013) 133–137.

[155] L.P. Zhang, Y.C. Jiang, X.F. Yu, H.L. Xu, M. Li, X.Z. Zhao, D.Y. Sui, Ginsenoside Rg3 improves cardiac function after myocardial ischemia/reperfusion via attenuating apoptosis and inflammation, Evid. base Compl. Alternative Med.: eCAM 2016 (2016) 6967853.

[156] M. Guo, J. Xiao, X. Sheng, X. Zhang, Y. Tie, L. Wang, L. Zhao, X. Ji, Ginsenoside Rg3 mitigates atherosclerosis progression in diabetic apoE-/- mice by skewing macrophages to the M2 phenotype, Front. Pharmacol. 9 (2018) 464.

[157] B.M. Kim, D.H. Kim, J.H. Park, Y.J. Surh, H.K. Na, Ginsenoside Rg3 inhibits constitutive activation of NF-κB signaling in human breast cancer (MDA-MB-231) cells: ERK and Akt as potential upstream targets, J. Cancer Prev. 19 (1) (2014) 23–30.

[158] X. Yang, J. Zou, H. Cai, X. Huang, X. Yang, D. Guo, Y. Cao, Ginsenoside Rg3 inhibits colorectal tumor growth via down-regulation of C/EBPβ/NF-κB signaling, Biomed. Pharmacother. = Biomedecine & pharmacotherapie 96 (2017) 1240–1245.

[159] J. Hou, S. Kim, C. Sung, C. Choi, Ginsenoside Rg3 prevents oxidative stress-induced astrocytic senescence and ameliorates senescence paracrine effects on glioblastoma, Molecules 22 (9) (2017).

[160] S.S. Joo, Y.M. Yoo, B.W. Ahn, S.Y. Nam, Y.B. Kim, K.W. Hwang, D.I. Lee, Prevention of inflammation-mediated neurotoxicity by Rg3 and its role in microglial activation, Biol. Pharmaceut. Bull. 31 (7) (2008) 1392–1396.

[161] B. Lee, B. Sur, J. Park, S.H. Kim, S. Kwon, M. Yeom, I. Shim, H. Lee, D.H. Hahm, Ginsenoside rg3 alleviates lipopolysaccharide-induced learning and memory impairments by anti-inflammatory activity in rats, Biomolec. Therap. 21 (5) (2013) 381–390.

[162] M.H. Siddiqi, M.Z. Siddiqi, S. Kang, H.Y. Noh, S. Ahn, S.Y. Simu, M.A. Aziz, N. Sathishkumar, Z.E. Jimenez Perez, D.C. Yang, Inhibition of osteoclast differentiation by ginsenoside Rg3 in RAW264.7 cells via RANKL, JNK and p38 MAPK pathways through a modulation of Cathepsin K: an in silico and in vitro study, Phytother Res. : PTR 29 (9) (2015) 1286–1294.

[163] L.J. Kang, Y.J. Choi, S.G. Lee, Stimulation of TRAF6/TAK1 degradation and inhibition of JNK/AP-1 signalling by ginsenoside Rg3 attenuates hepatitis B virus replication, Int. J. Biochem. Cell Biol. 45 (11) (2013) 2612–2621.

[164] H.Y. Sun, J.H. Lee, Y.S. Han, Y.M. Yoon, C.W. Yun, J.H. Kim, Y.S. Song, S.H. Lee, Pivotal roles of ginsenoside Rg3 in tumor apoptosis through regulation of reactive oxygen species, Anticancer Res. 36 (9) (2016) 4647–4654.

[165] C. Zhang, C. Li, X. Jia, K. Wang, Y. Tu, R. Wang, K. Liu, T. Lu, C. He, In Vitro and in vivo anti-inflammatory effects of polyphyllin VII through downregulating MAPK and NF-κB pathways, Molecules 24 (5) (2019).

[166] C. Xin, J. Kim, H. Quan, M. Yin, S. Jeong, J.I. Choi, E.A. Jang, C.H. Lee, D.H. Kim, H.B. Bae, Ginsenoside Rg3 promotes Fc gamma receptor-mediated phagocytosis of bacteria by macrophages via an extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent mechanism, Int. Immunopharm. 77 (2019) 105945.

[167] D. Zhang, A. Wang, J. Feng, Q. Zhang, L. Liu, H. Ren, Ginsenoside Rg5 induces apoptosis in human esophageal cancer cells through the phosphoinositide-3 kinase/protein kinase B signaling pathway, Mol. Med. Rep. 19 (5) (2019) 4019–4026.

[168] Y. Liu, D. Fan, Ginsenoside Rg5 induces apoptosis and autophagy via the inhibition of the PI3K/Akt pathway against breast cancer in a mouse model, Food Funct. 9 (11) (2018) 5513–5527.

[169] T.W. Kim, E.H. Joh, B. Kim, D.H. Kim, Ginsenoside Rg5 ameliorates lung inflammation in mice by inhibiting the binding of LPS to toll-like receptor-4 on macrophages, Int. Immunopharm. 12 (1) (2012) 110–116.

[170] S. Chu, J. Gu, L. Feng, J. Liu, M. Zhang, X. Jia, M. Liu, D. Yao, Ginsenoside Rg5 improves cognitive dysfunction and beta-amyloid deposition in STZ-induced memory impaired rats via attenuating neuroinflammatory responses, Int. Immunopharm. 19 (2) (2014) 317–326.

[171] S. Ahn, M.H. Siddiqi, V.C. Aceituno, S.Y. Simu, J. Zhang, Z.E. Jimenez Perez, Y.J. Kim, D.C. Yang, Ginsenoside Rg5:Rk1 attenuates TNF-α/IFN-γ-induced production of thymus- and activation-regulated chemokine (TARC/CCL17) and LPS-induced NO production via downregulation of NF-κB/p38 MAPK/STAT1 signaling in human keratinocytes and macrophages, in vitro cellular & developmental biology, Animal 52 (3) (2016) 287–295.

[172] W. Chen, R. Li, S. Zhu, J. Ma, L. Pang, B. Ma, L. Du, Y. Jin, Nasal timosaponin BII dually sensitive in situ hydrogels for the prevention of Alzheimer's disease induced by lipopolysaccharides, Int. J. Pharm. 578 (2020) 119115.

[173] Y. Liu, D. Fan, Ginsenoside Rg5 induces G2/M phase arrest, apoptosis and autophagy via regulating ROS-mediated MAPK pathways against human gastric cancer, Biochem. Pharmacol. 168 (2019) 285–304.

[174] Y.W. Zhang, D.Q. Dou, L. Zhang, Y.J. Chen, X.S. Yao, Effects of ginsenosides from Panax ginseng on cell-to-cell communication function mediated by gap junctions, Planta Med. 67 (5) (2001) 417–422.

[175] J. Hou, J. Xue, M. Lee, J. Yu, C. Sung, Long-term administration of ginsenoside Rh1 enhances learning and memory by promoting cell survival in the mouse hippocampus, Int. J. Mol. Med. 33 (1) (2014) 234–240.

[176] X.J. Chen, W.J. Liu, M.L. Wen, H. Liang, S.M. Wu, Y.Z. Zhu, J.Y. Zhao, X.Q. Dong, M.G. Li, L. Bian, C.G. Zou, L.Q. Ma, Ameliorative effects of Compound K and ginsenoside Rh1 on non-alcoholic fatty liver disease in rats, Sci. Rep. 7 (2017) 41144.

[177] W. Gu, K.A. Kim, D.H. Kim, Ginsenoside Rh1 ameliorates high fat diet-induced obesity in mice by inhibiting adipocyte differentiation, Biol. Pharmaceut. Bull. 36 (1) (2013) 102–107.

[178] J. Li, J. Du, D. Liu, B. Cheng, F. Fang, L. Weng, C. Wang, C. Ling, Ginsenoside Rh1 potentiates dexamethasone's anti-inflammatory effects for chronic inflammatory disease by reversing dexamethasone-induced resistance, Arthritis Res. Ther. 16 (3) (2014) R106.

[179] W. Lee, S.H. Cho, J.E. Kim, C. Lee, J.H. Lee, M.C. Baek, G.Y. Song, J.S. Bae, Suppressive effects of ginsenoside Rh1 on HMGB1-mediated septic responses, Am. J. Chin. Med. 47 (1) (2019) 119–133.

[180] E.K. Park, M.K. Choo, M.J. Han, D.H. Kim, Ginsenoside Rh1 possesses antiallergic and anti-inflammatory activities, Int. Arch. Allergy Immunol. 133 (2) (2004) 113–120.

[181] J.S. Jung, D.H. Kim, H.S. Kim, Ginsenoside Rh1 suppresses inducible nitric oxide synthase gene expression in IFN-gamma-stimulated microglia via modulation of JAK/STAT and ERK signaling pathways, Biochem. Biophys. Res. Commun. 397 (2) (2010) 323–328.

[182] H. Zheng, Y. Jeong, J. Song, G.E. Ji, Oral administration of ginsenoside Rh1 inhibits the development of atopic dermatitis-like skin lesions induced by oxazolone in hairless mice, Int. Immunopharm. 11 (4) (2011) 511–518.

[183] Y.J. Choi, J.H. Yoon, S.W. Cha, S.G. Lee, Ginsenoside Rh1 inhibits the invasion and migration of THP-1 acute monocytic leukemia cells via inactivation of the MAPK signaling pathway, Fitoterapia 82 (6) (2011) 911–919.

[184] D.N.H. Tam, D.H. Truong, T.T.H. Nguyen, L.N. Quynh, L. Tran, H.D. Nguyen, B.E. Shamandy, T.M.H. Le, D.K. Tran, D. Sayed, V.V. Vu, S. Mizukami, K. Hirayama, N.T. Huy, Ginsenoside Rh1: a systematic review of its pharmacological properties, Planta Med. 84 (3) (2018) 139–152.

[185] J.H. Yoon, Y.J. Choi, S.G. Lee, Ginsenoside Rh1 suppresses matrix metalloproteinase-1 expression through inhibition of activator protein-1 and mitogen-activated protein kinase signaling pathway in human hepatocellular carcinoma cells, Eur. J. Pharmacol. 679 (1-3) (2012) 24–33.

[186] X. Lyu, X. Xu, A. Song, J. Guo, Y. Zhang, Y. Zhang, Ginsenoside Rh1 inhibits colorectal cancer cell migration and invasion in vitro and tumor growth in vivo, Oncol. Lett. 18 (4) (2019) 4160–4166.

[187] M.J. Kim, H. Yun, D.H. Kim, I. Kang, W. Choe, S.S. Kim, J. Ha, AMP-activated protein kinase determines apoptotic sensitivity of cancer cells to ginsenoside-Rh2, J. Ginseng Res. 38 (1) (2014) 16–21.

[188] J. Huang, K. Peng, L. Wang, B. Wen, L. Zhou, T. Luo, M. Su, J. Li, Z. Luo, Ginsenoside Rh2 inhibits proliferation and induces apoptosis in human leukemia cells via TNF-α signaling pathway, Acta Biochim. Biophys. Sin. 48 (8) (2016) 750–755.

[189] T. Xia, Y.N. Wang, C.X. Zhou, L.M. Wu, Y. Liu, Q.H. Zeng, X.L. Zhang, J.H. Yao, M. Wang, J.P. Fang, Ginsenoside Rh2 and Rg3 inhibit cell proliferation and induce apoptosis by increasing mitochondrial reactive oxygen species in human leukemia Jurkat cells, Mol. Med. Rep. 15 (6) (2017) 3591–3598.

[190] E.K. Park, M.K. Choo, E.J. Kim, M.J. Han, D.H. Kim, Antiallergic activity of ginsenoside Rh2, Biol. Pharmaceut. Bull. 26 (11) (2003) 1581–1584.

[191] K. Choi, M. Kim, J. Ryu, C. Choi, Ginsenosides compound K and Rh(2) inhibit tumor necrosis factor-alpha-induced activation of the NF-kappaB and JNK pathways in human astroglial cells, Neurosci. Lett. 421 (1) (2007) 37–41.

[192] L.C. Li, H.M. Piao, M.Y. Zheng, Z.H. Lin, Y.H. Choi, G.H. Yan, Ginsenoside Rh2 attenuates allergic airway inflammation by modulating nuclear factor-κB activation in a murine model of asthma, Mol. Med. Rep. 12 (5) (2015) 6946–6954.

[193] S.Y. Kim, D.H. Kim, S.J. Han, J.W. Hyun, H.S. Kim, Repression of matrix metalloproteinase gene expression by ginsenoside Rh2 in human astroglioma cells, Biochem. Pharmacol. 74 (11) (2007) 1642–1651.

[194] X.X. Liu, J. Xia, J.F. Tang, M.H. Zhou, D.L. Chen, Z.H. Liu, Ginsenoside Rh_2 induces apoptosis and autophagy of K562 cells by activating p38, Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China J. Chin. Mater. Med. 42 (1) (2017) 146–151.

[195] D.Y. Kim, M.S. Jung, Y.G. Park, H.D. Yuan, H.Y. Quan, S.H. Chung, Ginsenoside Rh2(S) induces the differentiation and mineralization of osteoblastic MC3T3-E1 cells through activation of PKD and p38 MAPK pathways, BMB Rep. 44 (10) (2011) 659–664.
[196] G. Ren, Z. Shi, C. Teng, Y. Yao, Antiproliferative activity of combined biochanin A and ginsenoside Rh_2 on MDA-MB-231 and MCF-7 human breast cancer cells, Molecules 23 (11) (2018).
[197] S. Sanada, N. Kondo, J. Shoji, O. Tanaka, S.J.C. Shibata, P. Bulletin, Studies on the saponins of ginseng. I. Structures of ginsenoside-Ro,-Rb1,-Rb2,-Rc and-Rd, Chem. Pharmaceut. Bull. 22 (2) (1974) 421–428.
[198] H.J. Kang, Y. Oh, S. Lee, I.W. Ryu, K. Kim, C.J. Lim, Antioxidative properties of ginsenoside Ro against UV-B-induced oxidative stress in human dermal fibroblasts, Biosci. Biotechnol. Biochem. 79 (12) (2015) 2018–2021.
[199] J.H. Shin, H.W. Kwon, H.J. Cho, M.H. Rhee, H.J. Park, Vasodilator-stimulated phosphoprotein-phosphorylation by ginsenoside Ro inhibits fibrinogen binding to αIIb/β(3) in thrombin-induced human platelets, J. Ginseng Res. 40 (4) (2016) 359–365.
[200] S.-w. Zheng, S.-y. Xiao, J. Wang, W. Hou, Y.-p. Wang, Inhibitory effects of ginsenoside Ro on the growth of B16F10 melanoma via its metabolites, Molecules 24 (16) (2019) 2985.
[201] H.W. Kwon, J.H. Shin, D.H. Lee, H.J. Park, Inhibitory effects of cytosolic Ca(2+) concentration by ginsenoside Ro are dependent on phosphorylation of IP3RI and dephosphorylation of ERK in human platelets, Evid. Base Compl. Alternative Med.: eCAM 2015 (2015) 764906.
[202] J.H. Shin, H.W. Kwon, M.H. Rhee, H.J. Park, Inhibitory effects of thromboxane A2 generation by ginsenoside Ro due to attenuation of cytosolic phospholipase A2 phosphorylation and arachidonic acid release, J. Ginseng Res. 43 (2) (2019) 236–241.
[203] J. Xiao, T. Zhu, Y.Z. Yin, B. Sun, Notoginsenoside R1, a unique constituent of Panax notoginseng, blinds proinflammatory monocytes to protect against cardiac hypertrophy in ApoE(-/-) mice, Eur. J. Pharmacol. 833 (2018) 441–450.
[204] C.Y. Lee, S.L. Hsieh, S. Hsieh, C.C. Tsai, L.C. Hsieh, Y.H. Kuo, C.C. Wu, Inhibition of human colorectal cancer metastasis by notoginsenoside R1, an important compound from Panax notoginseng, Oncol. Rep. 37 (1) (2017) 399–407.
[205] Y. Yu, G. Sun, Y. Luo, M. Wang, R. Chen, J. Zhang, Q. Ai, N. Xing, X. Sun, Cardioprotective effects of Notoginsenoside R1 against ischemia/reperfusion injuries by regulating oxidative stress- and endoplasmic reticulum stress- related signaling pathways, Sci. Rep. 6 (2016) 21730.
[206] Y. Sun, B. Liu, X. Zheng, D. Wang, Notoginsenoside R1 alleviates lipopolysaccharide-triggered PC-12 inflammatory damage via elevating microRNA-132, Artif. Cells Nanomed. Biotechnol. 47 (1) (2019) 1808–1814.
[207] W. Wang, L. Huang, Y. Hu, E.R. Thomas, X. Li, Neuroprotective effects of notoginsenoside R1 by upregulating Trx-1 on acrylamide-induced neurotoxicity in PC12, Hum. Exp. Toxicol. 39 (6) (2020) 797–807.
[208] Z.R. Ge, M.C. Xu, Y.U. Huang, C.J. Zhang, J.E. Lin, C.W. Ruan, Cardioprotective effect of notoginsenoside R1 in a rabbit lung remote ischemic postconditioning model via activation of the TGF-beta1/TAK1 signaling pathway, Exp. Therap. Med. 11 (6) (2016) 2341–2348.
[209] X. Qiu, M. Zheng, D. Song, L. Huang, L. Tang, L. Ying, W. Wang, Notoginsenoside Rb1 inhibits activation of ERK and p38 MAPK pathways induced by hypoxia and hypercapnia, Exp. Therap. Med. 11 (6) (2016) 2455–2461.
[210] S. Shibata, O. Tanaka, T. Ando, M. Sado, S. Tsushima, T. Ohsawa, Chemical studies on oriental plant drugs. XIV. Protopanaxadiol, a genuine sapogenin of ginseng saponins, Chem. Pharmaceut. Bull. 14 (6) (1966) 595–600.
[211] J. Ruan, F. Sun, Y. Zhang, D. Zheng, G. Xiang, W. Zhao, Y. Zhang, T. Wang, New 20(S)-protopanaxadiol type saponins from the leaves of Panax notoginseng and their potential anti-inflammatory activities, Steroids 162 (2020) 108696.
[212] N. Jiang, L. Jingwei, H. Wang, H. Huang, Q. Wang, G. Zeng, S. Li, X. Liu, Ginsenoside 20(S)-protopanaxadiol attenuates depressive-like behaviour and neuroinflammation in chronic unpredictable mild stress-induced depressive rats, Behav. Brain Res. 393 (2020) 112710.
[213] X. Wang, H.Y. Xia, H.Y. Qin, X.P. Kang, H.Y. Hu, J. Zheng, J.Y. Jiang, L.A. Yao, Y.W. Xu, T. Zhang, X.L. Zhang, 20(S)-protopanaxadiol induces apoptosis in human umbilical vein endothelial cells by activating the PERK-eIF2alpha-ATF4 signaling pathway, J. Cell. Biochem. 120 (4) (2019) 5085–5096.
[214] C. Lu, L. Dong, J. Lv, Y. Wang, B. Fan, F. Wang, X. Liu, 20(S)-protopanaxadiol (PPD) alleviates scopolamine-induced memory impairment via regulation of cholinergic and antioxidant systems, and expression of Egr-1, c-Fos and c-Jun in mice, Chem. Biol. Interact. 279 (2018) 64–72.
[215] C. Lu, J. Lv, L. Dong, N. Jiang, Y. Wang, B. Fan, F. Wang, X. Liu, The protective effect of 20(S)-protopanaxadiol (PPD) against chronic sleep deprivation (CSD)-induced memory impairments in mice, Brain Res. Bull. 137 (2018) 249–256.
[216] B. Peng, R. He, Q. Xu, Y. Yang, Q. Hu, H. Hou, X. Liu, J. Li, Ginsenoside 20(S)-protopanaxadiol inhibits triple-negative breast cancer metastasis in vivo by targeting EGFR-mediated MAPK pathway, Pharmacol. Res. 142 (2019) 1–13.
[217] S. Jang, Y. Lim, G. Valacchi, S. Sorn, H. Park, N.Y. Park, M. Lee, Preventive effects of protopanaxadiol and protopanaxatriol ginsenosides on liver inflammation and apoptosis in hyperlipidemic apoE KO mice, Genes Nutr. 7 (2) (2012) 319–329.
[218] O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem. 31 (2) (2010) 455–461.
[219] R. Azevedo, M. van Zeeland, H. Raaijmakers, B. Kazemier, J. de Vlieg, A. Oubrie, X-ray structure of p38α bound to TAK-715: comparison with three classic inhibitors, Acta Crystallogr. Sect. D Biol. Crystallogr. 68 (Pt 8) (2012) 1041–1050.
[220] Y. Zhu, C. Zhu, H. Yang, J. Deng, D. Fan, Protective effect of ginsenoside Rg5 against kidney injury via inhibition of NLRP3 inflammasome activation and the MAPK signaling pathway in high-fat diet/streptozotocin-induced diabetic mice, Pharmacol. Res. 155 (2020) 104746.