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Review Article

Panax ginseng: Inflammation, platelet aggregation, thrombus formation, and atherosclerosis crosstalk

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ABSTRACT

Ginseng has been widely studied due to its various therapeutic properties on various diseases such as cardiovascular disease (CVD). Cardiovascular disease has been canonically known to be caused by high levels of low-density lipoproteins (LDL) in the bloodstream, in addition to the impaired vasodilatory effects of cholesterol. However, current research on CVD has revealed a cascade of mechanisms involving a series of events that contribute to the progression of CVD. Although this has been elucidated and summarized in previous studies the detailed correlation between platelet aggregation and innate immunity that plays an important role in CVD progression has not been thoroughly summarized. Furthermore, immune cell subtypes also contribute to the progression of plaque formation in the subendothelial layer. Thrombus formation and the coagulation cascade also have a vital role in the progression of atherosclerosis. Hence, in this mini review we aim to elucidate, summarize, and propose the potent therapeutic effect of ginseng on CVD, mainly on platelet aggregation, plaque formation, and thrombus formation.

1. Introduction

Endothelial damage allows low-density lipoproteins (LDLs) in blood to penetrate the subendothelial layer. Consequently, LDLs are modified into oxidized-LDL (ox-LDL), which has been shown to bind to the CD36 or lectin-like oxidized low-density lipoprotein (LOX1) receptors on platelets [1,2], thus causing platelet activation. The main difference between oxLDL and native LDL is the speed with which each lipoprotein is uptaken by macrophages, where they form foam cells. In addition to inhibiting the motility of tissue macrophages that causes the accumulation of macrophages, oxLDLs are also chemoattractants for monocytes, thus contributing to lesion development [3] (see Fig. 1).

P-selectin is released from damaged endothelium. Furthermore, platelets also express roughly 350 sites/μm^2 of P-selectin when activated, which is roughly ten times the expression on endothelial cells *in vitro* [4]. In addition to P-selectin, intercellular adhesion molecule 1 (ICAM-1) is also expressed on endothelial cells; however, its expression is elevated by pro-inflammatory cytokines.

Recent studies have also shown the inseparable relationship between the inflammatory cascade and atherosclerosis progression. Like toll-like receptor 4 (TLR4), pattern recognition receptors recognize LDLs [5,6]. Therefore, anti-inflammatory agents are deemed to be therapeutic targets of atherosclerosis progression. Moreover, it was reported that M1 macrophages play an important role in atherosclerosis as they demonstrate increased expression in atherosclerotic plaques. T helper cell 1 (Th1) cytokines (TNF-α, IL-6 and IL-8) are responsible for the differentiation of M1 macrophages [7]. Therefore, it can be suggested that atherosclerosis could be suppressed by encouraging a shift to a M2 macrophage [8,9]. Furthermore, activated platelets secrete platelet factor 4 (PF4) that induces monocytes differentiation in macrophages, other than inducing an increase in oxLDL uptake by macrophages, thus facilitating the formation of foam cells [10,11].

2. Activation of the inflammatory cascade in the subendothelial layer

Monocyte *trans*-endothelial diapedesis (migration through the subendothelial layer) is faciliated by monocyte chemoattractant

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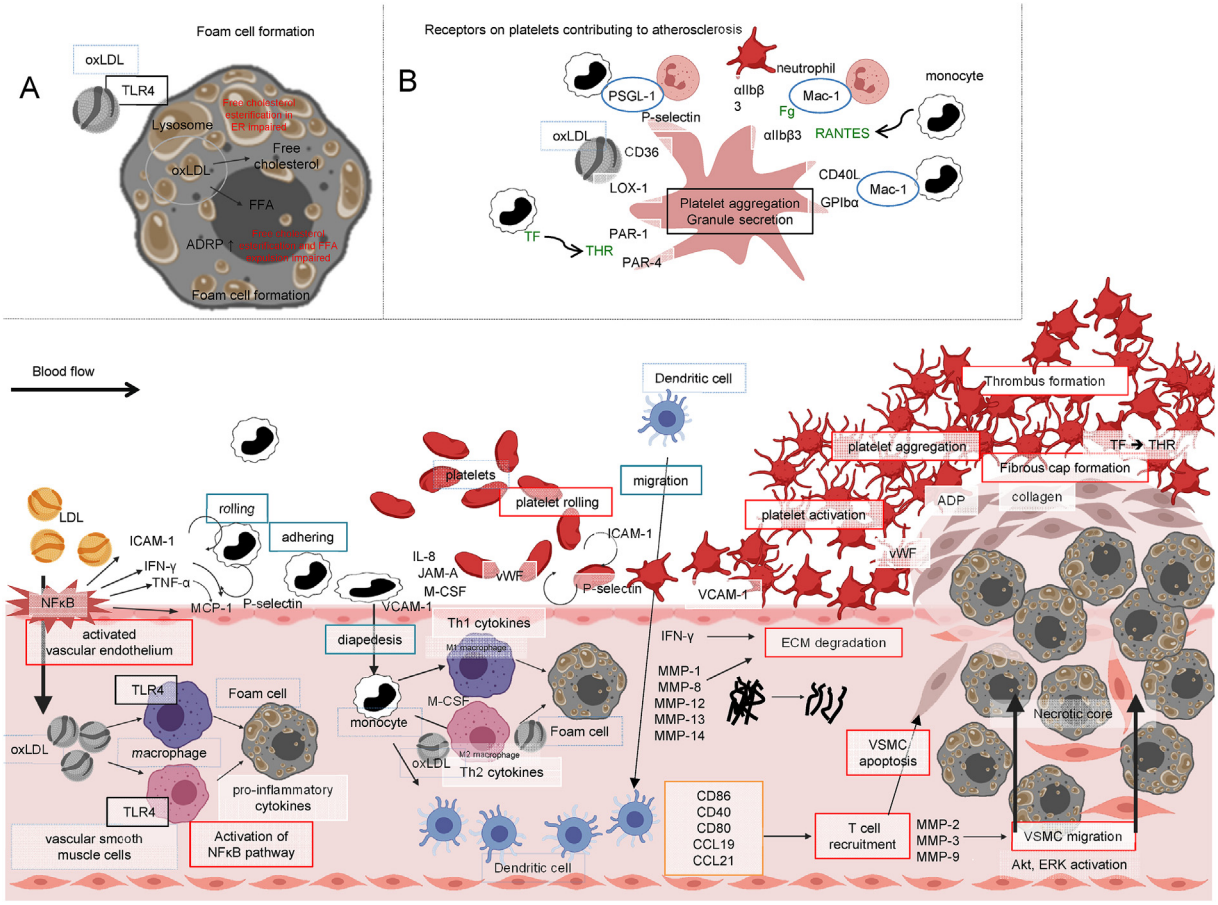

Fig. 1. Schematic diagram of the progression of atherosclerosis. A damaged subendothelium causes the secretion of pro-inflammatory cytokines and the activation of NFκB, allowing free flowing LDL in the periphery to enter the subendothelium where they are modified to oxidized oxLDL. Foam cells form macrophages take up oxLDL. With the release of adhesion factors, peripheral monocytes were attracted to the endothelium where they are able to migrate into the subendothelium. They are capable of differentiating into macrophages, which will also form foam cells. An accumulation of foam cells causes the formation of a necrotic core. Foam cells secrete factors that can causes ECM degradation, causing the formation of a vulnerable plaque. Monocytes can also differentiate into DCs. Other than that, DCs can also migrate into the subendothelium. They secrete factors that recruit T cells that eventually causes VSMC apoptosis and releases metalloproteinases that induces VSMC migration into the intima, forming a fibrous cap. An inflamed subendothelium also secretes factors like vWF, ADP, and collagen, which are agonists for platelet aggregation. With the activation of the coagulation cascade, THR is also released. This causes aggregation of platelets along with a clot formation. Formation of foam cells can also be due to the accumulation of free cholesterol and free fatty acid in macrophages (A). Platelets are an important player as platelet aggregation can be activated by other immune cells like neutrophils and monocytes, and oxLDL (B).

protein-1 (MCP-1) and macrophage-colony stimulating factor (M-CSF), platelet endothelial cell adhesion molecule-1, junction adhesion molecule-A, IL-8, and TNF-α [12,13]. At the same time, T lymphocytes are captured onto the vascular endothelium with the help of E-selectin and P-selectin. Using lymphocyte function-associated antigen-1 (LFA-1) and macrophage-1 antigen (Mac-1; or also known as integrin αMβ2), leukocytes (monocytes and neutrophils) adhere to the endothelium, and move through the vascular endothelium with the help of ICAM-1 [14]. In the intima, monocytes can differentiate into macrophages or dendritic cells (DCs). The main factor of differentiation to form macrophages is M-CSF. Macrophages can differentiate into M1 and M2 macrophages, and Th1 cytokines, such as IFN-γ and IL-1β, induce M1 macrophage polarization whereas Th2 cytokines, such as IL-4 and IL-13, induce M2 macrophage polarization. M1 macrophages secrete pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12, whereas M2 macrophages secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor beta 1 (TGF-β1). T helper cell 2 (Th2) cytokines are also known to induce a switch from M1 to M2 macrophages [15–17]. However, an imbalance in the ratio of M1 and M2 macrophages is also found in atherosclerotic lesions. Hence, Th1 and Th2 cytokine balance is crucial to prevent the progression of an atherosclerotic lesion [15].

DCs can be also recruited to the vulnerable atherosclerotic tissue, which, in turn, induces a reduced amount of circulating DCs [18]. Similar to the recruitment of monocytes, DCs are also recruited by P-selectin, E-selectin, and vascular cell adhesion molecule 1 (VCAM-1), which are secreted by the activated vascular endothelium [19,20]. Atherosclerotic lesions also secrete chemokines, such as MCP-1 (CCL2) and RANTES (CCL5), that generate a gradient for the migration of DCs through vascular endothelium [21]. DCs are activated by the detection of damage-associated molecular patterns, including TLRs, and pathogen-associated molecular patterns. Its activation leads to CD86, CD40 and CD80 secretion that, in turn, initiate adaptive immune responses. Platelets have also been shown to induce DC maturation and encourage DC-induced lymphocyte differentiation [22]. DCs secrete CCL19 and CCL21 that play an important role in T-cell attraction, other than secreting IL-12 that upregulates the CCR5 receptor in T cells, thus facilitating the accumulation of T cells in the atherosclerotic plaque due to an increased attracted towards RANTES, or CCL5 [23]. Another important role of DCs is that they have been reported to cause atherosclerotic plaque destabilization. The consequence of T cells

recruitment by DCs is that activated cytotoxic CD4 T cells are able to cause the apoptosis of vascular smooth muscle cells (VSMCs) and endothelial cells, which then destabilizes the atherosclerotic plaque. Furthermore, T-cell-derived IFN-γ induced extracellular matrix (ECM) degradation via matrix metalloproteinases (MMPs) [24].

Macrophages express TLR4, and oxLDL uptake causes macrophages to convert into foam cells [25]. When in foam cells, the cholesterol efflux mechanism is impaired, causing an increase in cellular cholesterol deposition. The imbalance in the lipoprotein uptake and cholesterol efflux contributes to the formation of foam cells [26]. This is also coupled by the intracellular protein network that stores, regulates and processes cholesterol by esterification, and macrophages take up oxLDL that is hydrolyzed into free cholesterol and fatty acids in the lysosomes. The endoplasmic reticulum will then esterify excessive cholesterol via acetyl-CoA acetyltransferase 1 (ACAT-1) [27,28]. Carnitine palmitoyl transferase-1 (CPT-1) determines fatty acid availability, whereas neutral cholesterol ester hydrolase plays a role in determining cholesterol accumulation in the cell, as it participates in cholesterol ester hydrolysis [28]. Adipocyte related differentiation protein (ADRP) has also been shown to enhance intracellular triacylglycerols (TAGs), thus contributing to its synthesis and preventing its expulsion [28]. The accumulation of fatty acids and cholesterol esters facilitates the formation a foamy macrophage that is termed as the "foam cell."

As mentioned above, M1 macrophages secrete IFN-γ which inhibits matrix formation by VSMCs. Macrophages also secrete proteinases, such as collagenases, gelatinases, stromolysin, and cathepsins, that cause matrix degradation [29]. In addition, MMPs, which are matrix-degrading enzymes, have been shown to contribute to atherosclerosis and to the formation of an unstable plaque [30]. MMP-2, -3, and 9 have been attributed to allowing VSMCs migration into the intima. In some ways, these MMPs are called plaque stabilizing MMPs as they facilitate plaque stabilization. However, this also contributes to the continuous increase in the size of the plaque which may also lead to vessel occlusion. In contrast, MMP-1, -8, -12, −13, and −14 are capable of degrading the ECM while simultaneously recruiting monocytes and macrophages, thus further contributing to the formation of a lipid rich core [31].

This is an important factor that contributes to the erosion and rupture of an atherosclerotic plaque. Macrophage-derived foam cells also release foam cell-derived extracellular vesicles that transport proteins to VSMCs, which then activates Akt and the extracellular signal-regulated kinase (ERK) pathways and promote their migration and adhesion [32]. It has been shown that CD36 regulates reactive oxygen species (ROS) in VSMCs [33], and VSMCs become proliferative and synthetic in atherosclerotic profile of patients [34]. VSMCs primed with IFN-γ have the ability to present antigen to Th1 and Th2 cells [35]. CD4 T-cell can also activate VSMCs via CD40 [36], which, in turn, causes extracellular matrix degradation, and encourages the migration and proliferation of VSMCs. At the same time, the increase in foam cells will eventually form a lipid rich core. VSMCs undergo remodeling, and they migrate to the intima (through and around foam cells), thus contributing to the thickening of the fibrous cap [37]. The thickening of the vascular endothelium has an increased amount of nanovasculatures that introduce more red blood cells due to the presence of a hypoxic environment. Consequently, the continual progression of a lipid rich core will then form a necrotic core. However, it should be stated that VSMCs, which migrated to the intima, are prone to apoptosis [38]. The simultaneous occurrence of this cascade of events will then facilitate a vulnerable plaque.

2.1. Platelet aggregation with leukocytes

In general, platelets are attracted to the endothelium with the help of the von Willebrand factor (vWF). This encourages the binding of platelets to P-selectin and collagen, secreted by an inflamed vessel, and directly leads to platelet activation. Collagen binds to the glycoprotein VI (GPVI) receptor on the platelet surface [39], whereas thrombin (THR) binds to the protease activated receptors (PAR) [40], which will be explained in more detail in the next subsection. Once the platelets are activated, a conformational change occurs on the integrin αIIbβ3, which allows platelets to bind to each other via fibrinogen and fibronectin [41,42]. Activated platelets also release adenosine diphosphate (ADP), serotonin, and thromboxane A2 (TXA2) that cause further platelet aggregation. These processes will eventually lead to the formation of clumps that we address as platelet aggregates.

Monocytes express P-selectin glycoprotein ligand-1 (PSGL-1), which is a ligand for P-selectin [43]. At the same time, P-selectin is secreted by activated platelets. In addition, activated platelets secrete RANTES that also attracts monocytes [44,45]. Monocytes can also bind to platelets because fibrinogen is a ligand of Mac-1 [46], which is also a ligand for αIIbβ3 on platelets. Thus, P-selectin enables the "binding" of platelets and monocytes, which constitutes a platelet-monocyte aggregate (PMA). PMAs can form via a series of receptors on monocytes, namely PSGL-1, Mac-1, and LFA-1. Seizer et al. (2008) has reviewed the different possible interactions between monocytes and platelets, and the authors summarized the main effects on monocytes based on the different interactions via various receptors. For example, Mac-1 on monocytes can bind to platelets via GPIbα, JAM-C, αIIbβ3, and CD40L. Consequently, this activates the NFκB pathway, increases the secretion of IL-1β, TNF-α and tissue factor (TF), and increases the amounts of adhesive receptors [47], which lead to the activation of the inflammatory cascade.

Other than PMAs, platelet-neutrophil aggregates are also an important player in atherothrombosis. When the vulnerable plaque ruptures, neutrophils start to accumulate at the site of injury that eventually causes platelet aggregation and also the activation of the coagulation cascade [48,49]. In atherosclerosis, there is also a notable increase in TNF-α and IL-1β in the plasma that causes the activation of neutrophils [50,51]. Activated neutrophils play a role in attracting platelets to the vascular endothelium, which, in turn, can attach to neutrophils via PSGL-1 to P-selectin, and Mac-1 to GPIb receptor on platelets [52]. Although neutrophils extracellular traps (NETs) are vital for the immune system in terms of combating microbes, NETs can contribute to the activation of leukocytes, endothelial cells, and platelets, kickstarting the coagulation system, and thus rendering it as a significant factor of atherothrombosis [52].

2.2. The coagulation cascade, thrombus formation, and plaque erosion

Platelet aggregation leads to thrombosis. Blood flow may cause erosion of platelet aggregates that will then continue to form aggregates (microemboli) in the blood. Microemboli have also been shown to cause coronary thrombosis [53]. In the injured vessel, platelets that continue to form aggregates with other platelets will form emboli. Platelets express an array of receptors, such as the thromboxane A2 receptor (TXA2R), multiple glycoproteins, P-selectin, CD40, TLRs, PAR, P2Y1, P2Y12, but also chemokines receptors, such as CX3CR1 and CXCR4, and also the junctional

adhesion molecules (JAMs) [54]. In addition to vWF and collagen that cause platelet aggregation, THR is also an important inducer of platelet aggregation, which is released in the occasion of a vascular injury [40]. When an injury occurs, the TF is released from the blood vessels, and, once released, it forms a complex with coagulation factor FVIIa and becomes FXa. This finally leads to THR formation that activates FXI. This is followed by the conversion of fibrinogen to fibrin, that will eventually form cross-links with FXIIIa that causes a clot formation consisting of platelets and erythrocytes, which is known as a thrombus [55]. Previous reports have also demonstrated that atherosclerotic plaques have high concentrations of TF. In a healthy vessel, coagulation does not occur because free TF is not exposed. However, the coagulation mechanism is important in cases of injury, and clot formation is vital to prevent further blood loss.

Thus, it can be deduced that the dysregulation of the endothelial layer kickstarts a complicated cascade of mechanisms. The progression of a vulnerable plaque causes VSMC apoptosis and fibrous cap thinning, which finally ruptures. A ruptured plaque causes the formation of a platelet-rich thrombus that finally leads to vessel occlusion.

3. Ginseng for atherosclerosis therapeutics

3.1. The effect on NFκB pathway

NFκB is an important marker of inflammation that plays an important role in the progression of atherosclerosis. *Panax ginseng* has been shown to effectively suppress the expression of NFκB in various pathophysiologies. Furthermore, *Panax ginseng* and its ginsenosides have been widely known for their anti-inflammatory activities. Gao et al. (2020) reported that ginsenoside Rb1 exerts anti-inflammatory effects against LPS-induced inflammatory responses in RAW 264.7 cells and bone marrow-derived macrophages via the NFκB and MAPK pathway, respectively. In fact, Rb1 has also rescued animals from induced septic shock and suppressed benzene-induced ear edema in BALB/c mice [56]. Our previous research has also demonstrated that Rg3-RGE and the Korean black ginseng (*Panax ginseng* roots that are steamed and dried nine times) show distinct anti-inflammatory effects that target the expression of NFκB and MAPK [57,58]. A study by Qin et al. (2017) showed that ginsenoside F1 could attenuate endothelial cell injuries, and thus prevent the progression of atherosclerosis in ApoE$^{-/-}$ mice via LOX-1 and NFκB inhibition [59]. As endothelial-to-mesenchymal transition (EndMT) is a cause of vascular disease, a recent study has shown that ginsenoside Rg3 can also reverse EndMT *via* the regulation of the miR-139-5p-NFκB axis [90].

3.2. The inhibitory effect of endothelial adhesion molecules

A study conducted on *Panax notoginseng* saponin fractions revealed that the saponin fraction and ginsnosides Rg1 and Rb1 have the ability to prevent monocyte adhesion on human coronary artery endothelial cells (HCAEC) induced with recombinant human TNF-α. Furthermore, they have also been shown to inhibit ICAM-1 and VCAM-1 expression, an effect that is attributed to their ability to prevent the translocation of NFκB into the HCAECs nuclei [60]. In a separate study, Rg3-RGE was shown to increase eNOS (vasodilatory effects), inhibit TNF-α mediated ICAM-1 and COX-2 in human umbilicalvein endothelial cells (HUVECs), and also improve vascular function in atherosclerotic Wistar rats [61]. It was also shown that TNF-α treated HUVECs and A7r5 cells had increased expressions of VCAM-1, ICAM-1, E-selectin, and P-selectin that were attenuated by the provision of the ginseng berry extract [62]. In ApoE$^{-/-}$ mice, Rb1 from *Panax notoginseng* managed to prevent the progression of atherosclerosis, and MCP-1 expression in the serum of ApoE$^{-/-}$ was also suppressed [63]. In a separate study, mice of C57/Bl6J background were given a western diet for 12-weeks that facilitated increased MCP-1 expression in the ex vivo culture medium of the aortic archs of the ApoE$^{-/-}$ mice. The authors then reported that PPD and PPT saponin from *Panax notoginseng* could prevent the development of atherosclerosis in ApoE$^{-/-}$ mice, thus suggesting their significant effect in inhibiting the increased levels of MCP-1 [64].

3.3. The effect of ginseng on the immune response and progression of atherosclerosis

Ginseng is well-known to regulate and modulate the immune system in various physiopathologies. Both the immune response and cytokines play a major role in determining the differentiation of monocytes to macrophages, thus contributing to the progression of atherosclerosis. A number of studies have shown that ginseng and ginsenosides can encourage the M2 polarization of macrophages to resolve inflammation. For instance, ginsenoside Rg3, Rg1 and Rb1 have been shown to encourage M2 polarization in macrophages and microglia [65]. Kang et al. (2018) underline that ginsenoside Rg3 has anti-inflammatory effects as a result of encouraging the polarization of M2 murine peritoneal macrophages and suppressing zymosan-induced peritonitis in C57/Bl6 mice [66]. In a model of LPS-induced parkinsonian symptoms in C57/Bl6 mice, Rg1 was also shown to alleviate the symptoms *via* NFκB signaling inhibition and encourage the markers of M2 macrophages [67]. In an ApoE$^{-/-}$ mice model, ginsenoside Rb1 has been shown to induce a skew of macrophages to the M2 phenotype, thus encouraging plaque stability by means of upregulating the expression of arginase-1 and macrophage mannose receptor (CD206), both of which are M2 macrophage markers [68]. Finally, an additional study revealed that ginsenoside Rg3 could encourage M2 macrophage phenotyping *via* PPARγ, which prevented the progression of atherosclerosis in diabetic ApoE$^{-/-}$ mice [69].

3.4. Activation of vascular smooth muscle cells by MMPs

MMPs are very essential in plaque formation due to their role in degrading the ECM. In addition to atherosclerosis, MMPs are important markers of skin aging and cancer metastasis. Inflammation has also been closely related to the degradation of MMPs. Furthermore, collagenases (MMP-1, MMP-8 and MMP-13) and gelatinases (MMP-2 and MMP-9) give rise to substrates such as collagen, gelatin, fibronectin and elastin [70]. Lee et al. (2013) found that *Panax ginseng* could prevent obesity via the inhibition of angiogenesis in HFD-fed C57/Bl6J mice. In fact, the authors showed that *Panax ginseng* decreased the mRNA expression of MMP-2 and MMP-9 in visceral and subcutaneous fat tissue [71]. This indicates that *Panax ginseng* has the potential to prevent the migration of VSMCs to the intima, as they were reported to suppress MMP-2 and MMP-9 expression. Further studies should be conducted to elucidate the potential of *Panax ginseng* against MMPs in atherosclerosis.

3.5. Inhibition of cholesterol efflux that prevents the formation of foam cells

The formation of macrophage-derived foam cells is a crucial part of atherosclerosis progression. It has been reported that autophagy can reduce oxLDL ingestion, thus inhibiting the formation of foam cells [72]. Qomaladewi et al. (2019) have summarized the roles of *Panax ginseng* extract and its components, such as Rb1, Rh2, F2, and compound K, and they have reported their effects in regulating

autophagy [73]. This finding proposes a novel mechanism of the inhibition of foam cell formation by *Panax ginseng*.

3.6. Potential of platelet-leukocyte aggregate inhibition

Leukocytes include both monocytes and neutrophils that can easily form aggregates with platelets when platelets are activated. Other than encouraging the migration of DCs through the sub-endothelium layer, RANTES is also known to attract monocytes. Consequently, this allows monocytes to come into contact with activated platelets. A previous study on atopic dermatitis has shown that *Panax ginseng* has the ability to inhibit RANTES secreted by phorbol 12-myristate 13-acetate and calcium ionophore A23187 in human mast-cell line (HMC-1) [74]. Inhibition of RANTES suggests that less platelet-monocyte aggregates will form. Secretion of ICAM-1 from an inflamed vessel can bind to LFA-1 and Mac-1. This also encourages the binding of platelets and leukocytes. The role of *Panax ginseng* on inhibiting ICAM-1 has been already mentioned above. CD40 plays an important role in the activation of VSMCs. Moreover, CD40L is expressed on platelets, and its inhibition may play a role in curbing the formation of PMAs (binding *via* Mac-1 and CD40L). In addition, CD40 can also be presented by infiltrated DCs to T cells, and thus activate the immune response. Although CD40 inhibition has not been specifically investigated for atherosclerosis, previous studies have shown that *Panax ginseng* can inhibit the expression of CD40 and its ligand, CD40L, in the lung tissue of BALB/c mice induced with airway inflammation (ovalbumin-sensitization) *via* immunohistochemistry [75]. In a separate study investigating the immunodulatory activity of Ginsan, a polysaccharide of *Panax ginseng*, it was demonstrated that Ginsan treatment increased the expression of MHC II in DCs even more than CD40-treated DCs [76]. From an immunodulatory perspective, increased expression of CD40 favors the appropriate activation of the immune response. Furthermore, there is still limited evidence in the literature regarding the inhibition of PSGL-1 by *Panax ginseng* treatment. Therefore, further investigation and research should be conducted to elucidate the role of *Panax ginseng*, particularly in atherosclerosis.

3.7. Inhibition of platelet aggregation and thrombus formation

The anti-platelet activity of *Panax ginseng* and its components has long been reported. These studies have also been summarized by our laboratory [77,91] and Luo et al. (2020) [78]. Our laboratory has previously reported that ginsenoside-Rp1 can inhibit platelet aggregation by collagen, THR, and ADP. In addition, Rp1 has also

Table 1
Summary of the therapeutic effects of *Panax ginseng* and its components against atherosclerosis.

Compound	Potential effects in atherosclerosis	Reference
Rb1	• Inhibited NFκB and MAPK in RAW 264.7 cells and BMDM • Rescued mice from septic shock and benzene-induced ear edema • Prevented monocyte adhesion on HCAEC • Inhibited ICAM-1 and VCAM-1 in HCAEC • Prevented translocation of NFκB into nucleus in HCAEC • Suppressed MCP-1 expression in the serum of ApoE$^{-/-}$ mice • Increased M2 macrophage polarization in macrophage and microglia • Increased arginase-1 and CD206 that increased plaque stability	[56,60,63,65,68]
Rg3-RGE	• Inhibited NFκB and MAPK pathway • Increased eNOS in HUVECs • Inhibited ICAM-1 and COX-2 in HUVECs • Inhibited platelet aggregation	[58,61]
Rg3	• Increased M2 macrophage polarization in macrophage and microglia • Induced M2 macrophage phenotyping via PPARγ and prevented atherosclerosis in diabetic ApoE$^{-/-}$ mice • Inhibited clotting factor FXa	[65,66,69,87]
F1	• Suppressed endothelial cell injury and inhibits atherosclerosis via LOX-1 and NFκB inhibition	[59]
Rg1	• Prevented monocyte adhesion on HCAEC • Inhibited ICAM-1 and VCAM-1 in HCAEC • Prevented translocation of NFκB into nucleus in HCAEC • Increased M2 macrophage polarization in macrophage and microglia • Inhibited platelet aggregation • Exhibited anti-coagulatory activities	[60,65,67,88],
Rg2	• Inhibited clotting factor FXa • Exhibited anti-coagulatory activities	[87,88]
Rp1	• Inhibited platelet aggregation induced by collagen, ADP and THR	[79]
Rk1	• Inhibited platelet aggregation and thrombus formation	[80]
Rp3	• Inhibited platelet aggregation and inhibited thrombus formation	[84]
Rp4	• Inhibited platelet aggregation induced by ADP	[85]
F4	• Inhibited platelet aggregation and thrombus formation	[82]
Ginseng berry extract	• VCAM-1, ICAM-1, E-selectin and P-selectin were inhibited in HUVECs and A7r5 cells • Upregulated aPTT and PT	[62,89]
PPD	• Inhibited atherosclerosis in ApoE$^{-/-}$ mice via inhibition of MCP-1	[64]
PPT	• Inhibited MCP-1 expression in ApoE$^{-/-}$ mice • Inhibited clotting factor FXa	[64,87]
***Panax ginseng* extract**	• Inhibited mRNA expression of MMP-2 and MMP-9 in visceral and subcutaneous fat tissue in C57/Bl6J mice • Inhibited RANTES in HMC-1 • Inhibited CD40 and CD40L in lungs of BALB/c mice induced with airway inflammation	[71,74,75]
Ginsan	• Increased expression of MHC II in dendritic cells	[76]
Black ginseng	• Inhibited NFκB and MAPK pathway	[57]
Gintonin	• Inhibited platelet aggregation via impairment of glycoprotein VI signaling and thrombus formation	[86]

BMDM, bone marrow-derived macrophages; MAPK, mitogen activated protein kinase; NFκB, nuclear factor kappa B; LOX-1, lectin-like oxidized low-density lipoprotein; HCAEC, human coronary artery endothelial cells; VCAM-1, vascular cell adhesion protein 1; ICAM-1, intracellular adhesion molecule 1; MCP-1, monocyte chemoattractant protein-1; ApoE, apolipoprotein E; eNOS, endothelial NOS; MMP, matrix metalloproteinase; PPARγ, peroxisome proliferator-activated receptor gamma; HMC-1, human mast-cell line 1; aPTT, activated partial thromboplastin time; PT, prothrombin time.

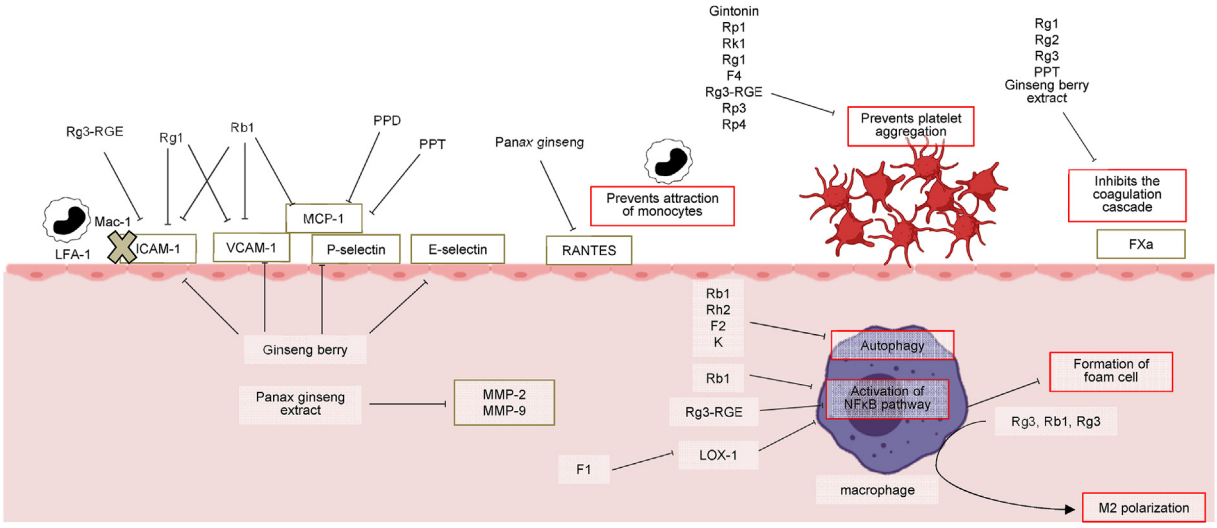

Fig. 2. *Panax ginseng* and their compounds have been reported to inhibit many factors involved in the progression of atherosclerosis, as summarized in this figure. This shows the potential of *Panax ginseng* as a therapeutic for atherosclerosis.

been found to inhibit granule secretion, calcium ion mobilization, activation of integrin αIIbβ3, while at the same time it could increase cAMP levels (hence the increment of VASP ser 157). Furthermore, Rp1 has also been found to inhibit the phosphorylation of Fyn, Lyn, Syk, PI3K, PLCγ2, and also the linker for activation of T cells (LATs). GPVI activation leads to Src family kinases and LAT phosphorylation [79]. LATs are expressed on platelets, and are essential for T-cell receptor mediated activation. This again demonstrates the important role of immune responses on atherosclerosis and platelet aggregation. Several studies have also reported the anti-platelet activity of Ginsenoside Rk1, Rg1, F4, Rg3-RGE, Rp3, Rp4, and gintonin [80–86], also summarized by Irfan et al. (2020) by covering the anti-platelet activity of ginsenosides, and how the schematic conversion of ginsenosides could affect their anti-platelet activity [77].

Other than platelet aggregation, *Panax ginseng* has also been reported to inhibit clotting factors such as the coagulation factor Xa (FXa). Ginsenoside Rg2, Rg3, and the PPT fraction have potent effects in inhibiting FXa [87]. In a separate study, ginsenoside Rg1 and Rg2 were reported to have anti-coagulatory activities as both Rg1 and Rg2 exhibit a prolonged clotting time [88]. Furthermore, an additional study conducted on rats fed with a high-fat diet (HFD) revealed that ginseng berry extract could regulate lipid metabolites and blood coagulation factors. In fact, this study also demonstrated that activated partial thromboplastin time (aPTT) was upregulated with ginseng berry extract, and prothrombin time was significantly recovered from the reduction caused by HFD [89]. This may indicate that ginseng may target the HFD-induced blood coagulation, and it may be explained that a HFD may increase serum LDL, which may cause atherosclerosis *via* a complicated inflammatory cascade that leads to platelet aggregation, thrombus formation, and vessel occlusion.

4. Future perspectives and research direction

This mini review highlights there are still a lot of issues that have not been verified in *in vivo* atherosclerosis models by ginseng (see Fig. 1). The majority of the studies presented were conducted with different immune or diet-based models, and, more specifically, platelet activation and its related downstream cascades. It can be understood that factors and processes that induce atherosclerosis are complicated and involve a series of events other than various pathophysiological disorders such as inflammation, vascular endothelial cell activation, recruitment of macrophages and monocytes, cholesterol efflux by macrophages, platelet activation, platelet-leukocyte aggregates, and blood clot. A previous study by Jang et al. (2021) has also shown that the treatment of Korean Red Ginseng shows therapeutic effects in db/db mice against cardiac-complication genes [92], which includes genes related to apoptosis, adhesion, differentiation, migration and immune response. As most of these areas have yet to be verified, we hope that this summary will initiate the implementation of further research specifically on the inflammation-related aspects of atherosclerosis. Although cardiovascular disease may have been long-investigated and well-established, new findings continue to unravel the critical involvement of inflammation in atherosclerosis. The beneficial roles of ginseng against atherosclerosis were also summarized by Xue et al. (2021) [93] and also summarized in Table 1 and Fig 2. However, the role of platelet aggregation and thrombosis should also be considered. Hence, further research should be conducted and which will elucidate the effect of *Panax ginseng* on this issue.

Declaration of competing interest

The authors declare no conflict of interest.

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