Book Chapter

Panax notoginseng Saponins for Treating Coronary Artery Disease: A Functional and Mechanistic Overview

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Abstract: Coronary artery disease (CAD) is a major public health problem and the chief cause of morbidity and mortality worldwide. Panax notoginseng, a valuable herb in traditional Chinese medicine (TCM) with obvious efficacy and favourable safety, shows a great promise as a novel option for CAD and is increasingly recognized clinically. Firstly, this review introduced recent clinical trials on treatment with PNS either alone or in combination with conventional drugs as novel treatment strategies. Then we discussed the mechanisms of panax notoginseng and panax notoginseng saponins (PNS), which can regulate signalling pathways associated with inflammation, lipid metabolism, the coagulation system, apoptosis, angiogenesis, atherosclerosis and myocardial ischaemia.
Keywords: Panax notoginseng, PNS, coronary artery disease, traditional Chinese medicine, review

Introduction

Coronary artery disease (CAD) is a major public health problem and a chief cause of morbidity and mortality worldwide. The number of deaths due to CAD was 56 million people globally during a decade from 2000 [1]. The sum of hospitalized cardiovascular operations rised by 28%, from about 6 million to

7.5 million [2]. The economic load of caring for patients also represents a huge cost for society. Revascularization represents innovative progress in the treatment for symptomatic CAD. However, by targeting one or two vascular lesions, it fails to completely solve the problem of plaque progress. A truly advance in the treatment of CAD will require more effective prevention. At the end of the nineteenth century, drug resistance to organic nitrates was observed [3, 4], while aspirin resistance was observed in 1994[5]. Clopidogrel has been widely used in various thrombotic diseases, especially in CAD patients with percutaneous coronary intervention (PCI) [6]. About a quarter of patients administering standard loading of clopidogrel exhibit poor responsiveness [7]. Due to the complexity of CAD, most patients require lifelong medication. Moreover, oral aspirin may directly stimulate the gastric mucosa and initiate abdominal discomfort, nausea and vomiting. The long-term use of aspirin can easily cause gastric mucosal damage [8]. The risk of diabetes greatly increases with large doses of statins. In addition, statins can cause abnormal liver enzymes and myopathy [9].Varying degrees of drug resistance and adverse reactions increase the difficulty and dissatisfaction with treatment.

In recent years, Traditional Chinese Medicine (TCM) has gained widespread popularity. Furthermore, an increasing number of studies have confirmed the efficacy of TCM for treating CAD. In 2007, nearly 4 out of 10 adults had used TCM therapy in the past 12 months, with natural products as the most commonly used therapies [10]. Of the various natural products, Panax notoginseng is one of the most commonly applied products because it has been evaluated with various beneficial effects, such as promotion of blood circulation, cerebrovascular protection [11,12], improvement of neurological function [13], reduction of oxidative stress [14] and mitigation of bone loss [15].

Panax notoginseng is particularly popular among patients with CAD because many studies have been associated the consumption of Panax notoginseng with CAD treatment. Panax notoginseng saponin (PNS) is the main active ingredient of Panax notoginseng. Over the past over 40 years, great energy has been devoted to confirming the effectiveness of the compounds

of Panax notoginseng on CAD. Many animal experiments have shown that PNS can improve the energy metabolism of myocardial cells, reduce myocardial damage, and inhibit ischaemia-induced cardiomyocyte apoptosis in acute MI rats [16,17]. Now the compound of PNS is available as an over-the-counter drug in both China and worldwide. In China alone, 5000 tons of Panax notoginseng products are produced annually [18]. The role of Panax notoginseng in cardiovascular diseases has been summarized [18,19], but no articles have focused on the effects of Panax notoginseng against CAD. This review summarizes extensively recent evidence on the use of Panax notoginseng in CAD therapy, its therapeutic effects and adverse events. Our current understanding of Panax notoginseng cardioprotective effects and mechanisms against CAD will also be discussed in detail.

Methodology

The terms "Panax notoginseng" or "Sanqi" or "Panax notoginseng saponins" were searched as "Title/Abstract" and MeSH terms in PubMed, China National Knowledge Infrastructure (CNKI) and SinoMed database. Articles related to therapeutic effects in coronary artery disease (CAD) were picked out manually. All articles with abstract were included and no language restrictions was applied.

Biological characteristics of Panax Notoginseng

Brief History

Panax notoginseng is a medicinal plant that was first used by ethnic minorities in China. It has been one of the most acclaimed herbs in China for 400 years. Panax notoginseng is traditionally applied as an anodyne and a haemorheologic-altering drug. The main medical component is the radix of Panax notoginseng, also known as Sanqi, Tianqi and Shanqi in East Asian countries [20]. "Compendium of Materia Medica" (Bencao Gangmu本草纲目) recorded the official detailed medical applications of Panax notoginseng in 1758, in which Panax notoginseng is called "more precious than gold"(jinbuhuan金不换) and written as "三

七” in Chinese (red box in Figure 1). As one species of ginseng, it was unrecognized worldwide until American ginseng was discovered in 1716. In 1843, the Russian botanist Carl Meyer nominate Asian ginseng the botanical name “Panax”, which implies “all-healing” in Greek [21]. “Noto” means “back, spine”, and “ginseng” represents “essence of men”.

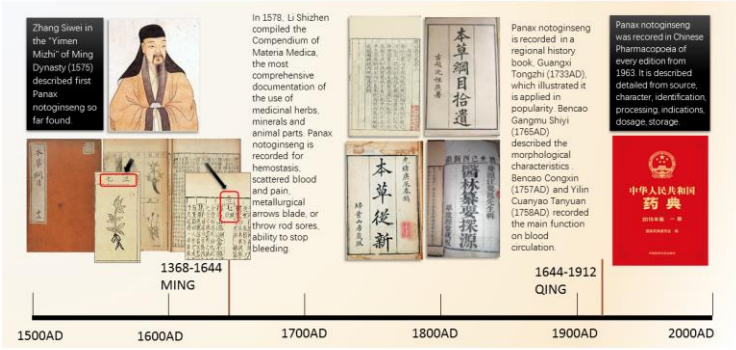

Figure 1: The important person and classic medical books in which Panax notoginseng was recorded. Zhang Siwei recorded first Panax notoginseng. The compendium of Materia Medica described the function of Panax notogingseng in detail. And then Panax notoginseng is captured in four significant ancient medical books and Chinese Pharmacopoeia.

Botanical Characteristics

Panax notoginseng F.H. chen is a hemitropous perennial herb with a short rhizome, a bamboo whip, and 2 to several fleshy roots [22]. The taproot looks conical or cylindrical with a length of 1-6 cm and a diameter of 1-4 cm. The surface is greyish brown or greyish yellow with intermittent vertical wrinkles and branch marks. There are stem scars on top with surrounding tumour-like bulges. The characteristics include dense, solid grey green, yellow green or grey sections (Figure 2).

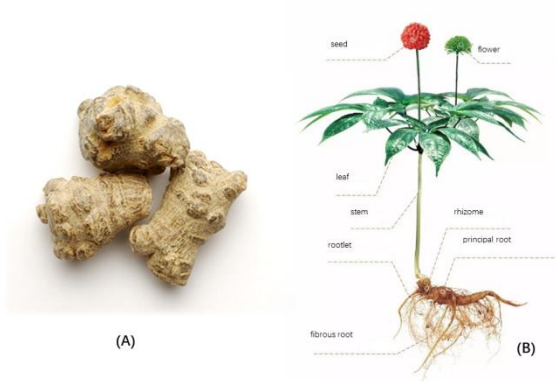

Figure 2: Radix (A) and plants pictures(B) for Panax notoginseng F.H. chen. The whole plant looks like B. The main part used for medical purpose is the principal root which looks like A after cleaning and pruning.

PNS: the Major Therapeutic Constituents of Panax Notoginseng

Panax notoginseng contains 3 key constituents, including saponins, polysaccharides, and dencichine[24]. Polysaccharides have many physiological functions, such as anti-tumour and immune regulation activity [25]. A special type of amino acid, dencichine, is an active substance of Panax notoginseng. Its structure is β-NoXalo-L-α,β diaminopropionic acid and can be artificially synthetized [26]. Saponins constitute one of the most important effective components of Panax notoginseng. So far, more than 80 kinds of monomer saponins have been isolated from Panax notoginseng parts (radix, stem, leaf, alabastrum, seed, etc.) since their first separation and identification in 1979 [27]. However, the most important components of PNS are ginsenoside Rg1, Rb1, Re and notoginsenoside R1 (NR1) (Figure 3). The amounts of these four components in PNS are 30%, 2.5%, 20%, and 2.5%, respectively. The radix of Panax notoginseng is the main part for extraction. According to the different aglycone structures, saponins are divided into 2 categories: dammarane tetracyclic triterpene and oleanane type pentacyclic triterpene. Based on whether the mother molecular nucleus structure of C6 displaces a hydroxyl group, dammarane-

type saponins can be divided into protopanaxadiol (PPD), protopanaxatriol (PPT), or octotillol [28]. Ginsenoside Rb1 is one of the major protopanaxadiol-type saponins. Ginsenoside Re, Rg1 and NR1 are the main raw ginseng triol saponins [28].

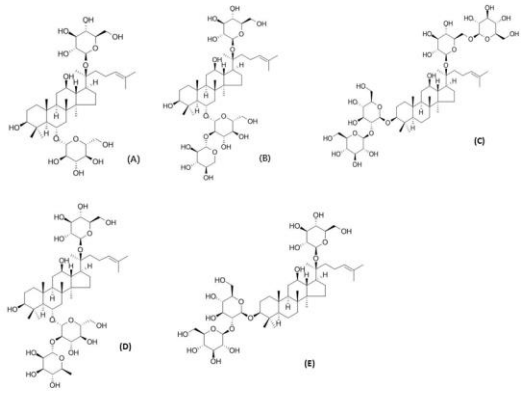

Figure 3: The chemical structure of the main active ingredients of PNS. (A) Notoginsenoside R1. (B) Ginsenoside Rg1. (C) Ginsenoside Re. (D) Ginsenoside Rd. (E) Ginsenoside Rb1 [147].

Quality Control

Many plant species are named Sanqi (Panax notoginseng). According to the statistics of the reference literature, except for Araliaceae Panax notoginseng, medicinal plants named Sanqi (Panax notoginseng) include as many as 20 species belonging to 11 families, which causes difficulty in distinguishing real Panax notoginseng. Pharmacological studies indicated that ginsenoside Rg1, ginsenoside Rb1 and NR1 are the main active constituents of Panax notoginseng. The quality control of Panax notoginseng also focuses on these three components. According to the "Chinese Pharmacopoeia", the distinction process is as follows: precisely extract the control solution and the test solution, pour into a liquid chromatograph and determine the species. The total amounts of ginsenoside Rg1 ($C_{42}H_{72}O_{14}$), ginsenoside Rb1 ($C_{54}H_{92}O_{23}$) and NR1 ($C_{47}H_{80}O_{18}$) should not be less than 5%. In standard Chinese Medicinal Materials in Hongkong [29], Panax notoginseng can be identified by thin layer

chromatography. The chromatographic results indicate that the Rb1, Rg1 and NR1 have the same colours and Rf values. In addition, the relative retention time of Panax notoginseng and the characteristic peaks of the 6 extraction liquids should be in accordance with the standard by HPLC fingerprint identification.

The therapeutic effects of PNS on CAD

Search Strategy

We conducted a systematic search of oral PNS for over 4 weeks against CAD on four English databases and four Chinese databases: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE Database, WHO Clinical Trials Registration Platform, Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), WANFANG and SinoMed. The search time frame ranged from the databases' inception until 20 Feb 2017. We also searched reference lists for further publications. The search expression used in MEDLINE was ((‘coronary heart disease’ [MeSH Terms] OR (‘coronary artery disease’ [MeSH Terms] AND (‘Panax notoginseng’ [MeSH Terms] OR sanqi[Text Word] OR sanchi[Text Word])) OR Xuesaitong[Text Word] OR Xueshuantong[Text Word])) AND ‘Randomized Controlled Trial’ [Publication Type:NoExp]. Similar expressions were used in the other databases. Outcome measures meet the primary or secondary outcomes.

Table 1: The basic information of the 17 RCTs of PNS on CAD.

Study ID	Sample(T/C)	Age, Mean±SD T,y	Age, Mean±SD C,y	M/F T	M/F C	Intervention group	Course (weeks)	Control group	Outcome measures	Ref.
Du 2009	56/56	58.8±9.2	58.8±9.2	unclear	unclear	XST + conventional drugs	4w	conventional drugs	FAA, DAA, DN	[30]
Feng 2016	36/35	69.3±4.8	69.4±5.2	21/15	20/15	PNS	12w	atorvastatin	lipid, PEP	[31]
Han 2008	30/30	64.1±10.8	63.7±11.7	23/7	21/9	XST + conventional drugs	12w	conventional drugs	FAA, DAA	[32]
Hou 2016	42/42	62.3±2.31	62.4±2.32	23/19	22/20	XST + conventional drugs	4w	conventional drugs	FAA, DAA, ECG	[33]
Kong 2006	52/52	61.2 ±5.73	60.77±5 .61	31/21	32/20	XST + conventional drugs	4w	conventional drugs	FAA, ECG	[34]
Kuang 2011	90/90	56.3±6.9	57.1±7.2	47/43	46/44	XST + conventional drugs	4w	conventional drugs	FAA, DAA	[35]
Liu 2008	30/30	64.6±5.4	63.6±4.5	unclear	unclear	XST + conventional drugs	4w	conventional drugs	ECG, lipid	[36]
Meng 2013	600/600	68±11	69±9	421/179	368/232	PNS tablet + conventional drugs	52w	conventional drugs	PEP	[37]
Song 2005	50/50	61.2±5.73	60.8±5.61	31/19	33/17	XST + conventional drugs	4w	conventional drugs	FAA, DN, ECG	[38]
Teng 2014	40/40	70.7±6.87	71.7±4.32	17/23	21/19	XST + conventional drugs	4w	conventional drugs+XST capsule placebo	FAA, lipid	[39]
Wan 2011	26/26	65.7	unclear	15/11	13/13	XST + conventional drugs	4w	conventional drugs	ECG	[40]
Wei 2010	90/90	60.4 ±3.5	60.4 ±3.5	unclear	unclear	XST +conventional drugs	4w	conventional drugs	FAA, DAA	[41]
Yan 2015	28/27	76.3±9.04	76.32±9.04	unclear	unclear	Sanqi Tongshu capsule +aspirin	24w	aspirin	PEP	[42]
Yu 2010	50/50	64.2±12.13	62.8±10.8	29/21	28/22	XST + conventional drugs	4w	conventional drugs	ECG	[43]
Zhang 2014	30/30	60±3.4	61±4.0	16/14	15/15	XST + trimetazidine	4w	trimetazidine	FAA, DAA	[44]
Zheng 2014	56/56	unclear	unclear	unclear	unclear	XST + conventional drugs	4w	conventional drugs	ECG	[45]
Zhou 2009	43/43	65±6	65±6	32/11	34/9	XST + conventional drugs	4w	conventional drugs	ECG	[46]

T/C: treatment group/control group; M/F: Male/female; XST: Xuesaitong soft capsule; FAA: frequency of angina attack; DAA: duration of angina attack; DN: dosage of nitroglycerin; PEP: the primary end point

Study Quality

Seventeen randomized clinical trials with 1747 participants was collected which randomly assigned to a conventional treatment versus a PN preparation evaluated cardiovascular outcomes (Table 1). The quality of the 17 RCTs was evaluated from 7 aspects using the ROB scale in the Cochrane handbook (Table 2). Three RCTs indicated the random way as random numbers. However, the other studies didn't describe the random method. 2 RCT [32,39] refers to random concealment and blindness.

Table 2: Risk of bias in the 17 RCTs of PNS on CAD.

References	A	B	C	D	E	F	G
Du 2009	?	?	?	?	?	?	?
Feng 2016	?	?	?	?	?	?	?
Han 2008	+	+	+	+			
Hou 2016	?	?	?	?	?	?	?
Kong 2006	?	?	?	?	?	?	?
Kuang 2011	?	?	?	?	?	?	?
Liu 2008	+	+	+	?	?	?	?
Meng 2013	+	?	?	?	?	?	?
Song 2005	?	?	?	?	?	?	?
Teng 2014	+	+	+	+	?	?	?
Wan 2011	?	?	?	?	?	?	?
Wei 2010	?	?	?	?	?	?	?
Yan 2015	?	?	?	?	?	?	?
Yu 2010	?	?	?	?	?	?	?
Zhang 2014	?	?	?	?	?	?	?
Zheng 2014	?	?	?	?	?	?	?
Zhou 2009	?	?	?	?	?	?	?

Note: A: random sequence generation, B: allocation concealment, C: blinding of participants and personnel, D: blinding for outcome assessment, E: incomplete outcome data, F: selective reporting, G: others bias, +: low risk of bias, -: high risk of bias, unclear risk of bias.

Primary Outcome

The primary outcome of CAD is the primary end point which was defined as the composite of all-cause mortality, myocardial infarction (MI), revascularization, and rehospitalization for unstable angina. PNS has been observed to have several

beneficial effects in patients with different stages of CAD. Several RCTs reported oral PNS could reduce the primary outcome. In 2008, a team underwent a RCT of 60 patients with CAD after PCI. The patients who had PNS (120 mg every time, 3 times every day) or a placebo was prescribed daily in combination with their conventional therapy for 3 months. The end point, rehospitalization, was focused on. The rehospitalization rate of patients with PNS was better than in the control group (1/30 and 3/30) [32] (Table 3). In 2013, furthermore, another team conducted a 1-year RCT with approximately 1200 CAD patents, 600 patients in the experimental group were given PNS (300 mg every time, 3 times every day). PNS increased the inhibitory effect of clopidogrel on platelet aggregation and reduced the primary end points. This trial compared the incidence of the primary end points in the experiment and control groups, which was 3.3% (20 cases) and 7.8% (47 cases) [37], resepctively. The primary end points included cardiac death, myocardial infarction, revascularization, stent thrombosis, of which most were related to revascularization.

Table 3: The end point with PNS+conventional drugs and conventional drugs alone.

		PNS+conventional drugs	conventional drugs	P value
Cardiac death	**52w**	1/600	1/600	>0.05
	12w	0/30	0/30	>0.05
Myocardial infarction	**52w**	2/600	4/600	<0.05
	12w	0/30	0/30	>0.05
Revascularization	**52w**	16/600	37/600	<0.05
	12w	0/30	0/30	>0.05
Stent thrombosis	**52w**	1/600	5/600	<0.05
Rehospitalization for unstable angina	**12w**	1/30	3/30	>0.05

Secondary Outcomes

Secondary outcomes include electrocardiogram (ECG), attack of angina pectoris, such as frequency of angina pectoris, duration of angina pectoris and dosage of nitroglycerin, quality of life. Two systematic reviews estimated current evidence for the benefit of

secondary outcomes and adverse events of PNS for CAD. One systematic review included 17 randomized clinical trials. Oral PN could alleviate angina pectoris [47]. Another systematic review including a total of 6 RCTs with 716 participants on unstable angina pectoris(UA) studied PNS alone or combined with conventional drugs versus conventional drugs alone. The results illustrated that PNS combined with conventional drugs displayed also a significant effect on relieving angina symptoms and improving ECG compared with conventional drugs alone [48].

Attack of Angina Pectoris

Angina pectoris is the symptoms for chest pain or discomfort due to CAD [49]. The patients may also feel the discomfort in your neck, jaw, shoulder, back or arm. Conventional drugs include anti-ischemic agents and vascular protective agents, such as nitroglycerin, aspirin, clopidogrel, beta-blockers and statin [50].

In this overview, 9 RCTs reviewed the therapeutic effects of PNS on angina pectoris compared PNS + conventional drugs with conventional drugs. It's demonstrated PNS is one effective agents to decrease frequency and duration of angina pectoris. PNS could decrease significantly frequency and duration of angina pectoris. 180 patients of unstable angina were randomly divided into treatment group and control group of respectively 90 patients. The treatment group added PNS (2 times/d for 4 weeks) on the basis of conventional treatment of angina pectoris. The control group administered conventional treatment of angina pectoris. The results showed that the frequency of unstable angina pectoris, pain intensity and duration were significantly reduced [35].

Ischemic Changes on ECG

ECG is the other important secondary outcome on evaluating the clinical efficacy against angina pectoris. A total of eight RCTs observed ECG changes with PNS on CAD patients. Positive correlations of PNS and improvements of ECG were reported that ischaemic changes on ECG were attenuated significantly. A

RCT divided 100 patients randomly into treatment group and control group. The two groups were given conventional drugs, treatment group plus PNS for 4 weeks. It's elucidated that ECG in the treatment group were better than those in the control group, in company with the curative effect of angina pectoris , FAA, the rate of stopping and the dosage of nitroglycerin [38]. Another RCT reported that with PNS treatment, ECG of 92% CAD patients returned to normal state or rise more than 0.05Mv of ST segment depression , different significantly with conventional drugs alone [33].

Lipid Metabolism

Lipid disorder is one of the main risk factors for CAD. A 20% reduction in major coronary events within 5 years was caused by a decrease of 1 mmol/L in LDL level [51]. All 3 RCTs reported effectiveness of PNS on lipids of CAD patients. PNS could decrease significantly TC, TG, LDL. PNS combined with conventional drugs was more effective than conventional drugs alone. In addition, some researches were trying to evaluate PNS alone with atorvastatin. 71 patients with CAD were randomly divided into two groups: PNS group (36 cases) and atorvastatin group (n=35). PNS was given 100 mg orally, while atorvastatin group received atorvastatin 20 mg orally. The results showed that there was no significant difference in the levels of TG, TC, CIMT and plaque between two groups before and after treatment. There was no significant difference in LDL-C before and after treatment in PNS group, while the LDL-C descended significantly in atorvastatin group. The incidence of abnormal liver function, gastrointestinal reaction and recurrent cardiovascular events in patients with atorvastatin was significantly higher than PNS [31].

In this overview, 15 RCTs observe the effect of PNS as alternative and complementary medicine on secondary outcomes, such as frequency of angina attack, duration of angina attack, ECG and lipid metabolism. And the results illustrated PNS combined with conventional drugs had also significant effects on changing the secondary outcomes.

Adverse Events

A systematic review evaluated the safety of PNS for UA, including 6 RCTs with 716 participants. Four of the included trials (66.7%) reported adverse effects related to treatment with PNS combined with conventional drugs. The only reported adverse effect was rash at 0.27% (1/363). No severe adverse events were reported [52]. Another systematic review evaluated an oral Panax notoginseng preparation for CAD and included 17 randomized clinical trials with 1747 participants. Nine trials reported adverse events. One trial reported reduced blood pressure and increased heart rates. One trial reported nausea, dizziness, and vomiting. One trial reported erythra, and 6 trials indicated no adverse events throughout the duration of treatment [53].

Focusing on PNS for CAD, 9 RCTs reported adverse events in all 17 RCTs. No observable toxicity in liver or kidney function was measured by serum markers. Several RCTs described adverse events that indicated that oral PNS for CAD is not related to adverse reactions (Table 4). Feng 2016 reported 2 cases with elevated transaminase, 1 case with muscle pain, and 1 case with gastrointestinal discomfort in the control group. No obvious adverse reactions were observed in the treatment group [31]. In the experimental group of Yan 2015, 1 case of subcutaneous haemorrhage and 1 case of positive faecal occult blood occurred. One case of nausea and 1 case of positive faecal occult blood occurred in the control group [42]. In Yu 2010, 1 case in the experimental group showed a small amount of rash after 3 d of treatment, which was not caused by the treatment [43]. No significant difference was observed in the incidence of adverse reactions. Furthermore, PNS was not related to any obvious abnormalities in liver and kidney function.

Table 4: The incidence of adverse reactions with PNS for CAD.

Adverse events	The incidence of adverse reactions (experimental)	The incidence of adverse reactions (control)	Ref.
elevated transaminase	0/36	2/35	[31]
gastrointestinal discomfort	0/36	1/35	[31]
muscle pain	0/36	1/35	[31]
subcutaneous haemorrhage	1/28	0/27	[42]
faecal occult blood positive	1/28	1/27	[42]
nausea	0/28	1/27	[42]
rash	1/50	0/50	[43]
Total	3/214	6/208	

The mechanisms of PNS on CAD

CAD occurs when atherosclerotic lesions impede blood flow in the coronary artery. The plaque activation causes ischaemia and infarction. Ruptures tend to happen near the thin and easy destroyed fibrous cap where activated immune cells, inflammatory molecules and proteolytic enzymes are abundant [54]. They can weaken the cap and transform stable plaque to an unstable vulnerable plaque that is more likely to rupture. The pathomechanism of atherosclerosis in CAD is related to inflammation, lipid metabolism, endothelial erosion, coagulation system dysfunction and apoptosis [55]. Plaque rupture is the major trigger of CAD [56], while hypoxia and ischaemia are the pathological manifestations of the disease. In addition, angiogenesis can improve blood flow in the presence of microvascular blockage in CAD.

Saponins are a group of natural compounds in plants and foods. PNS is the most important compound among Panax notoginseng's effective components. In the past ten years, it had received extensive attention in the treatment of CAD at home and abroad. Many studies showed that it had anti-inflammatory, anti-apoptotic, anti-hypoxic, lowering lipids, anti-coagulation and pro-angiogenesis properties (Figure 4, Table 5).

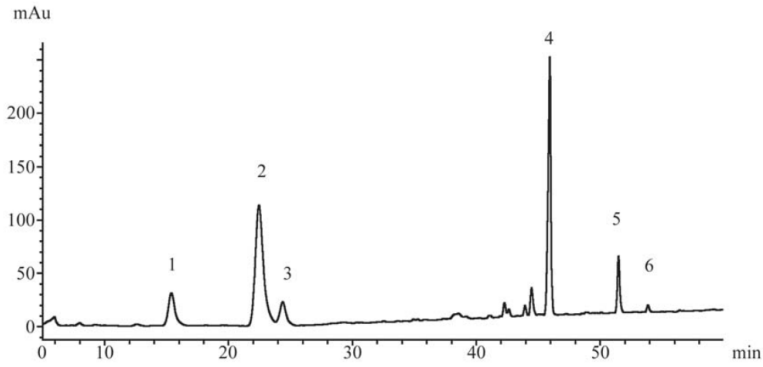

Figure 4: Summary of seven main functions of PNS in CAD.

Anti-Inflammation

Inflammation dominates in CAD and atherosclerosis. Immune cells gather in the early atherosclerotic lesions, where effector molecules promote the progress of inflammation which can induce acute coronary syndrome (ACS) [32]. In vulnerable plaques, the main characteristic is that inflammation exists widespread. Several studies showed that different systems of inflammation markers such as C-reactive protein in patients are related to an increased risk of ACS [57,58]. And inflammation associated with CAD includes MAPK activation, the role of NF-κB, TNF-α, ROS for signalling, modified lipoprotein on endothelial cells and other cell activation, leukocyte adhesion, formation of foam cells, macrophages (Figure 5A) and vascular smooth muscle cells (VSMCs).

First, NF-κB is critical for the trigger and development of atherosclerosis [59]. The elevated NF-κB activators such as osteoprotegerin were related to increased mortality, especially of cardiovascular diseases [60]. Activation of NF-κB led to regulation of many atherogenic genes, facilitation of inflammation, induction of chemokines and adhesion molecules on the surface of endothelial cell (ECs)(Figure 5B). Chemokines and adhesion molecules attracted the monocytes to the location prone to atheroma [61-63]. PNS inhibited NF-κB DNA binding activity [64] and secreting pro-inflammatory factors, interleukin (IL)-6 and MCP-1 in macrophages [65]. The size of

atherosclerotic lesions and the number of macrophages in apolipoprotein E (apoE) (-/-) mice were reduced by PNS. In addition, PNS reduced the expression of proinflammatory cytokines VCAM-1, ICAM-1 and MCP-1 with inhibition of NF-κB, JNK, p38 (MAPK) and ERK1/2 activation and RAGE [66]. Phagocytosis induced the expression of the pro-inflammatory factor COX-2 and the production by COX-2 regulated the functions of macrophage [67]. In the model of inflammation, the expression of COX-2 reached a peak. However, in the later stage COX-2 descended which leads to activation of PPARγ and inhibition of inflammation by NF-κB. Interestingly, PNS suppressed the expression of COX-2 at an early stage with promotion of phagocytosis, while PNS also elevated COX-2 expression at a later stage [68].

Figure 5: Illustration of the mechanism of PNS on (A) macrophage, (B) endothelial cell, (C) cardiomyocyte and (D) platelet aggregation. In the process of inflammation among macrophages (A), pro-inflammatory factors such as IL-6, MCP-1, VCAM-1, ICAM-1, MCR-1, and TNF-alpha are regulated by ROS and SOD. Prostaglandins produced by COX-2 is negatively related to phagocytosis. PNS can regulate pro-inflammatory factors by inhibiting ROS and promoting SOD. In addition, PNS also inhibit TNA alpha directly. The activated NF-κB regulates the expression of many atherogenic genes, creating a local inflammatory condition and inducing chemotactic factors and adhesion molecules on the surface of ECs (B). PNS can increase SOD activity by decreasing TNF alpha, IL-6 and ROS generation. Notoginsenoside R1 can

suppress inflammatory cytokines production by activating PPAR gamma and by suppressing ERK and PKB, inhibiting TNF-alpha. In addition, NR1 can inhibit NF-κB, MAPK, IL-1 beta and reduce cardiomyocyte apoptosis and inflammation through the activation of ER alpha and PI3K/Akt signalling (C). Ginsenoside Rg1 reduced intracellular ROS and LDH and suppressed the intracellular Ca2+ level by increasing the activity of endogenous antioxidants, including T-SOD, CAT and GSH. About (D), NG have an inhibitory effect on platelet aggregation. The effect of PNS in anti-platelet aggregation is related to the suppression of intracellular calcium mobilization and ERK2/p38 activation. Three main ginsenosides (Rg1, Re and R1) that exist in PNS also showed anti-platelet activity. Ft1 induced dose-dependent platelet aggregation mediated through P2Y12 receptors. NR1 significantly decreased TNF alpha-induced PAI-1.

Second, oxidation is generally considered as a facilitator or a modulator of inflammatory signalling [69], and also a major endothelial-derived hyperpolarizing factor (EDHF) mediator [70]. Oxidative stress involves the inflammation of vessels and the progression of atherosclerosis. Excessive reactive oxygen species (ROS) generation has been suggested to up-regulate pro-inflammatory cytokines and adhesion molecules which can result in atherosclerosis initiation consequently [71]. ROS facilitated the activation of ROS/Akt/IKK pathways that interact with NF-κB [72]. In addition, MDA(malondialdehyde) is a product of a free-radical peroxidatic reaction on lipids, and Superoxide dismutase (SOD) is a free-radical scavenger [73]. Myeloperoxidase (MPO), a peroxidase enzyme, could accurately predicted the mortality risk in patients with coronary angiography. The improvement of MPO and CRP ameliorated the long-term risk assessment of outcomes in CAD patients [74].

PNS also are considered as free radical-scavengers with antioxidant properties. PNS could impede the development of atherosclerotic lesions through the antioxidant and anti-inflammatory effects [67]. PNS protected a rat haemorrhagic shock model via antioxidative stress and anti-inflammatory pathways. PNS also increased SOD activity, decrease MDA, endotoxin, MPO, TNF alpha and IL-6 [75]. PNS could reduce oxidative stress and inhibit plaque progression. SOD and glutathione activities were elevated and ROS generation is impaired in apoE(-/-) mice treated with PNS [67].

Treatment with Notoginsengnosides (NG) could decrease the ROS level in platelets [53]. Ginsenoside-Rd significantly promoted H_2O_2-induced cell apoptosis with a concentration-dependent manner [77]. NR1 with the effect of phytoestrogen, was illustrated as a component with anti-inflammatory, antioxidative and anti-apoptotic properties. NR1 can restrict oxidized low-density lipoprotein (ox-LDL)-induced inflammatory cytokines including NF-κB, MAPK, TNF-alpha and IL-1 beta [78]. It also inhibits PAI-1 overexpression by TNF-alpha in human aortic smooth muscle cells (HASMCs) and the ERK/PKB pathways [79]. NR1 can protect the heart from septic shock, probably through the activation of ER alpha and PI3K/Akt pathway. This mechanism blocked NF-κB activation and attenuated inflammation and apoptosis in the myocardium [80,81]. In addition, the pretreatment with ginsenoside Rg1 decreased the release of lactate dehydrogenase (LDH) and increased cell viability dose-dependently. Ginsenoside Rg1 suppressed ROS and Ca^{2+} level intracellularly by raising the activity of endogenous antioxidants as T-SOD, CAT, GSH [82].

Regulation of Lipid Metabolism

Lipoprotein disorder is one of the main risk factors of CAD. A meta-analysis of 14 randomized trials showed that a decrease of 1 mmol/L in plasma LDL levels generates a 20% reduction in major coronary events including coronary revascularization and stroke within 5 years [83]. CAD is closely related to lipid metabolic disorders, specifically increased triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), ox-LDL and total cholesterol (TC) [84,85]. PNS can reduce remarkably the level of cholesterol ester in foam cells by up-regulation of ABCA1. This bioactivity may be related to the special chemical structures of PNS that are like the natural agonist of liver X receptor alpha (LXR alpha) [86]. LXRα as a key regulator of macrophage function, controls transcriptional programmes involved in lipid metabolism and inflammation [87]. PNS could regulate lipids by activation of the LXR alpha gene promoter which increased ABCA1 and ABCG1 subsequently and suppressed NF-κB DNA binding activity [88].

PNS could markedly reduce TC, TG, and LDL-C [89] and increase high-density lipoprotein cholesterol (HDL-C) significantly [90]. CPT-1A is a key enzyme in the process of fatty acid oxidation. While the fatty acid transporter protein 4 (FATP4) is associated with long and very long chain fatty acid uptake and promoting synthesis of acyl-CoA [91]. Fatty acid binding protein 4 (FABP4) and CPT-1A, were downregulated in ischemic zone of the heart. PNS could regulate lipid metabolism by increasing the expression of FABP4 and CPT-1A [92].

Lipid metabolic disorder can be caused by inflammation and can exasperate the inflammation [93]. Dyslipidemia and inflammation accelerate each other to form a detrimental cycle. Regulation of lipid metabolism disorders is conducive to inflammation alleviation and anti-inflammatory effects benefits the maintenance of balanced lipid metabolism. PNS could regulate lipid metabolism. Meanwhile, PNS decreased significantly the expressions of some inflammatory cytokines including integrins, IL-18, IL-1 beta and matrix metalloproteinases 2 (MMP2) and 9 [89].

In conclusion, CAD is closely related to lipid metabolic disorders, specifically including increased TG, LDL-C, ox-LDL and TC. PNS could depress the level of TC by elevating LXR alpha, ABCA1, and ABCG1 and reducing NF-κB. In addition, PNS can regulate lipid metabolism by inhibiting LPL and increasing FABP4 and CPT-1A. Furthermore, lipidosis is closely related to inflammation, which PNS have diverse effects on.

Regulation of Coagulation System

In CAD, antiplatelet therapy has become an important treatment according to several important guidelines [95,96]. Near wound, platelets are recruited to restore endothelial integrity to initiate thrombus formation [94]. Thrombosis is associated with platelet aggregation. Thromboxane A2 (TXA2), derived from platelets, induces powerfully release and aggregation of platelets.

PNS inhibited platelet activation by multiple ingredients and pathways. PNS could decrease platelet activation, inhibit

adhesion and aggregation of platelet, prevent thrombosis and improve microcirculation [97]. PNS protected ECs from injury by suppressing platelet adhesion, in which PNS was superior to aspirin. The underlying mechanism is related to the COX pathway in both ECs and platelets (Fig 5 (B)&(D)) [98]. NG could suppress platelet aggregation in vitro. Furthermore, in vivo NG could also significantly inhibit platelet aggregation of platelet rich plasma (PRP) [99]. The effect of PNS in anti-platelet aggregation is associated with inhibition of intracellular calcium mobilization and activation of ERK2/p38. Three main ginsenosides (Rg1, Re and NR1) existing in PNS also demonstrated anti-platelet activity, but their combination did not exhibit any synergistic effect on rabbit platelet aggregation [100]. Rg1 and Rg2 can significantly prolong the clotting time. Compared with Rg1, Rg2 showed a stronger anticoagulant effect [101].

However, in PNS, notoginsenoside Ft1(NFt1) as the potent procoagulant component induced platelet aggregation dose-dependently. The P2Y12 receptor serves as a crucial regulator of haemostasis and thrombosis on the platelet. When conditioned by ADP, the P2Y12 receptor activated a series of downstream events that result in platelet aggregation, shape change, dense granule secretion [102, 103]. Ft1 deceased plasma coagulation indexes and tail bleeding time and increased thrombogenesis and cytosolic Ca^{2+} accumulation.

Fibrinolysis is part of the coagulation cascade, which is adjusted by plasminogen activator (PA) and PA inhibitor (PAI-1). Abnormal fibrinolysis and high plasma concentrations of PAI-1 are related to an increased risk of CAD [104]. When human umbilical vein endothelial cells (HUVECs) were conditioned with purified NR1, tissue-type PA (TPA) synthesis increase in a dose- (0.01 to 100 mg of NR1/mL) and time-dependent manner. NR1 significantly decreased PAI-1 mRNA, protein and secretion in HASMCs in a dose-dependent manner [79]. TPA activity and TPA-PAI-1 complexes reached greater than twofold and threefold maximal stimulation, respectively NR1. In contrast, NR1 induced fivefold decrease in PAI-1 activity [105].

Anti-Apoptosis

Myocardial ischaemia can lead to widespread cell apoptosis [106]. PI3K/Akt pathway is an important regulator including proliferation, apoptosis and nitric oxide (NO) synthesis [107]. PI3K also strengthens the oxidative capacity of cardiac fatty acid. The PI3K signalling cascade diminishes myocardial damage by ischaemia via recruiting several endogenous cardioprotective pathways [108].

PNS could protect myocardial cells from apoptosis induced by ischaemia both in vitro and in vivo by activating the PI3K/Akt signalling pathway [115]. PNS significantly up-regulated p-Akt in H9c2 cells and ischaemic myocardial tissues. PNS attenuated cell apoptosis via chromatin concentration and condensation by up-regulating the antioxidative abilities of SOD and MDA [109]. PNS also improved cardiac function in the left ventricular ejection fractions (EF) of rats [16,110].

The pathological proliferation of VSMCs is a crucial factor involved in the pathogenesis of atherosclerosis, associated with inflammation, apoptosis, and matrix alterations [111]. PNS suppressed proliferation and induced apoptosis in VSMCs [112] by up-regulating p53, Bax, and caspase-3 and down-regulating Bcl-2 [113]. In addition, both atorvastatin and PNS have been observed to suppress VSMC proliferation by inhibiting the activation of the ERK signalling pathway [114].

Pro-angiogenesis

Angiogenesis is the stimulation of the endothelium to shape new blood vessels, which is implicated in the pathophysiology of CAD [115]. In CAD, inflammation related to atherogenesis contributes to the interaction of angiogenic factors [116], which lead to vascular repair [117]. Various angiogenic growth factors and progenitor cells can promote the formation of new blood vessels [118]. Angiogenesis is a potential treatment in many physiological processes such as MI, chronic cardiac ischaemia and stroke [119].

PNS could enhance angiogenesis and the proangiogenic effects including the VEGF-KDR/Flk-1 and PI3K-Akt-eNOS signalling pathways in vivo and in vitro [120]. NR1, similar to Rg1 and Re, had been shown to have pro-angiogenic effect, possibly by activation of the VEGF-KDR/Flk-1 and PI3K-Akt-eNOS signalling pathways in vivo and in vitro [121].
Ft1 can stimulate angiogenesis. Ft1 led to proliferation, migration and tube formation in HUVECs by activation of the PI3K/Akt and ERK1/2 pathways in rat mesenteric arteries. This leads to the phosphorylation of eNOS and release of NO, which triggers soluble guanylyl cyclase in the VSMCs [122].

Anti-atherosclerosis

Atherosclerosis is the pathological basis of CAD. Furthermore, the development of chronic atherosclerosis to form thrombosis is the pathogenesis of ACS [123]. ApoE is a ligand for cleansing receptors of chylomicrons and very low density lipoprotein residues. The lack of apoE can lead to the accumulation of cholesterol-rich residues in plasma, and long-time accumulation can generate atherosclerosis [124] with hypercholesterolemia and spontaneous arterial lesions [125]. PNS was able to decrease lipids, ox-LDL in serum and the expressions of CD40 and MMP-9 in apoE(-/-) mice [126]. Meanwhile, PNS lessened the size of atherosclerotic plaques, partly by progenitor cell mobilization. PNS also augmented endothelialization and reduced the VSMC content of the lesions [127].

A high-fat diet together with Zymosan (Zym) induces atherogenesis in rats. PNS reduced the levels of TC, TG, LDL-C, IL-6 and C-reactive protein and increased the HDL-C level significantly in serum of atherosclerosis rabbits by inhibiting FAK phosphorylation, integrins expression and NF-κB translocation [128]. And PNS significantly down-regulated MCP-1 and NF-κB/p65 with 8 weeks of treatment [90].

Ginsenoside Rd, isolated from PNS, is a voltage dependent Ca^{2+} channel blocker. Ginsenoside Rd decreased remarkably the size of atherosclerotic plaque and ox-LDL of macrophage in the apoE(-/-) rats. In vitro, ginsenoside Rd suppressed the formation

of foam cells induced by ox-LDL and cholesterol accumulation in macrophages [129].

Protection against Myocardial Ischaemia

PNS exerted a certain degree of improvement on myocardial ischaemia [130]. In fact, the earliest study to demonstrate the effects of Panax notoginseng on CAD was a study published in 1972, in which the oral administration of Panax notoginseng reduced the dosage requirement of nitroglycerin and improved ECG in clinic. And Panax notoginseng significantly increased coronary blood flow in dogs [131]. PNS was shown to obviously alleviate the degree of myocardial ischaemia and narrow the ischaemic area subjected to myocardial ischaemia and infarction [132]. PNS could enhance left ventricular systolic and diastolic functions, decrease peripheral resistance, and improve the cardiac function of rats with post-myocardial infarction left ventricular remodelling [133]. The endothelium was denudated completely after balloon endothelial denudation (BED). PNS could sustaine anti-restenotic effects after BED injury. PNS promoted endothelial regeneration and reduced ECM thickening [134]. In vitro, PNS exhibited an anti-apoptotic effect both in oxygen-deprived H9c2 cells and in ischaemic myocardial tissues [16]. In addition, PNS could decrease the pathological injury to cardiac myocytes with ischaemia and improve ventricular remodelling [135].

The PPAR family, a series of transcription factors, regulates cardiac energy metabolism and impacts metabolism of cardiac fatty acid and glucose [136]. PGC-1α is a transcriptional coactivator of the PPARs and a critical factor in myocardial metabolism [137]. In ischaemic rats, transcriptional factors were downregulated such as PPARs, RXRA and PGC-1 alpha [92]. PNS could up-regulate expressions of these factors.

In addition, salvianolic acids' compatibility with PNS could protect cardiomyocytes(Figure 5C) during hypoxia and reoxygenation injury by inhibiting apoptosis and improving energy metabolism compared to any single drug [138]. In the model of ischaemia/reperfusion, salvianolic acids (SA), NG and

a combination of SA and NG exhibited the cardioprotective effects. SA and NG displayed both similarities and differences in pathways such as energy metabolism, lipid metabolism, cell proliferation and apoptosis. [139]. The combination of SalB and Rg1, instead of SalB and Rb1, advanced cardiac contractility in rats with MI [140].

Table 5: Summary of animal and cell experiments of PNS on CAD.

Species	Experimental model	Effects	Signalling molecules involved	Ref.
PNS	human granulocytic HL-60, erythrocytic K562, megakaryocytic CHRF-288 and Meg-01 cell line	To promote proliferation and differentiation	kinase MEK-1↑, MEK-2↑, ERK-1↑, ERK-2↑, AKT-1↑, AKT-2↑, PI3K↑	[65]
PNS	THP-1 macrophage cells	To reduce secretion of inflammatory factors	LXRalpha↑, ABCA1↑, ABCG1↑, NF-κB↓, IL-6↓, MCP-1↓	[66]
PNS	apo-E-deficient mice	To inhibit the progression of atherosclerotic lesions via antioxidant/anti-inflammatory biological properties	VCAM-1↓, ICAM-1↓, MCP-1↓, RAGE↓, NF-κB↓, JNK, p38(MAPK) ↓, ERK1/2↓	[67]
PNS	peritoneal macrophage cells	To enhance phagocytosis	COX-2, PGE↓, PGD↑	[68]
PNS	haemorrhagic shock rats	protective to rat haemorrhagic shock model by antioxidative stress and anti-inflammation	ICAM-1↓, SOD↑, MDA↓, endotoxin↓, MPO↓, TNF alpha↓, IL-6↓	[75]
NG	rat washed platelets	To inhibit ADP-induced platelet aggregation	Grb2↑, thrombospondin 1↑, tubulin alpha 6↑, thioredoxin↑, Cu–Zn superoxide dismutase, DJ-1↑, peroxiredoxin 3↑, thioredoxin-like protein 2↑, ribonuclease inhibitor↑, potassium channel subfamily V member 2↑, myosin regulatory light chain 9↑, laminin receptor 1↑	[76]
Ginsenoside-Rd	basilar artery smooth muscle cells	To inhibit cell proliferation and reversed basilar artery remodelling	cytochrome C↑, caspase-9/caspase-3↑, MMP↓, Bcl-2/Bax↓, Cyclosporine A↓	[77]
NR1	human endothelial EA. hy926 cells	To suppress oxLDL-induced inflammatory cytokines production	PPARgamma↑, NF-κB↓, MAPK↓	[78]
NR1	human aortic smooth muscle cells	To inhibit TNF-alpha-induced PAI-1 production	ERK↓, PKB↓	[79]
NR1	H9c2 cardiomyocytes	To reduce cardiomyocyte apoptosis and inflammation	ERalpha↑	[80]
NR1	endotoxaemic mice	protection of cardiac function	ERalpha↑, phospho-Akt↑, phospho-GSK3beta↑, I-κB alpha↑	[81]
Ginsenoside Rg1	hypoxia/reoxygenation cardiomyocytes	antioxidative effect	ROS↓, T-SOD↑, CAT↑, GSH↑	[82]
PNS	foam cells	To decrease cholesterol ester	ABCA1↑	[86]
PNS	CAD rats	To improve lipid metabolism	LPL↑, FABP4↓, CPT-1A↓, cytochrome P450↑, PPARalpha↓, PPARgamma↓, RXRA↓, PGC-1alpha↓	[88]
PNS	atherosclerosis rats	To regulate the blood lipid profile and anti-inflammation	integrins↓, IL-18↓, IL-1beta↓, MMP-2↓, MMP-9↓, NF-κB/p65↓, IκBalpha↑	[89]
PNS	atherosclerosis rabbit	To regulate the blood lipid profile and anti-inflammation	IL-6↓, CRP↓, MCP-1↓, NF-κB/p65↓	[90]
PNS	apoE (-/-) mice	To prevent the development of atherosclerosis	Ca^{2+} influx↑, SR-A↓	[91]
Ginsenoside-Rd	macrophage cells	To inhibit ox-LDL-induced foam cell formation	Ca^{2+} influx↑	[91]
PNS	endothelial cells	To inhibit platelet activation	COX-2, 6-keto-PGF1alpha↑, COX-1↓, TXB2↓	[98]
PNS	Rats	To inhibit ADP-induced platelet		[99]

		aggregation of platelet rich plasma		
PNS	rabbit and human platelet	anti-platelet aggregation	ERK2↓, p38↓	[100]
PNS, ginsenosides (Rg1, Re and NR1)	human plasma	anticoagulation activity		[101]
Ginsenosides, Rg1, Rg2	rat washed platelets	To enhance platelet aggregation	Ca^{2+}↑, P2Y12 receptors↑	[103]
NFt1	HEK293 cells	None	Ca^{2+}↑, P2Y12 receptors↑, cAMP, phosphorylation of PI3K↑, Akt↑	[103]
NR1	cultured HUVECs	To activate tissue-type plasminogen	TPA↑, TPA-PAI-1 complexes↑	[105]
PNS	H9c2 cells	anti-apoptosis	PI3K↑, p-Akt↑	[109]
PNS	myocardial ischaemia injury rats	To improve cardiac function in rats	p-Akt↑	[110]
PNS	rat aorta after balloon angioplasty	To inhibit intima hyperplasia by inhibiting VSMCs proliferation	PCNA↓	[112]
PNS	VSMCs	To inhibit VSMCs proliferation and induce VSMCs apoptosis	p53↑, Bax↑, caspase-3↑, Bcl-2↓	[113]
PNS	VSMCs	To inhibit VSMCs proliferation	cyclinD1↓, CDK4↓, p21↓, P-ERK1/2↓, MKP-1↑	[114]
PNS	human umbilical vein endothelial cells(HUVECs)	To stimulate the proliferation of HUVECs	PI3K↑, Akt↑, eNOS↑	[120]
PNS	zebrafish	To promote changes in the subintestinal vessels	VEGF-KDR/Flk-1↑	[120]
NFt1	HUVECs	pro-angiogenesis, to stimulate the proliferation of HUVECs	VEGF-KDR/Flk-1↑, PI3K↑, eNOS↑, Akt↑	[121]
NFt1	rat mesenteric arteries	To induce endothelium-dependent relaxation	eNOS↑, ER beta↑, Akt↑, ERK1/2↓	[122]
PNS	apolipoprotein E-knockout mice	To lower serum lipid levels	CD40↓, MMP-9↓	[126]
PNS	apolipoprotein E-knockout mice	To reduce the size of atherosclerotic plaque	SDF-1 alpha↑, SCF↑, MMP-9↑, CXCR4↑	[127]
PNS	Zymosan A induced atherosclerosis rats	To inhibit atherogenesis	p-FAK↓, NF-κB↓	[105]
PNS	acute myocardial ischaemia in anaesthetic dogs	To attenuate the damage of myocardial ischaemia and infarction	ET↓, TXA2↓, MBF↑	[128]
PNS	post-myocardial infarction-ventricular rats	To reduce pathological injury of cardiac myocytes in myocardial ischaemia and cardiac muscle	ACE2↑, TNF-alpha↓	[135]
PNS	rabbits after balloon endothelial denudation (BED)	To promote endothelial, regeneration and reduce extracellular matrix thickening	VEGF↓, MMP-2↓	[126]
PNS	cardiomyocytes with hypoxia-reoxygenation	To inhibit apoptosis and improve energy metabolism		[138]
NG	rats of ischaemia-reperfusion (IR)	cardioprotective effect		[139]
Ginsenoside Rg1, Rb1	myocardial infarction rats	To improve heart contractility		[140]

Discussion

Summary of Current Evidence

In the past two decades, a breakthrough has been achieved in the pharmacology of PNS. The knowledge of PNS functions offers a new opportunity for the prevention and treatment of CAD. PNS has been observed to have multiple positive effects in the key processes of CAD, including anti-inflammation, the regulation of lipid metabolism and the coagulation system, anti-apoptosis, pro-angiogenesis, anti-atherosclerosis and anti-myocardial ischaemia (Figure 6). Several RCTs have shown that the long-term use of PNS can effectively reduce the end-point of CAD [37,42]. In addition, many RCTs found that PNS can also significantly improve performance on the ECG and reduce the frequency and the duration of angina attacks, greatly regulating the lipids [30,32-46].

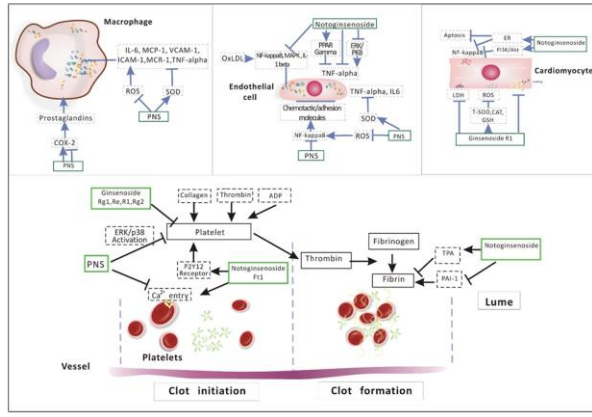

Figure 6: PNS on the evolution of atherosclerotic plaque. In the evolution of atherosclerosis plaque, PNS has effects on the oxidation of LDL, the accumulation of lipoprotein, chemoattractant cytokines related to macrophages, modified lipoprotein particles, platelet aggregation, the migration of smooth muscle cells(SMCs), apoptosis of SMCs and the development of foam cells.

The function of PNS on platelet aggregation resembles aspirin. For the patients with aspirin resistance (Arachidonic acid inhibitory rate<50%) and clopidogrel resistance (Adenosine diphosphate inhibition rate <30%), Ticagreloran, an oral reversibly binding P2Y12 inhibitor, is commonly used alternative drug [141]. However, Ticagrelor is unsuitable for patients with bleeding tendency, meanwhile it means a big financial burden on patients or the government. For those patients, PNS is recommend for anti-platelet aggregation. Several studies in vitro and vivo PNS may inhibit the activation of platelet through multiple components and multiple pathways. In a RCT, PNS alone is illustrated to decrease platelet aggregation and less adverse events [43].

Statins as a main drug by many guidelines have shown good effects in the primary and secondary prevention of CAD [142,143]. However, statins have side effects including elevated liver transaminase, myopathy, myalgia, myositis and even rhabdomyolysis. PNS could regulate lipid metabolism, not so strongly as statins, but with a higher safety. Meanwhile PNS has the roles of anti-inflammation and anti-platelet aggregation. So, for patients with liver damage, or the elderly without high TC, TG, LDL, we recommend PNS for lipid-lowering and anti-inflammation.

In addition, nitroglycerin is one of the oldest of cardiovascular drugs in clinics. Nitroglycerin exerts anti-ischemic effect mainly by expanding capacity vein, reducing preload and releasing coronary artery spasm. PNS could reduce myocardial ischemia and relieve angina pectoris. In clinic PNS has similar effects and different mechanisms with nitroglycerin. PNS was recommended when patients can't tolerate the side effects of nitroglycerin such as headache, dizziness, tachycardia. Patients with nitrate resistance were also recommended to administrate PNS.

Inflammation runs through the initiation, formation and onset of CAD. The widespread presence of inflammation generates the major feature of vulnerable plaques [144]. PNS exerts anti-inflammation by several signalling pathways. PNS can regulate pro-inflammatory factors by inhibiting ROS, TNA alpha, NF-κB

and promoting SOD. Interestingly, PNS has dual functions on COX-2 at different periods. An individual PNS, NR1 can suppress inflammatory cytokines production by activating PPAR gamma and by suppressing ERK and PKB, inhibiting TNF-alpha in vitro and vivo. Inflammation plays an important role in the whole process of CAD, PNS with less side effects could be administered for a long time. Meanwhile, long-term application of PNS could reduce the end point of CAD.

Different with western medicines, TCM acts on several targets to play a variety of roles on the mechanisms of the disease. PNS has effects simultaneously on anti-inflammation, the regulation of lipid metabolism and the coagulation system, anti-apoptosis, pro-angiogenesis, anti-atherosclerosis and anti-myocardial ischaemia. In the entire pathological process of CAD, at different pathological stages, PNS can effectively reduce the occurrence and the development of CAD. In several RCTs, PNS effectively reduce the end-point of CAD, greatly regulate the lipids, improve performance on the ECG and reduce the frequency and the duration of angina attacks. Thus, PNS is a potential agent against CAD.

Recently, the medical community has gradually assigned importance to the primary prevention of CAD with PNS due to their unique advantages. In primary prevention, PNS can regulate lipid metabolism and hypertension [145] and inhibit platelet aggregation. Aspirin has side effects such as gastrointestinal reactions and statins can cause liver injury. Especially in preventive treatment, long-term administration will increase the rate of side effects. And PNS appear to be safer. PNS have multiple targets, a wide range of therapeutic effects and high safety. Therefore, we believe that it has great potential in the treatment of CAD.

Limitations and Perspectives

Currently, increasing research is focusing on individual PNS. However, these studies are still rare compared to those on total PNS. Individual PNS could have contradictory functions, especially on platelets. Four main ginsenosides (Rg1, Re, NR1 and Rg2) that exist in PNS also showed anti-platelet and anticoagulation activity. Both Rg1 and Rg2 could significantly

extend blood clotting time. However, NFt1 was procoagulant and induced dose-dependent platelet aggregation. Therefore, PNS could be further separated in order to thoroughly investigate the function of Panax notoginseng. In addition, the mechanism of PNS in CAD is complicated, so the work of individual PNS multi-target networks will further raise the potential of Panax notoginseng for the effective treatment of CAD.

In addition, we need to further improve the drug purity and screen concentrations to reveal and enhance the medicinal value of PNS as an individual lipid-lowering drug or an antiplatelet agglutination drug. We have found some research that focuses on comparing PNS and aspirin or PNS and statins. The inhibitory effect of PNS on platelet activation was similar to aspirin, but the inhibitory effect of PNS on platelet adhesion to ECs was superior to aspirin [146]. In a RCT OF PNS group, aspirin group and PNS plus aspirin group, the results showed decreased D-dimer, platelet aggregation time, increased international standardization ratio of prothrombin time and prolonged prothrombin time in three groups. Compared with PNS, aspirin was more effective than PNS in improving platelet aggregation [42]. The purity and concentrate increase probably generate stronger effects on CAD.

However, the medical technology and the related animal experiments and RCTs are limited. Moreover, only one 1-year RCT has reported the effect of PNS on the end-point of CAD. However, we hope that some multi-centre, large-sample RCTs will provide high-level evidence for the effectiveness of PNS in CAD.

Conclusion

PNS have multiple positive effects in the key processes of CAD, including anti-inflammation, the regulation of lipid metabolism and the coagulation system, anti-apoptosis, pro-angiogenesis, anti-atherosclerosis and anti-myocardial ischaemia. Long-term use of PNS can effectively reduce the end point of CAD and improve angina pectoris, ECG and lipid metabolism which illustrates that PNS is potential agent on CAD. However, more high-level RCTs are expected to provide evidence for the efficacy of PNS in CAD.

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