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REVIEW

Focus on Notoginsenoside R1 in Metabolism and Prevention Against Human Diseases

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Abstract: Notoginsenoside (NG)-R1 is one of the main bioactive compounds from *Panax notoginseng* (PN) root, which is well known in the prescription for mediating the micro-circulatory hemostasis in human. In this article, we mainly discuss NG-R1 in metabolism and the biological activities, including cardiovascular protection, neuro-protection, anti-diabetes, liver protection, gastrointestinal protection, lung protection, bone metabolism regulation, renal protection, and anti-cancer. The metabolites produced by deglycosylation of NG-R1 exhibit higher permeability and bioavailability. It has been extensively verified that NG-R1 may ameliorate ischemia-reperfusion (IR)-induced injury in cardiovascular and neuronal systems mainly by upregulating the activity of estrogen receptor α-dependent phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and nuclear factor erythroid-2-related factor 2 (NRF2) pathways and downregulating nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. However, no specific targets for NG-R1 have been identified. Expectedly, NG-R1 has been used as a main bioactive compound in many Traditional Chinese Medicines clinically, such as Xuesaitong, Naodesheng, XueShuanTong, ShenMai, and QSYQ. These suggest that NG-R1 exhibits a significant potency in drug development.

Keywords: notoginsenoside (NG)-R1, *Panax notoginseng*, micro-circulatory hemostasis, permeability, bioavailability

Introduction

Panax notoginseng (PN), a member of the family Araliaceae, has been widely used as a Traditional Chinese Medicine (TCM) for thousands of years. Particularly, its root is often clinically prescribed to maintain the micro-circulatory homeostasis in the human body and manage various diseases, including cardiovascular,[1] neuronal,[2] and diabetic dysfunctions.[3] Xu et al (2018) reviewed the progress of PN in protection against inflammation-related chronic diseases.[4] Xie et al (2018) discussed the mechanisms of PN in anti-depressant or anxiolytic effects.[2] The bioactive compounds are the main factors responsible for the benefiting effects of TCM. More than 20 notoginsenosides (NGs), mainly belong to dammarane-type triterpenoidal saponins, have been identified and act as the main bioactive compounds responsible for the pharmacological effects of PN. These NGs include NG-R1, -R2, -R3, -R4, -R6, -Fa, -Fc, and -Fe, and ginsenoside-Rg1, -Rg2, -Rb1, -Rb2, -Rb3, -Rc, -Rd, -Re, -Rh, and -F2. Among them, NG-R1 (Figure 1), ginsenoside-Rg1, -Rd, and -Rb1 have been demonstrated to be the most effective.[5] Increasing evidence shows that NG-R1 exhibits a variety of biological activities, including cardiovascular protection,[6,7] neuroprotection,[8,9] anti-diabetes,[10,11] liver protection,[12] gastrointestinal protection,[13] lung protection,[14] bone metabolism regulation,[15] renal protection,[16] and anti-cancer.[17] Very recently, the effects

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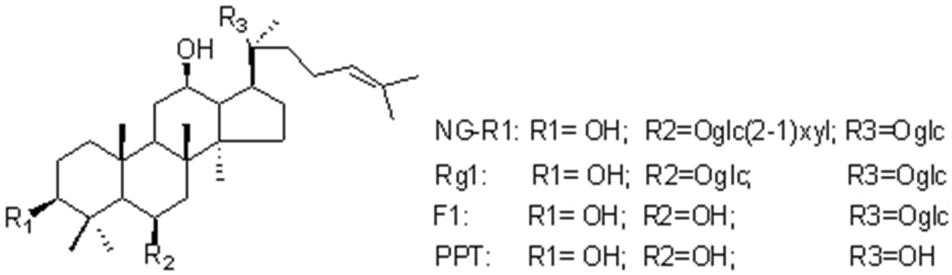

Figure 1 The chemical structure of NG-R1, Rg1, F1, and PPT.

of NG-R1 on organs ischemia/reperfusion injury have been discussed by meta-analysis, and NG-R1 has been indicated to be a novel drug candidate for ischemic diseases.[18] The versatile properties of NG-R1 have been discussed.[19] In this article, we will mainly discuss the metabolism and biological activities of NG-R1.

Metabolism of NG-R1

Generally, compounds with high concentration are responsible for the pharmacological activity of the herbs. However, the most abundant compounds in herbs are not necessary to produce the highest concentrations after administration. This might be associated with the different pharmacokinetic and distribution characteristics of each constituent in vivo. Expectedly, the concentrations of many ingredients in blood plasma are closely related to their pharmacological activity.[20–22] Pharmacokinetic research plays a crucial role in the development of drugs. The half-life of triterpenoid saponins is influenced by the number of sugar. Specifically, more sugar moieties indicate lower bioavailability and large polarity.[23] Deglycosylation of NGs has been observed as the major metabolic pathway in rats.[21] The absolute bioavailability of NG-R1, Rg1, and Rb1 in rats is 9.29%, 6.06%, and 1.18%, respectively[5] (Table 1). During the metabolism of NG-R1 (Figure 1), the metabolites ginsenosides Rg1, F1, and 20(*S*)-protopanaxatriol (PPT) are produced by intestinal bacteria on a Caco-2 monolayer model, and the stepwise hydrolysis by gut bacteria via NG-R1→Rg1→F1→PPT→dehydrogenated PPT reveals an ascending permeability.[24,25]

It has been demonstrated that NG-R1 exhibits poor membrane permeability and relatively low bioavailability and its transport primarily occurred by passive diffusion through the cell monolayer. The apparent permeability coefficient (Paff) of NG-R1 was about 1×10^{-7} cm/s, and the C_{max} of NG-R1 is significantly increased after oral administration combined with aspirin.[26] Borneol may act as a paracellular permeability enhancer to promote absorption. It has been demonstrated that the values of T_{max} and C_{max} of NG-R1 after oral administration to rats are 0.5 h and 6.45 μg/L, respectively. In borneol-included Fufang Danshen adhesive pellets (FDP) group, the T_{max} and C_{max} of NG-R1 are increased to 2.19 h and 10.13μg/L, respectively.[27] The tissue distribution study by measurement of PN saponin concentrations indicates that the overall trend of PN saponin concentration is as follows: liver > kidney > lung > spleen > heart.[28]

At least two phases of NG-R1 elimination by human intestinal bacteria in vitro are identified. NG-R1 is deglycosylated slowly at an average velocity of 0.18 μmol/h within the first 8 h (phase I). In Phase II, NG-R1 disappears 20 times faster than that in Phase I.[24] The rate of elimination of NG-R1 is reduced by co-administration with aspirin.[26] In addition, PPT formation rate is around 80% of NG-R1 elimination rate over the period of 8–48 h, and PPT is the most abundant metabolite after 12 h and reach > 70% of initial NG-R1 at 48 h.[24] In rats, NG-R1 is eliminated by excreting into the bile in 2 h and can be detected within 12 h. This indicates that the time course of NG-R1 metabolism is long in rats.[29] NG-R1 is quickly absorbed with the peak time (T_{max}) of 0.2 h in rats.[26] However, the pharmacokinetic parameters of NG-R1 in beagle dogs are showed that the value of $T_{1/2}$ is 4.833±1.609 h, T_{max} is 3.7±3.094 h, C_{max} is 70.907±38.79 ng/mL, and AUC is 404.234±131.891 ng/Lh[22] (Table 1). Another study in beagle dogs shows that the pharmacokinetic parameters of NG-R1 in the commercial capsules and the colon-specific osmotic pump capsules are different. In the commercial capsules, the value of $T_{1/2}$ is 0.63 h, T_{max} is 1.5 h, C_{max} is 23.59 ng/mL, and $AUC_{0\text{-}t}$ is 75.29 ngh/mL. In contrast, in the colon-specific cosmotic pump capsules, they are 5.84 h, 11 h, 16.63 ng/mL, and 203.25 ngh/mL, respectively.[30] Controversially, the pharmacokinetic parameters of NG-R1 in beagle dogs after a single oral dose of three-compound Danshen tablets are quite different. The value of $T_{1/2}$ is 4.82 h, T_{max} is 1.17 h, C_{max} is 1.91 ng/mL, and $AUC_{0\text{-}t}$ is 6.84 ngh/mL.[31] This difference

Table 1 The Biological Value of NG-R1 in Protection Against Diseases

Category		Models	Doses	Dosing Routes	Biological Value	Ref.
Metabolism	In vivo	Rats	300 mg/kg PN	Oral or intravenous administration	The absolute bioavailability of NG-R1 in rats is 9.29%	[5]
		Rats	31.25 mg/kg	Oral administration	Tmax is 0.2 h	[26]
		Beagle dogs	600 mg extraction	Oral administration	T1/2 is 4.833±1.609 h, Tmax is 3.7±3.094 h, Cmax is 70.907±38.79 ng/mL, and AUC is 404.234±131.891 ng/Lh	[22]
Cardiovascular protection	In vivo	Mice	25 mg/kg	Intraperitoneal administration	Improves cardiac functions, inhibits NF-κB, and activates PI3K/AKT pathway	[7]
		ApoE$^{-/-}$ mice	1–50 mg/kg	Intraperitoneal administration	Attenuates ISO-induced cardiac dysfunction, decreases atherosclerotic lesions, inhibits inflammatory cytokines accumulation	[41]
		Rabbits	25 mg/kg	Intravenous administration	Decreases the expression of TGFβ1/TAK1, caspase-3, −8, and −9	[42]
		Rat H9c2, rats	5,10,20 μM	Dissolved in perfusate	Suppresses oxidative stress and ER stress	[43]
		db/db mice	15, 30 mg/kg	Oral administration	Inhibits ROS generation and apoptosis, activates AKT and NRF2, and ameliorates fibrosis and hypertrophy	[49]
		ApoE$^{-/-}$ mice	25 mg/kg	Intraperitoneal administration	Decreases lipid deposition, inhibits oxidative stress, inflammation, fibrosis, and increases GSH and SOD levels	[50]
	In vitro	Rat H9c2	5, 10, 25 μM	Dissolved in the medium	Activates estrogen receptor α expression, inhibits inflammation and apoptosis	[40]
		Rat H9c2	20 μM	Dissolved in the medium	Increases cell viability and miR-21 expression, decreases PTEN and PI3K/AKT activity	[44]
		HUVECs	0.1, 1, 10,100 μg/mL	Dissolved in the medium	Increases TPA expression, enhances the formation of TPA/TPA complex	[46]
		HASMCs	0.1,1,10 μM	Dissolved in the medium	Decreases the expression PAI-1, ERK, and PKB	[47]
		EA.hy926	1,10,100 μM	Dissolved in the medium	Attenuates oxLDL-induced inflammation, inhibits the activity of NF-κB and MAPK	[51]
		VSMCs	0.1,1,10 μM	Dissolved in the medium	Decreases proliferation and migration, increases the activity of PI3K/AKT	[52]
Neuroprotection	In vivo	Rats	30 mg/kg PN	Intraperitoneal administration	Inhibits the expression of inflammatory cytokines, decreases edema and cell apoptosis	[56]
		Rats	100 mg/kg	Intragastric administration	Decreases infarction volume and apoptosis, increases BDNF and Bcl-2 expression	[8]
		C57BL/6 mice	10 mg/kg	Oral administration	Decreases the expression of TNFα, ICAM-1, p-JAK, caspase-12, p-STAT1, and NF-κB↓, increases the expression of GRP78, ATP, ADP, AMP, TAN, p-AMPK1/2, and GLUT3	[58]
		Rats	5, 10, 15 mg/kg	Intraperitoneal administration	Decreases the activity of PERK/CHOP, IRE1α, ERO1α, and caspase-12, increases the expression of Bcl-2	[61]
		OGD/R rats	15 mg/kg	Intraperitoneal administration	Reduces brain damage, increases PI3K/AKT/mTOR activity, decreases the expression of JNK	[63]
	In vitro	PC-12	50 μM	Dissolved in the medium	Decreases the expression of IL-6, −8, TNFα, and JNK, increases the expression of miR-132	[60]
		PC12	12.5, 25 μM	Dissolved in the medium	Inhibits ROS generation, lipid peroxidation, protein oxidation, and DNA fragmentation, increases the expression of NRF2/ARE signaling.	[65]
		HEK293	0.1,1,10 μM	Dissolved in the medium	Increases the levels of intracellular Ca^{2+}, decreases the activity of NMDA	[66]
		Neuronal cells	10 μM	Dissolved in the medium	Increases cell viability, inhibits oxidative damage, restored mitochondrial membrane potential, decreases the expression of MAPK	[67]

(*Continued*)

Table 1 (Continued).

Category		Models	Doses	Dosing Routes	Biological Value	Ref.
Antidiabetes	In vivo	Rats	5, 10, 20 mg/kg	Oral administration	Activates PI3K/AKT signaling, inhibits p-p65 activity, decreases inflammation and apoptosis	[74]
	In vitro	RSC96	50 μM	Dissolved in the medium	Decreases the expression of caspase-3, miR-503, PARP, and ROS, activates PI3K/AKT and Wnt/β-catenin pathways	[10]
		Min6	50 μM	Dissolved in the medium	Increased the expression of miR-29a, Wnt/β-catenin, and PI3K/AKT/GSK-3β	[69]
		HK-2	25μmol/L	Dissolved in the medium	Reduces mitochondrial damage, ROS generation, and apoptosis. activates NRF2-HO-1, inhibits TGFβ and collagen I expression	[70]
		Muller	20 μM	Dissolved in the medium	Inhibits oxidative stress, inflammation, and apoptosis, decreases VEGF and p62/SQSTM1 expression, increases PINK1, Parkin, and LC3-II/LC3-I ratio	[72]
Liver protection	In vivo	C57BL/6 mice	10 mg/kg	Dissolved in perfusate	Decreases the expression of E-selectin, CD18, LDH, ALT, and AST, reduces leukocyte rolling and adhesion	[12]
	In vitro	L02	10, 20, 40 μg/mL	Dissolved in the medium	Increases CYP7α expression, decreases HMG-CoAR and SREBP-2 expression	[76]
Bone metabolism	In vivo	C57BL/6 mice	10, 20 mg/kg	Intraperitoneal administration	Decreases MAPK and NF-κB activity, inhibits osteoclastogenesis and bone resorption	[15]
	In vitro	MC3T3-E1	50 μmol/L	Dissolved in the medium	Increases the expression of Runx-2, Osx, ALP, MAPK, JAK1, STAT3, and miR-23a	[78]
Gastrointestinal protection	In vivo	Rats	5, 10, 20 mg/kg	Oral administration	Increases the expression of somatostatin, gastrin, motilin, secretory IgA, GSH, Bcl-2, decreased the expression of IL-1β, IL-6, PGE2, NOS, endothelin, and Bax	[81]
		Mice	25 mg/kg	Oral administration	Decreases the activity of inflammatory cytokines, myeloperoxidase, and NF-κB	[82]
Lung protection	In vitro	WI-38	50 μM	Dissolved in the medium	Decreases the expression of IL-1β, TNFα, IL-6, NF-κB, and TAK1/JNK	[14]
		MRC-5	20, 30, 40 μM	Dissolved in the medium	Increases miR-132 expression, decreases the activity of NF-κB and JNK.	[83]
Renal protection	In vivo	Rats	20, 40 mg/kg	Intraperitoneal administration	Inhibits inflammation and apoptosis, decreases p38 MAPK and NF-κB, increased Bcl-2 expression	[16]
	In vitro	HK-2, RPTECs	30 μM	Dissolved in the medium	Increases cell viability, decreases the activity of ROS, inflammatory stress, apoptosis, and NF-κB, increases the expression of miR-26a	[84]
Anticancer	In vitro	EA.hy926	75,150,300 μM	Dissolved in the medium	Inhibits the expression of MMP-9, E-selectin, and ICAM-1	[17]
Others	In vivo	Rats	100 mg/kg	Intraperitoneal administration	Increases autologous fat graft quality and the expression of VEGF, bFGF, ANG, and HGF	[91]
	In vitro	HaCaT	60 μM	Dissolved in the medium	Decreases the expression of MyD88, p38 MAPK, NF-κB, and inhibits apoptosis	[93]

Abbreviations: NG-R1, notoginsenoside-R1; NF-κB, nuclear factor κ-B; PI3K, phosphoinositide 3-kinase; AKT (PKB), protein kinase B; ISO, isoproterenol; TGFβ1, transforming growth factor-β1; TAK1, TGF beta-activated kinase 1; ROS, reactive oxygen species; NRF2, nuclear factor erythroid-2-related factor 2; GSH, glutathione; SOD, superoxide dismutase; PTEN, gene of phosphate and tension homology deleted on chromsome ten; TPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; MAPK, mitogen-activated protein kinase; BDNF, brain-derived neurotrophic factor; ICAM-1, intercellular cell adhesion molecule-1; STAT1, signal transducer and activator of transcription; PERK, protein kinase R-like ER kinase; CHOP, C/EBP homologous protein; IRE1α, inositol-requiring enzyme 1α; ERO1α, endoplasmic reticulum oxidoreductin 1-α; NMDA, N-methyl-D-aspartic acid receptor; PINK1, PTEN induced putative kinase 1; HMG-CoAR, Hydroxymethylglutaryl-CoA reductase; SREBP-2, sterol regulatory element binding protein-2; MMP-9, matrix metalloprotein-9; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; HGF, hepatocyte growth factor; MyD88, myeloid differentiation factor 88.

might be explained by different species. However, more efforts are needed for better understanding the difference. NG-R1 has been demonstrated to show the inhibitory effects on cytochrome P450 1A2 (CYP1A2) but not on CYP2C11, CYP2D1, and CYP3A1/2, as indicated by increased caffeine C_{max} (43.13%) and $AUC_{0-\infty}$ (40.57%) and decreased CL/F (62.16%).[32]

Due to the low bioavailability of NG-R1, its application in the clinic has been greatly affected. Many strategies have been investigated for improving drug bioavailability,

such as extending the time of pharmaceutical preparations's effects on target sites, increase of the contact with the absorption membrane, change of membrane fluidity, and increase of drug penetration to the epithelial cells. Recently, it has been reported that core-shell hybrid liposomal vesicles (HLV) nanocarriers for NG-R1 dramatically influence its release profiles, inhibiting brain edema and reducing the infarct volume, accompanied by downregulation of lactate dehydrogenase (LDH), malondialdehyde (MDA), and H_2O_2 and upregulation of superoxide dismutase (SOD).[33] Consistently, poly ($_{D,L}$-lactide-*co*-glycolide acid) (PLGA) nanoparticles (NPs) carrying NG-R1 have been showed to greatly improve pharmacokinetic activity and enhance bioavailability, as showed that the value of AUC_{0-t} is 4 folds greater and C_{max} is 14.4 folds higher.[34] Another study reports that the bio-adhesive tablet prepared by chitosan as the main excipient significantly improves the bioavailability of PN saponins in beagle dogs than the normal tablet. Compared with that of the normal tablets, the relative bioavailability of bio-adhesive tablets after oral administration is 204.05% for NG-R1. Similar improvements for T_{max}, C_{max}, and AUC are observed.[35]

Drug–drug interaction may occur during the process of absorption. Borneol may enhance the bioavailability of NG-R1 by attenuating the intercellular tight junctions, as showed by increase of intestinal absorption and distribution and decrease of NG-R1 metabolism in Caco-2 cells.[36] Similarly, aspirin and salicylic acid may negatively affect the integrity and configuration of tight junction proteins and positively increase the permeability, and PN NGs increase the stability of gastrointestinal tract, absorption, and clinical efficacy in MDCK-MDR1 monolayer cells.[26] In Caco-2 cell monolayer, the AUC of NG-R1 may also be increased 2.24 folds by sodium N-[8-(2-hydrobenzoyl)amino] caprylate (SNAC), which facilitates passive transport of polar charged drugs, indicating improvement of absorption.[37] Sodium glycocholate (SGC)-mediated liposomes (@SGC-Liposomes) have been designed as a nanovesicle, which may improve the intestinal permeability and absorption of NG-R1 with a 2.68-fold higher AUC_{0-t} after oral administration in rats.[38] Interestingly, NG-R1 may increase the intestinal absorption and subsequent oral bioavailability of geniposide by inhibiting P-glycoprotein (P-gp) activity in a way similar to that of a P-gp inhibitor.[39]

Roles of NG-R1 in Cardiovascular Diseases

A comprehensive overview of the protective effects of PN saponins on cardiovascular diseases has been discussed.[6] NG-R1 has been demonstrated to improve the cardiac functions, as showed by attenuation of NF-κB signaling and subsequent reduction of inflammation and apoptosis responses (Figure 2). The possible mechanisms might be associated with the stimulatory activity of NG-R1 on estrogen receptor α and PI3K/AKT signaling pathways[7] (Figure 3). Consistently, NG-R1 protects against endotoxin-induced toxicity by upregulating the expression of estrogen receptor α, but not estrogen receptor β, leading to blockage of inflammation and apoptosis in rat H9c2 cardiomyocytes[40] (Table 1). The anti-inflammatory effects of NG-R1 contribute to the improvement of isoproterenol (ISO)-induced hypertrophied hearts of atherosclerosis-prone mice. In $ApoE^{-/-}$ mice, NG-R1 suppresses ISO-induced cardiac dysfunction, atherosclerotic lesions, and accumulation of inflammatory cytokines. These can be partially attenuated by the induction of CC chemokine receptor 2 (CCR2), which plays a critical role in recruiting pro-inflammatory monocytes to the inflamed hypertrophic heart tissues.[41]

In an ischemia-reperfusion (IR)-induced myocardial injury rabbit model, NG-R1 exhibits protective effects against IR injury by deactivating TGFβ1/TGFβ1 activated kinase 1 (TAK1) signaling pathway, as indicated by reduced expression of caspase-3, −8, and −9.[42] Consistently, NG-R1 has showed cardioprotective effects against IR injury by amelioration of oxidative stress and endoplasmic reticulum (ER) stress in H9c2 cardiomyocytes and Langendorf-perfused rat hearts, as demonstrated by decreased expression of GRP78, PERK, ATF6, IRE1, CHOP, JNK, and caspase-12[43] (Figure 2). Oxygen-glucose deprivation (OGD) produces negative effects on cardiomyocytes. In OGD-induced H9c2 cells, NG-R1 at the dose of 20 μM promotes cell viability and reduces the expression of Bax, cleaved caspase-3, and caspase-9. The possible underlying mechanism might be associated with the effects of NG-R1 on upregulation of miR-21 expression and downregulation of PTEN (a target of miR-21) expression and PI3K/AKT signaling pathway[44] (Table 1). Consistently, NG-R1 decreases myocardial infarction and injury and cardiac dysfunction induced by OGD in H9c2 cells, as showed by the improvement of cell viability, maintenance of actin skeleton and mitochondrial morphology, and attenuation of apoptosis. These might be related to the effects of NG-R1 on

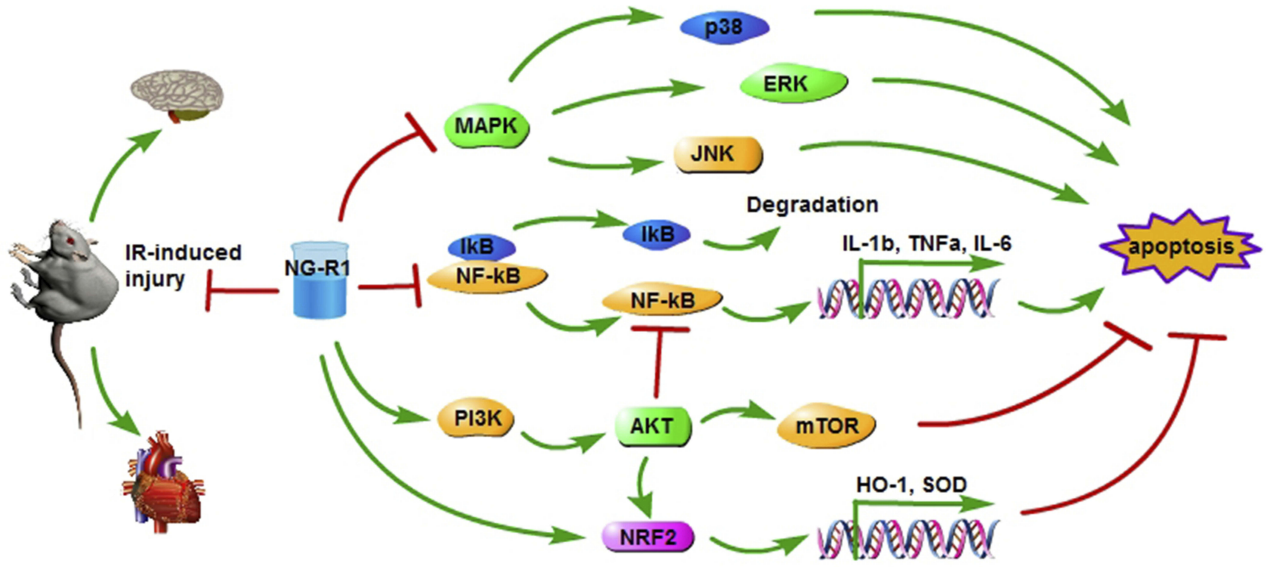

Figure 2 The protective effects of NG-R1 on IR-induced injury in heart and brain have been indicated, as indicated by downregulation of MAPK and NF-κB signaling pathways and upregulation of PI3K/AKT and NRF2 signaling pathways in rats.
Abbreviations: NG-R1, notoginsenoside-R1; NF-κB, nuclear factor κ-B; PI3K, phosphoinositide 3-kinase; AKT (PKB), protein kinase B; NRF2, nuclear factor erythroid-2-related factor 2; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; HO-1, heme oxygenase-1; SOD, superoxide dismutase.

inhibiting the ROCK signaling pathway and increasing ATP synthase δ-subunits activity.[45]

To investigate the effects of NG-R1 on the hemostatic system, the fibrinolytic parameters of cultured HUVECs have been studied. The antigen production of tissue-type plasminogen activator (TPA) and the complex formation of TPA and plasminogen activator inhibitor-1 (PAI-1) have been upregulated by NG-R1, while no effects on the expression of urokinase-type plasminogen activator and PAI-1 are found[46] (Table 1). In human aortic smooth muscle cells (HASMCs), NG-R1 dose-dependently decreases TNFα-induced PAI-1 expression by suppressing the activity of extracellular regulated protein kinases (ERK) and protein kinase B (PKB) signaling pathways.[47] Consistently, NG-R1 attenuates TNFα-induced ROS generation and ERK activation, leading to suppression of fibronectin expression and HASMC migration.[48] The protective effects of NG-R1 on advanced glycation end products (AGEs)-treated H9c2 cardiomyocytes and diabetic db/db mice have been investigated. Expectedly, NG-R1 significantly ameliorates AGEs-induced mitochondrial damage, decreases reactive oxygen species (ROS) production, and attenuates apoptosis by activating estrogen receptor α-dependent AKT and nuclear factor-erythroid 2-related factor 2 (NRF2) signaling pathways, leading to suppression of cardiac fibrosis and hypertrophy[49] (Figure 3).

Atherosclerosis, the leading cause of stroke and cardiovascular disease, is characterized by the accumulation of lipids and fibrous lesions. It has been reported that NG-R1 attenuates lipid deposition, oxidative stress, inflammation, and fibrosis and increases the levels of glutathione (GSH) and SOD in ApoE$^{-/-}$ mice. Additionally, NG-R1 pretreatment may induce downregulated expression of miR-21, miR-26a, and miR-126 and upregulated expression of miR-20a[50] (Table 1). In human endothelial EA.hy926 cells, NG-R1 exhibits protective effects against oxidized low-density lipoprotein (oxLDL)-induced inflammatory damage, as showed by suppression of NF-κB and MAPK signaling pathways and enhancement of PPARγ expression[51] (Figure 2). Neointimal hyperplasia-induced restenosis produces decreased long-term efficacy for dealing with coronary and peripheral arterial diseases. Abnormal proliferation and migration of vascular smooth muscle cells (VSMCs) is one of the main factors for the formation of neointima. It has been demonstrated that NG-R1 inhibits the proliferation and migration of VSMCs by mediating the activity of actin cytoskeleton dynamics and inhibiting the activation of the PI3K/AKT signaling pathway[52] (Figure 3).

Hypertension may contribute to the development of cardiovascular accidents. NG-R1 has been investigated for its role in vasodilation and found that it dose-dependently induces vessel relaxation by regulating NO pathway, but not cyclooxygenase (COX) pathway, in isolated aortic rings with intact endothelium.[53] Another report shows that NG-R1 may induce the expression of inducible nitric oxide synthase (iNOS)/NO signaling by downregulating the expression of LncRNA

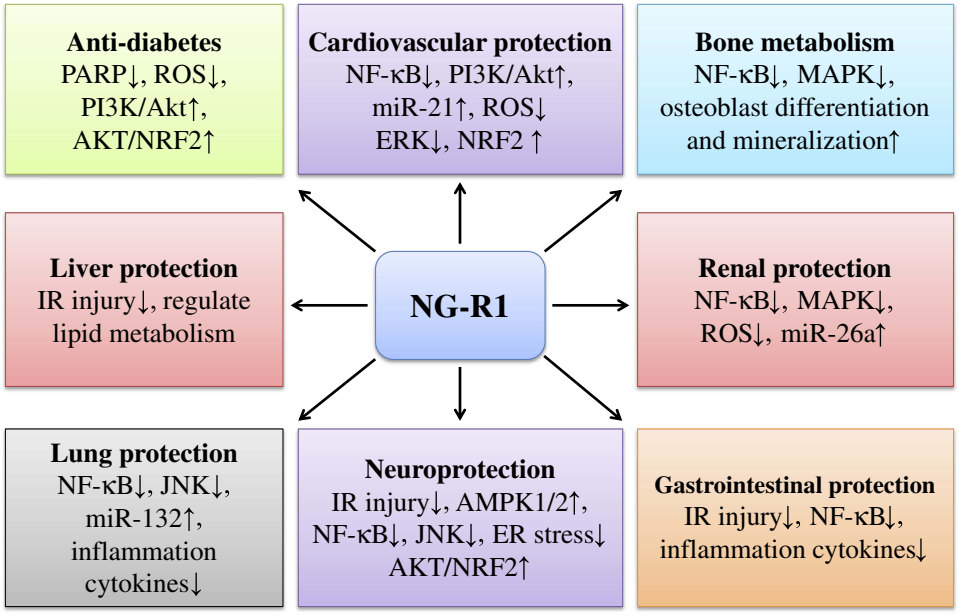

Figure 3 The various biological activities of NG-R1 in cardiovascular protection, neuroprotection, anti-diabetes, liver protection, lung protection, bone metabolism regulation, renal protection, and gastrointestinal protection have been indicated. NG-R1 has been demonstrated to downregulate NF-κB and upregulate PI3K/AKT and NRF2 signaling pathways in LPS-induced heart damage. Similar mechanisms are found in the protection of NG-R1 against IR-induced injury in the heart and brain. The anti-inflammatory activity of NG-R1 has been reported in protection against high glucose-induced diseases, promotion of osteoblast differentiation, and amelioration of renal, gastrointestinal, and lung diseases.

Abbreviations: NG-R1, notoginsenoside-R1; NF-κB, nuclear factor κ-B; PI3K, phosphoinositide 3-kinase; AKT (PKB), protein kinase B; PARP, poly ADP-ribose polymerase; NRF2, nuclear factor erythroid-2-related factor 2; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase.

AK094457 in vascular endothelial cells from spontaneously hypertensive rats.[54] Furthermore, NG-R1 may dramatically attenuate lipopolysaccharide (LPS)-induced red blood cell velocity, leukocyte adhesion, mast cell degranulation, cytokine production, and neutrophil CD11b/CD18 expression, blocking LPS-induced micro-circulatory disturbance.[55]

Roles of NG-R1 in Neuronal Diseases

PN is commonly used for treating micro-circulatory diseases in China. Recently, Nasal administration of PN saponin has been developed, and this indicates the benefiting roles of PN saponin in the brain.[9] PN exhibits protective effects against spinal cord IR-induced injury by downregulating inflammatory cytokine expression and decreasing edema and cell apoptosis[56] (Figure 2). Focal cerebral IR surgery may change intestinal flora and decrease the population of *Bifidobacterium longum*, which may induce the downregulated expression of GABA receptor in rats. These effects can be compromised by treatment with PN extracts.[57] NG-R1 may dramatically reduce the volume of cerebral infarction and hippocampal neuron apoptosis and protect against cerebral IR-induced injury by activating the expression of brain-derived neurotrophic factor (BDNF) and Bcl-2 and inhibiting the expression of Bax[8] (Table 1). It has been demonstrated NG-R1 prevents from IR-induced injury by inhibiting inflammation and ER stress-induced apoptosis, as showed by downregulating the expression of TNFα, intercellular cell adhesion molecule-1 (ICAM-1), p-JAK, caspase-12, p-STAT1, and nuclear translocation of NF-κB and upregulating the expression of glucose-regulated protein 78 (GRP78). In addition, NG-R1 also increases the contents of ATP, ADP, AMP, the total adenine nucleotides (TAN), the phosphorylation of AMPK1/2, and the expression of glucose transporter 3 (GLUT3) (Figure 2). Combination of Astragaloside IV, Rg1, Rb1, and NG-R1 may further strengthen these benefiting effects.[58,59] LPS may be neurotoxic, decrease cell viability, induce apoptosis, and increase the expression of IL-6, −8, and TNFα in PC-12 cells. NG-R1 may compromise the effects of LPS by upregulating the expression of miR-132 and suppressing the activity of the JNK signaling pathway in PC-12 cells[60] (Figure 3).

ER stress, known to be mediated by estrogen, is critical for the development of cell apoptosis during ischemia. The neuroprotective activity of NG-R1 by amelioration of ER stress has been demonstrated in neonatal rat hypoxia-ischemic

encephalopathy, as showed by decreased expression of protein kinase R-like ER kinase (PERK)/C/EBP homologous protein (CHOP), inositol-requiring enzyme 1α (IRE1α), endoplasmic reticulum oxidoreductin 1-α (ERO1α), and caspase-12 and increased expression of Bcl-2. However, the inhibitor of estrogen receptor ICI-182780 may attenuate the protective effects of NG-R1[61] (Figure 3). ER maintains the homeostasis of calcium, and imbalance of calcium may induce ER stress. Further study shows that NG-R1 may positively improve the binding of GRP78 to PERK and IRE1α, suppress PLC/IP3R signaling pathway, and decrease cell apoptosis in oxygen-glucose deprivation/reoxygenation (OGD/R) rat model.[62] Consistently, NG-R1 protects against brain damage in OGD/R rat model, upregulates the expression of PI3K/AKT/mTOR signaling pathway, and downregulates JNK signaling pathway by activating estrogen receptors[63] (Figure 2). NG-R1 has been demonstrated to prevent OGD/R-induced oxidative stress by inhibiting the generation of NADPH oxidase- and mitochondria-based superoxide, malondialdehyde, protein carbonyl, and 8-hydroxydeoxyguanosine in vivo and in vitro. These changes are associated with activation of estrogen receptor-dependent AKT/NRF2 signaling pathways by NG-R1, which significantly improves neurologic outcomes and decreases cerebral infarct volume.[64]

Oxidative stress contributes to the development of neurodegenerative diseases. NG-R1 exhibits neuroprotective effects in PC12 cells by inhibiting ROS generation, lipid peroxidation, protein oxidation, DNA fragmentation, and mitochondrial membrane depolarization induced by H_2O_2. The underlying mechanism might be associated with cross-talk between AKT and ERK1/2 signaling pathways in an estrogen receptor-dependent manner, and subsequently with upregulation of NRF2/ARE signaling and Phase II antioxidant enzyme expression[65] (Figure 2). The neurotoxicity of glutamate (Glu) has been associated with various intracellular signals in neurons. NG-R1 has been reported to significantly attenuate Glu-induced increase of intracellular Ca^{2+} concentration and ROS production and depolarization of mitochondrial membrane potential by inhibiting the activity of N-methyl-$_D$-aspartate (NMDA) receptor, leading to inhibition of cell apoptosis in HEK293 cells[66] (Table 1).

Amyloid β (Aβ) accumulation promotes the development of Alzheimer's disease (AD), which is indicated by neurodegeneration and synaptic dysfunction. Aβ may induce oxidative stress and cell death in neuronal cells. It has been showed that NG-R1 can compromise the effects of Aβ, as indicated by increased viability, reduced oxidative damage, restored mitochondrial membrane potential, and attenuated MAPK signaling pathway[67] (Table 1). The effects of NG-R1 on the neuronal excitability and synaptic and memory dysfunction under the condition of Aβ accumulation are investigated. NG-R1 may significantly enhance the membrane excitability of CA1 pyramidal neurons by inhibiting voltage-gated K^+ currents and lowering the spike threshold. Furthermore, NGR-R1 protects against impairment in long-term potentiation induced by Aβ1-42 and improves learning performance in the APP/PSI mice models.[68]

Roles of NG-R1 in Diabetes

Recently, it has been reported that NG-R1 produces protective effects against diabetes and its clinical complications. NG-R1 may prevent against high glucose-stimulated damage in RSC96 cells, as showed by downregulation of caspase-3 and miR-503, decrease of PARP cleavage and ROS generation, and activation of PI3K/AKT and Wnt/β-catenin signaling pathways[10] (Figure 3). The pro-inflammatory factor TNFα may produce damage in Min6 and rat primary islet β cells. NG-R1 has been demonstrated to ameliorate the effects of TNFα by positively regulating the expression of miR-29a, which is also mediated by Wnt/β-catenin and PI3K/AKT/GSK-3β signaling pathways, alleviating cell dysfunctions[69] (Table 1). Diabetic encephalopathy is aggravated by oxidative stress and inflammation. NG-R1 has been showed to activate AKT/NRF2 signaling pathway and inhibit the activation of NLRP3 inflammasome in db/db mice and high-glucose triggered HT22 hippocampal neurons.[11]

In AGEs-treated db/db mice, NG-R1 greatly increases the levels of serum lipid, β2-microglobulin, creatinine, and blood urea nitrogen and reduces glomerular volume and fibrosis. In vitro, NG-R1 protects HK-2 cells against AGEs-induced mitochondrial damage, ROS generation, and cell apoptosis by upregulating the NRF2-HO-1 signaling pathway and downregulating the expression of TGFβ and collagen[70] (Table 1). In high glucose-treated rat retinal capillary endothelial cells (RCECs), NG-R1 may monitor the cellular redox status and protect RCECs against damage, as showed by reduced production of ROS and nitrotyrosine, decreased activity of NADPH oxidase and PARP, and increased CAT activity.[71] Diabetic retinopathy may be managed by the involvement of NG-R1, which exhibits inhibitory effects on VEGF expression, oxidative stress, inflammation, and apoptosis in rat retinal Muller cells induced by high glucose and in the retinas of db/db mice. In addition, NG-R1 may also increase the expression

of PTEN induced putative kinase 1 (PINK1) and Parkin and the ratio of LC3-II/LC3-I and decrease the expression of p62/SQSTM1.[72]

Deficiency of α3β1 integrin induces reduced adhesion to the glomerular basement membrane, resulting in the development of diabetic kidney disease. NG-R1 has been showed to improve the expression of α3β1 integrin and increase podocyte adherence impaired by high glucose.[73] Consistently, NG-R1 ameliorates podocyte injury by activation of PI3K/AKT signaling pathway and inhibition of inflammation and apoptosis, as indicated by increased phosphorylation of PI3K and AKT and decreased phosphorylation of p65 in streptozotocin-induced rat diabetic nephropathy.[74] Furthermore, NG-R1 promotes the activity of the PI3K/AKT/mTOR signaling pathway and protects podocytes from high glucose-induced apoptosis[75] (Figure 3).

Roles of NG-R1 in Liver Diseases

Gut IR-induced injury in the liver may initiate the rate-limiting step of recruiting leukocytes to vascular endothelium, disturbing hepatic microcirculation. NG-R1 has been showed to ameliorate the effects of IR-induced injury (Figure 3), as indicated that NG-R1 attenuated the expression of E-selectin, CD18, LDH, ALT, and AST and the activity of leukocyte rolling and adhesion[12] (Table 1). Furthermore, PN and NG-R1 may regulate lipid metabolism by increasing the content of CYP7α and decreasing the levels of HMG-CoAR and SREBP-2 in steatotic L02 hepatocytes[76] (Table 1).

Roles of NG-R1 in Bone Metabolism Regulation

Recently, it has been demonstrated that PN saponins promote osteogenesis, including proliferation, differentiation, and mineralization activity in osteoblasts.[77] Accordingly, NG-R1 significantly induces bone development by inhibition of RNAKL-mediated MAPK and NF-κB signaling pathways and suppression of osteoclastogenesis and bone resorption.[15] In addition, NG-R1 may significantly induce the expression of Runx-2 and Osx as well as the activity of ALP in MC3T3-E1 cells dose-dependently.[78,79] The possible mechanism of NG-R1 in promotion on MC3T3-E1 differentiation is related to increased phosphorylation of MAPK, JAK1, and STAT3 and expression of miR-23a[78] (Table 1). Furthermore, the promoting effects of NG-R1 on osteoblast differentiation and mineralization have been demonstrated to be associated with activation of estrogen receptor signaling pathway, as showed that the transcriptional activity of phosphorylated estrogen response element-luciferase is activated and knockdown by the antagonist ICI-182780 may abolish the effects of NG-R1 on human BMSCs[80] (Figure 3).

Roles of NG-R1 in Gastrointestinal Diseases

IR-induced injury may occur in various conditions, including mesenteric artery embolism, abdominal aortic aneurysm surgery, and hemorrhagic shock. Intestinal IR-induced injury often causes high mortality clinically. NG-R1 significantly ameliorates IR-induced microvascular hyperpermeability, inflammatory cytokine generation, gap junction protein loss, and NF-κB activation[13] (Figure 3). The effects of NG-R1 on chronic atrophic gastritis in rats have been investigated, and it demonstrates that NG-R1 may increase the levels of somatostatin, gastrin, motilin, secretory IgA, GSH, and Bcl-2 and decrease IL-1β, IL-6, PGE2, NOS, endothelin, and Bax.[81] Inflammatory bowel disease (IBD) occurs in the gastrointestinal tract. It has been demonstrated that NG-R1 may significantly ameliorate the expression of inflammatory cytokines and the activity of myeloperoxidase and the NF-κB signaling pathway by acting a ligand to activate pregnane X receptor (PXR) and upregulating the expression of xenobiotic-metabolizing enzymes[82] (Table 1).

Roles of NG-R1 in Lung Diseases

Another report shows that NG-R1 exhibits protective effects against neonatal pneumonia. In LPS-treated WI-38 cells, NG-R1 decreases the expression of IL-1β, TNFα, and IL-6, decreases cell viability, and promotes apoptosis. These might be related to enhanced expression of miR-181a (targeting TLR4) and decreased activity of NF-κB and TAK1/JNK signaling pathways[14] (Figure 3). In MRC-5 cells, NG-R1 protects against LPS-induced cell proliferation inhibition, apoptosis, and increased production of inflammatory cytokines by increasing the expression of miR-132 and inactivating NF-κB and JNK signaling pathways[83] (Table 1).

Roles of NG-R1 in Renal Diseases

IR-induced injury, a major cause of renal failure, is associated with activation of inflammatory responses and apoptosis. NG-R1 has been reported to attenuate IR-induced renal dysfunction by suppressing inflammatory responses and inhibiting apoptosis in rats, as showed by downregulated

the expression of p38 MAPK and NF-κB signaling pathway and upregulated the expression of Bcl-2[16] (Figure 3). In human renal proximal tubular epithelial cell lines HK-2 and RPTECs, NG-R1 protects against LPS-induced viability reduction, ROS generation, inflammatory stress, and apoptosis by enhancing the expression of miR-26a and inactivating NF-κB signaling pathway[84] (Table 1).

Roles of NG-R1 in Cancer

PN saponins can maintain immune homeostasis and inhibit the proliferative activity of cancer cells. The anti-cancer potentials of PN saponins have been reviewed by Wang et al (2016).[85] PN saponins have been reported to reduce the survival of Lewis lung carcinoma (LLC) cells and decreasetumor growth. The bioinformatics analysis of gene expression profiles indicates that PN saponins may decrease the expression of genes responsible for tumorigenesis and progression, including Hgf, Met, Notch3, Scd1, Epas1, Col1a1, Raf1, Braf1, and CDK6, and factors responsible for tumor suppression, including p27 and PTEN.[86] The fermentation medium containing 10 g of raw PN powder and 90 mL of water has been demonstrated to counteract the proliferation against hepatoma Hep3B cells. However, the production of NG-R1 has been found to be decreased during fermentation, and ginsenosides Rh1 and Rg3 increase.[87] Hepatocellular carcinoma (HCC) is one of the most common malignancies with high morbidity and mortality. NG-R1 may inhibit cell viability, increase LDH release, suppress invasion, and enhance caspase-3/-7 activity in HCC cells by inactivation of PI3K/AKT and downregulation of miR-21.[88] Consistently, assays of notoginseng extracts and saponins in regulating SW480 cell apoptosis show that not NG-R1 but ginsenosides Rb1, Rb3, and Rg1 are the main bioactive compounds responsible for the suppression of human colorectal cancer cells.[89]

The regulatory activity of NG-R1 on the migration and invasion of cancer cells has been investigated. It indicates that NG-R1 may significantly reduce the expression of metalloproteinase (MMP)-9, E-selectin, ICAM-1 in HCT-116 cells and increase the capacity of the trans-epithelial electrical resistance in EA.hy926 endothelial cell monolayer[17] (Table 1). Angiogenesis is a morphogenetic process of neovessel growth, which is tightly controlled by angiogenic factors and inhibitors. The pro-angiogenic action of NG-R1 has been involved in the proliferation of HUVECs, as indicated by the increased number of cross-membrane, enhanced tube formation by activation of VEGF/KDR signaling and upregulating the activity of PI3K/AKT signaling. In addition, NG-R1 triggers pro-angiogenic activity in chemically induced blood vessel loss model in zebrafish.[90]

Other Biological Activities of NG-R1

Autologous fat tissue transplantation has been popularly used in surgery. However, the accompanied responses of inflammation may negatively aggravate graft volume maintenance and survival rate. NG-R1 has been demonstrated to improve the quality of autologous fat graft and survival rate by increasing the expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin (ANG), and hepatocyte growth factor (HGF)[91] (Table 1).

Due to side effects and antibody responses, many adjuvants are limited for their application in vaccines. NG-R1 has been found to exhibit significant adjuvant effects on immune responses and specific antibody against ovalbumin in mice, accompanied by a slight hemolytic activity. Structural activity relationship study shows that the type of sugar at the terminal of the C-6 chain of PPT may regulate the hemolytic activity, adjuvant potentials, and immune responses.[92]

Burn injury shows dramatically negative effects on patients by triggering inflammation at least. NG-R1 has been demonstrated to counteract inflammatory injury in LPS-treated human keratinocyte HaCaT cells, as indicated by downregulation of MyD88 expression, inactivation of p38 MAPK and NF-κB signaling pathways, and suppression of cell apoptosis[93] (Table 1).

Clinical Perspectives

Returning back to nature becomes a trend throughout the world, and it dramatically poses great enthusiasm in the exploration of traditional medicines for the management of complex diseases. However, traditional medicines generally contain complex mixtures of different chemical constituents, and this might raise a serious issue with quality uncertainty. Nowadays, characterization and quantification of the substances in traditional medicines are not of difficulty. Individual chemical markers may ensure the quality control of phytotherapeutic agents. NG-R1 has been identified as one of the bioactive chemical markers of Xuesaitong Injection (XST),[94] which is made of the saponins from *P. notoginseng* and has been extensively employed in clinic for managing cardiovascular and cerebrovascular diseases in China.[95] Naodesheng (NDS) is the TCM prescription widely used for clinic management of cerebral infarction

in China. NG-R1 is one of the bioactive compounds in NDS, which has been demonstrated to improve neurobehavioral activity, decrease the cerebral infarct area, and attenuate pathological features in middle cerebral artery occlusion (MCAO) rat models. In addition, NDS also exhibits significant antioxidative activity, as showed by a decrease of LDH and MDA production, increase of SOD generation in plasma, and enhancement of brain levels of leucine, isoleucine, choline, and myo-inositol.[96] NG-R1 is also the main bioactive and circulating compound of XueShuanTong, which has been predicted to show high potentials for drug interactions mediated by organic anion-transporting polypeptide (OATP)1B.[97]

Conventional pharmacotherapy has been implicated in the treatment of complex diseases, and the use of herbal medicinal products or botanical dietary supplements is prevalent in China. NG-R1 is one of the main bioactive compounds from a traditional Chinese medicine ShenMai Injection (SMI). In the excretion study, high concentration of prototype of NG-R1 has been observed in the rat kidney, and NG-R1 has been showed to be exclusively detected in rat urine, but not in feces.[98] QiShenYiQi (QSYQ) pill, a Chinese medicine, contains NG-R1 as the bioactive ingredient and contributes to anti-hypertrophic effects in the management of cardiac hypertrophy. It has been verified that each ingredient such as NG-R1 exhibits similar effects as QSYQ but to a lesser extent in rats. The possible mechanism might be associated with the enhancement of energy metabolism and amelioration of oxidative stress.[99] Further study shows that QSYQ may decrease IR-induced infarct size, ameliorate myocardial fibrosis, and inhibit monocyte infiltration and macrophage polarization towards M2 by downregulating the expression of TGFβ and TGFβRII in rats.[100] The clinically therapeutic effects of NG-R1 have been observed, the chemical basis for understanding the underlying mechanisms responsible for NG-R1-drug interactions is still limited.

Combinational, rather than single, chemotherapy strategy is often a more effective for the management of complex diseases. Botanical products, either as herbal medicines or as dietary supplements, can result in clinically important drug interactions. Increasing understanding of botanical products-drug interactions may ensure safe co-administration. Gap junctions (GJs), the specialized cell-cell junctions, have been linked to homeostasis maintenance, morphogenesis, cell differentiation, and growth control. Enhancement of GJs functions increases the cytotoxic activity of cisplatin, and both NG-R1 and Rg1 have been identified as the active compounds in PN for enhancing cisplatin-induced cytotoxic activity by inhibiting Cx32/Cx26 degradation and/or modulating translation in transfected HeLa cells. Unfortunately, Rb1 produces not any effects.[101] A monoclonal antibody has been developed by immunization of NG-R1-bovine albumin conjugates with BALB/c male mice. Interestingly, this monoclonal antibody exclusively recognizes free NG-R1 during the indirect competitive ELISA, establishing a reliable system for various applications in pharmaceutical and food fields.[102]

Conclusion

Herbal medicines with multi-compounds have been considered to exhibit pharmaceutical effects on multi-targets in a co-operative manner. The integrated pharmaceutical activity produced by different compounds with the same mother nuclear structure may be more reasonable than that of adding up all compounds with different groups. In addition, the components of herb and their concentrations in the blood plasma are statistically associated with the pharmacological activity of the herb. Simultaneous, rather than solitary, determination of these compounds in the blood plasma may provide a holistic understanding of pharmacokinetic characteristics. Although the sugar moiety increases the polarity, it may decrease the bioavailability of NGs. However, the underlying mechanisms of the chemical and spatial structures of sugar moiety on regulating the biological activity of NGs are still unclear. NG-R1 may be degraded to be ginsenoside Rg1, F1, and PPT, which exhibit dramatic biological effects. Whether these metabolites are involved in the regulatory activity of NG-R1 in the management of human diseases is still unknown. Thus, the reported activity of NG-R1, particularly in vivo, might be derived from the parent compound or the metabolites, alone or combination. In addition, the specific targets of NG-R1 are not identified. The limitation of research on NG-R1 in this article is that all data are from Asia, and this might be explained by the situation that the herbs are mainly found and used in Asia. The human-benefiting functions of PN saponins and NG-R1 are versatile, and they should be known worldwide. More efforts are still needed.

Collectively, we update the biological activities of NG-R1 in cardiovascular protection, neuro-protection, anti-diabetes, liver protection, gastrointestinal protection, lung protection, bone metabolism regulation, renal protection, and anti-cancer.

Data Sharing Statement

The experimental data used to support the findings of this study are included within the article.

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Author Contributions

Shouying Du provided the idea of this paper and resolved the problems in research process. Hai Liu and Jianqiong Yang contributed equally to this manuscript for collecting materials and writing the paper, Wanqing Yang, Shaonan Hu, Yali Wu helped with literature screening and paper writing. Bo Zhao, Haiyan Hu organized the information and edited the article pictures. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflict of interests.

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