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# From raw to steamed *Panax notoginseng*: A systematic review of saponin transformations and their functional consequences

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**Abstract**: **Background**: Notoginseng Radix et Rhizoma (NRR), derived from *Panax notoginseng*, serves as both a functional food and a key medicinal material in traditional Chinese medicine. Its bioactivity is largely attributed to saponins, which undergo significant chemical transformations during processing (e.g., steaming), altering its pharmacological profile. **Objective**: This review aims to systematically consolidate experimentally verified metabolites from authenticated NRR, elucidate the chemical transformations induced by processing and clarify the resulting shift in pharmacological effects, thereby providing a scientific basis for its targeted application. **Method**: A comprehensive literature search was conducted using CNKI, Wanfang Data, National Science and Technology Library, the Pharmacopoeia of the People's Republic of China, PubMed and Web of Science. Keywords included *Panax notoginseng* (Burk.) F. H. Chen; Pharmacological activities; Phytochemisity; Saponin transformation; Traditional processing; Traditional Chinese medicine. Data were also sourced from classic texts, dissertations and unpublished materials. **Results**: Processing, particularly steaming, converts high-polarity saponins into less polar ones via deglycosylation, dehydration and hydroxylation. This chemical shift underlies a functional transition: raw NRR primarily promotes blood activation and stasis dispersion, while processed NRR exhibits enhanced blood-nourishing, antioxidant, anti-inflammatory and immunomodulatory activities. **Conclusion**: The integration of ethnopharmacological knowledge with modern scientific perspectives clarifies the metabolite pathways and mechanistic basis for processing-induced changes in NRR. This review provides a reliable foundation for the precise use and further development of NRR in functional foods, nutraceuticals and evidence-based therapy.

**Keywords**: *Panax notoginseng* (Burk.) F. H. Chen; Pharmacological activities; Phytochemisity; Saponin transformation; Traditional processing; Traditional Chinese medicine

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## INTRODUCTION

Notoginseng Radix et Rhizoma (NRR) is a highly esteemed botanical in traditional Chinese medicine (TCM), derived from the dried roots and rhizomes of *Panax notoginseng* (Burk.) F. H. Chen. Known traditionally as Sanqi or Tianqi, it has been revered as "gold that cannot be exchanged" and a "miraculous herb of the southern country." According to TCM theory, NRR possesses a warm nature, a sweet and slightly bitter taste and affinity with the liver and stomach meridians. It is recognized for its abilities to disperse blood stasis, stop bleeding, reduce swelling and alleviate pain (Pharmacopoeia of the People's Republic of China, 2020). With a documented history spanning over 500 years, NRR has been widely used to treat hemoptysis, hematemesis, epistaxis, hematochezia, metrorrhagia, traumatic bleeding and pain from injuries.

NRR holds a distinctive position in TCM due to its unique ability to "stop bleeding without retaining blood stasis and dissolve stasis without damaging healthy tissues." Its application follows a well-established principle: used raw, it primarily stops bleeding, disperses blood stasis and alleviates pain in traumatic injuries; after processing via steaming, frying, or roasting—methods analogous to Chinese culinary techniques—it acquires enhanced tonic properties, such as promoting tissue regeneration, nourishing blood, generating fluids and supplementing *Qi* (Zhu, 2021). Like many traditional herbs, NRR serves a dual role, functioning not only as a therapeutic agent but also as a dietary supplement integrated into daily nutrition (Wang *et al*., 2025). This practice is particularly prevalent in its native Wenshan, Yunnan, where locals regularly incorporate NRR into various foods. Its status as a health food was officially endorsed in 2002 when the Chinese Ministry of Health included NRR in the "Catalog of Substances That Can Be Used in Health Foods."

Although the phytochemistry and pharmacology of NRR have been extensively reviewed, a critical research gap

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remains in systematically delineating how traditional processing drives the transformation of its key compounds—particularly saponins—and how these chemical changes precisely account for its altered pharmacological profiles. The TCM axiom that raw NRR "dispels" while processed NRR "tonifies" is well-recognized; however, a comprehensive understanding of the chemical underpinnings and resultant mechanistic shifts behind this dichotomy is still evolving. Previous reviews have often treated processing as a peripheral topic rather than the central theme. Therefore, the compelling rationale for this review is to provide a focused analysis bridging traditional processing practices with modern scientific evidence. We specifically center on the impact of processing—especially steaming—on the conversion of primary ginsenosides (e.g., Rb1, Rg1) into rare ginsenosides (e.g., Rk1, Rg5, Rg3) and the consequential efficacy enhancement in areas such as hematopoiesis, immunomodulation and neuroprotection. This focus addresses the pressing need to elucidate the "processing-compound-pharmacology" axis, which is paramount for rational clinical application, quality control and future development of NRR-based products.

Given that NRR exhibits a wide spectrum of pharmacological effects and that processing critically modulates its compound composition and bioactivity, this review comprehensively explores the historical documentation, traditional uses, phytochemistry, pharmacological effects and processing methods of NRR, with particular emphasis on the impact of processing. By clarifying the historical evolution and scientific basis of NRR processing, we aim to provide a robust reference for future pharmacological research and the clinical application of both raw and processed NRR.

## MATERIALS AND METHODS

### *Literature search strategy*

A systematic literature search was conducted to identify relevant studies on Notoginseng Radix et Rhizoma (NRR) published between January 2005 and April 2025. The search encompassed multiple electronic databases: China National Knowledge Infrastructure (CNKI), Wanfang Data, National Science and Technology Library (NSTL), PubMed and Web of Science. Official monographs, including the "Pharmacopoeia of the People's Republic of China" were also consulted. Search terms combined Medical Subject Headings (MeSH) and keywords: "Notoginseng Radix et Rhizoma", "*Panax notoginseng*", "Sanqi", "processing", "steaming", "pharmacology", "saponins" and "ginsenosides".

### *Inclusion and exclusion criteria*

*Inclusion criteria*: Studies were included if they primarily investigated: (1) the impact of processing (e.g., steaming, roasting) on NRR's chemical constituents; or (2) pharmacological activities of raw or processed NRR. *Exclusion criteria*: non-primary research (e.g., reviews without original data), studies focusing solely on other parts of *Panax notoginseng* without involving roots/rhizomes, or unavailability in English or Chinese.

### *Literature screening and data extraction*

Retrieved records were initially screened by title and abstract assessment. Potentially eligible articles underwent full-text review against inclusion criteria. Key data—including processing methods, identified compounds, tested extracts/compounds, pharmacological models, main findings and mechanisms of action—were systematically extracted from selected studies.

## RESULTS

### *The traditional uses*

Ancient physicians progressively documented and understood the medicinal properties of NRR through clinical practice. Initially, NRR was recognized for its ability to reduce swelling and alleviate pain in treating surgical injuries. Over time, its documented applications expanded to include hemostatic, blood-activating and blood-tonifying effects for managing various hematological disorders. Additionally, it was found to possess detoxifying and tissue-regenerating properties.

The earliest medicinal record of NRR appears in the "Compendium of Materia Medica", which notably did not mention its blood-tonifying effects. This omission influenced subsequent texts to emphasize primarily its hemostatic, blood-dispersing and pain-alleviating properties. A significant advancement came with the "Dian Nan Materia Medica", which first proposed the crucial distinction that raw NRR breaks up blood stasis, while roasted NRR tonifies blood, highlighting how processing fundamentally alters its therapeutic properties (Law and Au, 2025). This perspective was later supported by the "Supplement to the Compendium of Materia Medica", which authoritatively stated that "ginseng is the supreme herb for tonifying *Qi* and Sanqi is the supreme herb for tonifying blood."

### *Phytochemistry*

TCM has long served as a valuable source of natural compounds, with remarkable progress being made in recent years in the discovery and investigation of these natural products (Gu *et al*., 2022; Yan *et al.*, 2025; Ma *et al.*, 2025). To date, more than 170 compounds have been identified in NRR, with new compounds continually being discovered (as shown in Table 1). Modern research confirms that this complex chemical profile underpins NRR's therapeutic efficacy. The constituents are primarily categorized into *P. notoginseng* saponins (PNS) and non-saponin compounds. The saponins mainly include ginsenosides and notoginsenosides, while non-saponin compounds comprise flavonoids, cyclic peptides, polyacetylenes, polysaccharides, sterols and amino acids (Tao *et al*., 2024).

**Table 1**: The compounds in NRR

| No. | Compounds | Resource | References |
|---|---|---|---|
| *Saponins* | | | |
| 1 | Ginsenoside Ra3 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 2 | Ginsenoside Rb1 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 3 | Ginsenoside Rb2 | Ro; Rh | (Yu *et al*., 2013; Shi *et al*., 2022) |
| 4 | Ginsenoside Rb3 | Ro | (Yoshikawa *et al*., 2001) |
| 5 | Ginsenoside Rd | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 6 | Ginsenoside Rg3 | Ro; Rh | (Yu *et al*., 2013; Wei *et al*., 2024) |
| 7 | Ginsenoside F2 | Ro; Rh | (Yu *et al*., 2013; Sakah *et al*., 2013) |
| 8 | Malonyl-ginsenoside Rb1 | Ro | (Wan *et al*., 2010) |
| 9 | Notoginsenoside D | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 10 | Notoginsenoside Fa | Ro; Rh | |
| 11 | Notoginsenoside R4 | Ro; Rh | |
| 12 | Notoginsenoside S | Rh | (Zhang *et al*.,2013) |
| 13* | Notoginsenoside ST-4 | Ro | (Cui *et al*., 2008) |
| 14 | Notoginsenoside T | Ro; Rh | (Wan *et al*., 2010;Zhang *et al*.,2013) |
| 15 | Gypenoside XVII | Ro; Rh | (Yu *et al*., 2013;Sakah *et al*., 2013) |
| 16 | Notoginsenoside L | Ro | (Shi *et al*., 2022) |
| 17 | Quinquenoside R1 | Ro | (Wan *et al*., 2010) |
| 18 | Notoginsenoside K | Ro | (Shi *et al*., 2022) |
| 19 | Ginsenoside Rs3 | Ro | (Pei *et al*., 2011) |
| 20 | Chikusetsusaponin L5 | Ro | (Wan *et al*., 2010) |
| 21 | Ginsenoside F1 | Ro; Rh | (Qiu *et al*., 2014) |
| 22 | Ginsenoside Re | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 23 | Ginsenoside Rf | Ro; Rh | (Zhang *et al*.,2013; Han *et al*., 2014) |
| 24 | Ginsenoside Rg1 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 25 | 20(S)-Ginsenoside Rg2 | Ro; Rh | |
| 26 | Ginsenoside Rh1 | Ro; Rh | (Yu *et al*., 2013;Wan *et al*., 2012) |
| 27 | 20-O-glucoginsenoside Rf | Ro; Rh | (Zhang *et al*.,2013; Peng *et al*., 2018) |
| 28 | Koryoginsenoside R1 | Ro; Rh | (Zhang *et al*.,2013; Han *et al*., 2014) |
| 29 | Notoginsenoside M | Ro | (Shi *et al*., 2022) |
| 30 | Notoginsenoside N | Ro | |
| 31 | Notoginsenoside R1 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 32 | Notoginsenoside R2 | Ro; Rh | |
| 33 | Notoginsenoside R3 | Ro | (Wang *et al*.,2012) |
| 34 | Notoginsenoside R6 | Ro | |
| 35 | Notoginsenoside RW-1 | Rh | (Zhang *et al*.,2013) |
| 36 | Notoginsenoside U | Ro | (Sun *et al*., 2006) |
| 37* | Yesanchinoside D | Ro | (Liao *et al*., 2008) |
| 38 | Pseudoginsenoside RT3 | Ro | (Han *et al*., 2014) |
| 39 | 20(S)-6-O-[β-D-xylopyranosyl-(1→2)-β-D-xylopyranosyl] dammar-24-ene-3β,6α,12β,20-tetrol | Ro | (Qiu *et al*., 2014) |
| 40* | 20(S)-ProtopanaxtRool | Ro | (Liao *et al*., 2008) |
| 41 | 20(S)-20-O-[β-D-xylopyranosyl-(1→6-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl] dammar-24-ene-3β,6α,12β,20-tetrol | Ro | (Qiu *et al*., 2014) |
| 42 | 6'-O-Acetyl ginsenoside Rh1 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 43 | 20(S)-protopanaxatRool-20-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside | Ro | (Qiu *et al*., 2014) |

*Continue Table. 1……*

| No. | Compounds | Resource | References |
|---|---|---|---|
| 44 | 20(S)-sanchirhinosides A1 | Ro | |
| 45 | 20(S)-sanchirhinosides A2 | Ro | |
| 46 | 20(S)-sanchirhinosides A3 | Ro | (Zhang *et al*.,2013) |
| 47 | 20(S)-sanchirhinosides A4 | Ro | |
| 48 | 20(S)-sanchirhinosides A5 | Ro | |
| 49 | 20(S)-sanchirhinosides A6 | Ro | |
| 50 | 6-O-(β-D-glucopyranosyl)-20-O-(β-D-xylopyranosyl)-3β,6α,12β,20(S)-tetrahydroxydammar-24-ene | Ro | (Qiu *et al*., 2014) |
| 51 | Notoginsenoside A | Ro | |
| 52 | Notoginsenoside B | Ro | (Peng *et al*., 2018) |
| 53 | Notoginsenoside C | Ro | |
| 54 | Notoginsenoside E | Ro; Rh | |
| 55 | Ginsenoside II | Rh | (Song *et al*., 2007) |
| 56 | Ginsenoside V | Ro | (Sakah *et al*., 2013) |
| 57 | Notoginsenoside H | Ro | (Peng *et al*., 2018) |
| 58 | Notoginsenoside J | Ro | |
| 59 | Notoginsenoside RW-2 | Rh | (Zhang *et al*.,2013) |
| 60 | Vinaginsenoside R15 | Ro | (Liu *et al*., 2011) |
| 61 | Notopanaxoside A | Ro | (Komakine *et al*., 2006) |
| 62 | Vinaginsenoside R22 | Ro | (Han *et al*., 2014) |
| 63 | Notoginsenoside R8 | Ro | (Tung and Hai, 2016) |
| 64* | Ginsenoside Rg5 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013;Liao *et al*., 2008 ) |
| 65 | Ginsenoside Rh4 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 66* | Ginsenoside Rk1 | Ro; Rh | (Yu *et al*., 2013; Liao *et al*., 2008) |
| 67 | Ginsenoside Rk3 | Ro; Rh | (Yu *et al*., 2013; Han *et al*., 2014) |
| 68 | Notoginsenoside R7 | Ro | (Wang *et al*., 2023) |
| 69* | Notoginsenoside ST-1 | Ro | |
| 70* | Notoginsenoside ST-2 | Ro | (Liao *et al*., 2008) |
| 71* | Notoginsenoside ST-4 | Ro | |
| 72* | Notoginsenoside ST-5 | Ro | |
| 73 | Notoginsenoside T5 | Rh | (Zhang *et al*.,2013) |
| 74 | Sanchinoside B1 | Ro | (Liao *et al*., 2008) |
| 75 | 20(S)-Panaxadiol | Rh | (Zhou *et al*., 2007) |
| 76* | 3β,6α,12β-tRohydroxydammar-20(21),24-diene | Ro | (Liao *et al*., 2008) |
| 77 | Vinaginsenoside R4 | Ro | (Qiu *et al*., 2014) |
| 78 | Pseudoginsenoside F11 | Ro | (Wang *et al*., 2014) |
| 79 | 3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside-12β,25-dihydroxydammar-(E)20(22)-ene | Ro | (Liu *et al*., 2011) |
| 80 | Ginsenoside F4 | Ro | (Pei *et al*., 2011) |
| 81 | Notoginsenoside Spt1 | Ro | |
| 82 | 20(S)-panaxatriol | Rh | (Zhou *et al*., 2007) |
| 83 | Sanchirhinoside D | Ro | (Sakah *et al*., 2013) |
| 84 | Pseudoginsenoside Rt5 | Ro | |
| 85 | 3β,12β-dihydroxydammar-(E)-20(22),24-diene-6-O-β-D-xylopyranosyl-(1→2)-β-D-glucopyranoside | Ro | (Han *et al*., 2014) |
| 86 | Notoginsenoside R10 | Ro | (Li *et al*., 2001a) |
| 87 | 20(R)-Ginsenoside Rg3 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 88* | 6″-O-acetylginsenoside Rg3 | Ro | (Liao *et al*., 2008) |
| 89 | 20(R)-protopanaxadiol | Rh | (Zhang *et al*.,2013) |
| 90 | 3β,6α-20(S)-6,20-bis(β-D-glucopyranosyloxy)-3-hydroxy dammar-24-en-12-one | Ro | (Sakah *et al*., 2013) |
| 91 | Notoginsenoside I | Ro | (Peng *et al*., 2018) |

*Continue Table. 1……*

| No. | Compounds | Resource | References |
|---|---|---|---|
| 92 | Vinaginsenoside R3 | Ro | (Liu *et al*., 2011) |
| 93 | 5,6-Didehydroginsenoside Rd | Ro | (Wan *et al*., 2010) |
| 94 | Notoginsenoside G | Ro | (Peng *et al*., 2018) |
| 95 | 5,6-Didehydroginsenoside Rb1 | Ro | (Wan *et al*., 2010) |
| 96* | 20(R)-Protopanaxtriol | Ro; Rh | (Zhang *et al*.,2013; Liao *et al*., 2008) |
| 97 | 20(R)-Ginsenoside Rh1 | Ro; Rh | (Qiu *et al*., 2014;Yu *et al*., 2013) |
| 98 | Ginsenoside U | Ro | (Han *et al*., 2014) |
| 99* | 25-Hydroxy-20(R)-ginsenoside Rh1 | Ro | (Liao *et al*., 2008) |
| 100 | Notoginsenoside R9 | Ro | (Tung and Hai, 2016) |
| 101 | Sanchirhinoside B | Ro | (Zhang *et al*.,2013) |
| 102 | 6-O-β-D-glucopyranosyl-20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol-3-one | Ro | (Fu *et al*., 2013) |
| 103 | Daucosterol | Ro; Rh | (Komakine *et al*., 2006) |
| 104 | Notoginsenoside ST-6 | Ro | |
| 105 | Notoginsenoside ST-7 | Ro | |
| 106 | Notoginsenoside ST-8 | Ro | |
| 107 | Notoginsenoside ST-9 | Ro | |
| 108 | Notoginsenoside ST-10 | Ro | (Gu *et al*., 2015) |
| 109 | Notoginsenoside ST-11 | Ro | |
| 110 | Notoginsenoside ST-12 | Ro | |
| 111 | Notoginsenoside ST-13 | Ro | |
| 112 | Notoginsenoside ST-14 | Ro | |
| 113 | Notoginsenoside SP20 | Ro | (Gu *et al*., 2018) |
| 114 | Notoginsenoside SP21 | Ro | |
| 115 | Elatoside C | Ro | (Cao *et al*., 2019) |
| *Flavonoids* | | | |
| 116 | Quercetin3-O-β-D-xylopyranosyl-β-D-galactopyranoside | Ro | (Choi *et al*., 2010) |
| *Cyclopeptides* | | | |
| 117 | Cyclo-(Leu-Thr) | Ro | |
| 118 | Cyclo-(Leu-Ile) | Ro | |
| 119 | Cyclo-(Leu-Val) | Ro | |
| 120 | Cyclo-(Ile-Val) | Ro | |
| 121 | Cyclo-(Leu-Ser) | Ro | |
| 122 | Cyclo-(Leu-Tyr） | Ro | |
| 123 | Cyclo-(Val-Pro) | Ro | (Wang *et al*., 2004) |
| 124 | Cyclo-(Ala-Pro) | Ro | |
| 125 | Cyclo-(Phe-Tyr) | Ro | |
| 126 | Cyclo-(Phe-Ala) | Ro | |
| 127 | Cyclo-(Phe-Val) | Ro | |
| 128 | Cyclo-(Leu-Ala) | Ro | |
| 129 | Cyclo-(Ile-Ala) | Ro | |
| 130 | Cyclo-(Val-Ala) | Ro | |
| *Po1yacetylenes* | | | |
| 131 | Falcarindiol | Rh | (Liu *et al*., 2004) |
| 132 | Panaxytriol | Ro; Rh | (Komakine *et al*., 2006; Liu *et al*., 2004) |
| 133 | Panaxynol | Ro | (Komakine *et al*., 2006) |
| 134 | Panaxydol | Ro; Rh | (Komakine *et al*., 2006; Zhou *et al*., 2007) |
| 135 | PQ-2 | Ro | |
| 136 | Panaxydol chlorohydRone | Ro | (Komakine *et al*., 2006) |
| 137 | (8E)-1,8-hepatadecadiene-4,6-diyene-3,10-diol | Ro | |
| 138 | Ginsenoyne E | Ro | |

*Continue Table. 1……*

| No. | Compounds | Resource | References |
|---|---|---|---|
| 139 | Notoginsenic acid β-sophoroside | Ro | (Yoshikawa *et al*., 2001) |
| 140 | PQ-1 | Ro | |
| *Polysaccharides* | | | |
| 141 | PF3111 | Ro | |
| 142 | PF3112 | Ro | (Wang *et al*., 2016) |
| 143 | PBGA11 | Ro | |
| 144 | PBGA12 | Ro | |
| 145 | PNPSI | Ro | (Sheng *et al*., 2007) |
| 146 | PNPSIIb | Ro | |
| 147 | Sanchinan A | Ro | (Ma *et al*., 2016) |
| 148 | MRP5 | Ro | (Feng *et al*., 2019) |
| 149 | MRP5A | Ro | |
| 150 | PNPB1 | Ro | (Jiang *et al*., 2023) |
| *Amino acids* | | | |
| 151 | Dencichine | Ro | (Xie *et al*., 2007) |
| *Others* | | | |
| 152 | 3-Hydroxy-4-methoxybenzoic acid | Ro | (Komakine *et al*., 2006) |
| 153 | 2-(1′,2′,3′,4′-Tetrahydroxybutyl)-6-(2",3",4"-tRohydroxybutyl)-pyrazine | Ro | (Li *et al*., 2001b) |
| 154 | Cinnamic acid | Ro | |
| 155 | 1β,6α-dihydroxyeudesm-4(15)ene | Ro | (Komakine *et al*., 2006) |
| 156 | 2-Methoxy-1H-pyrrole | Ro | |
| 157 | 5-Hydroxymethyl-2-furancarboxaldehyde | Ro | (Liao *et al*., 2008) |
| 158 | Aromadendrane-7α ,11α -diol | Ro | |
| 159 | Aromadendrane-7β,11α -diol | Ro | (Komakine *et al*., 2006) |
| 160 | Alloaromadendrane-7α,11α-diol | Ro | |
| 161 | Spathulenol | Ro | |
| 162 | (Z,Z)-9,12-octadecadienoic acid 2-hydroxy-1, 3-propanedinyl ester | Ro | (Liao *et al*., 2008) |
| 163 | Panaphthaloside | Ro | |
| 164 | Panapyranone | Ro | |
| 165 | Isodauc-6-ene-10β,14-diol | Ro | (Qiu *et al*., 2024) |
| 166 | Nitidumine D | Ro | |
| 167 | Nitidumine C | Ro | |
| 168 | 3E-5-methoxy-6-hydroxy-6-methyl-3-hepten-2-one | Ro | (Qiu *et al*., 2024) |
| 169 | Succinic acid methyl ester | Ro | |
| 170 | Succinic acid monobuthyl ester | Ro | (Komakine *et al*., 2006) |
| 171 | 5-Hydroxy-3-methoxydec-2-enoic acid | Ro | |
| 172 | Aromadendrane-4β,10β-diol | Rh | (Zhou *et al*., 2007) |
| 173 | p-Coumaric acid 4-hydroxyphenyl ester | Ro | (Komakine *et al*., 2006) |
| 174 | Pananotin | Ro | (Chan *et al*., 2019) |

Notes: * The compounds were isolated from processed (steamed) NRR. Ro, Root; Rh, Rhizome

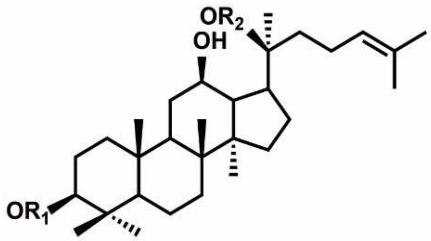
***Saponins***

Saponins represent the most abundant class of compounds in NRR, as illustrated in Fig. 1. These saponins are primarily dammarane-type tetracyclic triterpenes, classified into 20(S)-protopanaxadiol and 20(S)-protopanaxatriol aglycone moieties. The most prevalent saponins are ginsenoside Rg1 and ginsenoside Rb1.

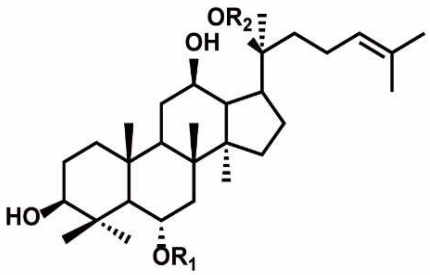
The "Pharmacopoeia of the People's Republic of China" stipulates that the combined content of ginsenoside Rg1, ginsenoside Rb1 and notoginsenoside R1 must be no less than 5.0% as the quality standard for NRR (Pharmacopoeia of the People's Republic of China, 2020). PNS inhibits thrombin-induced platelet aggregation (Dai *et al*., 2022), establishing them as the main active components responsible for NRR's blood-activating effects. Specifically, ginsenoside Rg1 and ginsenoside Rg2 have been shown to inhibit platelet aggregation to varying degrees (Yan *et al*., 2024).

***Flavonoids***

Although flavonoids are widely distributed in nature, only a limited number have been isolated from NRR, predominantly flavonols. One identified compound is Quercetin 3-O-β-D-xylopyranosyl-β-D-galactopyranoside, as shown in Fig. 2.

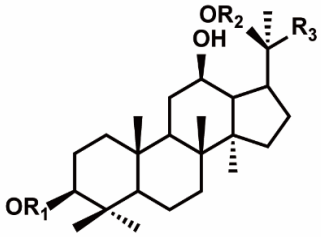


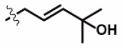
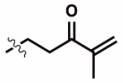
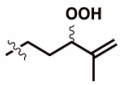
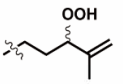
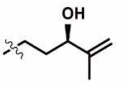
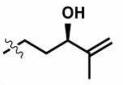

| | $R_1$ | $R_2$ |
|---|---|---|
| 1 | Glc(2 - 1)Glc | Glc(6 - 1)Glc(3 - 1)Xyl |
| 2 | Glc(2 - 1)Glc | Glc(6 - 1)Glc |
| 3 | Glc(2 - 1)Glc | Glc(6 - 1)Ara(p) |
| 4 | Glc(2 - 1)Glc | Glc(6 - 1)Xyl |
| 5 | Glc(2 - 1)Glc | Glc |
| 6 | Glc(2 - 1)Glc | H |
| 7 | Glc | Glc(6 - 1)Glc |
| 8 | Glc(2 - 1)Glc(6 - 1)Malonyl | Glc(6 - 1)Glc |
| 9 | Glc(2 - 1)Glc(2 - 1)Xyl | Glc(6 - 1)Glc(6 - 1)Xyl |
| 10 | Glc(2 - 1)Glc(2 - 1)Xyl | Glc(6 - 1)(6 - 1) |
| 11 | Glc(2 - 1)Glc | Glc(6 - 1)Glc(6 - 1)Xyl |
| 12 | Glc(2 - 1)Glc(2 - 1)Xyl | Glc(6 - 1)Ara(f)(5 - 1)Xyl |
| 13 | Glc(2 - 1)Glc(2 - 1)Xyl | H |
| 14 | Glc(2 - 1)Glc(2 - 1)Xyl | Glc(6 - 1)Glc(3 - 1)Xyl |
| 15 | Glc(2 - 1)Xyl | Glc(6 - 1)Glc |
| 16 | Glc | Glc(6 - 1)Glc |
| 17 | Glc(2 - 1)Glc(6 - 1)Ac | Glc(6 - 1)Glc |
| 18 | Glc(6 - 1)Glc | Glc |
| 19 | Glc(2 - 6)Glc(6 - 1)Ac | H |

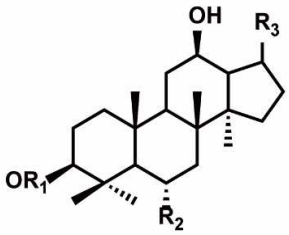


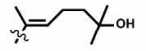
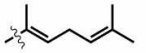
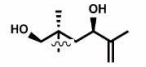
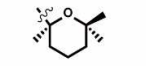
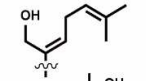
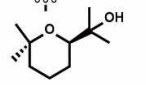
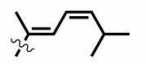
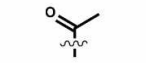

| | $R_1$ | $R_2$ |
|---|---|---|
| 20 | H | Glc(6-1)Ara(p)(4-1)Xyl |
| 21 | H | Glc |
| 22 | Glc(2-1)Rha | Glc |
| 23 | Glc(2-1)Glc | H |
| 24 | Glc | Glc |
| 25 | Glc(2-1)Rha | H |
| 26 | Glc | H |
| 27 | Glc(2-1)Glc | Glc |
| 28 | Glc(6-1)COCH=CHCH$_3$ | Glc |
| 29 | Glc(6-1)Glc | Glc |
| 30 | Glc(4-1)Glc | Glc |
| 31 | Glc(2-1)Xyl | Glc |
| 32 | Glc(2-1)Xyl | H |
| 33 | Glc | Glc(6-1)Glc |
| 34 | Glc | Glc(6-1)Glc |
| 35 | Xyl | Glc(6-1)Xyl |
| 36 | H | Glc(6-1)Glc |
| 37 | Glc(6-1)Ac | Glc |
| 38 | Xyl | Glc |
| 39 | Xyl(2-1)Xyl | H |
| 40 | H | H |
| 41 | H | Glc(6-1)Glc(6-1)Xyl |
| 42 | Glc(6-1)Ac | H |
| 43 | H | Glc(6-1)Glc |
| 44 | 6'-CH$_3$CH=CH-C=OGlc | H |
| 45 | 6'-AcGlc(2-1)Xyl | H |
| 46 | Glc | Ara(p) |
| 47 | Ara(p) | Glc |
| 48 | Glc(2-1)Ara(f) | Glc |
| 49 | Glc(2-1)Xyl | Glc(6-1)Glc |
| 50 | Glc | Xyl |

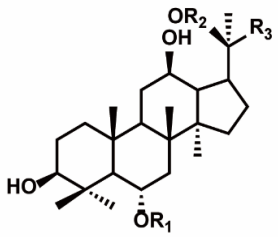
*Fig. 1: is continue……..*

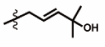
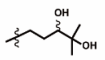
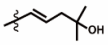
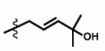
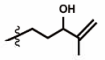
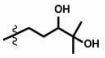
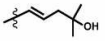



| | R1 | R2 | R3 |
|---|---|---|---|
| 51 | Glc(2-1)Glc | Glc(6-1)Glc |  |
| 52 | Glc(2-1)Glc | Glc(6-1)Glc |  |
| 53 | Glc(2-1)Glc | Glc(6-1)Glc |  |
| 54 | Glc(2-1)Glc | Glc |  |
| 55 | Glc(2-1)Glc | Glc |  |
| 56 | Glc(2-1)Glc | Glc(6-1)Glc |  |




| | R1 | R2 | R3 |
|---|---|---|---|
| 78 | H | OGlc(2-1)Rha |  |
| 79 | Glc(2-1)Gle | H |  |
| 80 | H | OGle-Rha |  |
| 81 | Glc | H |  |
| 82 | H | OH |  |
| 83 | Glc(2-1)Glc | H |  |
| 84 | H | OGle |  |
| 85 | H | OGlc(1-2)Xyl |  |
| 86 | H | OGle |  |




| | R1 | R2 | R3 |
|---|---|---|---|
| 57 | Glc(2-1)Xyl | Glc |  |
| 58 | Glc | Glc |  |
| 59 | Glc(2-1)Xyl | H |  |
| 60 | Glc | Glc |  |
| 61 | Glc | H |  |
| 62 | Glc | Glc |  |
| 63 | Glc | H |  |

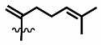
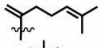
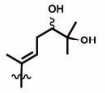
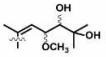
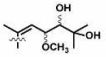
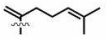
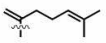
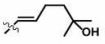
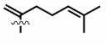
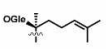
| | R1 | R2 | R3 |
|---|---|---|---|
| 64 | Glc(2-1)Glc | H |  |
| 65 | H | O-Gle |  |
| 66 | Glc(2-1)Glc | H |  |
| 67 | H | O-Gle |  |
| 68 | Gle | H |  |
| 69 | H | O-Gle |  |
| 70 | Glc(2-1)Glc | H |  |
| 71 | Glc(2-1)Glc | H |  |
| 72 | Glc(2-1)Glc(2-1)Xyl | H |  |
| 73 | H | O-Glc(3-1)Xyl |  |
| 74 | H | O-Glc |  |
| 75 | H | H |  |
| 76 | H | OH |  |
| 77 | Glc(2-1)Glc | OH |  |

*Fig. 1: is continue…….*

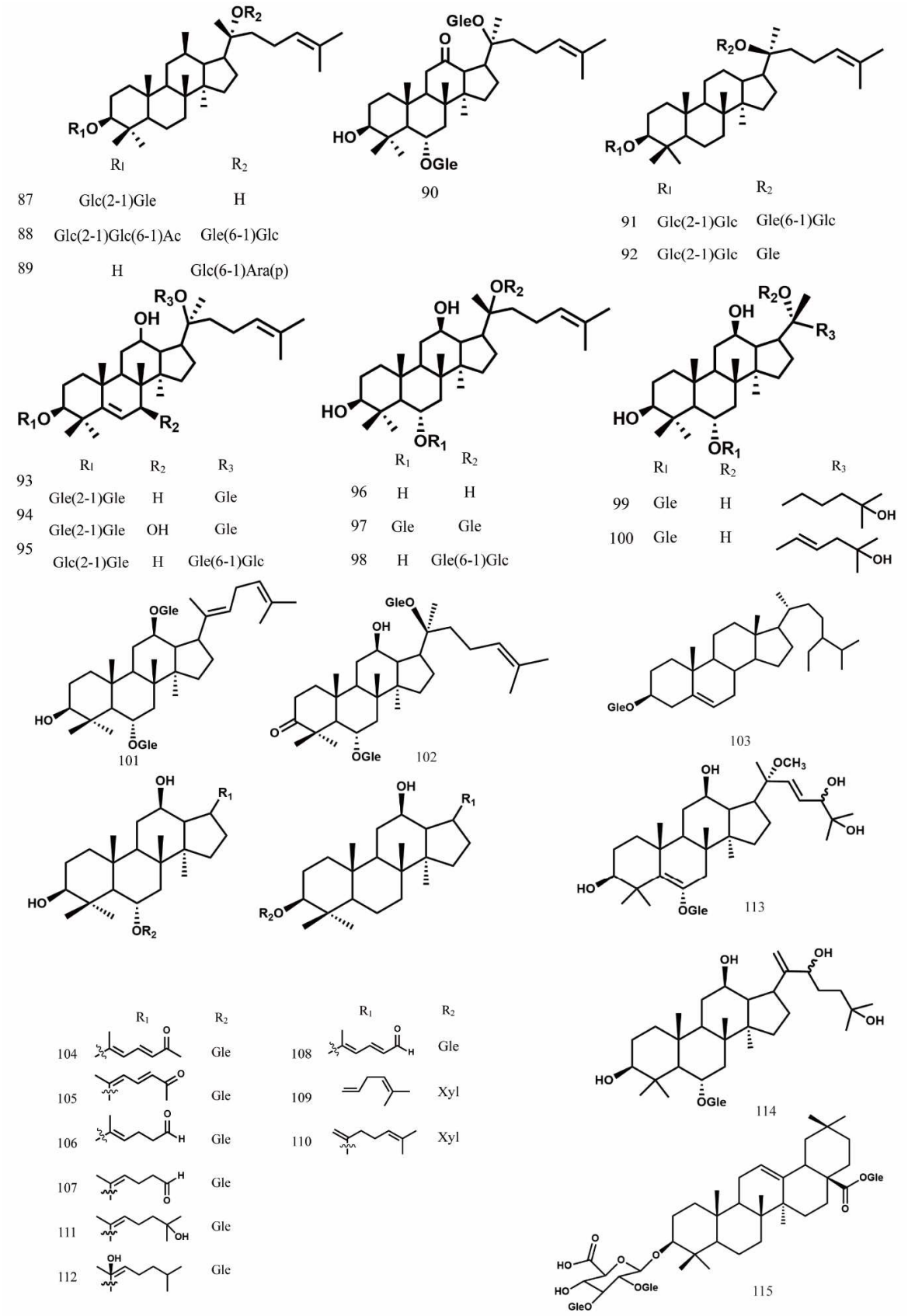
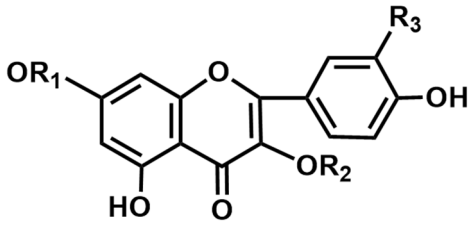


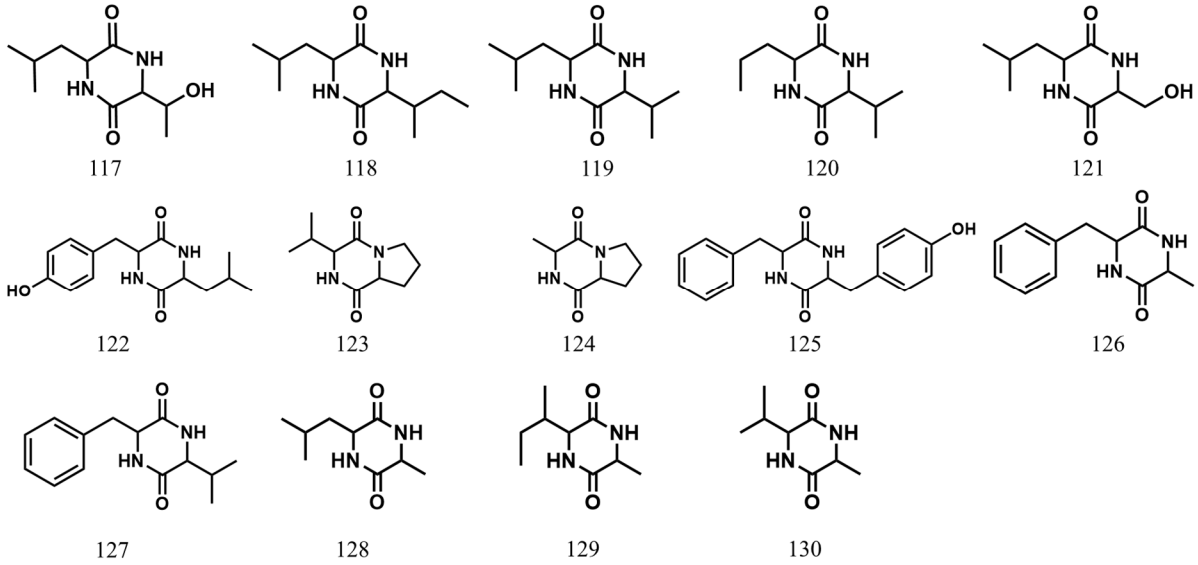

**Fig. 1**: The structures of saponins isolated from NRR.



116

$R_1 = H$ $R_2 = Gal(2\text{-}1)Xyl$ $R_3 = OH$

**Fig. 2**: The structure of the flavonoid isolated from NRR.

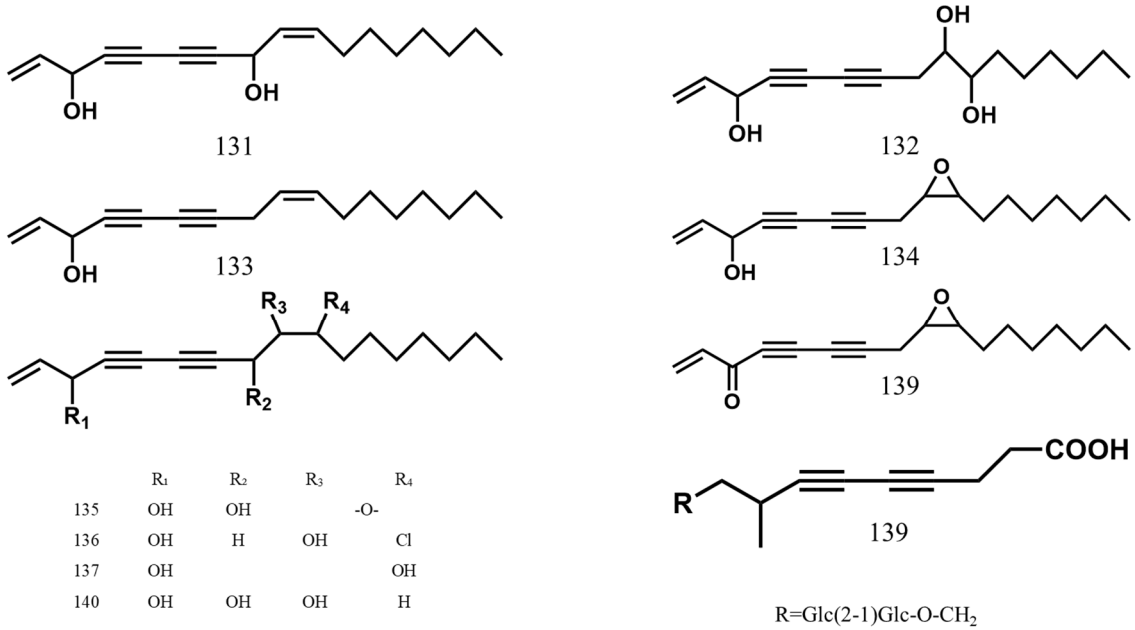


117 118 119 120 121

122 123 124 125 126

127 128 129 130

**Fig. 3**: The structures of cyclopeptides isolated from NRR.



131 132 133 134 139 139

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 135 | OH | OH | | -O- |
| 136 | OH | H | OH | Cl |
| 137 | OH | | | OH |
| 140 | OH | OH | OH | H |

R=Glc(2-1)Glc-O-$CH_2$

**Fig. 4**: The structures of polyacetylenes isolated from NRR.

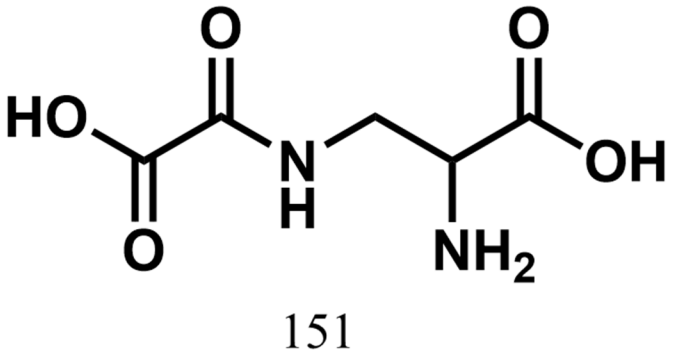



**Fig. 5**: The structure of the dencichine isolated from NRR.

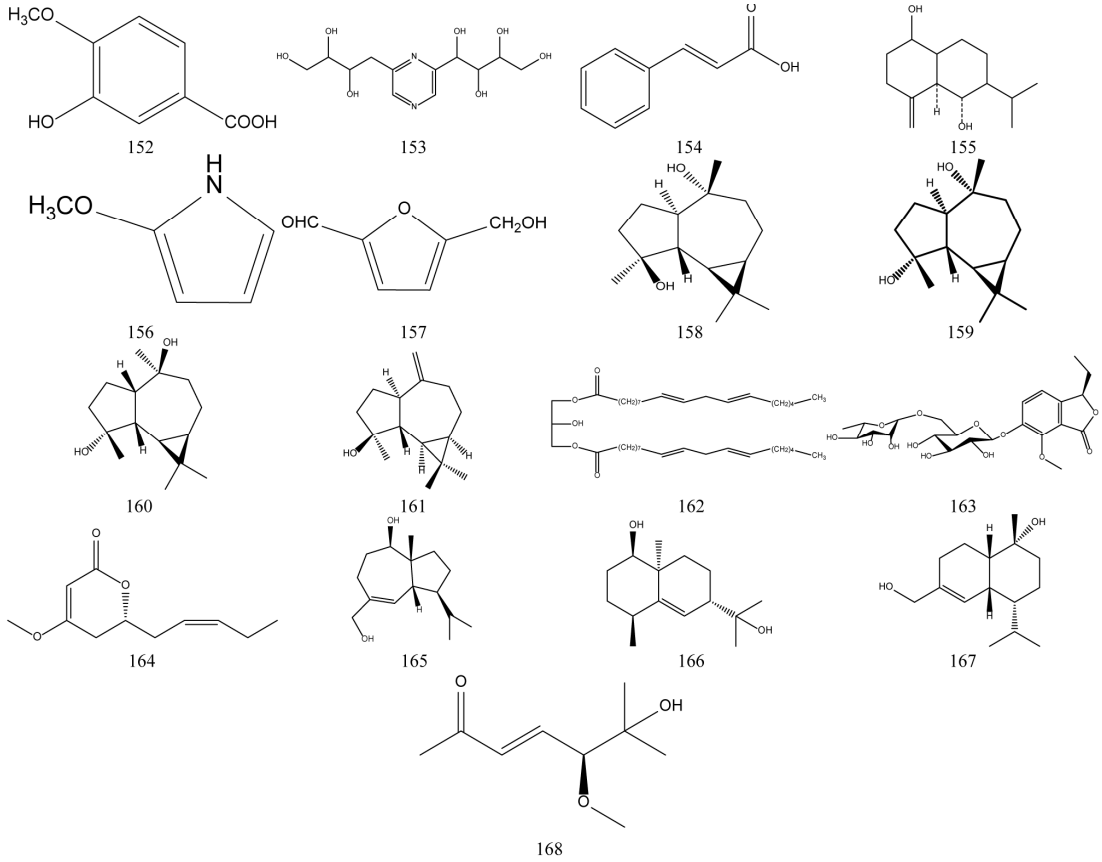



**Fig. 6**: The structure of other compounds isolated from NRR.

*In-vitro* experiments demonstrated that this flavonoid inhibits Aβ-induced cell death in cortical neurons and PC12 cells in a dose-dependent manner, while also suppressing Aβ-induced DNA fragmentation and caspase-3 activation (Choi *et al*., 2010). It is noteworthy that research on flavonoids in NRR remains relatively scarce, indicating a promising area for future compound isolation and pharmacological investigation.

***Cyclopeptides***

Fourteen cyclopeptides have been isolated from NRR, all characterized as cyclic dipeptides, as shown in fig. 3. Their structures were determined through spectral analysis and include: cyclo-(Leu-Thr), cyclo-(Leu-Ile), cyclo-(Leu-Val), cyclo-(Ile-Val), cyclo-(Leu-Ser), cyclo-(Leu-Tyr), cyclo-(Val-Pro), cyclo-(Ala-Pro), cyclo-(Phe-Tyr), cyclo-(Phe-Ala), cyclo-(Phe-Val), cyclo-(Leu-Ala), cyclo-(Ile-Ala) and cyclo-(Val-Ala).

***Po1yacetylenes***

Several polyacetylenes have been isolated from NRR, as depicted in fig. 4. Among them, panaxynol and panaxydol exhibit notable biological activities. Panaxynol demonstrates cytotoxicity against various human tumor cell lines *in-vitro* (McDonald *et al*., 2023) and effectively ameliorates colitis in a dextran sulfate sodium-induced

mouse model by targeting macrophage DNA damage and apoptosis (Chaparala *et al*., 2020). Panaxydol inhibits proliferation and induces differentiation of the human hepatocarcinoma cell line HepG2, causing cell cycle arrest at the G1 to S phase transition (Kim *et al*., 2024).

***Polysaccharides***

Polysaccharides are distributed throughout the *P. notoginseng* plant, with the highest concentration and diversity found in the main root (Shen *et al*., 2022). Research indicates that NRR polysaccharides exhibit adjuvant and immunostimulatory activities, suggesting significant potential for preventing and supporting the treatment of infections and immunodeficiency-related diseases (Wang *et al*., 2016).

***Amino acids***

Like all plants, NRR contains various amino acids. Analytical studies using standard comparison methods have identified at least 19 amino acids in NRR, seven of which are essential amino acids (Ji *et al*., 2022). However, a unique non-protein amino acid, dencichine (β-N-oxalyl-L-α,β-diaminopropionic acid), has been isolated from NRR, as shown in fig. 5. This compound, found almost exclusively in the *Panax* genus, exerts hemostatic effects by enhancing platelet activation and increasing platelet count (Zhang *et al*., 2025). Studies indicate that dencichine exhibits hemostatic effects at low doses but demonstrates neurotoxicity at high doses (Zhang *et al*.,2023), highlighting the need for further investigation into NRR's safety profile.

***Others***

In addition to the aforementioned classes, NRR contains various other compounds (Fig. 6). Notably, 2-(1′,2′,3′,4′-tetrahydroxybutyl)-6-(2″,3″,4″-trihydroxybutyl)-pyrazine has demonstrated toxicity toward liver cancer cells, with an $IC_{50}$ of 0.05 mg/mL (Li *et al*., 2001b). This finding further underscores the importance of comprehensive safety evaluation of NRR.

***Impact of processing on NRR***

*The processing methods of NRR*

The impact of various processing methods on NRR is summarized in Fig. 7. Traditional processing techniques documented in ancient texts include pulverization, chewing, grinding, roasting, frying and steaming. Methods such as grinding into powder, chewing and simple grinding are considered raw preparations, while roasting, frying and steaming constitute processed preparations. This distinction correlates directly with therapeutic intentions: raw preparations are primarily employed for hemostasis, blood dispersion and pain relief, whereas processed preparations are used for tissue regeneration, blood nourishment and replenishing deficiencies. This functional dichotomy aligns with the traditional axiom that raw NRR 'disperses' while processed NRR 'nourishes'.

Ancient practitioners believed that high—temperature processing methods—including roasting, frying and steaming-could enhance NRR's restorative properties, such as promoting tissue regeneration, generating fluids, supplementing *Qi* and nourishing blood. Throughout historical records, the method of pulverizing NRR into powder consistently maintains prominence, particularly for treating traumatic bleeding. Topical application of NRR powder effectively achieves rapid hemostasis. This hemostatic effect is attributed to dencichine, a unique amino acid in NRR that promotes thrombin formation, shortens bleeding and clotting times and induces local vasoconstriction while increasing platelet count (Wang *et al*., 2014). Additionally, the physical properties of NRR powder itself facilitate thrombus formation by filling vascular injuries. NRR powder (raw product) remains in contemporary use, with the current "Pharmacopoeia of the People's Republic of China" still prescribing its preparation through grinding. However, modern pharmacopoeial standards specify more refined procedures compared to ancient methods, requiring finer powder particle sizes and specific sieve mesh specifications.

***Effects of processing on the compounds of NRR***

In-depth research on NRR has demonstrated that processing significantly alters the composition and content of its chemical compounds, particularly ginsenosides. A comprehensive analysis employing a Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry (MALDI-MS) strategy delineated the chemical diversity and dynamic transformation patterns of ginsenosides during processing, while also mapping their spatial distribution. This approach provided mechanistic insights into the bioactivity differences between fresh and processed ginseng by elucidating the holistic impact of processing on natural product chemistry. For the first time, the transformation pathways of ginsenosides—including deglycosylation, dehydration, hydration, acetylation and isomerization—were systematically elucidated through a combination of precursor ion scanning and simulated processing. Mass spectrometry imaging further revealed that major ginsenosides, including M-Rb1, R1, Rg1, Rb1, Rd and Re, exhibited distinct spatial distributions, with high abundance in the xylem and a marked decline during processing (Fan *et al*., 2022). Although the above study revealed spatial distribution and transformation patterns of ginsenosides and identified certain quality markers in both raw and processed NRR, further well-designed pharmacological studies are necessary to fully elucidate the underlying processing mechanisms. For instance, comparative assessments should be conducted to evaluate the differential effects of raw and processed NRR on characteristic bioactivities such as hemostasis and blood circulation activation. Additionally, the pharmacological roles of the identified quality markers require experimental validation.

It is noteworthy that high-temperature steam processing enhances the content of rare ginsenosides in NRR—such as Rk1, Rg5 and other compounds—which are not naturally present in the plant. A processing-chemical profiling-pharmacodynamics integrated analysis further revealed that NRR steamed at 140ºC for 2 hours exhibited peak levels of Rk1, Rg5 and other rare ginsenosides, along with significantly enhanced antiplatelet aggregation activity. The study also partially clarified the chemical basis for these changes: molar-based dynamic profiling showed that low-bioactivity ginsenosides Rb1 and Rd are converted into moderately active 20(S/R)-Rg3, which is further transformed into highly active Rk1 and Rg5. Subsequent conversion to Rk2 and Rh3 was associated with reduced bioactivity. Notably, the increase in rare ginsenosides (Rg3, Rk1, Rg5) closely corresponded to the decrease in primary ginsenosides (Rb1, Rd), thereby validating the transformation pathway of ginsenosides during steaming (Fan *et al*., 2024). Although preliminary identification of potential ginsenosides lacking reference compounds was also performed, further isolation and bioactivity validation are required to comprehensively elucidate the impact of steaming on other chemical constituents in NRR.

Ginsenosides are classified into protopanaxadiol (PPD) and protopanaxatriol (PPT) types based on the presence of hydroxyl groups at the C-6 position. Representative PPD-type ginsenosides include Rb1, Rd, Rg3, Rk1 and Rg5, while PPT-type ginsenosides include Re, Rg6, F4, Rk3 and Rh4. Studies indicate that upon heating and steaming, most native saponins undergo dehydration and isomerization at the C-20 position. Concurrently, rare saponins are generated through sugar chain cleavage at the C-3 and C-6 positions. The enhanced therapeutic efficacy of processed P. notoginseng is closely associated with the formation of these rare saponins. Furthermore, increases in steaming temperature, environmental acidity and processing duration were found to elevate the content of rare saponins such as Rh1, Rh4, Rk3 and Rg3 in NRR, which correlates with enhanced anticoagulant and blood-nourishing activities (Zhao *et al*., 2024).

Indeed, the impact of processing on NRR extends beyond ginsenosides, also significantly influencing its polysaccharide profile. Chemical analyses showed a slight increase in polysaccharide content and a decrease in protein content. Monosaccharide composition analysis indicated a significant rise in glucose content in steamed NRR polysaccharides compared to raw NRR. Fourier transform infrared spectroscopy further revealed partial changes in polysaccharide functional groups between steamed and raw NRR polysaccharides. Moreover, steamed NRR polysaccharides exhibited superior immunomodulatory activity in both *in vivo* and *In-vitro* assays (Xing *et al*., 2021).

***Pharmacological effects and impact of processing***

Scientific research has demonstrated that NRR exhibits a broad spectrum of pharmacological activities, including beneficial effects on cardiovascular and cerebrovascular diseases, inflammation, traumatic bleeding, tumors and neuroprotection, as summarized in table 2. Processing-induced alterations in NRR's compound profile drive significant changes in its pharmacological effects.

***Effects on cardiovascular and cerebrovascular health***

TCM has demonstrated distinctive advantages in preventing and treating cardiovascular and cerebrovascular diseases. NRR is widely used throughout China and East Asia for managing ischemic heart and cerebrovascular conditions. The PNS in NRR confer cardioprotective effects in acute myocardial infarction through multiple mechanisms, including induction of cardiomyocyte autophagy, inhibition of platelet aggregation and enhancement of endothelial migration and angiogenesis (Wang *et al*., 2021). Additionally, PNS ameliorates myocardial ischemia-reperfusion injury via the HIF-1α/Bcl-2/BNIP3 autophagy pathway (Liu *et al*., 2019).

Notoginsenoside R1, a key compound of PNS, demonstrates cardioprotective mechanisms in both *in-vivo* and *in-vitro* models of myocardial ischemia/reperfusion (MI/R) injury. It mitigates MI/R injury by inhibiting the phosphorylation of TAK1, JNK and p38, thereby reducing myocardial apoptosis through suppression of the TAK1-JNK/p38 signaling pathway (Zeng *et al*., 2023). Furthermore, Notoginsenoside R1 exhibits protective effects against hypoxia-induced cardiac injury by reducing levels of CK, CK-MB, LDH and BNP, consequently improving cardiac function and decreasing arrhythmia incidence. It also enhances Nrf2 nuclear translocation, regulating the SLC7A11/GPX4/HO-1 pathway and iron metabolism to suppress ferroptosis, thereby alleviating hypoxia-induced cardiac inflammation and oxidative stress (Wang *et al*., 2024).

While previous PNS research predominantly focused on ischemic cardiovascular diseases, cerebral ischemic conditions have received comparatively less attention until recently. PNS improves various cerebral ischemia models: it enhances neurological function and reduces infarct size in rats with middle cerebral artery occlusion; improves motor coordination while reducing $Ca^{2+}$ concentration and energy metabolism disturbances in global cerebral ischemia models; and decreases thrombosis in carotid artery-jugular vein shunt models (Dong *et al*., 2022). PNS also protects brain microvascular endothelial cells from necroptosis induced by transient oxygen-glucose deprivation by inhibiting the RIP1-RIP3-MLKL signaling pathway and mitigating mitochondrial damage (Hu *et al*., 2022).

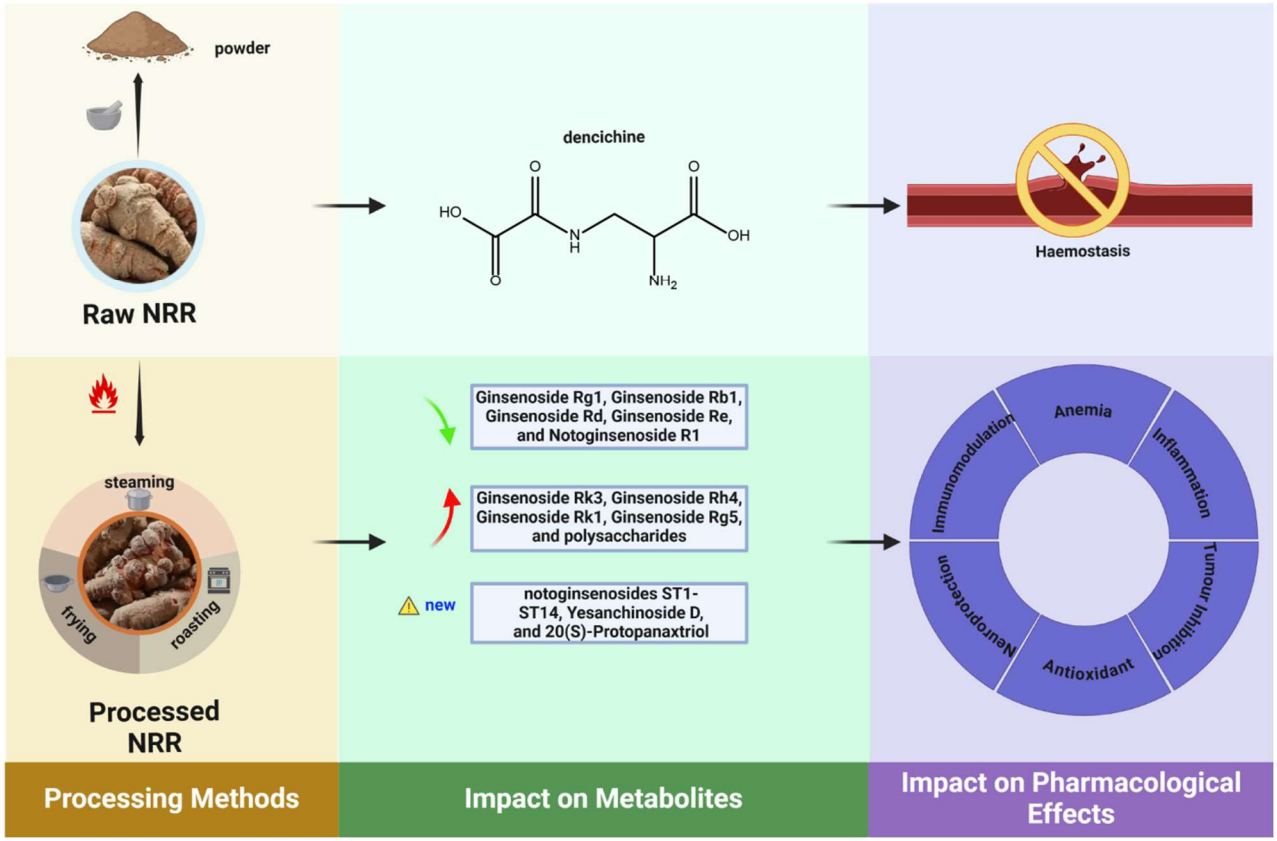



**Fig. 7**: The impact of processing methods on NRR

Processing significantly influences NRR's cardiovascular and cerebrovascular effects. A standardized extract from steamed NRR demonstrates cardioprotection by attenuating endoplasmic reticulum stress-induced apoptosis via the TXNIP/NLRP3 pathway, with these active saponins being either undetectable or present in minimal amounts in raw NRR (Wang *et al*., 2015). Both raw and steamed NRR ethanol extracts reduce neurological deficit scores and infarct volume in mice, protecting brain tissue by inhibiting MAPK signaling pathway activation and decreasing MMP-2 and MMP-9 protein expression.

However, raw NRR exhibits significantly superior pharmacodynamic effects compared to steamed NRR (Zhu, 2021), providing a scientific basis for the traditional preference for raw NRR in treating such conditions.

***Effects on haemostasis and wound healing***

NRR has been traditionally employed for various bleeding disorders, with its hemostatic effects being well-documented. Research indicates that PNS exerts hemostatic effects through multiple mechanisms. It demonstrates anti-proliferative effects on fibroblasts, promoting wound healing in mouse skin while suppressing scar formation (Men *et al*., 2020). PNS also facilitates proliferation and migration of anterior cruciate ligament fibroblasts, increases collagen and fibronectin expression and mediates these effects through phosphorylation of PI3K, AKT and ERK. Additionally, PNS mitigates inflammation by reducing TNF-α, IL-6 and IL-1β levels, providing protection against ACL injuries (Yu *et al*., 2015).

With increasing diabetes incidence and associated complications like chronic non-healing wounds, research shows that PNS improves wound healing in hyperglycemic rats by promoting endothelial cell proliferation, invasion, migration, angiogenesis, inhibiting apoptosis and oxidative damage and activating the GSK-3β/β-catenin pathway (Lei *et al*., 2022).

***Effects on coagulation***

Interestingly, the two most abundant PNS compounds, ginsenoside Rg1 and ginsenoside Rb1, exhibit opposing effects—ginsenoside Rg1 promotes angiogenesis while ginsenoside Rb1 inhibits it (Zhou *et al*., 2020b). This duality reflects the traditional understanding that NRR both stops bleeding and activates blood circulation. Modern medicine partially attributes NRR's blood-activating effects to its antithrombotic properties. PNS inhibits thrombin-induced platelet aggregation *in-vitro* and significantly reverses thrombin-induced hypercoagulability in rats, with activation of PPAR-γ and its downstream PI3K/Akt/eNOS pathway playing a central role (Dai *et al*., 2022).

Comparative studies reveal that raw NRR exhibits stronger anticoagulant effects, while steamed NRR is more effective in improving hemolytic anemia (Xiao *et al*., 2020).

***Effects on anemia***

Steamed NRR significantly increases peripheral blood cell counts, improves erythrocyte fragility and promotes overall hematopoiesis by enhancing EPO mRNA expression in kidneys and EPO receptor mRNA in bone marrow nucleated cells, ultimately alleviating renal anemia (Gao *et al*., 2022). Furthermore, steamed NRR enhances hematopoietic function in mice with blood deficiency syndrome by participating in cell cycle responses and immune cell activation through the JAK-STAT pathway, increasing peripheral blood cells in a dose-dependent manner and reversing splenomegaly (Zhang *et al*., 2020a).

***Effects on the liver***

Classical TCM theory posits that the liver stores blood and consequently, NRR is believed to possess hepatoprotective effects—a claim substantiated by numerous modern studies. Notoginsenoside R1 inhibits hepatic stellate cell activation, exerting antioxidant and anti-inflammatory effects by inactivating NF-κB and MAPK signaling pathways, thereby improving liver injury (Gong *et al*., 2022). Both methanol and water extracts of NRR demonstrate significant hepatoprotective effects, with ginsenosides Re and Rg1 from the methanol extract showing particularly notable activity. PNS prevents acute ethanol-induced liver injury, likely by ameliorating hepatic lipid accumulation and reducing CYP2E1-mediated oxidative stress.

***Effects on inflammation***

As previously noted, NRR exhibits anti-inflammatory effects in cardiovascular and cerebrovascular contexts. The cardioprotective effects of PNS associate with reduction of NLRP3 inflammasome and inflammatory mediators including IL-6, MCP-1 and TNF-α in injured myocardium, mediated by KATP channel activation that suppresses inflammatory responses (Ning *et al*., 2020). However, anti-inflammatory activity diminishes after steaming. Chemometric analysis identifies notoginsenoside R1, ginsenoside Rg1, ginsenoside Re and ginsenoside Rb1 as the primary anti-inflammatory compounds in raw NRR, while ginsenoside 20(S)-Rg3 serves as the effective anti-inflammatory compound in steamed NRR. Moreover, raw NRR contains higher concentrations of anti-inflammatory compounds (Zhang *et al*., 2019).

***Effects on immunomodulation***

NRR demonstrates considerable potential for treating immune disorders, with PNS and polysaccharides considered the primary immunomodulatory compounds. PNS enhances immune responses in piglets vaccinated with a modified live virus vaccine against PRRSV-2, suggesting potential as an oral immunomodulatory supplement (Yang *et al*., 2024a). PNPB1, a recently isolated NRR polysaccharide, significantly enhances splenocyte proliferation, NO and cytokine (TNF-α, IL-2, IL-10 and IFN-γ) production, peritoneal macrophage phagocytosis and TLR2 expression in cyclophosphamide-induced immunosuppressed mice, demonstrating potent immunoenhancing effects (Jiang *et al*., 2023).

Studies using a zebrafish tail-fin amputation model reveal processing effects on immunomodulation. Fingerprint-effect relationship analysis shows that ethanol extracts of NRR steamed at higher temperatures for longer durations contain increased amounts of ginsenosides Rh1, Rk3, Rh4, 20(S)-Rg3 and 20(R)-Rg3, which exhibit stronger neutrophil suppression effects (Xiong *et al*., 2022).

***Effects on tumour inhibition***

NRR demonstrates antitumor effects across various cancers. Its ethanol extract inhibits prostate cancer progression by reducing IL-4 secretion, blocking cell cycle progression and inducing apoptosis in prostate cancer cells (Hawthorne *et al*., 2022). PNS exhibits significant chemopreventive and immunomodulatory properties against colorectal cancer by reducing macrophage accumulation and Treg cell differentiation, thereby reshaping the tumor immune microenvironment (Li *et al*., 2022). PNS inhibits breast cancer proliferation and metastasis by normalizing tumor vasculature through suppression of EphA2 expression, thus improving the breast cancer immune microenvironment (Xia *et al*., 2023). Additionally, PNS exerts cytotoxic effects on pancreatic cancer cells by inhibiting autophagy and inducing apoptosis, enhancing chemosensitivity to gemcitabine and providing novel strategic options for pancreatic cancer treatment (Yao *et al*., 2021).

Research indicates that steaming alters NRR's saponin profile, converting native ginsenosides into anticancer compounds, thereby enhancing anticolorectal cancer efficacy. Steaming decreases contents of notoginsenoside R1, ginsenosides Rg1, Re, Rb1, Rc, R2, Rb3 and Rd, while increasing levels of Rh1, Rg2, 20R-Rg2, Rg3 and Rh2. When NRR is steamed at 120$^{o}$C for hours, the anticancer compound ginsenoside Rg3 content increases 5.23-fold compared to NRR steamed at 100$^{o}$C.

***Effects on antioxidant activity***

As a tonic herb, NRR possesses excellent antioxidant properties. Intervertebral disc degeneration represents a common cause of back pain and PNS injection has been clinically employed to alleviate IDD-related back pain. Recent studies indicate that PNS protects human nucleus pulposus cells from oxidative stress-induced apoptosis by inhibiting autophagy and activating the Akt/mTOR pathway, suggesting potential for treating IDD by preventing apoptosis and extracellular matrix degradation under oxidative stress (Guo *et al*., 2024).

**Table 2.** Pharmacological activities of NRR

| Pharmacological activity | Tested substance | Experimental animals/cell | Model | Tested living system/organ/cell | Dose range and administration route | Time period of application | Results | References |
|---|---|---|---|---|---|---|---|---|
| Effects on cardiovascular and cerebrovascular health | | | | | | | | |
| | PNS | Rats | Acute myocardial infarction | Heart and plasms | 100 mg/kg; oral | 2 weeks | ↑Ejection fraction, fractional shortening, LV wall thickness<br>↓Fibrosis area, cell size, LDH, CTNI | (Wang *et al.*, 2021) |
| | | | glucose deprivation | H9c2 rat cardiomyoblast cells | 10,100 μg/mL | 0-24 h | ↑LC3II/I, P62/HSP90, p-mTOR/mTOR, p-AMPK/AMPK, p-CaMKII/CaMKII, VEGF, p-Selection<br>↓vWF, platelet aggregation | |
| | PNS | Rats | myocardial ischemia-reperfusion injury | Serum and heart | 30 and 60 mg/kg; i.p. | 7 d | ↑HIF-1α, BNIP3, Atg5, Bcl-1, mitochondria autophagosome in myocardial cells, LC3II/LC3I<br>↓CK, MDA, lactate dehydrogenase, SOD, ROS | (Liu *et al.*, 2019) |
| | Notoginsenoside R1 | Mice | Myocardial ischemia/reperfusion | Heart and plasms | 25 mg/kg; i.p. | 6 h | ↑Bcl-2, LVEF, LVFS, attenuated fibrotic effect,<br>↓cTn-I, CK-MB, TUNEL-positive cells, Bax , α-SMA, Collagen I, fibronectin | (Zeng *et al.*, 2023) |
| | | Murine neonatal cardiomyocytes | Murine neonatal cardiomyocytes | Murine neonatal cardiomyocytes | 25 μM | 24 h | ↑Bcl-2<br>↓TUNEL-positive cells, Bax, p-p38/p38, p-JNK/JNK, p-ERK/ERK, p-TAK1/TAK1 | |
| | Notoginsenoside R1 | Rats | Hypobaric hypoxia model | Blood and heart tissues | 50,100 mg/kg; i.p. | 3 d | ↑suppressed hypoxia-induced damage in cardiomyocytes, Nrf2 nuclear, Keap1, TFRC<br>↓BNP, CK, CK-MB, LDH, MDA, ROS, TNF-α, IL-1β, Nrf2 cytosolic, GPX4, SLC7A11, FTH1, HO-1 | (Wang *et al.*, 2024) |
| | PNS | Rats | Middle Cerebral Artery Occlusion | Brains | 18.3,36.5,73 mg/kg; i.v. | 0,12 h | ↑the neurocoordination function<br>↓cerebral infarction, the neurobehavioral scores | (Dong *et al.*, 2022) |
| | | Rats | Cerebral Ischemia in Rats Subjected to Four-Vessel Occlusion | Brains | 18.3,36.5,73 mg/kg; i.v. | 0,24h | ↑ATP , PCr<br>↓LA, FFA , $Ca^{2+}$ | |
| | | Mice | Collagen-Adrenaline-Induced Thrombosis in Mice | The number of dead mice | 26.2,52.4,104.8 mg/kg; i.v. | 15 min | ↓the number of dead mice | |

*Table. 2 is continue……..*

| Pharmacological activity | Tested substance | Experimental animals/cell | Model | Tested living system/organ/cell | Dose range and administration route | Time period of application | Results | References |
|---|---|---|---|---|---|---|---|---|
| | | Rats | Carotid Artery-Jugular Vein Thrombosis in Rats | The thrombus weight | 18.3,36.5,73 mg/kg; i.v. | 15 min | ↑the thrombosis inhibition rates ↓the thrombus weight | |
| | PNS | The brain microvascular endothelial cells of rats | The necroptosis model of rat BMECs | The brain microvascular endothelial cells of rats | 22μg/ml | 2 h | ↑the integrity of nucleus and cell membrane ↓mitochondrial swelling, organelle damage, RIP1, RIP3, MLKL, PGAM5, Drp1 | (Hu *et al.*, 2022) |
| | A rare ginsenoside-standardized extract from steamed NRR | Rats | Myocardial infarction | Serum and heart | 25,50,100 mg/kg; oral | 3 d | ↑LVSP/LVDEP, SOD, ↓Infarct size, CM-MB, LDH, MDA, ROS, TXNIP, NLRP3, IL-1β, GRP94, BiP/GRP78, p-IRE1α, CHOP | (Wang *et al.*, 2015) |
| | Ethanol extract of raw and steamed NRR | Mice | Cerebral ischemia reperfusion injury | Brains | 200,400 mg/kg; oral | 3 d | ↑ ZO-1, Occludin ↓MDA, MPO, MMP-2, MMP-9, p-p38/p38, p-ERK/ERK, p-JNK/JNK | (Zhu, 2021) |
| Effects on haemostasis and wound healing | | | | | | | | |
| | PNS | Mice | Murine dorsal skin wound model | Skins | 0.001, 0.01, 10 mM; i.v. | 10 d | ↓scar area (%), α-SMA, the accumulation of fibroblasts in the wound area | (Men *et al.*, 2020) |
| | | Mouse fibroblast NIH/3T3 | Mouse fibroblast NIH/3T3 | Mouse fibroblast NIH/3T3 | 0.1 mM | 24,48,72 h | ↑NO levels, NO synthase activities ↓cell proliferation | |
| | PNS | Anterior cruciate ligament (ACL) fibroblasts | Anterior cruciate ligament fibroblasts | Anterior cruciate ligament fibroblasts | 0.05,0.1,0.2,0.4 mg/mL | 24 h | ↑the proliferation and migration of ACL fibroblasts, collagen I, collagen III, fibronectin, p-PI3K/PI3K, p-AKT/AKT, p-ERK/ERK ↓TNF-α, IL-6, IL-1β, MMP-2, MMP-9 | (Yu *et al.*, 2015) |
| | PNS | Human umbilical vein endothelial cells | Human umbilical vein endothelial cells | Human umbilical vein endothelial cells | 200 μg/mL | 48 h | ↑proliferation, invasion, migration, angiogenesis, MDA , NO, p-GSK3β, VEGF ↓cell apoptosis, LDH, GSK3β | (Lei *et al.*, 2022) |

*Table. 2 is continue……..*

| Pharmacological activity | Tested substance | Experimental animals/cell | Model | Tested living system/organ/cell | Dose range and administration route | Time period of application | Results | References |
|---|---|---|---|---|---|---|---|---|
| | | Rats | Diabetic model with back skin wound | Skins | T.D. | 14 d | ↑cutaneous wound healing | |
| Effects on coagulation | | | | | | | | |
| | PNS | Rats | Rat hypercoagulable model | Blood and lungs tissues | 10,100,200 mg/kg; oral | 1 h | ↑PPAR-γ, PI3K, p-Akt, p-Enos, APTT, PT, FIB, p21, FABP4 | (Dai *et al.*, 2022) |
| | PNS of raw NRR/steamed NRR; Polysaccharides of raw NRR/steamed NRR; Water extracts of raw NRR/steamed NRR | Mice | Model of acute Xueyu | Blood, liver and spleen | 0.22,0.40,1.62 g/kg; oral | 9 d | ↑red blood cells, hemoglobin, ↓hemosiderin deposition, inflammatory cell infiltration, whole blood shear rate, plasma viscosity | (Xiao *et al.*, 2020) |
| Effects on anemia | | | | | | | | |
| | Water extract of steamed NRR | Mice | Renal anemia | Blood and kidney tissues | 0.45,0.90,1.80 g/kg | 3 weeks | ↑the numbers of peripheral blood cells, the erythrocyte fragility, EPO, EPO receptor, HGF, Bcl-2 ↓TGF-β1, Bax | (Gao *et al.*, 2022) |
| | Water extract of steamed NRR | Mice | Blood Deficiency Syndrome | Blood, liver, spleen and kidney tissues | 0.4,0.8,1.6 g/kg | 12 d | ↑WBC, RBC, Hb, PLT, IL-2, STAT1, SHP2, Bcl2, Bcl-XL, c-Myc, p21 ↓p-JAK1 | (Zhang *et al.*,2020a) |
| Effects on the liver | | | | | | | | |
| | Notoginsenoside R1 | Rats | Liver fibrosis | Blood and liver | 25,50 mg/kg; i.p. | 6 weeks | ↑ALB, TP, p65, p-p65, p-ERK, p-JNK, p-p38, PPAR-γ, GSH, SOD, GST ↓ALP, AST, ALT, Coll-a1, α -SMA, TIMP1, MDA, IL-B, IL-1β, TNF-α | (Gong *et al.*, 2022) |
| Effects on inflammation | | | | | | | | |

*Table. 2 is continue……..*

| Pharmacological activity | Tested substance | Experimental animals/cell | Model | Tested living system/organ/cell | Dose range and administration route | Time period of application | Results | References |
|---|---|---|---|---|---|---|---|---|
| | PNS | Rats | Myocardial ischaemia–reperfusion injury | | 50 mg/kg; i.p. | 1 h | ↑−dp/dt max, mLVDP, Kir6.1, Kir6.2, SUR1, SUR2<br>↓+dp/dt max, mLVSP, NLRP3, IL-6, TNF-α, MCP-1, p-NF κB/NF κB | (Ning *et al.*, 2020) |
| | Water extract of raw NRR and steamed NRR; Notoginsenoside R1, Ginsenoside Rg1 , Ginsenoside Re, Ginsenoside Rb1 and Ginsenoside 20(S)-Rg3 | RAW264.7 cell | LPS-induced inflammatory response | RAW264.7 cell | 1.0 μg/mL; 2.5, 5.0, 10, 20 and 40 μmol/L | 24 h | ↓TNF-α, IL-6 | (Zhang *et al.*,2019) |
| Effects on immunomodulation | | | | | | | | |
| | PNS | Piglets | Piglets infected with Porcine Reproductive and Respiratory Syndrome Virus | Blood, lungs, thymus, and lymph nodes | 10 mg/kg; oral | 28 d | ↑IFN-α, IFN-β, PRRSV-neutralizing antibodies<br>↓HP-PRRSV viremia and tissue viral load | (Yang *et al.*, 2024a) |
| | PNPB1 | Mice | Cyclophosphamide induced immunosuppressive mice | Immune organs | 5,20 mg/kg; i.p. | 14 d | ↑body weight, WBC, thymus and spleen indices, splenic lymphocyte proliferation, TNF-α, IL-2, IL-10, IFN-γ, TLR2 | (Jiang *et al.*, 2023) |
| | Ethanol extract of raw and steamed NRR | Zebrafish | Zebrafish tail-fin amputation model | Zebrafish | 30,50 μg/mL | 2,4 h | ↑apoptosis of neutrophils<br>↓the number neutrophils, | (Xiong *et al.*, 2022) |
| Effects on tumour inhibition | | | | | | | | |

*Table. 2 is continue……..*

| Pharmacological activity | Tested substance | Experimental animals/cell | Model | Tested living system/organ/cell | Dose range and administration route | Time period of application | Results | References |
|---|---|---|---|---|---|---|---|---|
| | Ethanol extract of NRR | LNCaP cells, 22Rv1 cells, HPrEC | LNCaP cells, 22Rv1 cells, HPrEC | LNCaP cells, 22Rv1 cells, HPrEC | 1,2, 3, 4 , 5 mg/mL | 24,48 h | ↓IL-4 | (Hawthorne *et al*., 2022) |
| | PNS | Mice | Colitis-associated colorectal cancer model | Blood and colon tissues | 75,150 mg/kg | 5 d | ↓IL-1β, macrophage accumulation, Treg cells proportion, IDO1 | (Li *et al*., 2022) |
| | PNS | Mice | MMTV-PyMT (FVB) spontaneous breast cancer transgenic mouse model | Tumor tissue | 80,160 mg/kg; oral | 21 d | ↑Body weight, AOD CD31, CD4+, CD8+ ↓Weight of tumor, IL-6, IL-10, TNF-α, EphA2 | (Xia *et al*., 2023) |
| | PNS | Pancreatic cancer Miapaca2 and PANC-1 cells | Pancreatic cancer Miapaca2 and PANC-1 cells | Pancreatic cancer Miapaca2 and PANC-1 cells | 100 μM | 48 h | ↑Bax, p62 ↓MMP2, MMP9, Bcl2, LC3B-II/LC3B-I | (Yao *et al*., 2021) |
| Effects on antioxidant | | | | | | | | |
| | PNS | Rats | Disc degeneration in a puncture-induced rat model. | Co8/9 segments | 160, 200 mg/kg; i.p. | 8 weeks | ↑COL2A1 ↓MMP13 | (Guo *et al*., 2024) |
| | | Human nucleus pulposus cells | Human nucleus pulposus cells | Human nucleus pulposus cells | 0.01,0.1, 1, 5, 1 0,50 μg/mL | 24 h | ↑ COL2A1, ACAN, p-AKT, p-MTOR, P62 ↓caspase 3, Bax/Bcl-2, MMP13, LC3II, Atg7, ADAMTS-5 | |
| | PNS | Human umbilical vein endothelial cells | Human umbilical vein endothelial cells | Human umbilical vein endothelial cells | 0.05, 0.5,1 mg/mL | 48 h | ↑SOD, SIRT1, TGF-β1 ↓caspase-3, MCP-1, MDA, iNOS, COX-2 | (Yang *et al*., 2020) |
| | Water extract of raw NRR and steamed NRR | PC12 cell | PC12 cell | PC12 cell | 50, 100,200 μg /mL | 24 h | ↑the ORAC value | (Ma *et al*., 2022) |

*Table. 2 is continue……..*

| Pharmacological activity | Tested substance | Experimental animals/cell | Model | Tested living system/organ/cell | Dose range and administration route | Time period of application | Results | References |
|---|---|---|---|---|---|---|---|---|
| Effects on neuroprotection | | | | | | | | |
| | PNS | Mice | Age-related Alzheimer's disease | The brain and hippocampal tissues | 50,100 mg/kg; i.p. | 8 weeks | ↑GSH-Px activity, SOD, GSH, LC3-II/I, PINK, Parkin, OPTN, NDP52 ↓8-OHdG, MDA | (Yang *et al.*, 2024b) |
| | PNS | PC12 cell | Aβ1-42-induced cell damage | PC12 cell | 0.78,1.56,3.12,6.25,12.5,25,50,100,200,400,800 mg/L | 24 h | ↑LC3II/I, Parkin ↓p62, OPTN | (Jiang *et al.*, 2022) |
| | PNS | Rats | CCL2-induced cognitive deficits | Hippocampus | 50,100,200 mg/kg; bilateral hippocampal injection | 14 d | ↑GLT-1, GLAST, SOD ↓PAG, MDA, IL-6, IL-1β, IL-18, CXCL-10, Caspas-8, Caspase-9, Caspase-3, Bax/BCL-2 | (Zhou *et al.*, 2020a) |
| Effects on the kidney | | | | | | | | |
| | PNS | Mice | Diabetic Nephropathy | Urine, blood and the bilateral kidneys | 50,100,200 mg/kg; oral | 8 weeks | ↑SOD, GSH, Nrf2, HO-1 ↓urine volume, UPro, UAlb, BG level, Scr, BUN, MDA, CRP, TGF-β1, IL-6 | (Mi *et al.*, 2022) |
| | PNS | Rats | Chronic kidney | The kidney, ileum, colon tissues, blood and urine | 40, 80, 160 mg/kg; oral | 28 d | ↑Occludin, ZO-1, SIgA levels ↓TNF-α, MCP-1, IL-1β, IL-18, TMAO, p65, NLRP3, α-SMA, smad3, DAO levels, D-LA levels | (Xie *et al.*, 2022) |
| Effects on aging | | | | | | | | |
| | Panax notoginseng oligosaccharides | NIH-3T3 cells | The Replicative Senescence Cell Model | NIH-3T3 cells | 15.63,31.25,62.5 μg/mL | 24,48 h | ↑migration ability, COL-I, PCNA, cyclin E, cyclin D1, CDK4, p-MEK/MEK, p-p38/p38, p-ERK1/ERK1, p-ERK2/ERK2, p-Pax/Pax, p-Smad2/Smad2, p-Smad3/Smad3, TGF-β1 ↓SA-β-Gal activity, p61, p62 | (Zhai *et al.*, 2021) |
| | PNS | Chondrocytes | TNF-α induced osteoarthritis model | Chondrocytes | 100,200 μg/mL | 24 h | ↑MiMP, Bcl-2 ↓IL-1β, HMGB1, caspase-8, p16, MPTP, caspase-3, Bax | (Zhang *et al.*,2020b) |
| | | Rats | The osteoarthritis model | The cartilage sections | 75 μg/mL; intra-articular injection | 2 months | ↑Bcl-1, LC3II/LC3I, COL-II ↓p-PI3K/PI3K, p-AKT/AKT, p-mTOR/mTOR, MMP-3, MMP-13 | |

*Table. 2 is continue……..*

Additionally, PNS reduces oxidative stress-induced apoptosis in human umbilical vein endothelial cells by upregulating SIRT1 and antioxidant expression levels, thereby mitigating cardiovascular damage induced by advanced glycation end products (Yang *et al*., 2020).

With increased steaming time and temperature, native saponins significantly convert into less polar derivatives. The antioxidant activity of NRR increases with higher processing temperatures, indicating that steaming temperature represents a more critical factor than duration in enhancing antioxidant activity (Ma et al., 2022).

***Effects on neuroprotection***

NRR has been used for centuries in China to treat neurological damage from cerebral ischemia and other conditions. Mitochondrial dysfunction characterizes neuronal damage in Alzheimer's disease, where selective engulfment and degradation of damaged mitochondria via autophagosomes alleviates neuronal impairment. PNS enhances the PINK1/Parkin pathway, promoting hippocampal mitophagy, thereby preventing brain oxidative stress and ultimately improving cognitive function (Yang *et al*., 2024b). PNS also protects Aβ-damaged PC12 cells by activating mitophagy independently of PINK1, thus mitigating neuronal injury (Jiang *et al*., 2022). Additionally, PNS alleviates CCL2-induced learning and memory impairments, potentially by reducing NMDA receptor overactivation through mitigation of glutamate metabolism dysfunction (Zhou *et al*., 2020a). Similarly, steaming enhances NRR's neuroprotective capabilities (Ma *et al*., 2022).

***Effects on the kidney***

PNS, as NRR's primary active compound group, significantly contributes to treating kidney diseases. Diabetic nephropathy, a chronic diabetic complication and leading cause of end-stage renal disease, can be improved by PNS through activation of the Nrf2/HO-1 axis, exerting antioxidant and anti-inflammatory effects (Mi *et al*., 2022). Additionally, PNS benefits chronic kidney disease. Research indicates that PNS modulates gut microbiota and inhibits activation of pro-inflammatory and pro-fibrotic proteins in kidneys, thereby suppressing renal inflammation and fibrosis. This may be achieved by restoring gut microbiome composition, enhancing microbial barrier function and regulating microbial compounds (Xie *et al*., 2022).

***Effects on aging***

Skin aging typically accompanies replicative senescence of dermal fibroblasts, characterized by proliferative capacity loss, cell cycle arrest, reduced cell elongation and decreased extracellular matrix synthesis (Gu *et al*., 2020). TCM proposes that blood-nourishing effects impart rosy, lustrous complexion, implying anti-aging benefits—a vibrant research area for NRR (Fan *et al.*, 2025).

Oligosaccharides purified from NRR reverse replicative senescence of fibroblasts by promoting proliferation, migration and collagen-I synthesis, thereby improving skin aging (Zhai *et al*., 2021). PNS ameliorates cartilage degradation in osteoarthritis, potentially by protecting chondrocytes from senescence and apoptosis through PI3K-AKT pathway inhibition (Zhang *et al*., 2020b).

Moreover, two novel polysaccharides, MRP5 and MRP5A, identified in NRR, demonstrate relatively low antioxidant capacity *in-vitro* but exhibit strong antioxidant stress and lifespan-extending effects in *Caenorhabditis elegans* (Feng *et al*., 2019). These findings highlight NRR's potential in anti-aging product development.

## DISCUSSION

This review systematically establishes that processing serves as a decisive scientific intervention that fundamentally reprograms the therapeutic identity of Notoginseng Radix et Rhizoma (NRR). Through meticulous analysis of compound transformations and their corresponding pharmacological consequences, we demonstrate that the traditional axiom of "raw for dispersion, processed for tonification" represents more than empirical wisdom—it embodies a sophisticated system of bioactivity modulation rooted in molecular restructuring. The conversion of primary ginsenosides into rare analogues through thermal processing does not merely modify individual compound profiles but orchestrates a comprehensive shift in therapeutic signature, quantitatively evidenced by the suppression of hemostatic functions (Dai *et al*., 2022) and simultaneous enhancement of hematopoietic (Gao *et al*., 2022; Zhang *et al*.,2020a), immunomodulatory (Jiang *et al*., 2023; Yang *et al*., 2024a) and neuroprotective capacities (Yang *et al*., 2024b; Jiang *et al*., 2022).

The implications of these findings extend beyond NRR itself, positioning this herb as a paradigmatic model for understanding a fundamental principle in herbal medicine: that processing constitutes a critical determinant of therapeutic outcomes. This principle finds consistent validation across diverse medicinal species (Yang *et al*., 2023a; Yang *et al*., 2023b), suggesting a universal pharmacological paradigm where controlled processing unlocks latent therapeutic potentials. However, our synthesis reveals significant asymmetries in current research priorities. While saponin transformations have received substantial attention, the parallel modifications occurring in polysaccharide architectures and other non-saponin compounds remain largely uncharted territory. Furthermore, the almost exclusive focus on steaming has marginalized investigation of alternative processing methods, creating a fragmented understanding of NRR's full processing potential. Most critically, the capacity of processing to mitigate inherent toxicity—a well-

documented phenomenon in herbal processing—remains virtually unexplored in the NRR context, representing a critical frontier for safety optimization (Shan *et al*., 2024).

To advance beyond these limitations, the field must embrace an integrated research paradigm that simultaneously addresses multiple knowledge gaps. Future investigations should pursue comprehensive characterization of diverse processing techniques to establish chemistry-driven protocols aligned with specific clinical applications. Parallel efforts must systematically decode the therapeutic contributions of non-saponin compounds to realize both full pharmacological potential and resource sustainability. Concurrently, elucidating the biosynthetic regulation of key compounds will enable quality optimization through synergistic agricultural and processing interventions. This multidimensional approach will transform NRR from a traditionally used herb into a precisely characterizable therapeutic agent with defined chemical and pharmacological properties.

In conclusion, this review recontextualizes NRR processing from traditional practice to scientifically grounded strategy for therapeutic optimization. By mapping compound transitions to specific pharmacological outcomes, we provide a robust framework that not only validates traditional knowledge but also establishes a definitive trajectory for future research. This integrated perspective promises to accelerate the transition of NRR from ethnopharmacological tradition to evidence-based medicine while establishing new standards for herbal medicine research that harmonize traditional wisdom with contemporary scientific rigor.

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***Authors' contributions***
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***Ethical approval***
Not applicable.

***Data availability statement***
All data generated or analysed during this study are included in this published article.

***Conflict of interest***
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper and its supplementary information files.

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