Drug Design, Development and Therapy

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REVIEW

A Review of the Therapeutic Potential of Ginseng and Its Bioactive Components in Nonalcoholic Fatty Liver Disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is the major cause of chronic liver disease worldwide, with no universally recognized effective treatments currently available. In recent years, ginseng and its principal active components, such as ginsenosides, have shown potential protective effects in the treatment of these liver diseases. In NAFLD, studies have demonstrated that ginseng can improve hepatic lipid metabolism, reduce inflammatory responses, and inhibit oxidative stress and fibrosis, thereby attenuating the progression of NAFLD. Additionally, ginseng inhibits oxidative stress by scavenging free radicals and enhancing antioxidant enzyme activities, and it can impede fibrosis by interfering with the fibrotic signaling pathways. These combined effects contribute to attenuating the progression of NAFLD. These findings highlight the promise of ginseng as a potential therapeutic candidate for the treatment of NAFLD. However, despite the significant efficacy of ginseng in human NAFLD treatment, the number and quality of clinical studies remain limited, with a lack of large-scale, multicenter clinical trials to confirm these effects. Moreover, the pharmacokinetic properties of different ginsenosides, optimal therapeutic dosages, and the safety of long-term use require further investigation. This review summarizes the existing evidence on the mechanisms of action of ginseng and its active components in human NAFLD, assesses their potential as therapeutic options, and proposes future research directions to provide stronger scientific support for clinical application. Additionally, we performed a network pharmacology analysis of ginseng in relation to NAFLD to identify and investigate potential targets of ginseng in the treatment of NAFLD. This analysis aims to provide a theoretical foundation for the development of ginseng -based drugs for combating NAFLD.

Keywords: ginseng, bioactive components, NAFLD, NASH

Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as a rapidly escalating global health concern that demands our immediate attention. It is estimated to impact approximately one-quarter of the adult population.[1] NAFLD represents the hepatic manifestation of metabolic syndrome and encompasses a broad spectrum of liver conditions. This spectrum progresses from the relatively mild simple steatosis to the more severe non-alcoholic steatohepatitis (NASH), which can further lead to fibrosis, cirrhosis, and ultimately, the life-threatening hepatocellular carcinoma (HCC).[2] The high prevalence of NAFLD, along with its associated morbidity and the potential for such a serious progression, makes it a critical public health issue. Significantly, despite its prevalence and severity, there is currently a lack of approved pharmacotherapy that specifically targets NAFLD. This absence of targeted treatment options strongly emphasizes the urgent need for the development of novel and effective therapeutic approaches.

Received: 13 October 2024
Accepted: 10 December 2024
Published: 8 January 2025

Ginseng, a traditional medicinal or functional food with a long history of use in East Asia,[3] has gained significant attention in recent years for its potential therapeutic effects in metabolic disorders, including NAFLD.[4] The primary bioactive constituents of ginseng, known as ginsenosides, have been extensively studied for their hepatoprotective properties. Among these, ginsenosides Rg1, Rg3 and Rb1 have shown particular promise in preclinical models of NAFLD.[5] Ginsenoside Rb1 has been demonstrated to enhance lipid metabolism by activating AMP-activated protein kinase (AMPK), leading to reduced hepatic lipid accumulation.[6] This suggests that ginseng and its ginsenosides may hold great potential in the management of NAFLD.

However, despite these promising findings, the clinical application of ginseng in the treatment of NAFLD is hampered by several significant challenges. One of the primary obstacles is the poor bioavailability of ginsenosides, which undergo extensive metabolism in the gastrointestinal tract and liver, resulting in low systemic concentrations and limited therapeutic efficacy.[7] Furthermore, variability in ginseng composition due to differences in species, cultivation conditions, and extraction methods complicates the standardization of ginseng-based treatments.[8,9] These factors, coupled with a lack of large-scale, well-designed clinical trials, have limited the translation of preclinical successes into clinical practice.

In light of these challenges, this review is of crucial importance as it aims to comprehensively and critically evaluate the existing evidence regarding the efficacy of ginseng and its ginsenosides in treating NAFLD. We will delve deep into the molecular mechanisms that underlie their hepatoprotective effects, thoroughly discuss the limitations associated with their clinical application, and identify the key areas that require further research to enhance the therapeutic potential of ginseng in the management of NAFLD. By doing so, we hope to provide a clearer understanding of the current state of knowledge and pave the way for future investigations and potential improvements in the treatment of this prevalent liver disease.

The Role of Ginseng and Its Constituents in Ameliorating Nonalcoholic Fatty Liver Disease

Improve Lipid Metabolism

In recent years, the incidence of NAFLD has gradually increased and has become one of the most common chronic liver diseases in the world. With further research into the pathogenesis of NAFLD, there is increasing evidence that ginseng and its active ingredients have significant therapeutic potential in the population, especially in improving lipid metabolism.[10] Ginseng and its components play an important role in NAFLD and NASH (Figure 1 and Table 1). Several studies have reported the therapeutic effect of ginsenoside extracts in NAFLD (Figure 2). For example,

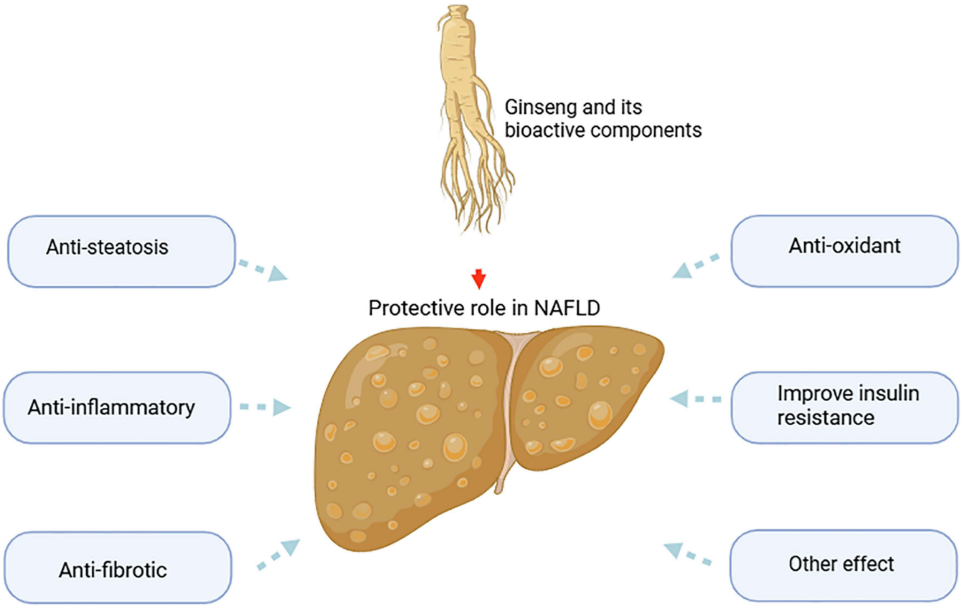

Figure 1 Protective effect of ginseng and its components on NAFLD.

 https://doi.org/10.2147/DDDT.S500719

Table 1 Pharmacological Effects of Ginseng and Its Components in NAFLD

Name	Regulatory Mechanism	Dose	Cell Line/ Experiment	References
Ginsenoside Rf	Reduces lipid accumulation	12.5 and 25μM	HepG2 cells	[11]
Ginsenoside Re	Inhibits lipid metabolism disorders and inflammatory responses by modulating the PI3K/AKT and TLR4/NF-κB signaling pathways	20 and 40mg/kg	Male C57BL/6 mice	[4]
Ginsenoside Rb1	Reduces fatty liver by activating AMPK	10mg/kg	Rats	[6]
Ginsenoside Rb2	Alleviates hepatic lipid accumulation by restoring autophagy via the induction of sirt1 and activation of AMPK	10mg/kg	C57BL/KsJ-Lepdb (db/db) mice	[12]
Ginsenoside Rg1	Exerts anti-apoptotic effects on non-alcoholic fatty liver cells by downregulating the expression of SGPL1	0.2, 0.4 and 0.6mM	HHL-5 cells	[13]
Ginsenoside Rg1	Inhibits lipogenesis, and decreases intracellular lipid content, adipocyte size, and adipose weight.	20mg/kg	Male KM mice	[14]
Ginsenoside Rg1	Improves liver function in NAFLD	100mg/kg	Male SD rats	[15]
Notoginsenoside R1, ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rd, and ginsenoside Re	Reduce TG and TC	6.9%, 28.0%, 29.7%, 7.3%, and 3.8%	L02	[16]
PDS-C	Reduces blood lipids, anti-inflammatory, and antioxidant properties as well as improves insulin resistance	80mg/kg	C57BL/6 male mice	[17]
Ginsenoside compound K	Reduces LD accumulation and LD marker protein PLIN2 expression	1μM	HuH7 cells	[19]
CMCs	Prevents lipid accumulation and mitochondrial oxidative stress, and enhances mitochondrial biogenesis	75, 150 and 300mg/kg	Male C57BL/6 mice	[20]
NabCK	Inhibits lipid-induced differentiation	20μg/mL	3T3-L1 peadipocytes and HepG2 hepatocytes	[21]
Ginseng berry	Normalizes mitochondrial function and glucose metabolism	100mg/kg	Male C57BL/6 mice	[22]
Lactobacillus fermentum KP-3-fermented ginseng	Ameliorates hyperlipidemia and liver injury	450mg/kg	Male mice	[23]
Ginsenoside Rg3	Suppresses VCAM-1 expression in liver sinusoidal endothelium	5mg/kg	Male C57BL/6 mice	[24]
Ginsenoside Rd	Reduces peroxidative damage and inflammation	5, 10, 15mg/kg	C57BL/6 mice	[25]
Ginsenoside Rg1	Inhibits inflammation and promotes metabolic homeostasis	40mg/kg	Male C57BL/6 mice	[26]
Ginsenoside Rg1	Alleviates liver inflammation	20 and 40mg/kg	Female C57BL/6 mice	[27]
Ginsenosides Rc	Attenuates hepatocytes' damage and oxidative stress in ALD by up-regulating the SIRT6/NRF2 pathway	5, 10 and 20mg/kg	Wild-type C57BL/6 mice and liver specific Sirt6-deficient mice	[28]
Compound K and ginsenoside Rh1	Ameliorate the liver function impairment	3mg/kg	SD rats	[29]
Ginseng saponin enriched in Rh1 and Rg2	Inhibits inflammation-mediated pathological inflammasome activation in macrophages	50 and 150mg/kg	Male C57BL/6 mice	[30]
Total saponins of Panax japonicus	Improves liver function and decreases the lipid level in the serum	100 and 300mg/kg	BABL/c mice	[31]

(*Continued*)

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Table 1 (Continued).

Name	Regulatory Mechanism	Dose	Cell Line/ Experiment	References
KRG	Reduces NASH related inflammation	50, 100, 200ng/mL or 100, 200, 400mg/kg	RAW 264.7 cells and mice	[32]
GBCK25	Ameliorates steatosis and inflammation	10, 20, 100, 200 and 400mg/kg	Male C57BL/6 wild-type mice	[33]
Panax ginseng extract	Prevents obesity and histological features of nonalcoholic steatohepatitis	100mg/kg	Wistar rats	[34]
Panaxydol	Reduces tissue inflammations through disruption of NLRP3 inflammasome	20μg/mL	Primary mouse bone-marrow-derived macrophage	[35]
JRG-M	Reduces lipogenesis by modulating AMPK	50, 100, 200 and 400mg/kg	Male C57BL/6 mice	[36]
Ginseng seed oil	Ameliorates hepatic lipid accumulation	25,50μg/mL and 500mg/kg	HepG2 cells and C57BL/6 mice	[37]
Ginsenoside Re	Reduces blood glucose and lipid levels	0–80μM and 5, 10, 20mg/kg	HepG2 cells and C57BL/6 mice	[38]
Ginsenoside Rg1	Ameliorates palmitic acid-induced insulin resistance	10–80μM	HepG2 cells	[39]
Ginsenoside Rg3	Reduces lipid accumulation and TGs	0, 5, 25, 50μM and 1mg/kg	3T3-L1 cells and C57BL/6 male mice	[40]
Ginsenoside Mc1	Improves liver steatosis and insulin resistance by attenuating ER stress	50, 100μg/mL and 10mg/kg	HepG2 cells and male C57BL/6 mice	[41]
Protopanaxatriol	Reduces body weight, serum lipid levels and improves insulin resistance,	50μM and 100mg/kg	3T3-L1 adipocytes and FemaleC57BL/6 mice	[42]
Chinese ginseng	Prevents the development of obesity and insulin resistance	0.5g/kg	Male C57BL/6 mice	[43]
GE	Improves HFD-induced NAFLD	100 and 200mg/kg	C57BL/6 male mice	[44]

ginsenoside Rf significantly reduced lipid accumulation in the liver, showing its potential in improving NAFLD-associated abnormal lipid metabolism.[11] In addition, ginsenoside Re improves NAFLD-induced lipid metabolism disorders and inflammatory responses by regulating the phosphoinositol-3 kinase (PI3K)/protein kinase B (AKT) and Toll-like receptor 4 (TLR4)/NF-κB signaling pathways.[4] Ginsenoside Rb1 has demonstrated a significant ability to reduce hepatic fat accumulation, making it a promising candidate for treating fatty liver disease.[6] Similarly, ginsenoside Rb2 improves NAFLD and glucose tolerance by restoring autophagy and reducing hepatic lipid accumulation through the induction of sirtuin-1 (SIRT1) and activation of AMPK.[12] Ginsenoside Rg1 not only reduces hepatic steatosis but also inhibits apoptosis, showing potential clinical value in NAFLD patients.[13] Further studies have revealed that ginsenoside Rg1 exerts anti-lipogenic and anti-obesity effects by inducing AMPK activation, inhibiting lipogenesis, and reducing intracellular lipid content and adipose tissue mass.[14] Additionally, ginsenoside Rg1 improves the pathological process of NAFLD through mechanisms closely associated with the Atf3 and Acox2 genes.[15] In the treatment of NAFLD and related disorders, raw and processed Notoginseng Radix et Rhizome (NRR) exhibits superior lipid-regulating effects compared to other preparation methods, primarily due to its active components, including notoginsenoside R1, ginsenoside Rg1, ginsenoside Rb1, and ginsenoside Rd. These components exert lipid-lowering effects by regulating molecules such as hydroxymethyl glutaric acyl coenzyme A reductase (HMG-CoAR), sterol regulating element binding protein-2

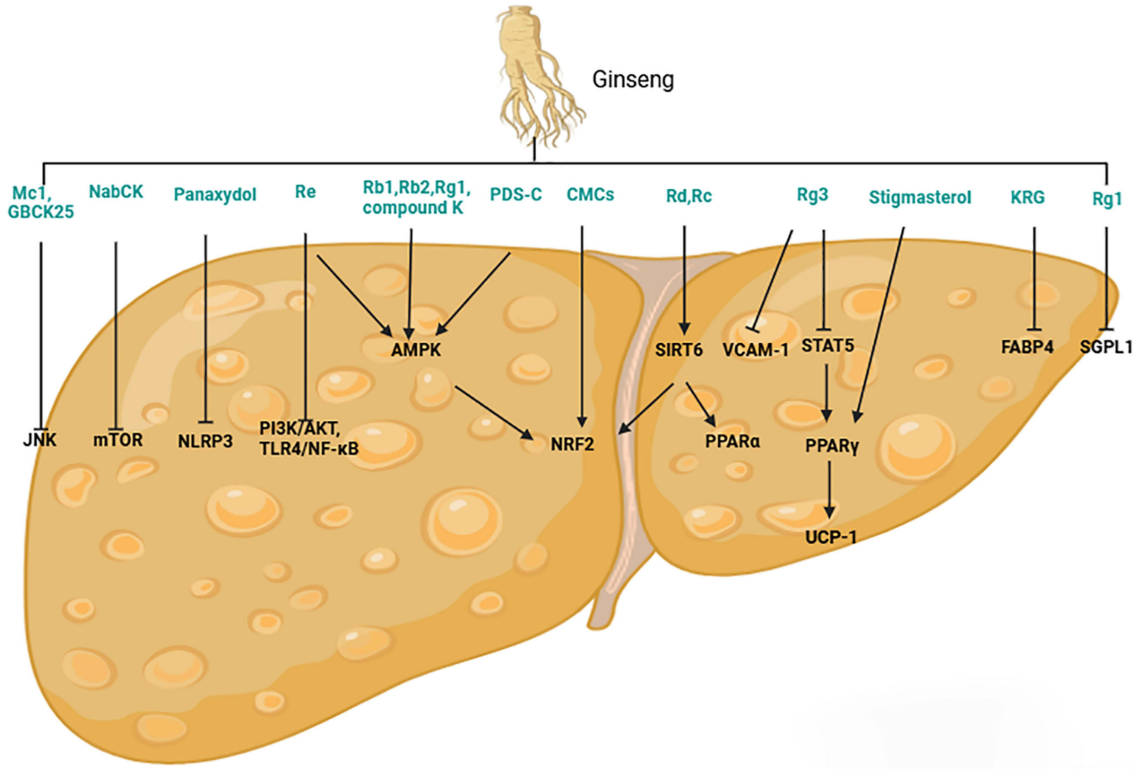

Figure 2 Mechanism of ginseng and its components against NAFLD.

(SREBP-2), and cholesterol 7α-hydroxylase (CYP7α).[16] Moreover, the panaxadiol saponin component (PDS-C) isolated from total ginsenosides has shown significant hepatoprotective effects in NAFLD mice, ameliorating hepatic steatosis and blood lipid levels while reducing oxidative stress and inflammation.[17] Compound K, a major active metabolite of ginsenosides, reduces lipid accumulation and lipogenesis in hepatocytes by upregulating AMPK activity and peroxisome proliferator-activated receptor (PPAR)-α-related pathways, highlighting its therapeutic potential for hepatic steatosis and related diseases.[18,19] Wild ginseng cambial meristematic cells (CMCs) improve high-fat diet (HFD)-induced hepatic injury by enhancing mitochondrial function and alleviating oxidative stress.[20] NabCK, composed of the natural compound ginsenoside CK and albumin, restores lipid homeostasis and alleviates lipotoxicity in steatotic hepatocytes by promoting lipid export, inhibiting de novo lipogenesis (DNL), and forming a mammalian target of rapamycin (mTOR)-regulated feedback network.[21] Metabolomic analysis revealed significant changes in overall liver metabolites in mice fed with HFD supplemented with ginseng berry, indicating that many metabolites involved in pathways such as mitochondrial function, glucose, lipid, and amino acid metabolism were altered.[22] Furthermore, *Lactobacillus fermentum* KP-3-fermented ginseng significantly lowers serum TC and LDL levels, inhibits hepatic aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and reduces hepatic lipid accumulation induced by a HFD.[23] These findings suggest that ginseng and its components hold substantial potential for the treatment of metabolic diseases, particularly NAFLD.

In summary, while the potential of ginseng and its components for NAFLD treatment is evident from the existing findings, more rigorous research efforts, including extensive clinical trials and detailed mechanistic studies, are required to fully confirm their efficacy and pave the way for their successful clinical application.

Anti-Oxidant, Anti-Inflammatory and Anti-Fibrosis

Ginseng and its components have demonstrated significant antioxidant, anti-inflammatory, and anti-fibrotic effects in the treatment of NAFLD. Ginsenoside Rg3 has been shown to improve NAFLD lesions in mice by inhibiting the adhesion of inflammatory cells to the vascular endothelium.[24] Ginsenoside Rd, on the other hand, ameliorates NAFLD symptoms by

https://doi.org/10.2147/DDDT.S500719

activating the SIRT6/PPAR-α signaling pathway, which reduces reactive oxygen species (ROS) production, inflammation, and enhances fatty acid β-oxidation.[25] Additionally, ginsenoside Rg1 protects the liver from age-related fatty liver disease by maintaining hepatic forkhead box protein O1 (FOXO1) activity, thereby enhancing its antioxidant capacity and reducing the senescence-associated secretory phenotype (SASP) and inflammation.[26] Ginsenoside Rg1 not only improves hyperlipidemia and lipid peroxidation but also alleviates endoplasmic reticulum stress and inflammation, thus protecting liver function and providing effective protection against NAFLD.[27] Ginsenoside Rc improves mitochondrial stress, oxidative stress, and inflammatory damage induced by a high-fat diet by activating the SIRT6-PPAR-α axis.[28] Studies have also shown that ginsenosides compound K and Rh1 can reverse hepatocyte damage and liver fibrosis induced by a HFD.[29] Saponin extract reduces mtROS production and protects against NAFLD by inhibiting the NLRP3 inflammasome and promoting mitochondrial autophagy.[30] The total saponins of Panax japonicus have shown potential protective effects against hepatic fibrosis in fatty liver disease by inhibiting endoplasmic reticulum stress and C/EBP homologous protein (CHOP) and c-Jun NH2-terminal kinase (JNK)-mediated apoptosis and inflammatory pathways.[31] KRG has demonstrated significant efficacy in the treatment of inflammation and fibrosis related to NAFLD and NASH.[5,32,45] Fermented ginseng, GBCK25, alleviates NASH severity by regulating cytochrome P450 2E1 (CYP2E1) and its associated c-Jun N-terminal kinase (JNK)-mediated cellular damage.[33] Panax ginseng extract can prevent the histological features of obesity and non-alcoholic steatohepatitis, such as steatosis and inflammation.[34] Panax ginseng extract and its component panaxydol effectively inhibit the expression of the NLRP3 inflammasome and various adipogenesis-regulating genes, thereby ameliorating inflammation and fibrosis in NASH.[35] Panax ginseng berry extract effectively inhibits adipogenesis in 3T3-L1 adipocytes, significantly reducing lipid accumulation. It is hypothesized that ginseng extract may inhibit adipocyte differentiation and lipid accumulation by activating various adipogenesis-regulating genes, such as PPARγ and CCAAT/enhancer-binding protein (C/EBP-α).[46] JRG-single (JRG-S) and JRG mixtures (JRG-M) have been found to consistently reduce inflammation and fibrosis in NAFLD mice by modulating the AMPK signaling pathway.[36] These studies have provided valuable insights, revealing that ginseng and its active components exhibit remarkable potential in multiple crucial aspects. Specifically, they show great promise in antioxidant activities, which can help combat oxidative stress often associated with NAFLD and NASH. Moreover, their anti-inflammatory properties are also of significance. Inflammation plays a key role in the progression of these liver conditions, and the ability of ginseng and its components to counteract such inflammation positions them as potentially effective agents in treatment. Furthermore, their anti-fibrotic activities cannot be overlooked. Fibrosis is a serious consequence of NAFLD and NASH that can lead to further liver damage and complications. The presence of anti-fibrotic capabilities in ginseng and its active components suggests they could play a vital role in halting or even reversing the fibrotic process.

In summary, the evidence from these studies indicates that ginseng and its active components, with their antioxidant, anti-inflammatory, and anti-fibrotic potential, are highly promising candidates for the treatment of NAFLD and NASH. However, further research, including well-designed clinical trials, is still needed to fully confirm their efficacy and safety in actual clinical settings.

Improve Insulin Resistance

Numerous studies have shown that ginseng and its extracts play a significant role in regulating glucose and lipid metabolism, improving insulin sensitivity, particularly in obesity models induced by a HFD, where they exhibit strong metabolic regulatory potential. Saponins found in fermented ginseng root (FGR) and fermented ginseng berry (FGB) have demonstrated substantial benefits in counteracting HFD-induced obesity, with FGR showing stronger anti-hyperglycemic and anti-obesity effects. Notably, only FGB significantly inhibited the expression of inflammatory markers in adipose tissue.[47] Ginseng seed oil (GSO) effectively reduced hepatic steatosis and improved metabolic profiles, including dyslipidemia and insulin resistance, in HFD-fed mice. This anti-steatotic effect is likely mediated by the upregulation of Ppara, Sirt1, and Ppargc1a, which regulate the transcription of enzymes involved in fatty acid β-oxidation.[37] Ginsenoside Re exerts its effects by inducing SHP expression, inhibiting hepatic gluconeogenesis through the suppression of the CREB-CRTC2 complex, and reducing hepatic triglyceride synthesis by downregulating SREBP-1c and related lipogenic enzymes.[38] Ginsenoside Rg1 reverses palmitic acid-induced reduction in glucose uptake in HepG2

cells by downregulating the gluconeogenic genes glucose-6-phosphate (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK).[39] Ginsenoside Rg3 ameliorates insulin resistance and lipotoxicity associated with obesity both in vivo and in vitro via the STAT5-PPAR-γ pathway.[40] Ginsenoside Mc1 offers protective effects against endoplasmic reticulum stress-induced apoptosis, insulin resistance, and lipogenesis in palmitic acid-treated hepatocytes and obese mice, suggesting that Mc1 supplementation could be a potential therapeutic strategy for preventing NAFLD in patients with obesity and insulin resistance.[41] Protopanaxatriol has been shown to improve insulin resistance, reduce body weight, and alleviate hepatic steatosis in diet-induced obese mice and ob/ob mice.[42] Long-term dietary supplementation with Chinese ginseng has been found to prevent HFD-induced obesity in mice by improving insulin and leptin sensitivity, glucose tolerance, blood pressure, hepatic fatty acid oxidation, and plasma lipid profiles.[43] These findings have indeed shed light on an important aspect regarding ginseng and its active components. It has been observed that they possess a notable potential when it comes to improving insulin resistance. Insulin resistance is a crucial factor in the development and progression of various metabolic disorders, and the fact that ginseng and its active constituents show promise in this regard is quite significant. Moreover, their potential is not limited to just insulin resistance improvement. They also hold promise in addressing other associated metabolic disorders. This broader scope of potential impact on the overall metabolic health landscape further emphasizes their possible value in the realm of metabolic disease management.

In summary, the findings clearly suggest that ginseng and its active components have substantial potential in enhancing insulin resistance and dealing with associated metabolic disorders. However, while this initial indication is promising, it is by no means conclusive.

Regulate Intestinal Flora

In recent years, the modulation of gut microbiota has garnered significant attention in the treatment of NAFLD. A study found that ginsenoside extract (GE) improves HFD-induced NAFLD by maintaining energy balance, modulating gut dysbiosis, and enhancing gut integrity and metabolic inflammation. GE enhances the diversity of the bacterial community and causes dramatic changes in the composition of the gut microbiome by reducing the F/B ratio. In addition, GE promotes the popularity of beneficial bacteria (Parabacteroides, Muribaculaceae, Akkermansia, and Ruminococcus_torques_group) and decreases the prevalence of harmful bacteria (Lachnospiraceae and *Helicobacter*).[44] Specifically, GE's impact on NAFLD is closely linked to its role in the synergistic regulation of LPS- and SCFA-producing bacteria, the dysbiosis-mediated metabolic endotoxemia, and LPS-mediated NF-κB/IκB signaling pathway.[44] The gut microbiota plays a crucial role in various physiological processes, and its imbalance has been closely associated with the development and progression of NAFLD and related metabolic disorders. By having the potential to modulate the gut microbiota, ginseng and its active components could potentially influence these conditions in a positive way. This discovery thus offers new and valuable insights into the possible mechanisms through which ginseng and its components might work to improve NAFLD and related metabolic disorders. It also points towards promising directions for future therapeutic strategies, suggesting that targeting the gut microbiota with ginseng and its active components could be a fruitful approach in the treatment and management of these conditions.

In summary, these findings firmly underscore the significant potential of ginseng and its active components in modulating gut microbiota for the improvement of NAFLD and related metabolic disorders. This not only provides new perspectives on the role of ginseng and its components but also paves the way for further research and the development of more effective therapeutic strategies in the future.

Network Pharmacological Analysis

To explore and validate the action targets and molecular pathways of ginseng and its bioactive components in NAFLD, we conducted a network pharmacology analysis. Initially, we screened potential drug targets using The Encyclopedia of Traditional Chinese Medicine (ETCM) database (http://www.tcmip.cn/ETCM/index.php/Home/)[48] and the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (https://old.tcmsp-e.com/browse.php?qc=herbs).[49] The identified targets were submitted to the UniProt database[50] (https://www.uniprot.org/), with the species limited to "Homo sapiens".

Subsequently, we searched for NAFLD-related disease targets using the keywords "non-alcoholic fatty liver disease" in the GeneCards (https://www.genecards.org/),[51] therapeutic target database (TTD, https://db.idrblab.net/ttd/)[52] and Comparative Toxicogenomics Database (CTD, https://ctdbase.org/)[53] databases, resulting in 38130 unique disease target genes after eliminating duplicates. We then used the Venny 2.1.0 online tool (http://www.liuxiaoyuyuan.cn/)[54] to intersect the identified drug target genes with the disease target genes. This analysis revealed 820 overlapping genes associated with both "ginseng" and "NAFLD" (Figure 3).

These intersecting genes have been identified as potential targets for the treatment of NAFLD using ginseng. To explore these targets, we conducted a series of analyses. Initially, the genes were uploaded to the STRING (https://cn.string-db.org/)[55] database to generate a protein-protein interaction (PPI) network. We set the species to "human" and used a comprehensive score of >0.4 as the threshold for inclusion in the network. The results were further visualized using Cytoscape 3.8.2 to identify the key targets of ginseng. The top 10 key intersection targets include protein kinase B (AKT1), interleukin-6 (IL-6), insulin gene (INS), SRC proto-oncogene (SRC), cAMP-dependent protein kinase catalytic subunit alpha (PRKACA), tumor necrosis factor (TNF), beta-actin (ACTB), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), heat shock protein 90 alpha family class A member 1 (HSP90AA1), hexose-6-phosphate dehydrogenase (H6PD) (Figure 3).

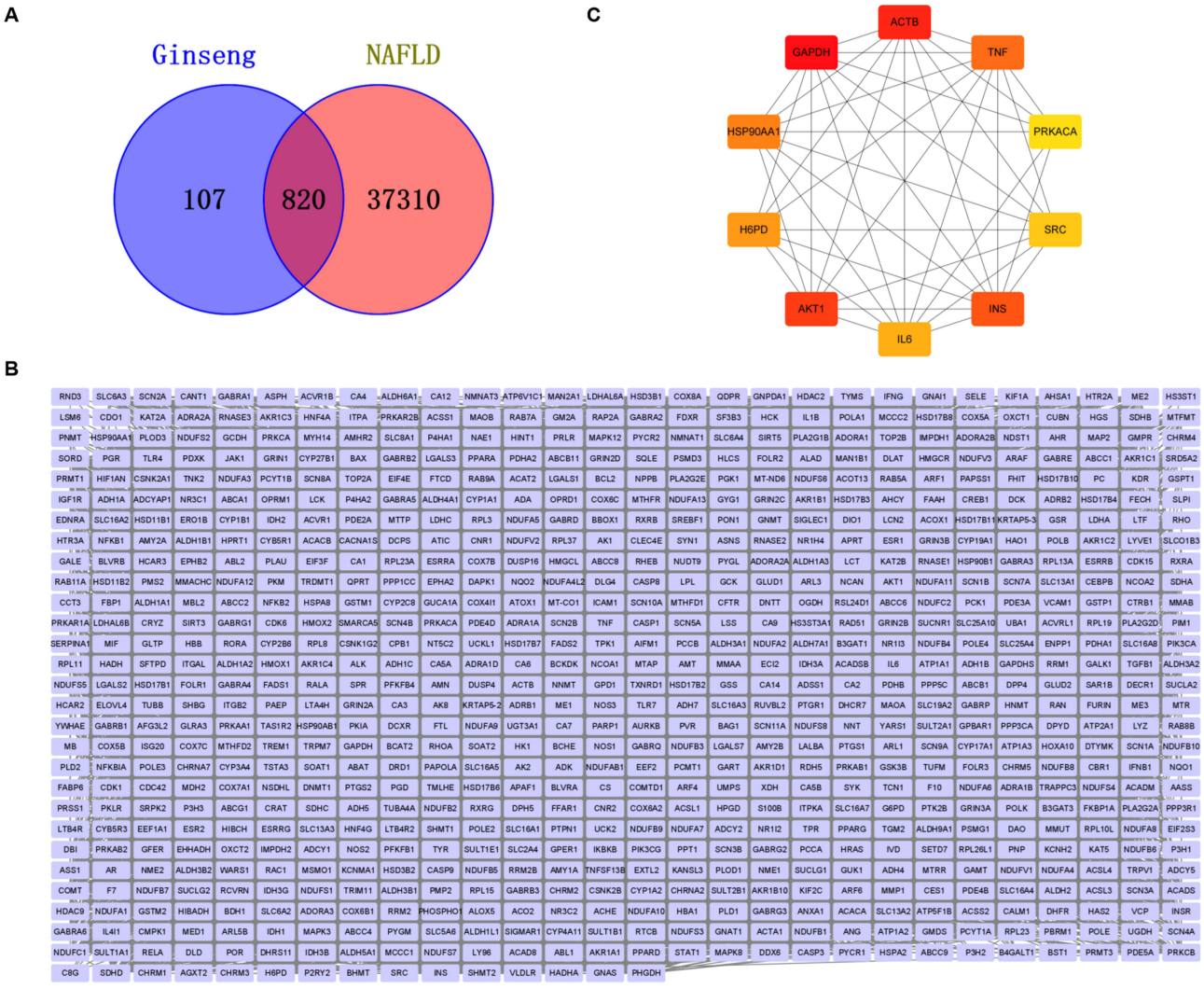

Figure 3 Identification of key targets. (**A**) Venn diagram of ginseng and NAFLD. (**B**) PPI networks of key targets. (**C**) Top 10 key targets.

Our findings demonstrate that ginseng exhibits strong targeting activity against NAFLD. Key components such as Adenosine Triphosphate, Adenosine, Adenine Nucleoside, Cetylic Acid, Hexadecanoic Acid, Palmitic Acid, Stigmasterol, Kaempferol, Cis-9, Cis-12-Linoleic Acid, Inositol, Linoleic, Linoleic Acid, Protopanaxadiol, Protopanaxatriol, Campesterol, M-Cresol and Î′-Sitosterol-3-(6-Linoleoyl) Glucopyranoside play crucial roles in the therapeutic effects of ginseng against NAFLD. Previous studies have indeed confirmed that stigmasterol and protopanaxatriol play important roles in the treatment of NAFLD.[56] These bioactive compounds target key proteins such as GABA receptor subunit beta3 (GABRB3), Nuclear receptor subfamily 3 group C member 1 (NR3C1), sodium/potassium-transporting ATPase subunit alpha-2 (ATP1A2), ATP1A3, nuclear factor NF-kappa-B p105 subunit (NFKB1), NFKB2, Solute carrier organic anion transporter family member 1B3 (SLCO1B3), Vitamin D3 receptor (VDR), 11-beta-hydroxysteroid dehydrogenase 1 (HSD11B1), and Serine/threonine-protein phosphatase PP1-gamma catalytic subunit (PPP1CC), which are critical in mediating ginseng's protective effects against NAFLD (Table 2). Consistently, studies have shown that ginseng and its active components exert effects in various diseases by targeting NR3C1,[57] NFKB1,[58] SLCO1B3,[59] VDR,[60] and HSD11B1.[61]

Concurrently, we conducted gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses. The gene data were input into the The Database for Annotation, Visualization and Integrated Discovery (DAVID)[62] database (https://david.ncifcrf.gov/), with the species set to "Homo sapiens", to analyze the enrichment of ginseng-related biological processes (BP), cellular components (CC), molecular functions (MF), and signaling pathways associated with NAFLD. We applied a *P*-value threshold of <0.05 and selected the top 10 enriched terms for BP, CC, and MF, along with the top 20 KEGG pathways, based on gene count. The results were then visualized using the Bioinformatics[63] online platform (https://www.bioinformatics.com.cn/). Furthermore, GO enrichment analysis primarily involve biological processes, cellular components, and molecular functions related to mitochondrial function, energy metabolism, transmembrane transport, neural signal transmission, and response to external stimuli. Additionally, KEGG pathway analysis revealed that the cAMP signaling pathway, Glucagon signaling pathway, cGMP-PKG signaling pathway, HIF-1 signaling pathway, Insulin signaling pathway, AGE-RAGE signaling pathway in diabetic complications, Thyroid hormone signaling pathway, Adipocytokine signaling pathway, C-type lectin receptor signaling pathway and

Table 2 The Top 10 Targets and Components of Ginseng in the Treatment of NAFLD

Degree	Name
398	Adenosine Triphosphate
154	Adenosine, Adenine Nucleoside
86	Cetylic Acid, Hexadecanoic Acid, Palmitic Acid
73	Stigmasterol
72	Kaempferol
64	Cis-9, Cis-12-Linoleic Acid, Inositol, Linoleic, Linoleic Acid
52	Protopanaxadiol
51	Protopanaxatriol
47	Campesterol, M-Cresol
44	Î′-Sitosterol-3-(6-Linoleoyl)Glucopyranoside
52	GABRB3
52	NR3C1
52	ATP1A2
52	ATP1A3
52	NFKB1
52	NFKB2
52	SLCO1B3
51	VDR
51	HSD11B1
51	PPP1CC

https://doi.org/10.2147/DDDT.S500719

Calcium signaling pathway are crucial in ginseng's anti-NAFLD effects. These pathways significantly contribute to the progression of NAFLD (Figure 4). Similar studies have also demonstrated that ginseng and its active components improve disease treatment by targeting multiple signaling pathways, including cAMP,[64] HIF-1,[65] Insulin,[66] AGE-RAGE,[67] and Calcium.[68]

Conclusions and Prospects

Ginseng, especially its major active components such as ginsenoside Rb1 and Rg3, has shown significant potential in ameliorating NAFLD. For instance, studies have demonstrated that ginsenoside Rb1 can effectively reduce hepatic steatosis by activating the AMPK pathway, which subsequently inhibits lipogenesis via downregulation of SREBP-1c expression.[69] Similarly, ginsenoside Rg3 has been reported to attenuate liver inflammation and fibrosis by modulating the NF-κB signaling pathway, thus preventing the progression of NAFLD to NASH.[70]

In addition to these well-studied components, network pharmacology has revealed several other bioactive compounds in ginseng, such as adenosine triphosphate, adenosine, adenine nucleoside, cetylic acid, hexadecanoic acid, palmitic acid, kaempferol, cis-9, cis-12-linoleic acid, inositol, linoleic acid, protopanaxadiol, campesterol, m-cresol, and Î′-Sitosterol-3-(6-Linoleoyl) Glucopyranoside. These compounds have shown the potential to target key molecular pathways, including the cAMP signaling pathway, glucagon signaling pathway, cGMP-PKG signaling pathway, HIF-1 signaling pathway, insulin signaling pathway, AGE-RAGE signaling pathway, thyroid hormone signaling pathway, adipocytokine signaling pathway, C-type lectin receptor signaling pathway, and calcium signaling pathway. Molecular targets such as GABRB3, ATP1A2, ATP1A3, NFKB2, and PPP1CC may also be crucial in mediating ginseng's therapeutic effects on NAFLD. Future studies should focus on these components and pathways to further explore their potential and better understand the mechanisms underlying ginseng's efficacy in NAFLD treatment.

However, despite these encouraging results, the clinical application of ginseng in NAFLD treatment remains limited by several factors. A primary concern is the poor bioavailability of ginsenosides, which are subject to extensive metabolism in the gastrointestinal tract and liver, significantly reducing their systemic concentration and therapeutic efficacy. For example, ginsenoside Rb1 undergoes deglycosylation in the intestine, resulting in less active metabolites with lower bioactivity.[71] Additionally, the variability in ginseng composition, influenced by factors such as the species, cultivation conditions, and extraction methods, complicates the standardization of ginseng-based therapies. For instance, Panax ginseng, commonly used in Asia, contains different ginsenoside profiles compared to American ginseng (Panax quinquefolius), leading to inconsistent therapeutic outcomes across studies.[72]

A few small-scale clinical studies have indicated potential benefits of ginseng in reducing liver fat content and improving liver enzyme levels in NAFLD patients, but these studies often suffer from small sample sizes, short durations, and lack of control groups, thereby limiting their generalizability. Furthermore, the potential for drug-herb interactions, particularly in patients with polypharmacy, poses an additional risk, as ginseng can influence the metabolism of other medications through cytochrome P450 enzymes, potentially leading to adverse effects. Moreover, while preclinical models have shown promising results, the translation to human clinical trials has been limited.

To overcome these challenges, future research should focus on enhancing the bioavailability of ginsenosides, possibly through novel delivery systems such as nanoparticles or liposomes. Additionally, standardized extraction and processing methods need to be developed to ensure consistent therapeutic outcomes. Well-designed, large-scale clinical trials are essential to confirm the efficacy and safety of ginseng in the treatment of NAFLD and to establish standardized dosing regimens.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

The authors acknowledge using Biorender (https://app.biorender.com/) to create the schemata (Figures 1 and 2).

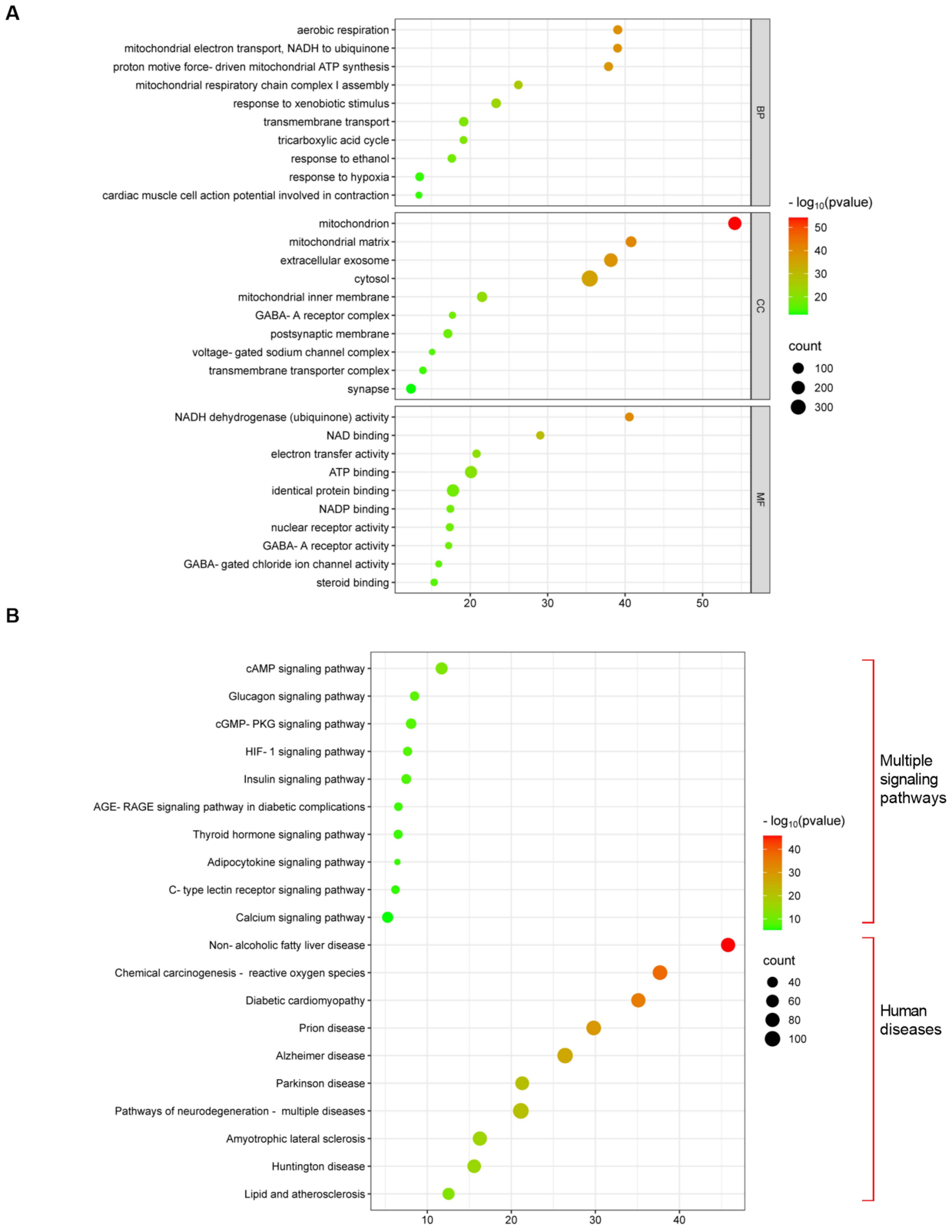

Figure 4 GO and KEGG. (**A**) GO analysis of intersection targets. (**B**) KEGG analysis of intersection targets.

https://doi.org/10.2147/DDDT.S500719

Declarations

All authors read and approved the initial manuscript.

Funding

The present study was financially supported by the Science and Technology Program of Hebei (223777156D); Clinical Medical School Graduate Research Innovation Practice Project (2023KCY06); National Natural Science Foundation of China (No. 81973840 and No. 81273748).

Disclosure

The authors declare that they have no competing interests.

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