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Berberine's impact on health: Comprehensive biological, pharmacological, and nutritional perspectives

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ABSTRACT

Berberine (BBR) exhibits significant anti-diabetic effects by enhancing insulin sensitivity, promoting glycolysis, and inhibiting gluconeogenesis. It also shows promise in treating non-alcoholic fatty liver disease (NAFLD) by reducing hepatic fat content and improving liver enzyme levels, lipid profiles, and insulin sensitivity. Studies show that BBR inhibits tumor growth, metastasis, and cell proliferation while inducing apoptosis and cell cycle arrest. Additionally, it enhances autophagy, regulates gut microbiota, and boosts the effectiveness of other anti-tumor drugs. Clinical trials indicate that BBR reduces the recurrence of colorectal adenomas and offers radio-protective benefits, although mild side effects such as constipation have been noted. Additionally, BBR's cardiovascular benefits include lowering cholesterol, improving lipid metabolism, and reducing inflammation, thus potentially attenuating the progression of atherosclerosis. Numerous randomized clinical trials have demonstrated BBR's therapeutic efficacy, suggesting that it may be a safe and useful adjuvant treatment for diabetes, NAFLD, cancer, and cardiovascular disease (CVD). However, we need to acknowledge limitations like low bioavailability and trial heterogeneity, which could affect how well the findings apply more broadly. Notwithstanding these encouraging results, more investigation is required to develop uniform treatment regimens and to completely comprehend the processes underlying the benefits of BBR.

1. Introduction

Recently, natural products have garnered considerable interest for their unique pharmacological qualities, which allow them to be utilized clinically in a variety of healthcare environments [1,2]. Alkaloids are among the several types of substances that have been widely used in traditional medicine [3]. One alkaloid, called berberine (BBR), is found in the roots, rhizomes, and bark of plants from various families like Annonaceae, Berberidaceae, Menispermaceae, Papaveraceae, Rutaceae, and numerous more [1]. It is also one of the primary bioactive constituents of Coptis chinensis Franch (Rhizoma Coptidis, Coptis, Ranunculaceae), which is a traditional Chinese medicine [4].

It's interesting to note that BBR is thought to be relatively safe at standard dosages with little chance of adverse effects. It is a crystalline powder that is yellow, odorless, and has a strong bitter flavor. It is only sparingly soluble in water and only minimally soluble in ethanol or methanol [1].

Many disorders, such as malignancies, endocrine disorders, cardiovascular diseases (CVDs), neurological disorders, and digestive problems, are treated with BBR [5]. BBR has proven to promote insulin secretion, enhance insulin sensitivity, inhibit gluconeogenesis, reduce fat accumulation, avert steatosis and fibrosis, display anti-inflammatory and antioxidant properties, and modulate the immune system in both animal and human studies [5]. Despite the wealth of research in this area, the aim of this investigation was to offer a comprehensive review of BBR's structure, physiological and pharmacological properties, its

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impact on cardiometabolic health, and its role in managing chronic diseases. The study particularly focused on the health benefits and safety of BBR.

2. Methodology

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, with the last search performed on August 21, 2024. The search strategy used combinations of relevant keywords, including: Berberine OR Berberine derivative AND Cardiovascular Disease OR Heart disease OR CVD OR Atherosclerosis OR Hypertension OR blood pressure OR Hyperlipidemia OR Dyslipidemia OR Hypercholesterolemia OR Myocardial Ischemia OR Ischemic heart disease OR Myocardial infarction; Berberine AND Diabetes OR type 2 diabetes; Berberine AND Toxicology AND Side Effects AND adverse events AND complaints; Berberine AND Safety AND Drug Interactions AND Lethal Dose AND pharmacological interactions; Berberine AND Bilirubin AND kernicterus; Berberine AND Pharmacokinetics AND bioavailability AND absorption; Berberine AND Chemical structure AND molecular formula; Berberine AND Chemical structure AND molecular formula; Berberine AND nonalcoholic fatty liver OR non-alcoholic fatty liver OR non-alcoholic OR nonalcoholic steatohepatitis OR NAFLD OR NASH OR steatohepatitis OR fatty liver; Berberine AND Tumors OR Neoplasia OR Neoplasm OR Tumor OR Cancer OR Cancers OR Malignant Neoplasm OR Malignancy OR Malignancies OR Malignant Neoplasms OR Neoplasm OR Benign Neoplasms OR Neoplasms.

Peer-reviewed narrative reviews, systematic reviews, randomized controlled trials, observational studies, and preclinical studies (both in vitro and in vivo) focusing on the pharmacology, pharmacokinetics, safety, drug interactions, toxicology, diabetes, cardiovascular disease, non-alcoholic fatty liver disease, cancer and chemical characterization of BBR were considered eligible. Case reports, conference abstracts, non–peer-reviewed sources, and studies lacking clear outcome measures were excluded. The reference lists of relevant papers were also screened manually to identify additional studies. When applicable, clinical studies were briefly appraised based on design, sample size, and primary outcomes to provide a balanced interpretation of the available evidence.

3. Berberine structure

BBR is an isoquinoline alkaloid, and it is a quaternary amine with the molecular formula $C_{20}H_{18}NO_4^+$ (2,3 methylenedioxy-9,10-dimethoxyprotoberberine chloride) and a molecular weight of 336.37 g/mol (Fig. 1) [6].

BBR hydrochloride (B·HCl·nH2O) is its most common form [7], characterized by a bitter taste and bright yellow crystalline appearance [8]. Its intense yellow color historically made it useful for dyeing materials [9]. Under UV light, BBR fluoresces yellow with a Color Index of 75,160 [10].

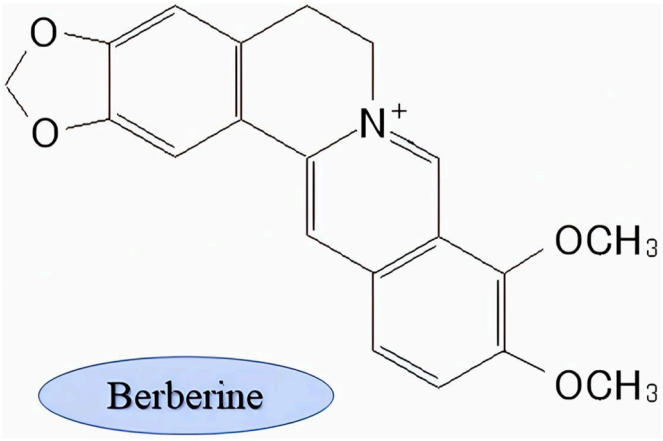

Fig. 1. Chemical structure of BBR.

4. Pharmacokinetics of berberine

After oral administration, BBR is absorbed in the gastrointestinal tract of both rats and humans. However, its poor water solubility results in low intestinal absorption and bioavailability [11,12]. In rats, absolute bioavailability is reported below 1 % [13]. In a pharmacokinetic study involving 20 human participants who received a single 400 mg oral dose of BBR, the maximum plasma concentration (Cmax) reached approximately 0.4 ng/mL, and the area under the concentration–time curve (AUC0–∞) was about 9.18 ng/mL [14]. Low absorption is primarily due to BBR's physicochemical properties [6]. Under physiological conditions, BBR is ionized and forms self-aggregates in acidic environments, such as the stomach, reducing solubility and intestinal permeability [15]. Additionally, BBR undergoes active efflux by P-glycoprotein (P-gp) in the intestinal epithelium, further decreasing its absorption (Fig. 2) [16]. Studies in rats have shown that co-administration with P-gp inhibitors can enhance BBR absorption up to sixfold, suggesting a significant role for this transporter in limiting its bioavailability [13,17]. After absorption, BBR shows wide tissue distribution [18]. Animal studies have demonstrated high concentrations of BBR in the liver, kidneys, lungs, heart, pancreas, brain, and skeletal muscles, often surpassing its plasma levels within 4 h post-administration [18,19]. The liver plays a central role in BBR metabolism via oxidative demethylation and glucuronidation, mainly through cytochrome P450 enzymes such as CYP2D6, CYP1A2, and CYP3A4 [15,20]. Major metabolites include berberrubine (A1), thalifendine (A2), demethyleneberberine (A3), and jatrorrhizine (A4), along with their glucuronide conjugates (Fig. 3). Elimination of BBR and its metabolites occurs primarily through bile, urine, and feces [21]. Although no comprehensive studies on BBR elimination in humans have been conducted [22], data from rat models suggest that approximately 22.83 % of the administered dose can be recovered, with berberrubine and thalifendine being the main excreted metabolites [22].

5. Berberine and cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, claiming about 17.9 million lives each year. CVDs are a group of heart and vascular diseases, including coronary heart disease, cerebrovascular disease, and rheumatic heart disease [23]. In 2019, ischemic heart disease and stroke collectively represented over 80 % of all cardiovascular fatalities across the globe [24]. The primary modifiable risk factors contributing to CVD worldwide included elevated systolic blood pressure, dietary risks, high levels of LDL cholesterol (LDL-C), tobacco consumption, increased fasting plasma glucose, and insufficient physical activity [24,25].

5.1. Atherosclerosis

Atherosclerosis (AS) is primarily a lipid metabolic condition that contributes to many cardiovascular and cerebrovascular disorders [26]. Atherosclerosis involves lipid accumulation, chronic inflammation, endothelial dysfunction, foam cell production, and plaque rupture [26]. BBR has the capability of reducing the risk of cardiometabolic diseases while also enhancing cardiovascular health [27]. It modulates blood pressure and the lipid profile, reduces hypercholesterolemia, suppresses vascular endothelial inflammation, and promotes endothelial function [27].

BBR possesses anti-hypercholesterolemic properties (Fig. 2). It lowers triglycerides (TG), total cholesterol (TC), LDL-C, increases HDL cholesterol (HDL-C), optimizes the leptin-to-adiponectin ratio, preventive activities against cellular damage induced by hyperglycemia, endothelial dysfunction, and improves endothelium-dependent

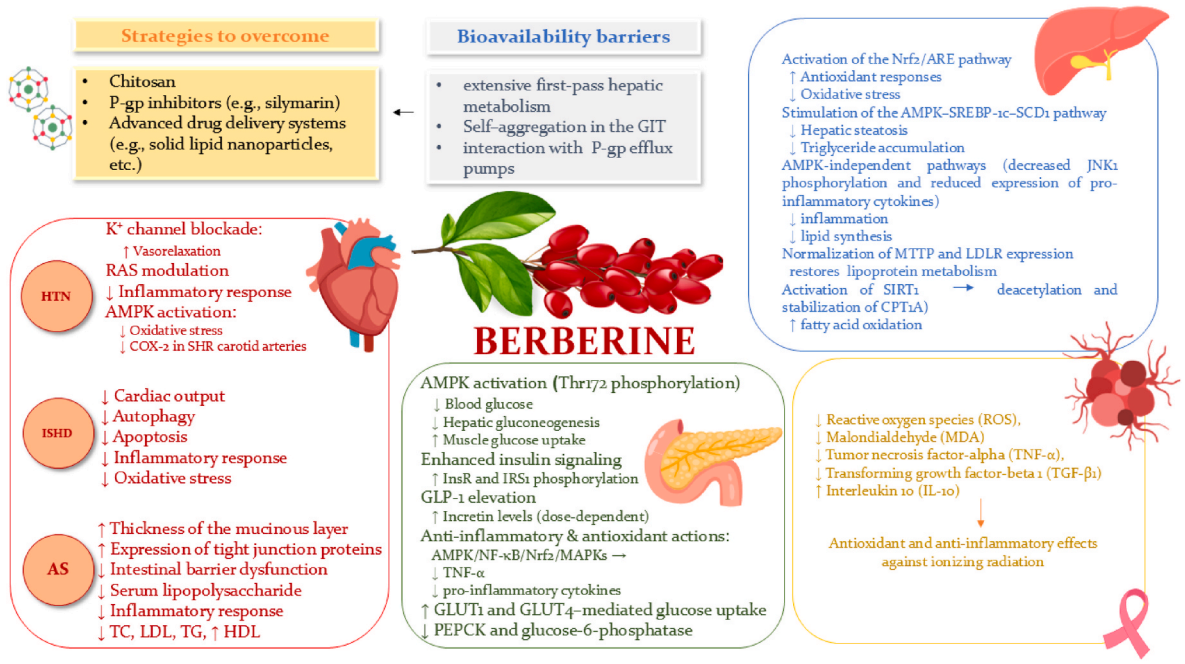

Fig. 2. The mechanism related to BBR and diseases
Abbreviations: AMPK; Adenosine monophosphate-activated protein kinase, AS; Atherosclerosis, GLP-1; Glucagon-like peptide-1, HTN; hypertension, ISHD; Ischemic heart disease, PEPCK; Phosphoenolpyruvate carboxykinase, RAS; Renin-angiotensin system.

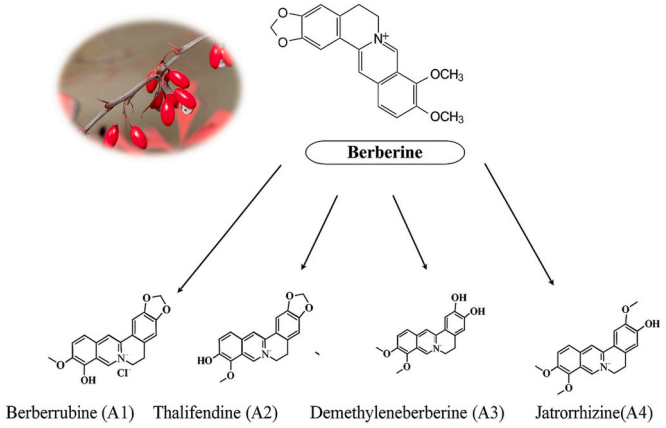

Fig. 3. The metabolites of BBR.

vasodilation [28,29]. Research from clinical trials shows that the BBR-silymarin association substantially improves cholesterol and glucose metabolism and could improve cardiovascular health [30]. Silymarin improves BBR oral bioavailability so as alleviates gastrointestinal discomfort [30].

Obesity and metabolic disorders lead to inflammation and atherosclerosis (AS) by damaging the intestinal barrier [31]. In AS, inflammation reduces the mucus layer and disrupts tight junctions, desmosomes, and adherens junctions that regulate epithelial permeability [31]. This damage allows gut bacteria and antigens to enter the bloodstream, activating systemic inflammation via toll-like receptors (TLRs) and inflammasomes [32]. Elevated serum lipopolysaccharide (LPS) indicates a compromised gut barrier and is linked to plaque formation and rupture in AS [33]. Increased concentrations of circulating LPS and inflammatory cytokines are linked to the formation and rupture of atherosclerotic plaques [34].

BBR has shown promise in AS models, particularly in high-fat diet (HFD) mice, where it reduced LPS levels and improved gut barrier function (Fig. 2) [35]. BBR lowered pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), mitigated HFD-induced metabolic endotoxemia, and improved obesity-related metabolic dysfunctions [36]. It also increased colonic mucin thickness and tight junction protein expression, partly by boosting Akkermansia, a beneficial gut bacterium [36,37]. In diabetic rats, BBR reduced inflammation-induced intestinal permeability and likely acted through the TLR4/MyD88/NF-κB pathway [38]. In type 2 diabetic rats induced by HFD and streptozotocin, BBR restored mucosal integrity, decreased LPS levels, and alleviated endotoxemia (Fig. 2) [39]. In obese mice, BBR's modulation of gut microbiota led to reduced LPS, metabolic endotoxemia, and systemic inflammation [40].

5.1.1. *Ischemic heart disease*

Coronary atherosclerosis and its complications are the main contributors to the development of ischemic heart disease (ISHD) [41], with myocardial infarction representing its most critical and fatal form [8]. Myocardial ischemia-reperfusion injury (MI/RI) can trigger various types of regulated cell death, such as apoptosis, ferroptosis, and autophagy-related cell death [42]. While reperfusion therapy offers advantages, it can also inadvertently worsen cardiac injury [41], highlighting the need for a more thorough exploration of the mechanisms involved in myocardial I/R injury to enhance treatment approaches [43].

Experimental investigations utilizing hypoxia-reoxygenation in isolated cardiomyocytes indicate that pretreatment with BBR markedly decreases the levels of lactate dehydrogenase (LDH) and malondialdehyde (MDA), which are indicators of I/R injury [44]. The cardioprotective properties of BBR are ascribed to multiple mechanisms: its antioxidant capabilities, anti-inflammatory effects following ischemia, promotion of coronary vasodilation, anti-apoptotic properties, inhibition of autophagy, and facilitation of angiogenesis after I/R injury (Fig. 2) [8].

5.2. *Cholesterol-lowering effect of berberine*

Elevated levels of LDL-C and/or decreased levels of HDL-C are significant risk factors for atherosclerosis (AS), with hypertriglyceridemia

also acting as an independent factor in the progression of the disease [45]. BBR decreases the absorption of intestinal cholesterol by interfering with micellization and encourages cholesterol excretion through enterocytes [46]. It boosts hepatic LDL-C receptor expression by inhibiting the activity of PCSK9 (proprotein convertase subtilisin/kexin type 9) [47], and reduces triglycerides via AMPK activation and inhibition of the MAPK/ERK pathway (Fig. 4) [48]. Furthermore, BBR enhances bile acid production, aids in cholesterol excretion, and regulates hepatic cholesterol synthesis by phosphorylating HMG-CoA reductase [49,50].

The side effects of BBR are typically mild and gastrointestinal [51]. Clinical trials indicate that BBR, when combined with chlorogenic acid and tocotrienols, effectively reduces LDL-C and total cholesterol levels after a 12-week period in menopausal women at risk for dyslipidemia [51]. In a separate study, administering 500 mg of BBR twice daily resulted in significant reductions in total cholesterol (29 %), triglycerides (35 %), and LDL-C (25 %) among 32 hyperlipidemic Asian patients compared to a placebo group [52]. A larger trial involving 116 patients with type 2 diabetes mellitus (T2DM) corroborated the lipid-lowering and glycemic control effects of BBR [53]. Additionally, a randomized controlled trial (RCT) involving patients who could not tolerate standard hyperlipidemia treatments found that a BBR–red yeast extract supplement significantly enhanced lipid profiles compared to diet alone [54]. These findings are summarized in Tables 1 and 2.

5.3. Hypertension

Hypertension (HTN), recognized as the most prevalent chronic condition globally, serves as a significant modifiable risk factor for early mortality. If left untreated, it heightens the risk of developing peripheral vascular disease, stroke, ischemic heart disease, and heart failure. BBR, when used in conjunction with lifestyle changes or antihypertensive drugs, has demonstrated a greater reduction in blood pressure compared to lifestyle modifications alone [71]. The hypotensive effects of BBR are summarized in Table 3.

Mechanistically, BBR lowers blood pressure by: (a) activating AMPK, which reduces endothelial ER stress and oxidative damage, while downregulating COX-2 in SHR carotid arteries [72]; (b) delaying the onset and progression of HTN by modulating the renin–angiotensin system (RAS) and inhibiting proinflammatory cytokines (IL-6, IL-17, IL-23) [73]; (c) inducing vasorelaxation and decreasing vascular stiffness [74]; and (d) functioning through potassium channel-dependent mechanisms, as vasodilation is diminished by K^+ channel blockade and the removal of endothelial cells (Fig. 2) [75].

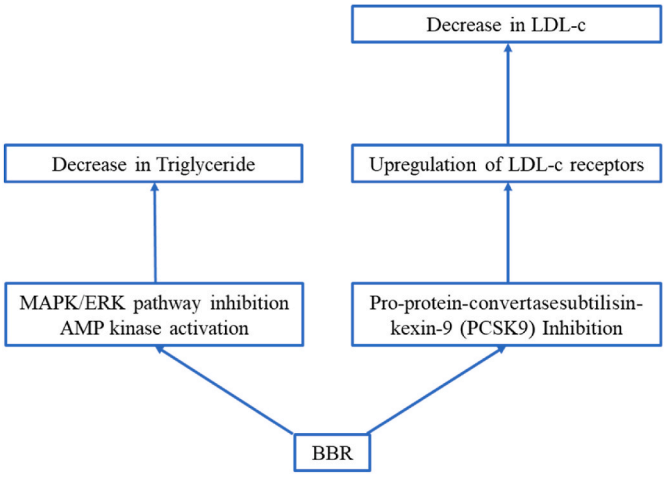

Fig. 4. The primary lipid-lowering action of BBR in human hepatic cells involves upregulating LDL receptor expression through inhibition of PCSK9, thereby reducing circulating LDL levels.

5.3.1. Berberine and diabetes

Diabetes mellitus (DM) represents a significant global health challenge, marked by disrupted glucose metabolism and chronic hyperglycemia [79]. It is anticipated that by 2030, the number of individuals with DM will reach 643 million, escalating to 783 million by 2045, with a particularly heavy impact on low- and middle-income nations such as Iran, India, and South Africa [79]. DM is responsible for approximately 6.7 million fatalities each year and is associated with various multi-organ complications, including retinopathy, nephropathy, neuropathy, cardiomyopathy, and infertility [80].

BBR has surfaced as a potential antidiabetic compound through several mechanisms: (a) activation of AMPK via Thr172 phosphorylation, which lowers blood glucose levels, inhibits hepatic gluconeogenesis, and promotes glucose uptake in muscles [81,82]; (b) phosphorylation of InsR and IRS1 to enhance insulin signaling [83]; (c) increased levels of GLP-1, especially at elevated doses [84]; (d) enhanced glucose uptake through GLUT1 and GLUT4 [85]; (e) inhibition of hepatic PEPCK and glucose-6-phosphatase, thereby decreasing gluconeogenesis [32]; and (f) reduction of inflammation and oxidative stress through signaling pathways involving AMPK, NF-κB, Nrf2, MAPKs, TNF-α, and pro-inflammatory cytokines (Fig. 2) [86,87].

The proposed mechanisms indicate that BBR holds significant promise as an oral antidiabetic agent. Numerous studies, demonstrate a marked enhancement in glycemic parameters, including FPG, 2h-OGTT, HbA1c, and HOMA-IR, when administered at a daily dosage of 500 mg over 12 weeks (Tables 4 and 5).

Zhang et al. reported that a daily intake of 1 g of BBR resulted in a 20 % reduction in blood glucose, a 12 % decrease in HbA1c, and an improvement in lipid profiles among 116 diabetic subjects [52]. In contrast to conventional antidiabetic medications, BBR also inhibits weight gain. A trial conducted by Hu et al., in 2012 demonstrated that 500 mg of BBR taken three times daily for 12 weeks resulted in a weight loss of 5 lbs. and a 3.6 % reduction in body fat [88].

6. Berberine and NAFLD

Non-alcoholic fatty liver disease (NAFLD), which represents the hepatic aspect of metabolic syndrome, encompasses a spectrum from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis [106]. NAFLD is a significant contributor to the development of chronic liver disease [107]. Approximately 25 % of the global population is affected [108], and its prevalence is increasing in tandem with obesity and T2DM [107]. Factors contributing to this condition include insulin resistance (IR), unhealthy lifestyle choices, imbalances in gut microbiota, and heightened hepatic fat production [109]. Current treatment strategies focus on lifestyle changes and the management of glycemic and lipid levels; however, there is currently no established pharmacotherapy available [109,110].

Research studies in Table 6 show strong evidence that BBR can help manage NAFLD, especially in patients with related health issues like T2DM. BBR has shown effectiveness in enhancing insulin sensitivity, glycemic control, lipid metabolism, and liver function in patients with NAFLD [111–114]. Also, combining BBR with metformin improved lipid levels and insulin sensitivity [113,115]. Furthermore, regarding the combined form of BBR, a related finding is that a BBR ursodeoxycholate derivative showed similar benefits in patients with NAFLD and T2DM, reducing liver fat, weight, liver enzymes, and improving blood sugar control at a daily dose of 2 g over 18 weeks [98]. While one study indicated no significant improvements [116]Table 6.

BBR exerts hepatoprotective effects through various mechanisms: (a) the activation of the Nrf2/ARE pathway enhances antioxidant responses and mitigates oxidative stress [117–119]; (b) stimulation of the AMPK–SREBP-1c–SCD1 pathway diminishes hepatic steatosis and triglyceride (TG) accumulation [120]; (c) suppression of inflammation and lipid synthesis occurs via AMPK-independent pathways, including decreased JNK1 phosphorylation and reduced expression of

Table 1
Summary of animal studies regarding the effect of berberine on cholesterol.

Author (Year)	Design	Diet and subject	Intervention	Daily dose	Duration	Result	Refs.
Singh AB et al. (2019)	Animal (Mice)	HFD and high-cholesterol diet	BBR	200 mg/kg	2 weeks	↓ LDL-C, TC, and TG	[55]
Zhou X et al. (2019)	Animal (Rat)	HFD	BBR	72.6 mg/kg	4 weeks	↓ LDL-C, TC, and TG	[56]
Zhu TL et al. (2017)	Animal (Rat)	Hyperlipoidemia rats	BBR	100, 200, and 300 mg/kg	4 weeks	↓ LDL-C, TC, and TG ↑ HDL-C	[57]
Wang Y et al. (2014)	Animal (Rat)	HFD and high-cholesterol diet	BBR	50, 100, and 150 mg/kg	8 weeks	↓ TC	[58]
He K et al. (2016)	Animal (hamsters)	HFD and high-cholesterol diet	BBR	46.7 mg/kg	140 days	↓ LDL-C, TC, and TG ↑ HDL-C	[59]
Dong S.-F. et al. (2011)	Animal (Rat)	HFD and high-sucrose diet	BBR	30 mg/kg	6 weeks	↓ LDL-C, and TG	[60]
Lee Y et al. (2006)	Animal (Mice)	HFD	BBR	380 mg/kg	2 weeks	↓ TG	[61]
Briand F. et al. (2013)	Animal (hamsters)	HFD and high-fructose diet	BBR	150 mg/kg	2 weeks	↓ LDL-C, and TG	[62]

Abbreviations: BBR: Berberine, HDL: High density lipoprotein, HFD: High fat diet, LDL: Low density lipoprotein, TC: Total cholesterol, TG: Triglyceride.

Table 2
Summary of clinical studies regarding the effect of berberine on cholesterol.

Author (Year)	Design	Subject (n)	Intervention	Daily dose	Duration	Result	Ref.
Wang S et al. (2022)	RCT	Type 2 diabetic (365)	BBR	BBR with 0.6 g per 6 pills, twice daily before a meal	3 months	↓ LDL-C, and TC	[63]
Chan M et al. (2022)	RCT	Schizophrenia spectrum disorders and metabolic syndrome (58)	BBR	600 mg	12 weeks	↓ LDL-C, and TC	[64]
Zhao, J.V. et al. (2021)	RCT	Hyperlipidemic (84)	BBR	500 mg, twice daily	12 weeks	↓ LDL-C, HDL-C, and TC	[65]
León-Martínez JM et al. (2020)	RCT	Dyslipidemia (12)	BBR	500 mg	3 months	↓ LDL-C, HDL-C, and TC	[66]
Spigoni V. et al. (2017)	RCT	Hyperlipidemic)30(	BBR	200 mg	12 weeks	↓ LDL-C	[67]
Wang L et al. (2016)	Crossover	Mild hyperlipemia (97)	BBR	300 mg	3 months	↓ LDL-C, TG, and TC ↑ HDL-C	[68]
Li L et al. (2015)	RCT	Polycystic ovary syndrome (98)	BBR	1200 mg, three times daily	4 months	↓ LDL-C, TG, and TC	[49]
Sola R et al. (2014)	RCT	Moderately hypercholesterolemic (51)	BBR	500 mg	12 weeks	↓ LDL-C, and TC	[69]
Derosa G et al. (2013)	RCT	Low risk of cardiovascular disease patients (71)	BBR	1 g, twice daily	3 months	↓ LDL-C, TG, and TC ↑ HDL-C	[29]
Cianci A et al. (2012)	RCT	Moderate dyslipidemia (60)	BBR	500 mg	12 weeks	↓ LDL-C, TG, and TC	[70]

Abbreviations: BBR: Berberine, HDL: High density lipoprotein, LDL: Low density lipoprotein, TC: Total cholesterol, TG: Triglyceride, RCT: Randomized clinical trial.

Table 3
Summary of clinical studies regarding the effect of berberine on blood pressure.

Author (Year)	Design	Subject (n)	Intervention	Daily dose	Duration	Result	Ref.
Chan M et al. (2022)	RCT	Schizophrenia and metabolic syndrome (58)	BBR	300 mg, twice daily	12 weeks	↓ SBP, and DBP	[64]
Zhao, J.V. et al. (2021)	RCT	Hyperlipidemia (84)	BBR	500 mg, twice daily	12 weeks	↓ SBP, and DBP	[65]
León-Martínez JM et al. (2020)	RCT	Dyslipidemia (12)	BBR	500 mg	3 months	↓ SBP, and DBP	[66]
M. Memon et al. (2018)	NRCT	Type 2 diabetic (100)	BBR	500 mg, three times daily	3 months	↓ SBP, and DBP	[76]
G. Huang (2013)	RCT	Moderate HTN and gout (84)	BBR	300 mg, three times daily	2 months	↓ SBP, and DBP	[77]
V. Trimarco et al. (2012)	RCT	Grade 1 essential HTN and low cardiovascular risk (18)	BBR	500 mg	4 weeks	↓ SBP, and DBP	[78]

Abbreviations: BBR: Berberine, DBP: diastolic blood pressure, HTN: Hypertension, SBP: Systolic blood pressure.

pro-inflammatory cytokines [121]; (d) normalization of MTTP and LDLR expression aids in restoring lipoprotein metabolism [122–124]; and (e) activation of SIRT1 promotes fatty acid oxidation through deacetylation and stabilization of CPT1A (Fig. 2) [125,126].

In summary, BBR offers a promising multifaceted treatment option for NAFLD by affecting lipid metabolism, inflammation, oxidative stress, and hepatic fat.

7. Anti-cancer effect of berberine

According to the World Health Organization's 2020 report, cancer was responsible for around 10 million fatalities and 19.3 million new diagnoses, primarily affecting the stomach, liver, lung, and breast [128]. Traditional treatments such as radiotherapy, chemotherapy, and surgery have their limitations and side effects, which have led to a growing interest in natural compounds like BBR. BBR is noted for its low toxicity and a range of therapeutic benefits, including anti-inflammatory, anti-oxidative, anti-diabetic, and anti-tumor properties [129].

BBR demonstrates anticancer effects through various mechanisms: it inhibits cell proliferation, angiogenesis, metastasis, and invasion; induces apoptosis, autophagy, and cell cycle arrest; modulates inflammatory responses and transcription factors; and disrupts epithelial-

Table 4
Summary of animal studies regarding the effect of berberine on glycemic parameters.

Author (Year)	Design	Subject	Intervention	Daily dose	Duration	Result	Ref.
Lyu Y et al. (2022)	Animal (Mice)	Diabetic	BBR	250 mg/kg	2 weeks	↑ Insulin sensitivity	[89]
Li CN et al. (2020)	Animal (Mice)	Diabetic	BBR	100 mg/kg	7 weeks	↓ FBG, ↑ oral glucose tolerance, and ↑ balance of α- and β-cells	[90]
Zhang W et al. (2019)	Animal (Mice)	Diabetic	BBR	136.5 mg/kg	14 weeks	↑ Gut microbiome, ↓ body weight, intestinal inflammation, and blood glucose levels	[91]
Li H-Y et al. (2018)	Animal (Mice)	Diabetic	BBR	50 mg/kg	10 weeks	↓ FBG, ↑ SIRT1, and ↓ ER stress	[92]
Xue M et al. (2015)	Animal (Mice)	Diabetic	BBR	100 mg/kg	5 weeks	↓ Lipogenesis, and ↑ lipolysis in the liver	[93]
Wang Z et al. (2015)	Animal (Mice)	Diabetic	BBR	50 mg/kg	8 weeks	↓ Blood glucose, and lipid metabolism	[94]
Zhou J et al. (2009)	Animal (Rat)	Diabetic	BBR	75, 150, 300 mg/kg	16 weeks	↓ lipid peroxidation, ↑ β-cell regeneration, and Insulin expression	[95]
Leng S-h (2004)	Animal (Rat)	Diabetic	BBR	187.5 and 562.5 mg/kg	4 weeks	↑ Insulin secretion	[96]

Abbreviations: BBR; Berberine, FBG; Fasting blood glucose.

Table 5
Summary of clinical studies regarding the effect of berberine on glycemic parameters.

Author (Year)	Design	Subject (n)	Intervention	Daily dose	Duration	Result	Ref.
Panigrahi A et al. (2023)	RCT	34 individuals with prediabetes	BBR	500 mg, three times daily	12 weeks	↓ FBG, 2 h-OGTT, HbA1c, and HOMA-IR	[97]
Harrison S.A et al. (2021)	RCT	100 non-alcoholic steatohepatitis and T2DM patients	BBR	1 g, twice daily	18 weeks	improvement in glycemic control ↓ weight, and liver-associated enzymes	[98]
Zhao MM et al. (2021)	RCT	15 patients with T2DM and obesity	BBR	1 g	2 weeks	↑ insulin secretion	[99]
Sartore G et al. (2021)	RCT	40 patients with T2DM	BBR	500 mg	12 weeks	↓ HbA1c, and FBG	[100]
Yan H et al. (2021)	RCT	185 patients with T2DM and NAFLD	BBR	500 mg, twice daily	16 weeks	↓ Liver fat content in women as compared to men	[101]
Zhang Y et al. (2020)	RCT	409 patients with T2DM	BBR	600 mg, twice daily	12 weeks	↓ blood glucose levels	[102]
Li ZY et al. (2018)	RCT	114 patients with T2DM	BBR	400 mg, three times daily	6 months	↓ HbA1c, BUN, SBP, and hs-CRP	[103]
Guarino G et al. (2017)	RCT	136 patients with T2DM	BBR	500 mg	52 weeks	↓ FBG and insulin, HOMA-IR, TC, HDL-C and LDL-C, TG, and uric acid	[104]
Zhang H et al. (2010)	RCT	97 patients with T2DM	BBR	1 g	2 months	↓ FBG, HbA1c, and TG	[105]
Yin J et al. (2008)	RCT	84 patients with T2DM	BBR	500 mg, twice daily	3 months	↓ FBG, TC, and LDL-C	[7]
Zhang Y et al. (2008)	RCT	116 patients withT2DM with dyslipidemia	BBR	1 g	3 months	↓ FBG and insulin, HOMA-IR, TG, TC, LDL-C, HDL-C and uric acid	[52]

Abbreviations: BUN; Blood urea nitrogen, hs-CRP; Highly sensitive C-reactive protein, SBP; Systolic blood pressure, FBG: Fasting blood glucose, HOMA-IR; Homeostatic Model Assessment for Insulin Resistance HDL; High-density lipoprotein, LDL; Low-density lipoprotein, TC; Total cholesterol, TG; Triglyceride, RCT; Randomized clinical trial.

mesenchymal transition proteins [130].

The Table 7 provides an overview of RCT research findings regarding the effectiveness of BBR supplementation in cancer patients, which indicates that supplementation with BBR effectively lowers the recurrence rate of colorectal adenomas [131–133] and has radioprotective effects [134,135].

Another meta-analysis found that BBR's effectiveness in preventing the recurrence of colorectal adenomas is similar to that of conventional treatments, although mild and reversible side effects, such as constipation, were reported more frequently than with placebo [136].

Recent research has found that berberine (BBR) has antioxidant and anti-inflammatory effects against ionizing radiation, according to a systematic review of clinical and experimental studies. This is because it reduces levels of reactive oxygen species (ROS), malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta 1 (TGF-β1), while increasing interleukin 10 (IL-10) levels. BBR also has radio-protective effects by minimizing apoptosis and cell cytotoxicity. However, in cancer cells, BBR blocks the upregulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 alpha (HIF-1α) by triggering oxidative stress, DNA damage, mitochondrial dysfunction, and hyperpolarization (Fig. 2) [137].

Overall, these results confirm BBR's anticancer effects, but future research on its safety is necessary.

8. Toxicology and side effects

Generally, BBR has shown low toxicity and side effects in animal studies [21]. Typical oral doses are well tolerated, with adverse events being rare and mostly mild [138]. Gastrointestinal symptoms such as nausea, diarrhea, constipation, abdominal distension, and pain are the most frequent side effects [71,138]. Rare cases of hypoglycemia have also been reported [139], but patients usually tolerate these without reducing the dose below 600 mg/day [139].

BBR appears to prolong small intestinal transit time, which may contribute to gastrointestinal side effects. This was shown using sorbitol and breath hydrogen tests [140]. In clinical studies, adverse events were reported in patients receiving BBR, either alone or as part of combination products. For example, in a study on 36 DM patients treated with BBR (500 mg three times daily) for 13 weeks, 34.5 % experienced flatulence, diarrhea, abdominal pain, or constipation [7]. These reactions

Table 6
Summary of clinical studies regarding the effect of berberine (derivatives) in NAFLD treatment.

Author (year)	Design	Subject (n)	Intervention	Daily dose	Duration	Result	Refs.
Nejati et al. (2022)	RCT	Patients with NAFLD (48)	BBR	6.25 g	6 weeks	↔ Lipid profile, fasting blood glucose, or liver enzymes	[116]
Harrison et al. (2021)	RCT	Patients with presumed NASH and type 2 diabetes (87)	BBR ursodeoxycholate	1 or 2 g	18 weeks	↓ Liver fat content, weight, ALT, GGT, and improved glycemic control (in a 2 g daily dose consumption)	[98]
Chang et al. (2016)	RCT	Adult NAFLD patients (80)	BBR	1.5 g	16 weeks	↓ Weight, WC, BMI, HFC, blood glucose, HbA1c, serum cholesterol, TG, LDL-C	[111]
Li et al. (2015)	RCT	Adult NAFLD patients (96)	BBR	0.3 g	12 weeks	↓ 2hPG, HbA1c, TC, LDL-C, ALT, AST	[127]
Yan et al. (2015)	RCT	Adult NAFLD patients (184)	BBR	1.5 g	16 weeks	↓ Weight, HFC, ALT, AST, GGT, glucose, HOMA-IR, TC, TG, LDL-C	[112]
Ning et al. (2013)	RCT	Adult NAFLD patients (44)	BBR + metformin	0.5 g	16 weeks	↓ HbA1c, TC, TG	[113]
Bai RuiMiao et al. (2011)	RCT	Adult NAFLD patients (68)	BBR + metformin	0.5 g	12 weeks	↓ FPG, TC, TG, LDL-C, FINS, HOMA-IR ↑ adiponectin	[115]
Xie et al. (2011)	RCT	Newly diagnosed patients with type 2 diabetes, combining NAFLD (60)	BBR	0.3 g	12 weeks	↓ TG, TC, LDL-C, ALT, AST ↑ HDL-C ↓ Liver lipid content	[114]

Abbreviations: RCT: randomized clinical trial, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, BBR: berberine, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, WC: waist circumference, BMI: body mass index, HFC: hepatic fat content, Hb A1c: hemoglobin A1c, TG: triglycerides, LDL-c: low-density lipoprotein cholesterol, 2hPG: Two-hour post-load glucose, TC: total cholesterol, AST: aspartate aminotransferase, FPG: Fasting plasma glucose, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, FINS: fasting insulin, IR: insulin resistance, HDL: high-density lipoprotein.

Table 7
Summary of clinical studies regarding the effect of berberine in cancer treatment.

Author (year)	Design	Subject (n)	Intervention	Daily Dosage	Duration	Results	Ref.
Chen et al. (2020)	RCT	Patients with colorectal adenoma (891)	BBR	0.6 g	2-year	↓ Recurrent adenoma	[131]
Wang et al. (2020)	RCT	Patients with colorectal adenoma (84)	BBR	0.3 g	18 months	↓ Recurrence rate	[132]
Liu (2018)	RCT	Patients with colorectal adenoma (101)	BBR	0.6 g	2-year	↓ Recurrence rate	[133]
Li et al. (2010)	RCT	Patients with seminoma or lymphoma (36) Patients with cervical cancer (42)	BBR	0.9 g	5 weeks	Delayed onset and severity of RIAIS. (In individuals who had received abdominal or entire pelvic radiation)	[135]
Liu et al. (2008)	RCT	patients with NSCLC (85)	BBR + radiation therapy	20 mg/kg	6 weeks	↓ occurrence of RILI	[134]

Abbreviations: RCT: randomized clinical trial, BBR: berberine, RIAIS: Radiation-induced acute intestinal symptoms, RILI:radiation-induced lung injury.

were generally mild and resolved within four weeks in most cases [21]. However, in 14 patients (24.1 %), the dosage had to be reduced from 0.5 g to 0.3 g three times daily due to gastrointestinal complaints [6].

A meta-analysis by Lan et al. involving 27 studies confirmed a dose-dependent relationship between BBR and adverse effects [71]. At higher doses (5–15 mg/kg), animal studies have shown a reduction in dopaminergic neurons in the substantia nigra and striatum, suggesting potential neurotoxicity that may impair motor and cognitive functions [141,142]. It should be noted that when combination products were used, some observed effects may reflect contributions from other components and not solely BBR. Furthermore, Mahmoudi et al. reported immunotoxic effects at 10 mg/kg, including reduced leukocyte, neutrophil, and lymphocyte counts, as well as spleen weight [143]. Decreased production and differentiation of B- and T-cells, including $CD19^+$ B-cells, $CD4^+$, and $CD8^+$ T-cells, have also been associated with BBR treatment [144].

9. Safety and drug interactions

Highly purified and concentrated berberine has generally shown a favorable safety profile. Although a relatively low median lethal dose ($LD_{50} \approx 25$ mg/kg) has been reported in mice, this value is route-dependent and was obtained primarily from parenteral animal models rather than oral administration [145]. In contrast, oral administration at standard therapeutic doses (500–1000 mg/day) is well tolerated in humans, with adverse effects being uncommon and usually mild [9]. The main safety concern with berberine lies in its potential for drug–drug interactions. Berberine can displace drugs such as warfarin and thiopental from plasma protein-binding sites, potentially increasing their circulating concentrations [146]. In a study with 17 healthy participants, oral administration of 300 mg berberine three times daily for two weeks significantly inhibited CYP2D6, CYP2C9, and CYP3A4 [147]. Since the bioavailability of cyclosporine depends on CYP3A4, CYP3A5, and P-glycoprotein [21], coadministration with berberine significantly increases cyclosporine blood levels [148,149].

This interaction has been confirmed clinically: in renal transplant recipients, 0.2 g berberine three times daily for three months increased cyclosporine AUC by ~34.5 % and prolonged its half-life by 2.7 h [150,151], while in heart transplant patients, a ~25 % increase in cyclosporine blood levels was observed [152]. Other interactions have also been reported. Li et al. noted mild splenic toxicity when berberine was combined with 5-ASA [153]. Kwon et al. showed that berberine increases the plasma concentration and AUC of metformin, likely due to inhibition of OCT1 and OCT2-mediated elimination [154]. Berberine has also demonstrated synergistic antibacterial activity with ciprofloxacin, potentially enabling dose reduction of the antibiotic [155]. Furthermore, interactions with tamoxifen, lovastatin, and ketoconazole have been observed [156–158].

Table 8
Major reported drug–drug interactions with berberine.

Drug/compound	Mechanism of interaction	Clinical consequence	Ref.
Warfarin, thiopental	Protein-binding displacement	↑ Plasma concentration, ↑ bleeding risk	[146]
Cyclosporine A	CYP3A4 & P-gp inhibition, delayed emptying	↑ AUC (~34.5 %), ↑ half-life, dose adjustment needed	[148–152]
Metformin	Inhibition of OCT1/OCT2	↑ AUC, ↑ plasma concentration	[154]
Ciprofloxacin	Synergistic antibacterial activity	Potential for antibiotic dose reduction	[155]
Tamoxifen, lovastatin, ketoconazole	CYP inhibition/competition	Altered plasma levels, possible ↑ toxicity	[156–158]
5-ASA	Additive splenic toxicity (animal study)	Mild splenic effects	[153]

Abbreviations: CYP3A4: Cytochrome P450 3A4, P-gp: P-glycoprotein, AUC: The area under the ROC curve, OCT: Organic cation transporter, ASA: Aspirin (acetylsalicylic acid).

Overall, oral berberine at therapeutic doses is considered safe for most individuals. However, caution is warranted when coadministered with drugs metabolized by CYP enzymes or transported by P-glycoprotein. A concise summary of reported interactions is provided in Table 8.

10. Effects on plasma bilirubin

BBR has been associated with increased plasma bilirubin levels under certain conditions. In infants with glucose-6-phosphate dehydrogenase deficiency, BBR may induce kernicterus, a severe neurological condition linked to hyperbilirubinemia [159]. In vitro studies have shown that BBR competes with bilirubin for binding to albumin, potentially displacing bilirubin into its unbound form [15]. In animal models, intraperitoneal administration of BBR at doses of 10 and 20 μg/g for seven consecutive days significantly elevated total and unbound bilirubin levels without affecting serum albumin concentrations [160]. Chan et al. demonstrated that BBR reduced bilirubin binding to serum proteins in adult rats, likely due to in vivo displacement or inhibition of bilirubin metabolism [160]. This persistent elevation of unbound bilirubin may pose a risk, particularly in neonates and pregnant individuals [160].

As a result, BBR-containing traditional Chinese remedies should be avoided in jaundiced neonates and during pregnancy [160]. Although some studies report no direct link between BBR and jaundice [161–163], caution remains warranted. During pregnancy, BBR-containing herbs are classified under category C and are not recommended during lactation [15].

11. Approaches for overcoming the pharmacokinetic problems

BBR has low intestinal absorption and poor oral bioavailability, with studies in rats showing bioavailability below 1 % [13,21]. Its limited absorption is attributed to several factors, including interaction with P-glycoprotein (P-gp) efflux pumps, self-aggregation in the acidic environment of the gastrointestinal tract, and extensive first-pass hepatic metabolism [17,164,165]. As a substrate of P-gp, BBR's absorption may be enhanced up to sixfold when co-administered with P-gp inhibitors [12]. Clinical evidence supports this strategy. In a study of 69 type 2 diabetic patients, the combination of BBR with silymarin (a known P-gp inhibitor) resulted in a more significant reduction in HbA1c compared to BBR alone [166]. Additionally, chitosan has been shown to improve BBR uptake by modulating intestinal tight junctions [16]. Advanced drug delivery systems such as solid lipid nanoparticles, liposomes, microemulsions, and micelles have also been widely used to enhance solubility and permeability of poorly absorbed compounds like BBR [21, 167]. These formulations offer promising approaches for improving BBR's pharmacokinetic profile. However, most data supporting these methods are derived from animal studies, and further evaluation in humans is essential.

12. Conclusion

Overall, in this review, BBR shows promise as a low-toxicity profile, and therapeutic agent for improving cardiovascular health by enhancing lipid profiles, reducing inflammation, and promoting endothelial function, despite bioavailability challenges. Its therapeutic effects on atherosclerosis and ischemic heart disease, lipid profiles, lowering blood pressure, and enhancing glycemic control offer a promising alternative to conventional treatments with fewer side effects, highlighting the value of incorporating natural supplements like BBR into lifestyle changes for better health outcomes in chronic conditions. Its multifaceted effects make it a valuable adjunct in managing NAFLD, especially amid rising obesity and T2DM rates. The research underscores the promising role of BBR as a potent anti-cancer agent, revealing its capabilities in modulating a range of cellular mechanisms critical to tumor growth and metastasis. BBR has been shown to influence various pathways involved in cell proliferation, apoptosis, and angiogenesis, which are fundamental processes in cancer development and progression. BBR appears to exhibit manageable side effects, making it a more tolerable option for patients. Despite these promising findings, the research also emphasizes the need for further investigation into the safety and pharmacokinetic properties of BBR. Understanding how BBR is absorbed, distributed, metabolized, and excreted in the body is crucial for optimizing its therapeutic application. Detailed studies are necessary to determine the appropriate dosing regimens, potential drug interactions, and long-term effects of BBR in cancer patients.

CRediT authorship contribution statement

Parastoo Asghari: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Arvin Babaei:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation. **Nazanin Zamanian:** Writing – review & editing, Writing – original draft, Investigation. **Elyas Nattagh- Eshtivani:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Ethics approval and consent to participate

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ABBREVIATIONS

ALT	Alanine aminotransferase	I/R	Ischemia-reperfusion
AMPK	AMP-activated protein kinase	ISHD	Ischemic heart disease
AS	Atherosclerosis	LD50	Lethal Dose 50
AST	Aspartate aminotransferase	LDH	Lactate dehydrogenase
BBR	Berberine	LDL-C	low-density lipoprotein cholesterol
BMI	Body mass index	MTTP	Microsomal triglyceride transfer protein
BUN	Blood urea nitrogen	NAFLD	Non-alcoholic fatty liver disease
CVD	Cardiovascular disease	NASH	Nonalcoholic steatohepatitis
Cmax	Average maximum plasma concentration	PCSK9	Protein-convertase subtilisin-kexin-9
DBP	Diastolic blood pressure	LPS	lipopolysaccharide
ER	Endoplasmic reticulum	MDA	liver Malondialdehyde
FBG	Fasting blood glucose	MDA	Malondialdehyde
FINS	Fasting insulin	P-gp	P-glycoprotein
GGT	Gamma-glutamyl transferase	PEPCK	Phosphoenolpyruvate carboxykinase
GLP-1	Glucagon-like peptide-1	RCT	Randomized clinical trial
GSH	Glutathione	ROS	Reactive oxygen species
HDL-C	High-density lipoprotein cholesterol	SBP	Systolic blood pressure
HF	Heart failure	SCD1	Stearyl-coenzyme A desaturase 1
HFC	Hepatic fat content	SRE	Sterol regulatory element
HFD	High-fat diet	SREBP-1c	Sterol regulatory element-binding protein-1c
HIF-1α	Hypoxia-inducible factor-1 alpha	SOD	Superoxide dismutase
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance	TLRs	Toll-like receptors
hs-CRP	Highly sensitive C-reactive protein	TC	Total cholesterol
HTN	Hypertension	TGF-β1	Transforming growth factor-beta 1
IGT	Impaired glucose tolerance	TG	Triglycerides
InsR	Insulin receptor	TNF-α	Tumor Necrosis Factor-alpha
IRS1	Insulin receptor substrate 1	T2DM	Type 2 diabetes mellitus
IR	Insulin resistance	VLDL	Very low-density lipoprotein
IL	Interleukin	WC	Waist circumference

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