



Promising Antioxidative Effect of Berberine in Cardiovascular Diseases

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Berberine (BBR), an important quaternary benzyloquinoline alkaloid, has been used in Chinese traditional medicine for over 3,000 years. BBR has been shown in both traditional and modern medicine to have a wide range of pharmacological actions, including hypoglycemic, hypolipidemic, anti-obesity, hepatoprotective, anti-inflammatory, and antioxidant activities. The unregulated reaction chain induced by oxidative stress as a crucial mechanism result in myocardial damage, which is involved in the pathogenesis and progression of many cardiovascular diseases (CVDs). Numerous researches have established that BBR protects myocardium and may be beneficial in the treatment of CVDs. Given that the pivotal role of oxidative stress in CVDs, the pharmacological effects of BBR in the treatment and/or management of CVDs have strongly attracted the attention of scholars. Therefore, this review sums up the prevention and treatment mechanisms of BBR in CVDs from *in vitro*, *in vivo*, and finally to the clinical field trials timely. We summarized the antioxidant stress of BBR in the management of coronary atherosclerosis and myocardial ischemia/reperfusion; it also analyzes the pathogenesis of oxidative stress in arrhythmia and heart failure and the therapeutic effects of BBR. In short, BBR is a hopeful drug candidate for the treatment of CVDs, which can intervene in the process of CVDs from multiple angles and different aspects. Therefore, if we want to apply it to the clinic on a large scale, more comprehensive, intensive, and detailed researches are needed to be carried out to clarify the molecular mechanism and targets of BBR.

Keywords: Berberine, cardiovascular disease, reactive oxygen species, coronary atherosclerosis, myocardial infarction/reperfusion

1 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in the world. The World Heart Federation reported that the number of people died of CVD is up to 17.3 million every year. It is estimated that by 2030, the number of deaths due to CVD will increase to 23.6 million (Smith et al., 2012; Hao et al., 2017). CVD accounts for up to 40% of the disease mortality in China, making it the first cause of death and premature death among Chinese residents. China and India have the highest burden of CVD in the world (Zhou et al., 2016; Zhao et al., 2019). Because of the unsatisfied demands of Western medicine for the management of CVD, some clinicians have focused on traditional Chinese medicine (TCM) to find out what role it can play in the prevention and treatment of CVD. A large number of studies in this area, both basic and

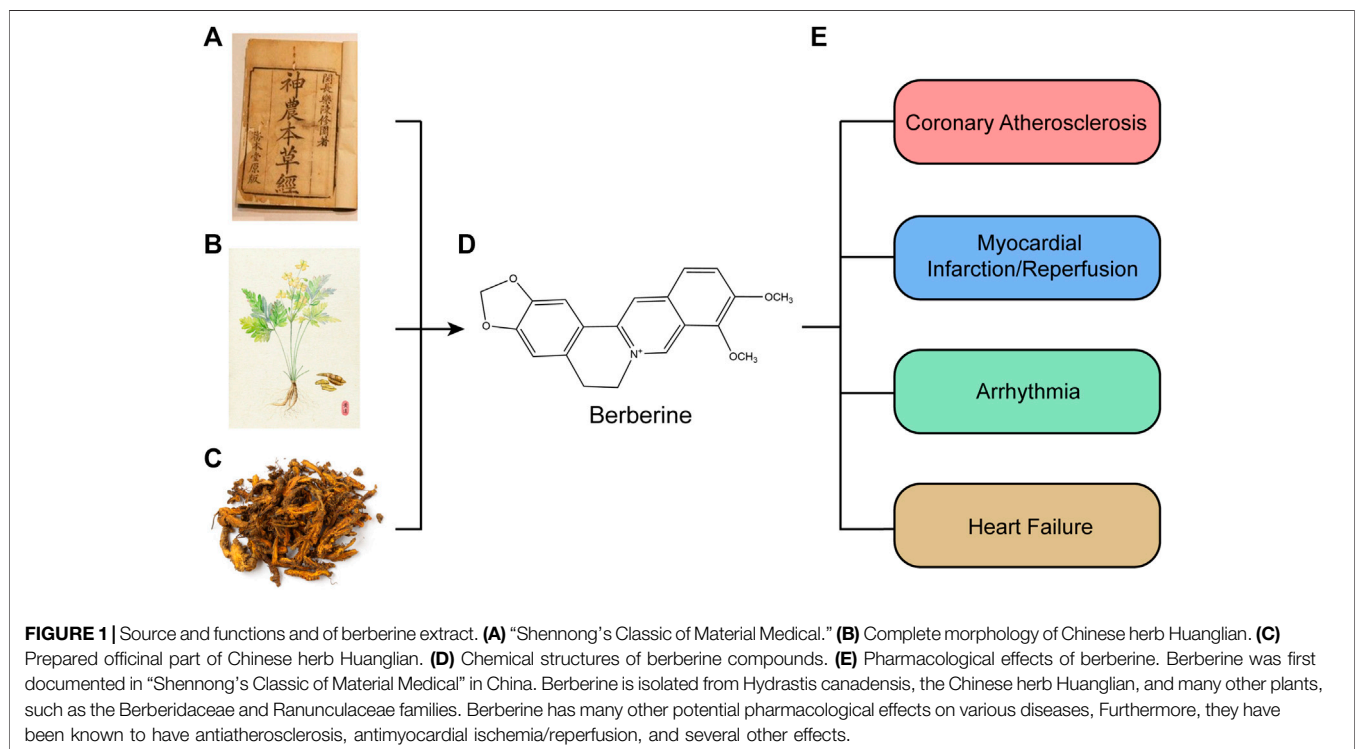
TABLE 1 | Detected studies reporting potential antioxidative stress effects of berberine in CVDs.

| Application | Experiment | Intervention measures | Model | Target | References |
|------------------------------------|-----------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------|
| Coronary atherosclerosis | <i>In vivo</i> | Berberine | C57BL/6 mice and ApoE ^{-/-} mice | Inflammatory and oxidative markers (NF- κ B, ICAM-1, IL-6, i-NOS) | Feng et al. (2017) |
| | <i>In vivo</i> | Berberine | ApoE ^{-/-} mice with hyperhomocysteinemia | Peroxisome proliferator-activated receptor- γ (PPAR γ) | Li H. et al. (2016) |
| | <i>In vivo</i> | Berberine | Male SHR and WKY rats | AMPK, endoplasmic reticulum (ER) stress, COX-2 | Liu et al. (2015) |
| | <i>In vivo</i> | Berberine | Male C57BLKS/J-Leprdb/Leprdb mice | AMPK | Jeong et al. (2009) |
| | <i>In vitro</i> | Berberine | The murine cell line J774A.1 | AMPK/mTOR | Fan et al. (2015) |
| | <i>In vitro</i> | Berberine | Human umbilical vein endothelial cells | LDL, oxLDL | Hsieh et al. (2007) |
| | <i>In vitro</i> | Berberine | Human peripheral blood mononuclear cells | NLRP3 inflammasome and IL-1 β | Jiang et al. (2017) |
| | <i>In vitro</i> | Berberine | The human acute monocytic leukemia cell line, THP-1 | oxLDL | Huang et al. (2013) |
| | <i>In vitro</i> | Berberine | Human umbilical vein endothelial cells | AMPK, eNOS, NOX4 | Zhang et al. (2013) |
| | <i>In vitro</i> | Berberine | Human umbilical vein endothelial cell line and the human premonocytic cell line U937 | Ang II | Ko et al. (2007) |
| Coronary atherosclerosis | <i>In vitro</i> | Berberine | Raw 264.7 macrophages and 3T3-L1 adipocytes | AMPK | Jeong et al. (2009) |
| | <i>In vitro</i> | Berberine | Human umbilical vein endothelial cells | oxLDL, TNF α | Caliceti et al. (2017) |
| | <i>In vitro</i> | Berberine | Monocytic THP-1 cells, human monocyte line | NLRP3 and IL-1 β | Liu et al. (2016) |
| | clinical trials | Berberine (500 mg, daily) | Bone marrow cells, Human THP-1 cells, Murine 3T3L-1 cells | NLRP3 inflammasome | Zhou et al. (2017) |
| Coronary atherosclerosis | Clinical trials | Berberine capsules (900 mg/d for 3 months) | Mild or moderate mixed hyperlipidemia patients | LDL and total triglycerides (TG) | Cicero et al. (2007) |
| | Clinical trials | Berberine nutritional agents (containing Berberis aristata d.e. 588 mg) | Patients with mild hyperlipidemia | Plasma total cholesterol (TC) and LDL-C | Wang et al. (2016) |
| | Clinical trials | Berberine nutritional agents (containing Berberis aristata d.e. 588 mg) | Patients with mild to moderate hypercholesterolemia | LDL-C | D'addato et al. (2017) |
| Myocardial infarction/ Reperfusion | <i>In vivo</i> | Berberine | Sprague Dawley (SD) rats | Phosphoinositide 3-kinase/AKT | Qin-Wei and Yong-Guang, (2016) |
| | <i>In vivo</i> | Berberine | Male Wistar rats | AMPK and the AKT/GSK3 β signaling pathway | Chang et al. (2016) |
| | <i>In vivo</i> | Berberine | Male Sprague-Dawley rats | Apoptosis and mitochondrial dysfunction | Wang et al. (2015) |
| | <i>In vivo</i> | Berberine | Male Sprague-Dawley rats | Silent information regulator 1 (SIRT1) | Yu et al. (2016) |
| | <i>In vivo</i> | Berberine | C57BL/6 mice | NF- κ B and PI3K/AKT | Wang et al. (2018) |
| | <i>In vitro</i> | Berberine | H9C2 embryonic rat myocardium-derived cells | JAK2/STAT3 | Zhao et al. (2016) |
| Myocardial infarction/ Reperfusion | <i>In vitro</i> | Berberine | H9C2 cardiomyocytes | Silent information regulator 1 (SIRT1) | Yu et al. (2016) |
| | Clinical trials | Berberine (300 mg (tid) in addition to the therapy of the general group) | In acute ischemic stroke (AIS) patients | The serum macrophage migration inhibitory factor and IL-6 levels | Li Y. et al. (2016b) |
| Arrhythmia (atrial fibrillation) | Clinical trials | Berberine tablets (0.3 g/ time, and three times/day) | Patients with acute myocardial infarction treated with percutaneous coronary intervention | Plasma level of C-reactive protein, tumor necrosis factor α and IL-6 | Qing et al. (2018) |
| | <i>In vivo</i> | — | p47 ^{-/-} mice; MsrA ^{-/-} mice; mice with genetic CaMKII inhibition | Oxidized CaMKII | Erickson et al. (2008), Swaminathan et al. (2011) |
| | <i>In vivo</i> | — | Male C57BL/6 | Reactive oxygen species signaling | Yang X. et al. (2020) |
| Heart failure | <i>In vitro</i> | — | Human Jurkat T cell line | Reactive oxygen intermediates/CaM kinases | Howe et al. (2004) |
| | <i>In vivo</i> | — | Nampt transgenic mice | NAD ⁺ synthesis | Hsu et al. (2009) |

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TABLE 1 | (Continued) Detected studies reporting potential antioxidative stress effects of berberine in CVDs.

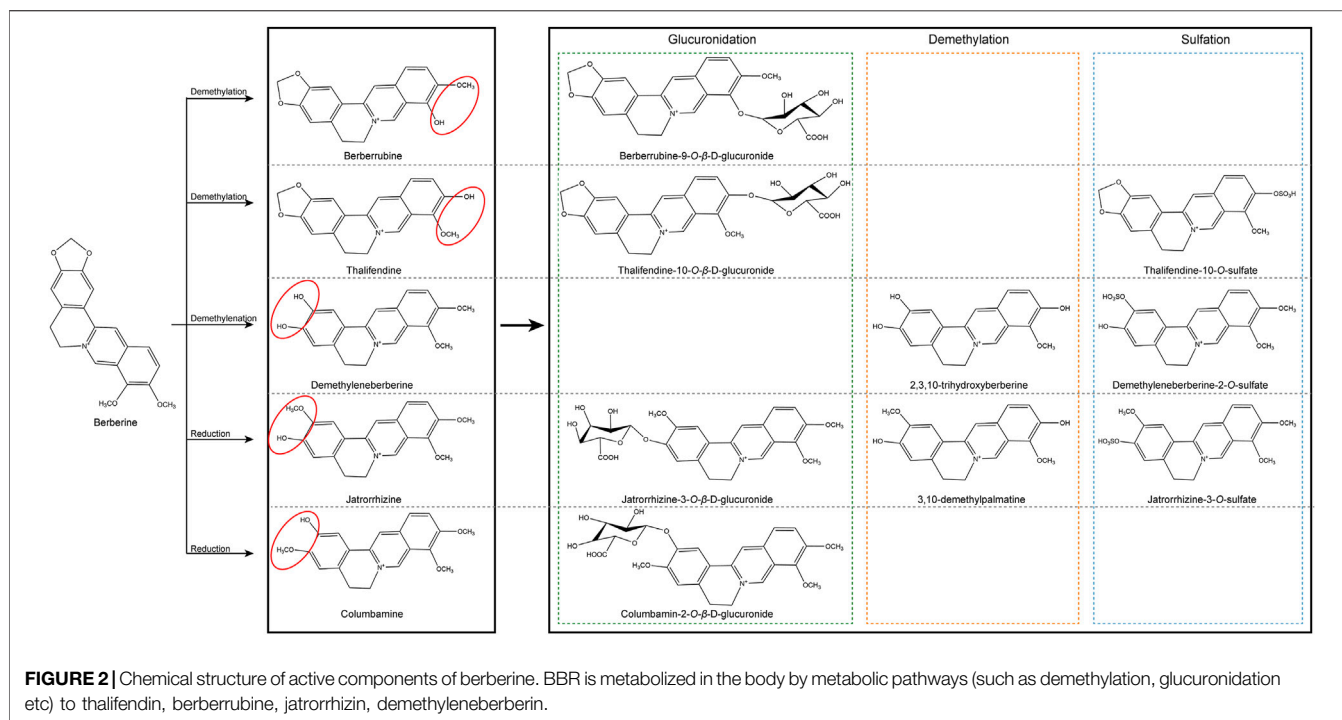
| Application | Experiment | Intervention measures | Model | Target | References |
|-------------|-----------------|-----------------------|----------------------------------------------------------------|------------------------------------------------|------------------------|
| | <i>In vivo</i> | — | Male NOS3-null (NOS3 ^{-/-}) mice and C57/BL6 WT mice | 151 | Takimoto et al. (2005) |
| | <i>In vivo</i> | — | p47 ^{phox} ^{-/-} mice and WT mice | NAD(P)H Oxidase Subunit p47 ^{phox} | Doerries et al. (2007) |
| | <i>In vivo</i> | — | SRF ^{HKO} and control (Sf/Sf) mice | NAD ⁺ | Diguet et al. (2018) |
| | <i>In vivo</i> | — | Wistar Kyoto and spontaneously hypertensive/HF (SHHF) rat | Xanthine Oxidoreductase | Minhas et al. (2006) |
| | <i>In vivo</i> | — | Dogs | Xanthine oxidase | Ukai et al. (2001) |
| | <i>In vitro</i> | — | Primary cultures of cardiac myocyte | NAD ⁺ and Sir2 α deacetylase | Pillai et al. (2005) |



clinical, have attracted increasing attention from the cardiovascular community (Hao et al., 2017). For many centuries, BBR has been widely used to treat various intestinal infections and fungal infections due to its well-known and powerful antimicrobial effects. In addition, BBR can also act on the cardiovascular system, such as regulating blood lipids and sugar, anti-arrhythmia, vasodilation effects (Shaffer, 1985; Marin-Neto et al., 1988). BBR may be cardioprotective by controlling oxidative stress and reducing injury to the myocardium, which protects the heart, according to recent *in vitro* and *in vivo* researches (Table 1). To promote pharmacological research, development, and utilization of BBR, this review describes the preventive effects of BBR in CVDs from the perspective of ROS.

2 CHEMISTRY AND BIOACTIVITY OF BERBERINE

Berberine (BBR) is a natural product extracted from the roots, rhizomes, and stem bulk of the Berberidaceae and Ranunculaceae families (such as *Hydrastis canadensis*, the Chinese herb Huanglian, and many other plants) (Pang et al., 2015; Tan et al., 2016; Ye et al., 2017; Neag et al., 2018; Feng X. et al., 2019) (Figure 1). It has the molecular formula [C₂₀H₁₈NO₄]⁺ and a molar weight of 336.36 g/mol (Battu et al., 2010; Tan et al., 2016). 5,6-dihydro-9,10-dimethoxybenzo [g]-1,3-benzodioxolo [5,6-á] quinolininium is the chemical name for BBR (Lau et al., 2001). BBR is a yellow needle-shaped crystal that may be precipitated in ether and has a melting temperature of 145°C. It exhibits antimicrobial



effects on hemolytic *Streptococcus*, *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and Freund's *Shigella*, and can improve leukocyte phagocytosis (Ye et al., 2017). Because of extensive antibacterial activity, extracts of BBR-containing plants or BBR have been the most successful folkloric therapy to against dysentery and infectious diarrhea in China for centuries (Lau et al., 2001; Neag et al., 2018). BBR has many other potential pharmacological effects on various diseases, it has been known to exert anti-inflammatory and anti-cancer effects (Neag et al., 2018); in addition, it can also induce anti-oxidative stress activities (Ye et al., 2017; Neag et al., 2018).

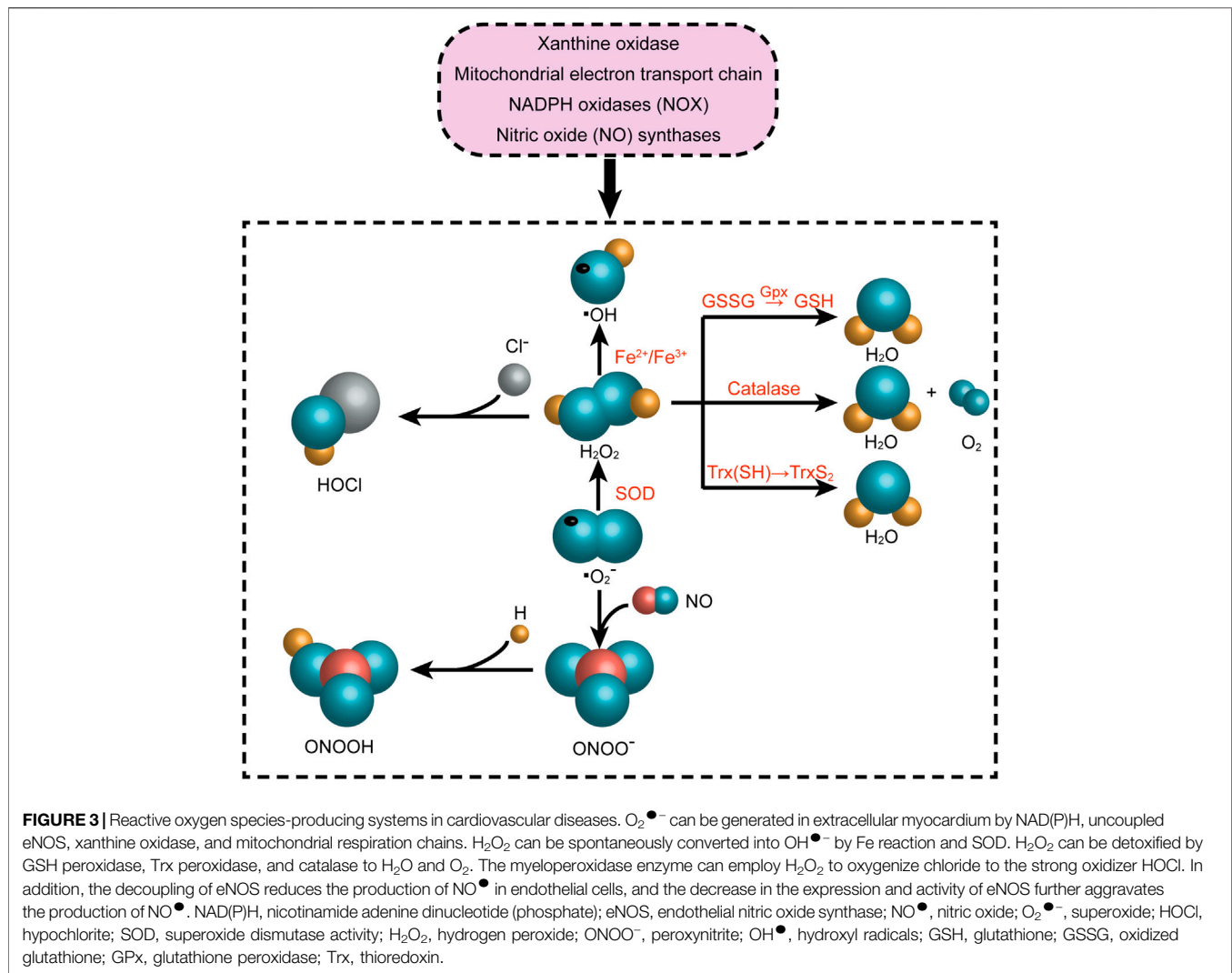
BBR is rapidly transformed after oral application into phase I products, which are then coupled with glucuronic acid or sulfuric acid to create phase II metabolites, which are finally discharged from urine and bile (Ma et al., 2013; Wang K. et al., 2017). The principal metabolic pathways (Figure 2) for BBR in humans and rats are demethylation, demethylenation or reduction and succedent interaction with glucuronic acid and sulfuric acid (Wang K. et al., 2017; Feng X. et al., 2019).

However, BBR itself is of low bioavailability (with a bioavailability of less than 1%), Feng W. et al. (2019), Feng et al. (2020) have described that gut microbiota metabolites of BBR could reveal the enigma between low bioavailability and powerful therapeutic effects. In gastrointestinal tract, nitroreductases are bacterial enzymes that could catalyze the reductive reaction of BBR (Li Y. H. et al., 2009). Nitroreductases regulates BBR absorption by converting BBR into absorbable dihydroberberine, which is 5–10 times more absorbed than BBR (Li Y. H. et al., 2009). After oral administration of BBR, the bioavailability of BBR was significantly increased in hamsters fed a high-fat diet

compared with hamsters fed a normal diet (Li Y. H. et al., 2009). Interestingly, BBR can reduce blood lipids in high-fat hamsters, but it has no obvious lipid-lowering effect on normal hamsters. The interaction of nitroreductases with BBR in the gut has also been demonstrated in rats (Feng et al., 2015). Clinical studies have shown that a positive relationship between blood concentration of BBR and activity of fecal nitroreductase (Li Y. H. et al., 2009; Wang Y. et al., 2017). There is a study showed that BBR could modulate branched-chain amino acids biosynthesis, degradation, and transport in gut microbiota, which alleviate insulin resistance in animals (Yue et al., 2019). The above-mentioned results indicate that by studying the interaction between gut microbiota and BBR, we can change the predicament of BBR's low bioavailability, which will make it better biologically.

3 MOLECULAR MECHANISMS OF OXIDATIVE STRESS IN CARDIOVASCULAR DISEASES

Reactive oxygen species (ROS) play a significant part in many CVDs, and their unregulated generation is related to myocardial tissue damage. The state of oxidative stress results from an imbalance in the formation of ROS and antioxidant defenses in the body, which resulting in an accumulation of ROS and eventually damage cells and tissues (Pizzino et al., 2017; Charlton et al., 2020). In physiological situations, appropriate amount of ROS exerts an influence on cellular signal transduction and physiological function, which is equivalent to their detoxification effect (Tsutsui et al., 2009). It is known as the redox signaling



characterized by specific and invertible oxidation/reduction modification of cell signal elements that can be modulated, and can affect gene expression, excitation-contraction coupling, or cell growth, migration, differentiation, and death (Burgoyne et al., 2012; Sack et al., 2017). The process of ROS production mainly includes enzymatic or non-enzymatic reactions, which are generated by oxidase and then eliminated by the scavenging system. The imbalance between ROS generation and removal systems results in increase in ROS levels and represent alarming stresses. Almost every subcellular organelle in the cell produces ROS (Corpas et al., 2015; Sun et al., 2020). At the cardiac level, the mitochondrial electron transport chain, xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and nitric oxide (NO) synthases are the primary producers of ROS (Figure 3). In our prior investigation, we discovered that the activity of ROS was increased by ibrutinib in mice, which boosted the synthesis of atrial fibrillation (AF) maintenance substrates, and ultimately making them more susceptible to AF. Apocynin is a NOX

inhibitor that can reduce the occurrence of AF and atrial remodeling (Yang X. et al., 2020). On the one side, NOXs (summarized as the NOX enzyme family) are the only major ROS resources (Drummond et al., 2011; Lassegue et al., 2012; Xu T. et al., 2019). There is ample evidence that NOX enzymes play a key role in the pathophysiology of several CVDs (Brandes et al., 2010; Lassegue et al., 2012; Senoner and Dichtl, 2019). On the other side, the activity of the mitochondrial electron transport chain (ETC) generates ATP to meet cellular energy requirements. In most cell types, oxygen acts as an electron acceptor, which is another ROS resource (Murphy, 2009; Xu T. et al., 2019). In addition, many other enzymes such as xanthine oxidase, nitric oxide synthase, cyclooxygenase, cytochrome P450 enzymes and lipoxygenase, as well as other organelles, such as peroxisomes and endoplasmic reticulum, can promote the production of ROS in cells (Senoner and Dichtl, 2019). Intracellular ROS is strongly linked to the pathogenesis of CVDs, such as atherosclerosis (AS), myocardial ischemia/

reperfusion (I/R) injury, arrhythmia, and HF (Xu T. et al., 2019; Sun et al., 2020).

4 EFFECT OF BERBERINE ON CARDIOVASCULAR DISEASES

4.1 Coronary Atherosclerosis

AS is currently considered a chronic inflammatory illness. Hyperactivated pro-inflammatory signaling pathways, increased oxidative stress and upregulated cytokines/chemokines expression are crucial factors in the pathogenesis of AS. The excessive production of ROS causes oxidative stress, which has become an essential and final common mechanism of AS (Kattoor et al., 2017). Some researches on mouse models of AS suggest that BBR may have an anti-atherosclerotic effect (Wu et al., 2020; Yang X.-J. et al., 2020). BBR plays a protective and ameliorative role in AS by regulating various cellular events that pro-atherogenic, including the reduction of oxidative stress (Cheng et al., 2013).

4.1.1 *In Vivo*

Endothelial dysfunction and cell damage is caused by oxidative stress, which plays a key role in the onset and progression of cardiovascular disorders, such as AS (Xi et al., 2007). In the ApoE^{-/-} mouse model, BBR, particularly 8-BBR-C16 administration, effectively inhibited nuclear factor kappa-B (NF-κB) activation and reduced the protein expression of ICAM-1, iNOS and interleukin (IL)-6. These results indicate that the inhibition of BBR and 8-BBR-C16 on the development of AS in ApoE^{-/-} mice can be achieved not only by reducing lipids levels, but also by enhancing anti-inflammatory and antioxidant capabilities (Feng et al., 2017). BBR is a protective agent for endothelial cells. There is a study has found that BBR improves the stability of atherosclerotic plaques in mice with hyperhomocysteinemia, which is associated with the stimulation of peroxisome proliferator-activated receptor-α and consequent reduction of oxidative stress in endothelial cells (Li H. et al., 2016). BBR treatment can inhibit endoplasmic reticulum stress and thereby eliminate ROS, resulting in cyclooxygenase (COX)-2 down-regulation (Liu et al., 2015) or reduction of endothelial microparticle-mediated oxidative stress, thereby improving endothelial function (Cheng et al., 2013). It has been demonstrated that probiotics can influence the lipid metabolism and effectively reduce AS by means of regulating gut microbiota to decrease trimethylamine oxide (Liang et al., 2020). The study has shown that different short chain fatty acids have different effects on the activation of Nod-like receptor family pyrin domain containing-3 (NLRP3) and formation of arterial neointima. Among short chain fatty acids, butyrate has promising therapeutic effects and can serve as a new source of therapeutic strategies for AS (Yuan et al., 2018). An article concluded that the regulatory role of BBR in metabolic abnormalities and AS is achieved through the interaction with the gut microbiota (Cao et al., 2021). The research indicated that in high-fat diet-fed rats, BBR restored the gut barrier, decreased inflammatory and oxidative stress markers, and improved gut peptide levels via

regulating gut microbiota (Xu et al., 2017). In ApoE^{-/-} mice fed a high-fat diet, BBR can improve serum lipid and systemic inflammation levels, and alleviate AS, which may be partly due to changes in composition and functions of gut microbiota (Wu et al., 2020). A similar animal study showed that BBR alleviated AS development and decreased inflammatory cytokine expression, which is related to alterations in gut microbiota compositions (Shi et al., 2018). Gut microbiota are of great value in the treatment of disease processes, and studies have found that modulating gut microbiota, especially increasing the abundance of Akkermansia, may be helpful to improve the anti-atherosclerotic and metabolic protective effects of BBR (Zhu et al., 2018).

4.1.2 *In Vitro*

Atherosclerosis is an inflammation-driven disease and macrophages have a central role in the modulation of inflammation. Two major macrophages phenotypes have been characterized according to the activation by different microenvironmental signals: pro-inflammatory M1 macrophages induced by bacterial lipopolysaccharide (LPS) and/or interferon gamma (IFN-γ) and anti-inflammatory M2 macrophages triggered by IL-4 or IL-13 (Kuznetsova et al., 2020; Yang et al., 2021). There is research suggested that BBR not only inhibit M1 macrophages polarization, but also promote M2 macrophages polarization (Yang et al., 2021). Activated macrophages produce a number of inflammation-related factors such as IL-1β, TNF-α, IL-6, IL-8, matrix metalloproteinase-9 (MMP-9), and so on, which initiate inflammation to induce AS (Kleemann et al., 2008). Some studies suggest that BBR significantly downregulated the proinflammatory cytokines (TNF-α, IL-6, IL-1β, and MCP-1) (Jeong et al., 2009; Wang et al., 2020). NOX may be the most important ROS generation system in the cardiovascular system (Kattoor et al., 2017). BBR inhibited the generation of ROS, which may be caused by the inhibition of the activated NOX content (Jiang et al., 2017). On the one hand, NOX activity in macrophages is an important part of the production of oxidized low-density lipoprotein (ox-LDL) (Kattoor et al., 2017). Ox-LDL, which stimulates circulating monocytes and increases their potential to penetrate blood vessel walls, is one of the novel and high-profile cardiovascular risk factors. Increased infiltration is a critical factor in the occurrence of AS (Huang et al., 1999; Cipolletta et al., 2005; Hulsmans and Holvoet, 2010). BBR can stimulate macrophage autophagy through AMPK/mTOR signaling pathway, thereby attenuating the inflammatory markers generated by ox-LDL (Fan et al., 2015). In human umbilical vein endothelial cells (HUVECs), oxidative stress is alleviated to a sufficient degree to normalize ApoB fragmentation after BBR treatment. It is suggested that BBR has strong antioxidant capacity and inhibits LDL oxidation (Hsieh et al., 2007). BBR significantly reduced the adhesion of monocytes and HUVECs induced by ox-LDL, and this effect was positively correlated with the dose. The experiments show that BBR has a protective effect in the early stage of AS (Huang et al., 2013). On the other hand, the activation of NOX can promote the formation of ROS, leading to endothelial dysfunction (Sena et al.,

2013). NOX4 is a subtype of NOX, which is mainly expressed in vascular endothelial cells and is the main source of endothelial cells to produce O_2^- (Zhang et al., 2013). In palmitic acid-treated HUVECs, BBR reduced ROS production and NOX4 protein expression (Zhang et al., 2013). Moreover, excessive ROS, up-regulated monocyte chemoattractant protein (MCP)-1, and increased adhesion of monocytes to endothelial cells induced by Ang II can all be effectively inhibited by BBR (Ko et al., 2007). According to research findings, BBR mainly inhibits the accumulation of ROS derived from NOX4 in HUVECs (Zhang et al., 2013) or the production of cellular ROS in macrophages by activating AMPK (Jeong et al., 2009). BBR treatment can reduce the level of ROS in endothelial cells after acute exposure to H_2O_2 (Caliceti et al., 2017). Furthermore, the activation of NLRP3 inflammasomes can also be suppressed by BBR: BBR reduces the activation of ROS-dependent NLRP3 inflammasomes in macrophages and inhibits NF- κ B, which inhibits the expression and release of IL-1 β (Jiang et al., 2017; An et al., 2019). BBR reduces the activation of inflammasomes induced by natriuretic acid crystals by inhibiting the expression of NLRP3 and IL-1 β (Liu et al., 2016). Furthermore, BBR also inhibits the action of NLRP3 inflammasomes and the production of IL-1 β induced by saturated fatty acids (palmitate) in adipose tissue-derived macrophages through activating AMPK-dependent autophagy (Zhou et al., 2017).

4.1.3 Clinical Trials

The lipids that cause AS, particularly low-density lipoprotein cholesterol (LDL-C), have occasional effects on the occurrence and development of atherosclerotic plaques (FERENCE et al., 2017; Fatahian et al., 2020). Numerous clinical trials have been conducted to investigate the role of BBR in the treatment of atherosclerotic lipids. It has been shown that in mild or moderate mixed hyperlipidemia patients, 500mg of BBR daily were able to significantly reduce LDL and total triglycerides (TG). And no adverse events were reported during the study (Cicero et al., 2007). A clinical randomized controlled trial concluded that oral BBR capsules (900 mg/d for 3 months) were effective in reducing plasma total cholesterol (TC) and LDL-C levels compared with placebo in patients with mild hyperlipidemia (Wang et al., 2016). A multicenter, randomized, double-blind, placebo, controlled trial confirmed the safety and efficacy of BBR in patients with mild to moderate hypercholesterolemia, where continuous daily oral BBR nutritional agents (red yeast rice, coenzyme Q10, and hydroxytyrosine, containing *Berberis aristata* d.e. 588 mg) for 4 weeks induced a 26% reduction in LDL-C (D'addato et al., 2017). The study suggests that combined administration of monacolin K and BBR could provide similar protection from CVDs compared to prescription statin therapy, with potentially lower risks for adverse effects (D'addato et al., 2017). In addition, there are some meta-analyses showed that BBR was successful in reducing TC and LDL cholesterol. A meta-analysis that included 19 controlled and cross-sectional trials indicated that the combination of BBR with silymarin significantly lowered cholesterol (Bertuccioli et al., 2020). Moreover, a meta-analysis including 16 randomized controlled trials with 2,147 participants strongly confirmed the BBR's efficacy and safety in the treatment

of dyslipidemia patients. They thought that the blood lipid status of patients with dyslipidemia was significantly improved after BBR treatment, and the safety was satisfactory, the contents of TC and LDL-C were significantly decreased, and no significant adverse events occurred (Ju et al., 2018). Another clinical study and meta-analysis showed that BBR combined with nutritional supplements or combined oral administration of BBR and drugs could reduce plasma LDL-C and TC levels without significant side effects (Affuso et al., 2010; Marazzi et al., 2011; Pisciotta et al., 2012; Cicero et al., 2019; Zhang et al., 2019). In conclusion, these studies all confirm that BBR regulates plasma cholesterol levels in patients with dyslipidemia and that this natural compound provides an exciting and encouraging preventive and therapeutic strategy for AS.

4.2 Myocardial Infarction/Reperfusion

Myocardial infarction is one of the common ischemic heart diseases and is the main cause of mortality in high-income societies (Kim et al., 2009). Reperfusion itself can lead to other injuries, such as cardiac dysfunction, reperfusion arrhythmia, and aggravated myocardial infarction. ROS is critical for organ damage during I/R (Cross et al., 1987; Halliwell et al., 1992; Jeroudi et al., 1994). Numerous researches have demonstrated that the formation of ROS increases regardless of whether it is during I/R (Minutoli et al., 2016). The mechanisms by which excessive ROS induce cellular injury involve interference with cell signal transduction, activation of inflammatory factors, lipid peroxidation (Davidson et al., 2012) and even direct cell death (Zhan et al., 2016). BBR has antioxidant and anti-inflammatory effects, meanwhile, BBR treatment has a cardioprotective effect on I/R injury, and can significantly improve cardiac function after I/R injury (Qi et al., 2010; Chang et al., 2012; Gao et al., 2012; Chang et al., 2016; Zhao et al., 2016).

4.2.1 *In Vivo*

There is a study offered direct evidence that BBR-treated rats played an antioxidant role by reducing cardiac superoxide production, gp91phox expression, malondialdehyde (MDA) concentration and promoting superoxide dismutase (SOD) activity (Yu et al., 2016). In previous research, the levels of MDA, a marker of lipid peroxidation (Chang et al., 2016), were significantly reduced in the BBR-treated diabetic rat model (Chang et al., 2016). Sirtuin 1 (SIRT1)-mediated antioxidant effects have been shown to exert a protective effect on I/R myocardium (Zhang et al., 2018). Mitochondria is the center of energy production. Ischemia triggers energy depletion, leading to mitochondrial dysfunction, which increases oxidative stress and induce apoptosis (Bulteau et al., 2005; Bhatti et al., 2017). In turn, oxidative stress aggravates ischemia reperfusion injury (Bulteau et al., 2005; Wang et al., 2015; Bhatti et al., 2017). In myocardial ischemia-reperfusion model of male Sprague-Dawley rats, the mitochondrial membrane potential (MMP) is improved due to BBR pretreatment, indicating that I/R-induced mitochondrial lesion was obviously reduced (Wang et al., 2015). Yu et al. (2016) found that SIRT1 inhibitors abrogated the antioxidant effect of BBR using a rat myocardial I/R injury model, suggesting an indispensable

role of SIRT1 in the cardioprotective effect of BBR. The anti-inflammatory effect of BBR is associated with its inhibition of phosphoinositide 3-kinase (PI3K)/AKT signaling pathway, which reduces the secretion of a variety of pro-inflammatory cytokines/mediators in cardiac myocytes and serum, such as IL-6, IL-1 β and tumor necrosis factor (TNF)- α in serum and cardiac myocytes (Shang et al., 2010; Li et al., 2014; Qin-Wei and Yong-Guang, 2016). In addition, BBR also alleviated inflammation by suppressing the NF- κ B signaling pathway (Wang et al., 2018). Moreover, it has been reported that the BBR derivative rainanberine protects pulmonary arterial ring and by inhibiting NOX and calcium influx (Gao et al., 2012). In addition, Liu et al. (2017) suggest a potential new strategy by which exercise benefits the cardiovascular system by altering the microbiome. Zununi Vahed et al. (2018) reviewed the development of microbiota dysbiosis after myocardial infarction and gave recent advances in a microbiota-based therapeutic strategy to delay or prevent myocardial infarction. Administration of antibiotics decrease or increase the abundance of specific bacterial groups in the rat intestine, which links to severity of myocardial infarction and may provide opportunities for novel diagnostic tests and interventions for prevention of CVD (Lam et al., 2012; Lam et al., 2016). Beneficial microbiota reduce MI risk factors or reduce post-MI events mainly by modulating lipogenesis and cholesterol metabolism and antioxidant production (Girard et al., 2009; Lam et al., 2012; Mccafferty et al., 2012; Gan et al., 2014). As a consequence, further studies are needed to devise the impact of BBR on intestinal microbiota and myocardial infarction through ROS.

4.2.2 *In Vitro*

In addition, the antioxidant effect of BBR was also observed in cultured cells (Tan et al., 2007; Chatuphonprasert et al., 2013). BBR significantly attenuated I/R injury in SIR-injured H9C2 cardiomyocytes, and the SIRT1 signaling pathway more or less mediated this cardioprotective property characterized by antioxidant and anti-inflammatory effects (Yu et al., 2016). Furthermore, SIR-induced cardiac apoptosis, oxidative stress and endoplasmic membrane stress were remarkably downregulated by BBR (Zhao et al., 2016).

4.2.3 Clinical Trials

Unfortunately, although a large number of preclinical studies have conclusively concluded that BBR has a preventive and curative effect on I/R, its clinical studies are scarce (Liu et al., 2019). For the first time, Li Y. et al. (2016) found evidence that neurological deficits and the prognosis were improved in acute ischemic stroke (AIS) patients. The BBR group received BBR 300 mg (tid) in addition to the therapy of the general group. They believe that BBR worked by downregulating the serum macrophage migration inhibitory factor and IL-6 levels. And there was no significant difference in the incidence of adverse reactions between the two groups (Li Y. et al., 2016). Similarly, the BBR group was given additional BBR tablets 0.3 g/time, and taken three times a day. The results suggest that BBR prolonged the life expectancy and improved the quality of life in patients with acute

myocardial infarction treated with percutaneous coronary intervention (Qing et al., 2018). Moreover, they also discovered that the plasma level of C-reactive protein, tumor necrosis factor α and IL-6 were considerably decreased by BBR treatment. In summary, all of these findings indicated that BBR may alleviate I/R injury by inhibiting the over-reactive inflammatory response.

4.3 Arrhythmia

Arrhythmia is defined as an abnormality of the heart rate or rhythm due to an abnormality in the frequency, rhythm, pacing site, conduction velocity, or sequence of excitation of the heart impulses, with AF being the most prevalent and closely linked to high cardiovascular morbidity and mortality (Nattel and Dobrev, 2016; Barangi et al., 2018).

4.3.1 Oxidative Stress in Atrial Fibrillation

Atrial structural remodeling, electrical remodeling, alterations in the autonomic nervous system, and Ca²⁺ disturbances are the four major mechanisms of AF pathogenesis. In addition, increased ROS might alter ion channel activity, thereby increasing AF susceptibility (Barangi et al., 2018). ROS via modifying proteins central to excitation–contraction coupling, including L-type calcium channels, sodium channels, potassium channels, and sodium-calcium exchangers, which may contribute to the pathogenesis of the arrhythmia (Takimoto and Kass, 2007). ROS also affects the function of the sarcoplasmic reticulum Ca²⁺-adenosine triphosphatase (SERCA) and changes the activity of calcium sensitivity in myofilaments. Additionally, ROS causes an energy deficit by interfering with the action of energy-metabolizing proteins. Eventually, ROS promotes fibrosis via increasing cardiac fibroblast proliferation and matrix metalloproteinases, which results in extracellular remodeling (Takimoto and Kass, 2007; Van Der Pol et al., 2019). On the one hand, excessive ROS was detected in cardiac tissue of several atrial pacing models, which leads to electrical changes in the atria and ultimately induces AF (Violi et al., 2014; Karam et al., 2017; Korantzopoulos et al., 2018). On the other hand, the role of oxidative stress in the pathogenesis of AF has been increasingly recognized. The risk factors that induce AF, such as adiposity, diabetes, age, and hypertension, may all be linked by oxidative stress (Ziolo and Mohler, 2015). Accelerated ROS in myocardial tissues causes DNA, protein, and lipid damage, as well as tissue injury. These events lead to heart structural and electrical remodeling, which increases susceptibility to AF (Barangi et al., 2018). Meanwhile, the multifunctional calcium/calmodulin-dependent protein kinase II (CaMKII) as a sensor is activated after being stimulated by ROS, thereby promoting the occurrence of arrhythmia (Erickson et al., 2008; Swaminathan et al., 2011). Ox-CaMKII could be regarded as a biomarker activated by ROS, mediating the development of AF (Howe et al., 2004; Erickson et al., 2008; Palomeque et al., 2008). In our previous study, we have proved the effects of ROS on atrial cardiomyocytes of mice, and it is possible that ROS activates ox-CaMKII and p-CaMKII (Thr-286) to increase AF susceptibility after ibrutinib treatment (Yang X. et al., 2020). Gut microbe-derived metabolites function primarily to modulate energy

metabolism, local and systemic immune systems, and neural activity (Liu et al., 2022). Based on a strategy of metagenomic and metabolomic analyses, the study shown that the disordered gut microbiota and microbial metabolite profiles in AF. Imbalances in gut microbial function and associated changes in metabolic patterns were observed in both feces and serum of patients with AF (Zuo et al., 2019). The heart-gut axis is a potential target for CVDs therapy. A high-fructose diet can induce inflammation of the heart-gut axis and metabolic disturbances that ultimately lead to arrhythmias (Cheng W. L. et al., 2021). The current study demonstrates that aged-associated microbiota dysbiosis promotes AF in part through a microbiota-gut-atria axis. It is indicating that in fecal microbiota transplantation rat model, the microbiota-intestinal barrier-atrial NLRP3 inflammasome axis may be a reasonable molecular target for the treatment of age-related arrhythmias (Zhang et al., 2021).

4.3.2 Berberine in Atrial Fibrillation

Huang et al. described the anti-arrhythmic activity of BBR for the first time in 1989 (Feng X. et al., 2019). BBR exerts its antiarrhythmic effect by prolonging action potential duration (APD), which is due to the mechanism that BBR blocks ion currents (Barangi et al., 2018). In cardiac myocytes, BBR significantly shortened the extended QTc interval while also stabilized the decreased transient outward potassium current (I_{to}) and L-type Ca^{2+} (I_{Ca}) currents (Wang et al., 2012) or depressed ATP-sensitive K^+ channel (K_{ATP}) channel activation (Wang et al., 1996). The effects of BBR on cell membrane ion currents was related to its concentration, with BBR at concentrations of 0.3–30 μ M blocking rapid (I_{Kr}) delayed rectifier K^+ channels and at higher dose inhibiting I_{to} (Sanchez-Chapula, 1996). Further studies revealed that BBR as well as the derivatives of BBR targets a variety of channels including the cardiac slow (I_{Ks}) delayed rectifier K^+ channels and I_{Kr} , K_{ATP} , inwardly-rectifying K^+ channel (I_{K1}), I_{Ca} (Chi et al., 1996; Chi et al., 1997; Lau et al., 2001; Li et al., 2008). Na channel activity plays a major role in mediating proper action potential conduction across the heart (Karam et al., 2017). Studies have shown that elevated intracellular NADH causes a decrease in cardiac Na^+ current (I_{Na}) signaled by an increase in mitochondrial ROS (Liu et al., 2009; Liu et al., 2010). Liu et al. (2013) demonstrated a reduction in mitochondrial ROS in cardiomyopathy will reverse the reduced I_{Na} and possibly some of the arrhythmic risk by improving conduction velocity. BBR increases myocardial contractility and cardiac output via blockade of K^+ channels, stimulation of Na^+ - Ca^{2+} exchanger, and elevation of coronary blood flow. It is considered that a transient inward current carried primarily by Na^+ , which is intimately associated with an increase in intracellular Ca^{2+} overload, is responsible for the delayed afterdepolarization. This effect is also likely to be involved in the antiarrhythmic effect of BBR (Lau et al., 2001). Recently, there are some studies that have shown that, through its favourable antioxidant and sodium channel inhibitory effects, Cannabidiol, is the main non-psychoactive constituent of the Cannabis sativa plant, may protect against high glucose-induced arrhythmia and

cytotoxicity (Fouda et al., 2020; Fouda and Ruben, 2021). Future studies may reveal the antiarrhythmic effect of BBR through ROS and sodium channels. In rabbit atrial myocytes, Acetylcholine-induced AF can be inhibited by the effects of BBR to prolong APD and increase the effective refractory period of the atrium. Notably, The RR interval and effective refractory period (ERP) were likewise prolonged by BBR. According to the above-mentioned mechanisms, BBR treatment results in the termination of the acetylcholine-induced AF (Zhou et al., 2015). The IC_{50} value indicates the concentration of the inhibitor which is required to inhibit a given biological or biochemical function by half (Caldwell et al., 2012). The research found that the drug at concentrations of 0.3–30 μ M blocked only the delayed rectifier (I_K) current with an $IC_{50} = 4.1 \mu$ M. BBR produced a tonic block and a phasic block that was increased with the duration of the depolarizing pulse (Sanchez-Chapula, 1996). CPU86017 is a novel Class III antiarrhythmic agent derived from BBR. It blocks $I_{Kr, tail}$, I_{Ks} , and I_{Ca} currents with IC_{50} values of 25, 14.4, and 11.5 μ M, respectively (Dai, 2006).

Although several experiments have shown that BBR has an anti-arrhythmic impact by changing ion channel activity. Few researches have focused on the antioxidative effects of BBR in AF condition. Therefore, further research *in vivo* and *in vitro* or clinical trials investigating the antiarrhythmic effect of BBR via ROS are warranted.

4.4 Heart Failure

HF is a complicated clinical syndrome caused by abnormalities in the cardiac structure or function, and its pathogenesis involves structural changes, neurohumoral, cells, and molecules (Van Der Meer et al., 2019). HF is an increasing global burden of disease characterized by altered excitation-contraction coupling, cardiac energy deficit, and oxidative stress (Weissman and Maack, 2021).

4.4.1 Oxidative Stress in HF

Nicotinamide adenine dinucleotide (NAD⁺) and its reduced dinucleotide NADH play a pivotal role in driving oxidation-reduction reactions refer to energy production (Mericskay, 2016; Hershberger et al., 2017). In addition to its function in regulating the energy metabolism of cardiomyocytes, NAD⁺, as a precursor for the phosphorylated dinucleotide pair NADP⁺/NADPH, is vital in the detoxification of ROS (Mericskay, 2016; Hershberger et al., 2017). Reduced myocardial NAD⁺ levels have been observed in HF murine models (Pillai et al., 2005; Hsu et al., 2009; Rajamohan et al., 2009). Excessive ROS triggered left ventricular (LV) dilatation, LV remodeling, and consequently LV systolic dysfunction in mice (Takimoto et al., 2005). In mice myocardial infarction models, NOX inhibition lacking the cytoplasmic NOX component p47phox attenuates ventricular remodeling and dysfunction (Doerries et al., 2007). In a murine HF model, cardiac function and redox status could be improved by supplementing NAD⁺ levels and nicotinamide riboside (NR), a precursor of NAD⁺ (Diguët et al., 2018). After inhibition of xanthine oxidase using oxypurinol (rats) or allopurinol (dogs), the heart from LV remodeling was protected, the LV contractile function and myocardial efficiency post-cardiac injury was improved. These observations suggest that

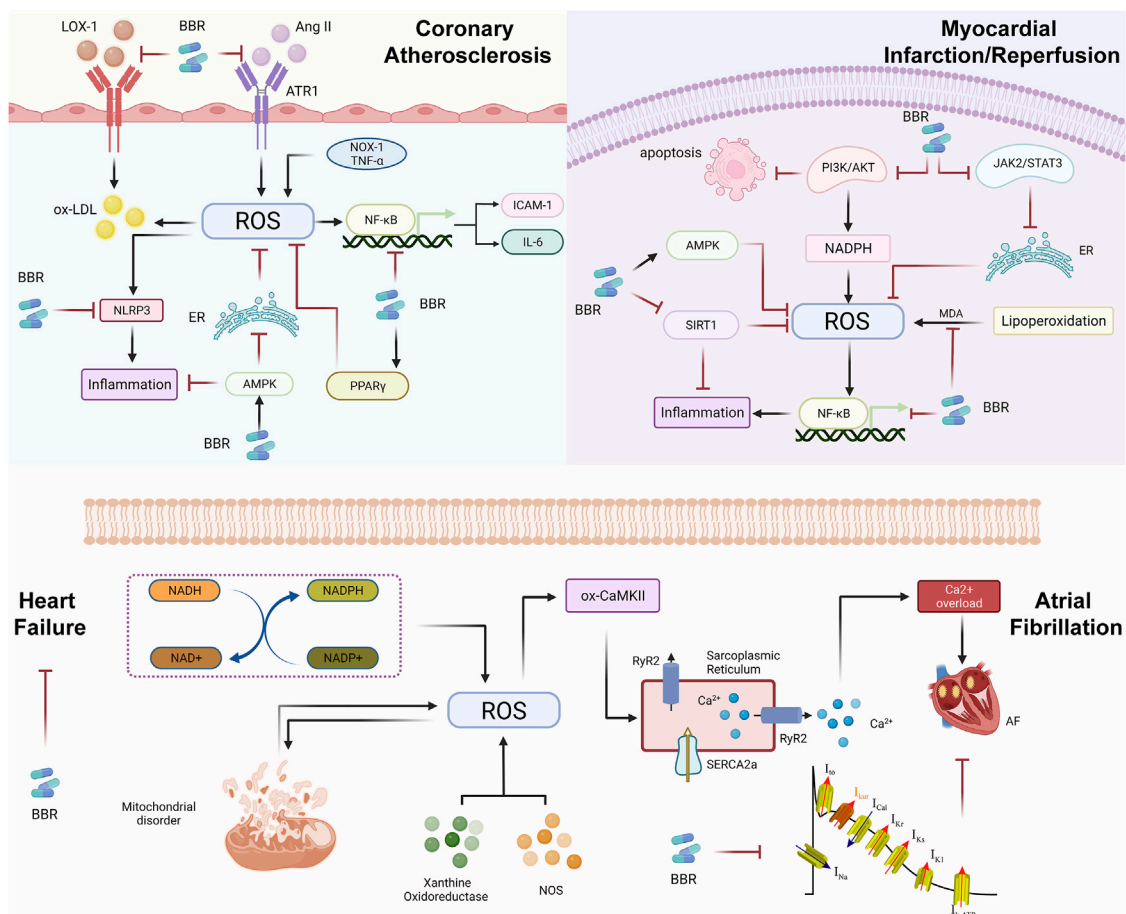


FIGURE 4 | Reactive oxygen species in the evolution of cardiovascular diseases (CVDs) and pharmacological mechanism of berberine (BBR). During the evolution of atherosclerotic plaques, the main role of berberine is to inhibit the oxidation of LDL, Ang II and inflammation, or activate AMPK and PPAR γ , and further inhibiting the oxidative stress response; BBR in MI/R regulates superoxide reaction by MDA, thereby preventing excessive myocardial injury. BBR may regulate oxidative stress through the NF- κ B signaling, PI3K/AKT signaling, JAK2/STAT3 signaling and so on. Oxidative stress mainly affects SR and RyR2 through ox-CaMKII and causes calcium overload, which eventually leads to AF. In terms of treatment, BBR mainly reduces the occurrence of AF by inhibiting ion channels. ROS-induced HF is mainly due to NADH/NADPH, mitochondrial disorders, XO and NOS, but the improvement of berberine in HF is mostly clinical research. Therefore, it is necessary to further study the mechanisms of BBR to treat HF through ROS and find for clinical treatment new targets.

xanthine oxidase inhibition restores cardiac structure and function, and may enhance myocardial calcium sensitivity in HF (Ukai et al., 2001; Minhas et al., 2006). The gut microbial modulation of inflammation through short-chain fatty acids production, which is important in disease states. In patients with HF, the abundance of Ruminococcaceae on the family level was decreased and abundance of Blautia from the Lachnospiraceae family on the genus level was reduced (Kamo et al., 2017), and the levels of Faecalibacterium prausnitzii was reduced (Cui et al., 2018). In HF, most of the microbes that were reduced belonged to the Lachnospiraceae family, in addition to Faecalibacterium from the Ruminococcaceae family (Kummen et al., 2018). Butyrate exerts local anti-inflammatory effects in the gut mucosa, and stimulates surrounding regulatory T cells (Arpaia et al., 2013). Kummen et al. (2018) reported that patients with chronic HF have reduced butyrate-producing potential bacteria (Kummen et al., 2018). Evidence suggests that elevated bacterial translocation during HF is the result of one

or more mechanisms, including altered gastrointestinal structure and function during visceral hyperemia, and abnormal host immune defenses (Tang et al., 2019). There are two main ways in which gut microbiota directly interact with BBR: 1) BBR modulates gut microbiota; 2) gut microbiota transforms BBR. Researching interactions between BBR and gut microbiota will be providing reference for clinical rational use of BBR in the treatment of diseases (Cheng H. et al., 2021).

4.4.2 Berberine in HF

Cardiac function in transverse aortic constriction (TAC) surgery induced chronic HF in mouse model can be remarkably ameliorated by BBR (Abudureyimu et al., 2020). In a high-dose isoprenaline (s.c.)-induced HF model in rats, 12 days of continuous administration of total saponins of Panax ginseng (20 mg/kg/d) combined with BBR (20 mg/kg/d) had similar therapeutic effects compared with captopril alone (Li Y. et al., 2009). BBR (63 mg/kg/d, p.o., 4 week) was further proven to be a

promising medicine to ameliorate HF by targeting the inhibition of cardiomyocyte Ca^{2+} overload (Zhang et al., 2008). Similarly, intravenous BBR administration reduced left ventricular end-diastolic pressure and systemic vascular resistance, thereby improving cardiac output in dogs with ischemic HF (Huang et al., 1992). This activity has also been validated in other animal models (Ko et al., 2000). A randomized, double-blind controlled study concluded that BBR significantly improved left ventricular ejection fraction (LVEF), exercise capacity, dyspnea-fatigue index, and lowered the frequency and complexity of ventricular premature complexes (VPCs) in patients with chronic HF (Zeng et al., 2003). However, despite the above mentioned abundant preclinical studies suggesting an important role for oxidative stress in the development of HF, unfortunately, there is currently a lack of clinically recognized treatments that directly target ROS (Weissman and Maack, 2021). This may be due to that in the experimental setting, the most of the researches to test the efficacy of anti-oxidative stress treatments in HF models, while in the clinical setting the treatments of anti-oxidative stress were primarily tested in patients with acute myocardial infarction and not HF (Van Der Pol et al., 2019). Hypertension is a major risk factor for CVDs, including coronary artery disease, stroke, HF, AF and so on (Yousefian et al., 2019). Several studies have demonstrated the therapeutic potential of BBR and its derivatives for hypertension (Liu et al., 1999; Zhang et al., 2005; Lan et al., 2015). A systematic review investigate BBR effect on blood pressure and CVD risk in five randomized controlled trials and two non-randomized controlled trials were included with 614 participants (Suadoni and Atherton, 2021). It has been reported that natural compounds can improve hypertension due to the formation of stable free radicals with ROS-derived NADPH oxidase and prevent the assembly of NOX subunits (Yousefian et al., 2019). It was showed that NOX4-derived ROS play an important role in endothelial microparticles-induced oxidative stress, and BBR can reverse cell damage caused by elevated endothelial microparticles (Cheng et al., 2013). Tian et al. (2019) suggest that in 2K1C renovascular hypertensive rats, BBR attenuates hypertension and sympathoexcitation through the ROS/Erk1/2/iNOS pathway. Therefore, more work should be taken to investigate the mechanisms of BBR or other clinical therapies on HF via ROS and find new targets for the clinical management.

5 CONCLUSION

In recent years, an increasing number of studies have begun to focus on the role of BBR in CVDs. In the last decade, there are also a growing number of studies showing the unexpected therapeutic effects of BBR on many CVDs, including AS, myocardial I/R, AF and so on (Figure 4, created with BioRender.com). In this paper, we systematically and comprehensively review the chemical properties,

bioavailability, and molecular mechanisms of BBR on CVDs via oxidative stress. Besides, the application of BBR in metabolic diseases is limited by its unsatisfied oral bioavailability. As a result, improving the bioavailability of BBR is a problem that needs to be addressed to expand its clinical application. It is fortunate that polymer materials and nanotechnology provide us a new idea (Zhu et al., 2013; Mirhadi et al., 2018; Xu H. Y. et al., 2019). There is research that shows that novel nanoemulsion provides a promising carrier to improve the hypoglycemic efficacy of BBR by overcoming its gastrointestinal deficiency. Nanoemulsion increased the oral bioavailability of BBR in rats by 212.02% (Xu H. Y. et al., 2019). Moreover, Mirhadi et al. (2018) describes different types of nanocarriers (polymeric based, magnetic mesoporous silica based, lipid based, dendrimer based, graphene based, silver and gold nanoparticles) have been used for encapsulation of BBR. Similarly, the self-microemulsifying drug delivery system formulation could be used as a possible alternative to traditional oral formulations of BBR to improve its bioavailability, which was enhanced about 2.42-fold compared with the commercial tablet in rats (Zhu et al., 2013). The information can be referred to for the future research related to BBR.

BBR is extensively used in clinical practice in traditional medicine. Therefore, it is worthwhile to explore the active ingredients of BBR and to elaborate the mechanism of BBR deeply from the perspectives of molecular biology and pharmacokinetics, which is beneficial to promote the broader clinical application of BBR. In short, the role of BBR in preventing and treating CVDs should not be underestimated, and rigorous, large-scale, long-term, high-quality, multicenter clinical trials need to be implemented to confirm the efficacy, safety, and economic benefits of BBR. What needs to be emphasized is that researches on the association between BBR, BBR structural analogs, BBR-containing plants and CVD, especially clinical investigations, needs to continue.

AUTHOR CONTRIBUTIONS

YX and YG designed the manuscript. NA and GZ drafted the manuscript. YL and CY revised the manuscript. FY and LZ aided in the design of the illustrations. All authors approved the manuscript for publication.

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