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Therapeutic Application of Berberine: a Consolidated Review

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Abstract
Berberine (BBR) is a naturally occurring alkaloid compound found in various plant parts linked to numerous health benefits. Its use in traditional Ayurvedic health practices dates back to ancient civilizations. The aim of this review is to provide an overview of current studies that examine the development and increased potency of BBR's therapeutic effects. This review highlights the potential therapeutic properties of this phytochemical compound and its potential use as an alternative to conventional treatment for chronic ailments such as diabetes, cardiovascular diseases, and cancer. Both animal and clinical researches have demonstrated the therapeutic effects of BBR on these diseases, and studies on its toxicity are also included. According to the studies reviewed, BBR has a positive effect on several physiological processes, including glucose and lipid metabolism, inflammation, oxidative stress, and endothelial function. It can also inhibit tumor growth and promote apoptosis in cancer cells. Furthermore, BBR has exhibited the capacity to ameliorate cardiac performance, diminish arterial blood pressure and serum cholesterol concentrations, and augment insulin responsiveness. Collectively, the extant body of knowledge posits that BBR holds therapeutic promise across a spectrum of pathological conditions. Nevertheless, an augmented investigation effort is requisite to ascertain its optimally efficacious dosage, administration modality, and potential untoward reactions. Moreover, extended examinations are imperative to appraise its enduring safety profile and efficaciousness, particularly when employed concomitantly with other pharmacotherapies. Despite a predominantly affirmative outcome within prevailing investigations, it remains imperative to conduct further exhaustive scrutiny, particularly via clinical trials, in order to substantiate its therapeutic security and efficacy in the management of ailments.

Keywords Berberine · Therapeutic applications · Alkaloid · Phyto-compounds

Introduction

Nowadays, pharmaceutical companies are dedicating their time and resources towards researching and developing herbal medication formulations that can be used to manage chronic diseases [1–4]. The World Health Organization also supports the use of conventional treatments that have natural origins because they are easily accessible and relatively inexpensive to produce [1, 5, 6]. This shift towards natural remedies is mainly due to the fact that some synthetic pharmaceutical drugs may have harmful side effects when used for long-term treatment of chronic diseases. The use of plant-based products as natural medication to treat chronic disorders is a traditional method that has been supported by Ayurveda, an ancient medical system originating from the Indian subcontinent that is now used as an alternative treatment worldwide [7–10].

Natural products have gained popularity as an alternative to conventional medicine due to their high effectiveness and minimal adverse effects, according to studies [11–14]. Berberine (BBR) which possesses potent antibacterial, antiprotozoal, antidiarrheal, and anti-trachoma effects, has been used in Ayurveda, Chinese medicine, and Middle Eastern folk medicine for more than 3000 years [15, 16]. In recent years, clinical research has revealed BBR's effectiveness against various disorders, including hypertension, arrhythmia, hyperglycemia, cancer, depression, inflammation,

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analgesia, and hypolipidemia [17, 18]. BBR has proven itself to be a promising drug with multispectral activities (Fig. 1).

This review focuses on recent studies to show the drug's delivery on therapeutic effects to increased potency rather than summarizing earlier findings on pharmacology of BBR.

BBR Chemical Structure and Plant Sources

BBR has a molecular weight of 336.37 g/mol and a chemical formula of C20H18NO4+(16,17-dimethoxy-5,7-dioxa-13-azoniapentacyclo[11.8.0.02,10.04,8.015,20] henicosa-1(13),2,4 (8),9,14,16,18,20-octaene) [19, 21]. It is a stable compound with a bitter taste and appears as a yellow crystalline powder. BBR is highly soluble in polar solvent like water and ethanol, but less soluble in organic solvents such as acetone and ether [22]. The hydrochloride form of BBR, which has a lower water solubility rate compared to its sulfate and phosphate forms, dissolves more readily in hot water. Ethanol and methanol are commonly used agents for obtaining BBR from different plant sources [19]. BBR extraction techniques have evolved in recent years, with both traditional methods like Soxhlet extraction, percolation, and maceration, as well as modern techniques like ultrahigh pressure method, supercritical fluid extraction, and microwave-assisted extraction being employed [15, 19, 23]. Raw extracted BBR is now used to make oral pills or capsules for clinical use. BBR is readily available from medicinal herbs conventionally used and is found in abundance in different parts of medicinally significant plants, such as the stem, tuber, and bark [19] (Table 1).

BBR has been used in normal diet as traditional medicine for centuries, particularly in Chinese medicine as antimicrobial, anti-fungal, antiprotozoal, and anti-effective against different viral, parasitic, and other infections [25]. Sometimes, Chinese people used it as dietary supplement to treat common cold, influenza, and other respiratory infections [26].

Therapeutic Applications of BBR

Anticancer Activity

BBR is one of the powerful substances utilized in anticancer therapy which is derived from a variety of plants. It is shown to have an effective activity against a wide range of cancer including breast cancer, lung cancer, cervical cancer and gastric cancer [21].

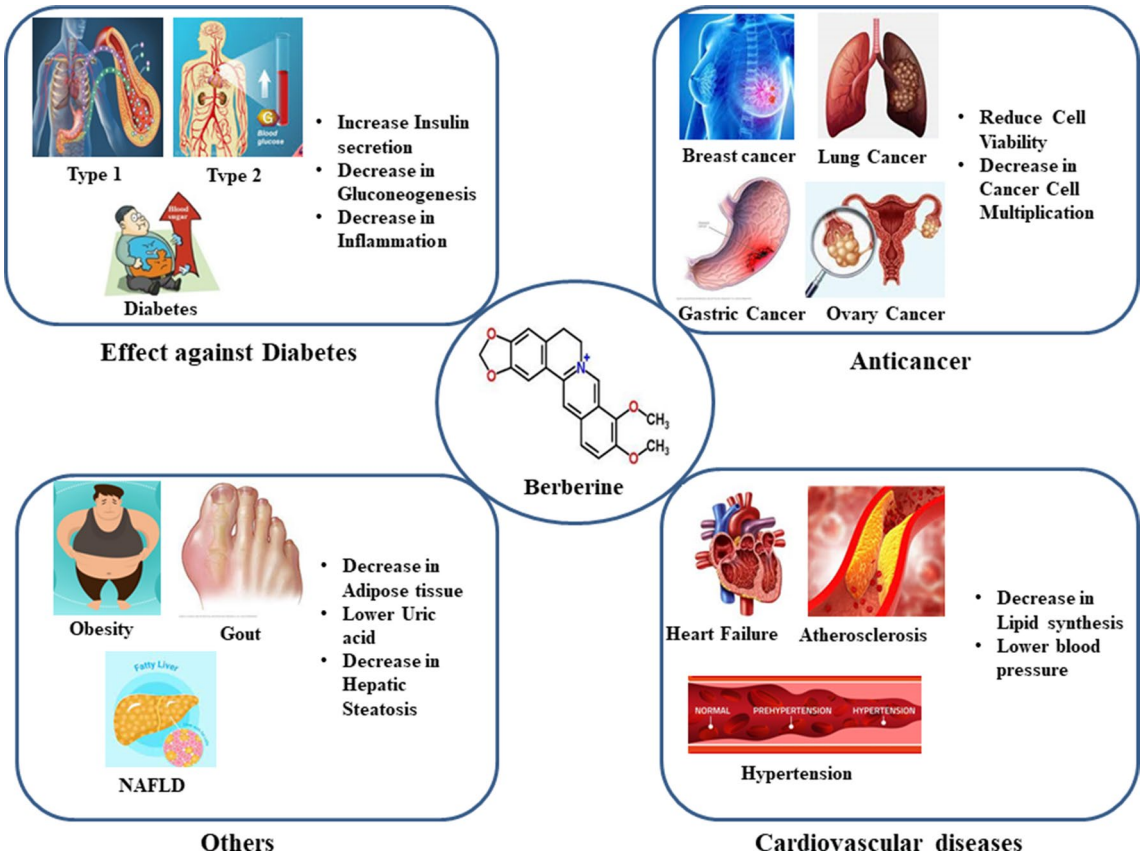

Fig. 1 BBR and its potential application in different health problems [19, 20]

Table 1 Natural sources of BBR [19, 22, 24]

Sl. no	Plant sources	Plant parts	BBR content (mg/g)
1	*Coptis chinensis* Franch	Rhizome	51–96
2	*Coptis teeta* Wall	Rhizome	72–91
3	*Berberis kansuensis* C.K. Schneid	Stem, bark	18–35
4	*Argemone mexicana* L.	Root, stems, leaves	0.69–11
5	*Berberis diaphana* M.	Stem, bark	8–24
6	*Thalictrum foliolosum* DC.	Root	5–11
7	*Berberis vulgaris* L.	Root	8
8	*Berberis croatica* Horvat	Root	8–14
9	*Berberis darwinii* Hook	Stem, bark	45
10	*Coscinium fenestratum* (Goetgh.) Colebr.	Stem	11–33

Breast Cancer

Breast cancer has become a major concern for women worldwide, claiming numerous lives over the years [27]. Studies have revealed that BBR can effectively reduce cell viability and inhibit the multiplication of cancerous cells [28]. Another study also indicated that BBR can lower the levels of metadherin, which acts as a catalyst for the growth of cancerous cells, thus preventing their proliferation [29]. BBR was found to inhibit the growth of MDA-MB-468 cells by blocking cyclin D/cyclin-dependent kinase 4 (CDK4) complexes and stimulating the cell growth inhibitor p38, leading to the arrest of the cell cycle at the G1/S stage. BBR also reduced the proliferation of MDA-MB-231 cells by blocking the cyclin A/CDK1 cell cycle kinase complex and the AKT/ERK pathways, inhibiting the cell cycle at the G2/M phase [28, 30]. BBR can help in reducing abnormal growth of the cell, apoptosis, and inflammation. It can also be used in coordination with other chemotherapy medicines like cisplatin, 5-fluorouracil, methyl methanesulfonate, and camptothecin to prevent and treat breast cancer [29, 30].

Lung Cancer

Lung cancer is a dangerous and widespread form of cancer that results in a significant number of deaths worldwide [31]. Studies have shown that BBR can reduce the growth of non-small cell lung cancer (NSCLC) xenograft tumors in humans via the SWI-independent-3 transcription regulator. Additionally, BBR can cause DNA damage by downregulating TOP2 levels, leading to NSCLC cell death. BBR also stimulates the miR19a/TF/MAPK signaling pathway, which further promotes NSCLC cell death [31, 32]. BBR has great potential to prevent lung cancer by reducing cell growth, self-destruction of cancer cells, and boosting the anticarcinogenic impact of tyrosine kinase inhibitors. However, future research is necessary to explore other potential mechanisms of BBR-based lung cancer prevention [31–33].

Ovarian Cancer

Ovarian cancer is a significant health hazard and prevalent malignancy in women worldwide [30, 34]. BBR has shown promise in enhancing the effectiveness of many anticancer drugs in preventing the growth of ovarian cancer cells. For example, in in-depth analysis of caspase-dependent and RIPK3-MLKL pathways, the conjunction with BBR and cisplatin can effectively induced the ovarian cancer cell to be inactivated, ceased cellular mechanism and gradually program cell death [35]. In another study, BBR was found to inhibit the independent phospholipase A2 (iPLA2)-arachidonic acid (AA)-cyclooxygenase-2 (COX-2)-prostaglandin E2 (PGE2) pathway and reverse the phosphorylation-induced growth of focal adhesion kinase (FAK) caused by the chemotherapeutic drug VP16 [36]. It was also known that BBR in association with drug niraparib has great potential to use as anticancer against ovarian cancer by inducing DNA damage [35, 36]. BBR has great potential to enhance the effectiveness of drugs in conjugation with anticancer drugs especially in ovarian cancer cells by following different cell mechanism and pathways. BBR-based ovarian cancer prevention and treatment need to be explored more with focus to the potential mechanisms of [35, 36].

Gastric Cancer

Stomach cancer is a prevalent disease across the world [30, 37]. Several studies have reported that BBR can prevent stomach cancer through various mechanisms. For example, BBR can inhibit the proliferation of SGC-7901 cells by blocking the cell cycle at G1 phase [38]. In in vitro and in vivo experiments, BBR can inhibit the growth of cancer cells and reduce the release of IL-8 by inactivating the MAPK signaling pathways [39]. Moreover, it is also known that the BBR can suppress and inhibit the STAT3 stimulation and phosphorylation of the epidermal growth factor receptor (EGFR) in the prevention of stomach cancer [37, 38].

Effect Against Diabetes

BBR has been found to have a significant impact on lipid and carbohydrate metabolism, particularly on glucose homeostasis, according to recent preclinical and clinical investigations [1]. It stimulates the insulin receptor in the liver and skeletal muscle by promoting kinase C–dependent protein, as reported in some studies [40]. Yin and colleagues demonstrated that BBR can be used to treat type 2 diabetes in humans [41]. According to their research findings, BBR had a significant impact on reducing both fasting blood glucose levels and postprandial blood glucose throughout the entire experiment, starting from the first week until the end. The study also revealed that fasting plasma insulin decreased by 28.1%, and the index for assessing insulin resistance (known as homeostasis model assessment) dropped by 44.7% (p 0.001). Additionally, the hemoglobin A1C level decreased from 8.1 ± 0.2 to 7.3 ± 0.3% (p 0.001). The trial showed that 20 (34.5%) of the participants experienced temporary gastrointestinal side effects, while there were no observations of liver or renal impairment. These findings suggested that BBR has a potent oral hypoglycemic effect and is effective in lipid metabolism, making it a promising drug for diabetes treatment [1, 41, 42].

Kong et al. carried out a study aimed at investigating the cellular mechanism by which BBR enhances insulin sensitivity, and they observed that it activates the insulin receptor (InsR), as reported in their publication [43]. Specifically, they found that BBR administration to human liver cells in vitro resulted in a dose- and time-dependent increase in InsR expression, InsR mRNA, and protein expression. When administered to diabetic mice with insulin-deficient type 2 diabetes, BBR reduced blood glucose levels; however, it was not effective against NOD/LtJ type 1 diabetes mellitus. From this, it can be concluded that BBR is a unique phytochemical component that could be useful for treating insulin resistance especially in type 2 diabetes mellitus [42, 44, 45].

Cardiovascular

Cardiovascular disease (CVD), encompassing atherosclerosis, hypertension, and heart failure, is the most prevalent cause of mortality globally [46–49]. Including the developed nations, cardiovascular diseases have greatly impact in mortality despite its preventive measures to mitigate its incidence; numerous patients remain vulnerable to it [50]. And moreover, in the last two decades, the prevalence of morbidity and mortality due to CVD is still alarmingly high [46–49].

Effect of BBR on Atherosclerosis

Atherosclerosis is a primary disorder of lipid metabolism, which is also associated with numerous cardiovascular and brain diseases [51–53]. The progression of atherosclerosis often goes unnoticed for several years, and patients typically become aware of their condition only after experiencing cardiovascular diseases, such as stroke or heart attack. Atherosclerosis is initiated due to the accumulation of low-density lipoprotein (LDL) particles in endothelial cells [54]. Therefore, effective strategies to prevent the progression of atherosclerosis include reducing endothelial dysfunction, reversing dyslipidemia, and suppressing inflammation. BBR has been shown to protect against atherosclerosis by lowering cholesterol levels [51, 52, 55, 56]. The other aspect of BBR includes atheroprotective effects, such as its ability to reduce inflammation, prevent vascular smooth muscle cell proliferation, and act as an antioxidant. Researchers Zimetti and colleagues have demonstrated that BBR also has a dual protective effect on cholesterol homeostasis and on the inflammatory phenotype in macrophages from both mice and humans [57]. In their study, treatment with BBR (150 mg/kg/d, p.o., 12 weeks) resulted in a significant reduction in atherosclerotic plaque area, as well as the suppression of inflammatory and oxidative markers [58]. By controlling different pro-atherogenic cellular events, BBR can effectively prevent the progression of atherosclerosis.

BBR on Hypertension

Hypertension is a widespread chronic medical condition worldwide and a major preventable risk factor for early mortality. Failure to detect hypertension early and provide effective treatment can lead to an increased risk of cardiovascular diseases, including ischemic heart disease, stroke, peripheral vascular disease, and heart failure. Nevertheless, decreasing blood pressure can considerably diminish the likelihood of fatality due to heart disease and stroke. A clinical study conducted in 1993 revealed the efficacy of BBR in treating hypertension in 42 cases [59, 60]. While the precise mechanism responsible for the modulatory impact of BBR on hypertension is currently under investigation, both clinical and experimental researches indicate that BBR and its derivatives exhibit properties that can counteract hypertension [40]. Control of high blood pressure is associated with a reduced risk of developing complications such as stroke, myocardial infarction, heart failure, and peripheral vascular disease [61]. BBR has potential effects to use as drugs for antihypertensive treatment as evidence in both clinical and experimental studies. According to a meta-analysis, taking BBR in combination with lifestyle changes is more effective in reducing blood pressure than just lifestyle changes or a placebo for treating hypertension. From a scientific

standpoint, it has been observed that the synergistic utilization of BBR alongside an oral antihypertensive medication yields superior outcomes in blood pressure reduction compared to the singular administration of the antihypertensive drug. Notably, the customary daily consumption of BBR falls within the range of 0.6 to 2.7 g. Furthermore, it is significant to highlight that 27 randomized controlled clinical trials employing sole BBR treatment have reported no significant adverse effects [40].

BBR combined with amlodipine has been shown to have a significant clinical impact on elderly patients with gout and hypertension by effectively lowering blood pressure and UA levels [62, 63]. While the exact mechanism of how BBR affects hypertension is not yet fully understood, clinical and experimental studies have indicated that BBR and its derivatives may possess antihypertensive properties. Hypertension pathogenesis is linked to endothelial cell oxidative stress and cell death caused by endoplasmic reticulum (ER) stress activation. In SHR carotid arteries, Liu et al. found that BBR could inhibit ER stress, activate AMPK, scavenge ROS, and reduce endothelium-dependent contractions by downregulating COX-2 [64]. A recent study revealed that BBR directly relaxes blood vessels to lower blood pressure in old mice while also reducing vascular stiffness [65]. It can lower high blood pressure by affecting vascular stiffness, and high blood pressure is achieved by inhibiting TRPV4, decreasing intracellular calcium levels, reducing MLC phosphorylation, and relaxing VSMCs [65]. Furthermore, in aging ApoE KO mice, BBR may function as a calcium channel blocker to reduce vascular stiffness and high blood pressure. Hypertension awareness and management challenges are widespread, but it is important to recognize that the burden of hypertension varies not only by country but also by ethnicity and socioeconomic status. Controlling blood pressure is associated with a 30–35% reduction in strokes, a 20% reduction in myocardial infarction, and a decreased risk of other hypertension complications such as heart failure, atrial fibrillation, and ventricular arrhythmias [66].

BBR on Heart Failure

Heart failure is associated to various cardiac diseases including cardiac remodeling, cardiac arrest, hypertrophy, and fibrosis [1, 5]. Effective interventions for cardiac remodeling are crucial for the treatment of heart failure [1]. Pathological cardiac hypertrophy is a key transitional stage that leads to heart failure and other cardiac diseases [1]. In the realm of scientific understanding, Pak1, belonging to the serine/threonine protein kinase family, plays a vital role in facilitating adaptive physiological cardiac remodeling. Exhaustive investigations have been conducted to explore its roles in upholding electrophysiological stability and maintaining ventricular Ca2+ homeostasis in the presence of physiological, β-adrenergic, and hypertrophic stress conditions [1]. Interestingly, BBR can be used against the heart failure and has been found to have multiple pharmacological activities [1]. In a clinical investigation involving 12 individuals afflicted with intractable congestive heart failure, berberine (BBR) exhibited a safeguarding influence. The intravenous administration of BBR, dosed at 0.2 mg/kg per minute, yielded noteworthy alterations in hemodynamic parameters [7].

Studies using animal models have demonstrated the potential of BBR to reduce the severity of heart failure (HF). As an illustration, the administration of BBR in canines afflicted with ischemic left ventricular heart failure has demonstrated a propensity to augment cardiac output and the apex rate of ascent of left ventricular pressure (+dp/dt), concomitantly with a reduction in left ventricular end-diastolic pressure (LVEDP), diastolic blood pressure (DBP), and systemic vascular resistance. In a parallel manner, within a rat model simulating heart failure (HF) induced by a heightened dosage of isoproterenol, the simultaneous administration of total saponins extracted from *Panax* ginseng (20 mg/kg/d), BBR (20 mg/kg/d), and captopril over a continuous period of 12 days showcased a discernible anti-heart failure effect in both experimental cohorts [67, 68].

Effect of BBR on Neurology

BBR plays a pivotal role as neuroprotective against ischemic damage by suppressing Bcl-2 phosphorylation. BBR has been shown to have a neuroprotective effect that improves survival of brain cells that are electrically excitable survive, develop, function, and be protected [69]. Therefore, it can be used as a powerful phytoconstituent in the treatment of a variety of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease [70–72]. BBR has been widely used in therapeutic against neurodegeneration as it has potential to prevent from neurodegeneration in various cases like Alzheimer's disease [73]. In the studies of administration of BBR on rat model of Alzheimer's disease, it was discovered after 2 weeks that intra-gastric administration of 50 mg kg of BBR chloride improves memory loss while enhancing the expression of interleukin 1 beta and inducible nitric oxide in the hippocampus of rat suffering from amyloid beta–induced Alzheimer's diseases [74]. According to reports, the study on BBR prevents glutamate-induced toxicity in astroglial cell cultures, including protein mis-folding, aggregation, mitochondrial fragmentation, and neurodegeneration [75, 76]. Berberine treatment increases the cytotoxicity of 6-hydroxydopamine in PC12 cells, which causes degeneration of dopaminergic neurons in substantia nigra of rats [77]. BBR significantly reduced behavioral functional impairment and artificially induced brain ischemia (caused by permanent occlusion of

the middle cerebral artery) [78]. The Akt/GSK3/ERK1/2 survival/apoptotic signaling pathway, Jun amino-terminal kinases (JNK), and caspase-3 activity inhibition are all involved in the neuroprotective effects of BBR [79].

Effect/Role of BBR on Antiviral Activities

In viral replication, BBR interferes to decrease the replication rate in the virus and host interaction. BBR interferes with DNA synthesis and reverse transcriptase activity by intercalating into DNA. It prevents from replication of human cytomegalovirus (HCMV), human papillomavirus (HPV), herpes simplex virus (HSV), and human immunodeficiency virus (HIV) [79]. Hong et al. have demonstrated that BBR inhibits the replication of the hepatitis C virus (HCV) by preventing entry of HCV by targeting the viral E2 glycoprotein. BBR interacts with the HCV E2 glycoprotein, according to molecular docking studies [80]. BBR also demonstrates antiviral activity against infections caused by the dengue virus (DENV) and the Zika virus (ZIKV). BBR shows antiviral activity against infections caused by the dengue virus (DENV) and the Zika virus (ZIKV). The four DENV serotypes—DENV-1, DENV-2, DENV-3, and DENV-4—transmit the virus to people when *Aedes aegypti* and *Aedes albopictus* mosquitoes bite. This virus causes a variety of illnesses such as asymptomatic infection, dengue fever, dengue hemorrhagic fever (DHF), and the potentially fatal dengue shock syndrome (DSS) [81].

]The severe acute respiratory syndrome coronavirus (SARS-CoV), which is the cause of the respiratory disease SARS, can also be treated with BBR. Additionally, BBR lowers the risk of ALI/ARDS in COVID-19 patients by preventing the release of inflammatory cytokines and the inflammatory signaling pathway [82]. COVID-19 caused immunological, inflammatory and an oxidative change; on the other hand, SARS-CoV-2 induces acute respiratory distress syndrome (ARDS), endothelial dysfunction (ED), acute lung injury (ALI), and multi-organ failure (MOF) [82–85] According to Warowicka et al., BBR has strong antiviral activity against various viruses which include coronaviruses, influenza, respiratory syncytial virus (RSV), herpes, and influenza [79]. BBR reduces the spread of SARS-CoV-2 and the inflammatory disorders; it is linked by activating the inflammatory signaling pathway.

Effect/Role of BBR on Antimicrobial Activities

BBR has shown promise potential treatment for a number of infections due to its capacity to inhibit a variety of microorganisms, such as bacteria, fungi, viruses, and protozoa. BBR is normally found as chloride and sulfate salts which are resistant against *Staphylococcus epidermidis*, *Neisseria meningitidis*, and *Escherichia coli.* BBR is found effective against *Salmonella*, *Shigella*, *Giardia*, and *cholera* in human beings [86]. According to Chinese herbal, Material medica, BBR sulfate exhibits significant antimicrobial activity against a variety of microorganisms, including *Salmonella*, *Candida*, *Staphylococcus* (Staph), *Klebsiella*, *Clostridium*, *Pseudomonas proteus*, *Shigella*, *Vibrio*, *Cryptococcus*, and *Entamoeba* species [87]. The National Institutes of Health stated that BBR has showed significant antimicrobial activity against bacteria, fungi, viruses, and chlamydia, demonstrating antimicrobial properties [88]. Bacteria, yeasts, and fungi were found to be moderate effects on BBR, but it had little effects on both Gram-positive and Gram-negative bacteria.

Mechanism of Action of BBR

On weight loss

Obesity represents a persistent illness distinguished by abnormal accumulation of fat that may have a negative impact on health. Globally, the rise in the proportion of overweight and obese people has caused great concern and is estimated to have resulted in 3.4 million deaths [89]. The primary repository for lipids and fatty acids is the adipocyte, which causes obesity, diabetes, and other related diseases. According to a new study conducted by Wu et al. (2019), therapy with BBR at a dose of 100 mg per day for 1 month increased the mass and activity of brown adipose tissue (BAT) in both humans and mice ($n = 10$) [90]. Thus, in modestly overweight individuals who have non-alcoholic fatty liver disease, weight loss will increase their sensitivity to insulin. Contrarily, in diet-induced obese mice and chow-fed mice, BBR promotes BAT growth by activating brown adipogenic genes, which increase BAT thermogenesis and overall consumption of energy. Han et al. [91] reported that the diabetic patients ($n = 10$) and mice ($n = 10$) who received BBR 500 mg/day for 10 weeks saw a significant decrease in the amounts of Firmicutes and Clostridia whereas an increase in the relative abundance of Bacteroidetes and Betaproteobacteria. For the NOD mice, however, oral probiotic therapy caused them to develop diabetes. BBR can modify gut flora without having any systemic anti-infective effects. By reducing the expression of LXRs, PPARs, and SREBPs in visceral white adipose tissue, BBR counteracts the effects of streptozotocin and aids in weight loss [92]. Peroxisome proliferator–activated receptors (PPARs) and liver X receptors (LXRs) are expressed more when BBR is present. The expression of PPAR2, C/EBP, adiponectin, and leptin mRNA is down regulated in pre-adipocytes after BBR administration on human fat in vitro [93].

On Cholesterol Metabolism

Cholesterol is a type of lipid (fat) molecule that is essential for various physiological functions in the body, such as building cell membranes and producing hormones. However, having excessively high levels of cholesterol in the bloodstream, particularly low-density lipoprotein (LDL) cholesterol, is associated with an increased risk of cardiovascular diseases like heart attacks and strokes. The cholesterol homeostasis is regulated by LDL receptor mediated in the liver [94]. Since the initial study showing that BBR reduced cholesterol through LDL receptor–mediated liver LDL cholesterol clearance [95], numerous studies have been carried out in vitro and in vivo to investigate this specific mechanism of action [96, 97]. Numerous studies have demonstrated that BBR increases the expression of hepatic LDL receptors [98]. BBR promotes LDL receptor expression in hepatocytes by stabilizing LDL receptor mRNA through activation of the ERK pathway [99].

The liver achieves cholesterol clearance by transforming cholesterol into bile acids, which are subsequently secreted either as free cholesterol in bile or as bile acids. Research has provided evidence that the utilization of BBR (berberine) amplifies the process of cholesterol excretion from the liver into bile, which is then eliminated from the body through fecal excretion. Supplementation with BBR induces notable alterations in the composition of bile acids, characterized by an increase in primary bile acids and a simultaneous decrease in secondary bile acids within both liver tissue and serum. Moreover, an in-depth analysis of gene expression patterns in liver tissue samples obtained from hamsters subjected to BBR treatment reveals a substantial surge in the expression of mitochondrial sterol 27-hydroxylase. This enzyme plays a pivotal role in regulating the synthesis of bile acids from cholesterol within the liver. When all these findings are considered together, it becomes evident that BBR contributes to the augmentation of both cholesterol breakdown and the excretion of bile acids. Consequently, this multifaceted impact culminates in the reduction of total cholesterol (T-C) and low-density lipoprotein cholesterol (LDL-C) levels in the bloodstream [100, 101].

On Tumor Suppression

According to research by Turner et al. (2008), BBR had been demonstrated to hinder mitochondrial respiratory complex I that may cause AMP levels to rise and AMPK to become activated [102]. However, a recent study by Xu et al. (2014) reveals that BBR blocks complex I, increasing glucose intake and lactate release independently of AMPK. The addition of BBR may induce cellular stress responses, such as activation of the p38 and JNK pathways, which may or may not be dependent on activation of AMPK. This is because blockage of the respiratory chain results in stress conditions. Additionally, we cannot rule out extra-mitochondrial processes induced by this medication [103].

On Endothelium and the Heart

An essential early stage in the development of atherosclerosis is endothelial dysfunction. Numerous factors that contribute to endothelium damage are connected to metabolic changes. The rise in secretion of proinflammatory cytokines and a reduction in the production of adiponectin, the increased levels of free fatty acids in the blood, and hyperglycemia in people with obesity and insulin resistance may affect gene expression and cell signaling in the vascular endothelium and alter the release of endothelium-derived factors. NADPH oxidase activation, eNOS uncoupling, increased endothelin-1 expression, an imbalance in the generation of vasodilators and vasoconstrictor mediators, and the induction of adhesion molecules are all signs of a dysfunctional endothelium [104]. In turn, the altered endothelium homeostasis aids in the formation and growth of plaque. According to Endemann and Schiffrin (2004), it is linked to the majority of cardiovascular diseases, including hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic kidney failure [105]. Due to LDLc's stimulation of endothelial eNOS downregulation, endothelial cells exposed to hypercholesterolemia exhibit a decreased capacity to release endothelium-derived relaxing factors [106]. Endothelial function appears to be promoted by decreasing cholesterol levels [107].

Xu et al. (2009) have highlighted additional processes that underlie BBR's actions on the endothelium [108] showed that BBR triggers an upregulation of endothelial progenitor cells (EPC-CFUs) through NO generation in healthy people. Following BBR treatment, the quantity of EPC-CFUs increased and the functions, including proliferation, adhesion, and migration, were improved. Additionally, the very same study group noticed that after BBR therapy, circulating endothelial microparticles (EMPs), which are typically linked to endothelial dysfunction, decreased. This finding demonstrates a clear connection between the fall of EMPs and an enhancement in flow-mediated vasodilation (FMD) in healthy patients. Additionally, the EMPs caused decreased eNOS protein expression in vitro, a negative consequence that BBR prevented [109]. A clinical, double-blind, placebo-controlled research in which BBR was given in combination with policosanols and RYR also recently showed the therapeutic effects of BBR treatment on FMD. In a population of hypercholesterolemic patients, this investigation showed that the medication resulted in a considerable improvement of FMD [110].

Toxicity

The Singapore government prohibited the use of BBR in 1976 due to concerns that it could cause hemolytic hepatitis in newborn babies if taken during pregnancy or nursing, as it may lead to a lack of glucose-6-phosphate dehydrogenase (G6PD) [111]. There were no sex-specific effects of BBR toxicity that were well-established and widely acknowledged. But the toxicity varies depending upon factors such as dosage, sensitivity of individuals, and its interaction with other medication.

BBR has been found to be the toxic component in mice, with the median acute oral lethal dose of the total RC extract being 2.95 g/kg [112]. However, when combined with other natural plants, BBR exhibited minimal toxicity and side effects [113]. When BBR is combined with other natural plants or compounds, it can exhibit synergistic effects. It may be possible to use lower individual doses of each plant while still getting the desired therapeutic result when BBR is combined with other plants. BBR may be less toxic and have fewer side effects at lower doses. The toxicity of BBR is dependent on the administration method and dose, with intravenous and intraperitoneal injections resulting in LD50 of 9.0386 g/kg and 57.6103 g/kg, respectively, while intragastric administration had no LD50 [114]. Administration of BBR sulfate at a dose of 50 mg/kg in rats resulted in diarrhea in 40% of cases [115]. Oral administration of BBR sulfate at a dose of 100 mg/kg in cats induced vomiting within 6–8 h and resulted in death after 8–10 days, with hemorrhagic inflammatory issues observed in the small and large intestines in cats given 50/100 mg/kg doses of BBR sulfate orally for 10 days [115]. Dogs administered low doses of BBR, and its compounds showed mild signs of poisoning, such as salivation, nausea, diarrhea, emesis, muscle tremor, and occasionally paralysis [116].

There have been some preliminary results regarding effect of BBR on the gut microbiome, but more extensive research is required to fully comprehend its effects. However, in some studies, BBR can change the gut microbiota's makeup by encouraging the growth of good bacteria while preventing the growth of harmful bacteria. The following are some possible BBR effects on the gut microbiome: (1) Change in the composition of the microbiome: BBR may affect the relative abundance of specific bacterial species in the gut, resulting in a more advantageous microbiome. (2) BBR has been shown to have antimicrobial properties, which suggests that it could aid in the fight against some pathogenic bacteria in the gut. (3) Anti-inflammatory properties: According to some studies, BBR may lessen gut inflammation, which might have an indirect effect on the gut microbiome by reducing the inflammatory environment [117]. (4) Metabolic effects: BBR may also affect the metabolic processes of the gut microbiome, which may have an impact on how nutrients are absorbed and processed. BBR has also been found to have some immunotoxic effects, leading to a decrease in leukocyte, neutrophil, and lymphocyte levels, as well as decreased generation and differentiation of B- and T-cells and splenic CD19+ B-cells, CD4+, and CD8+ T-cells. Exposure to BBR can also cause uterine contractions and have teratogenic effects [111–116, 118].

Mitigation of Side Effect of BBR

- Start with a low dose: It is good to start with a low dose of BBR and gradually increase it over time if we are new to supplementation. This strategy enables our body to get used to the substance and may lower your risk of experiencing serious side effects.
- Take with meals: BBR should be taken with meals to lessen its effects on the digestive system and the likelihood of stomach discomfort. BBR can be more easily absorbed if we eat.
- Divide the dose: Take the daily dose in two or three smaller doses as opposed to one larger dose. This may lessen side effects by lowering the amount of BBR present in the digestive tract at one time.
- By taking special precaution when applied to skin especially to pregnant women.
- Drink plenty of water to stay hydrated and to support our digestive system overall while taking BBR. This will help us avoid constipation.

Conclusion

BBR shows promising potential as a medication for a wide range of clinical applications. Evidence suggests that BBR and its derivatives may have positive outcomes for various medical conditions. The main objective of pharmaceutical research is to enhance a medication's bioavailability while minimizing harm. This review focuses on the potential therapeutic applications of BBR. Although various pharmacological effects of BBR have been discovered through clinical research over the years, further investigation is necessary to understand its practical application in treating diseases. Numerous studies have demonstrated the efficacy of BBR in treating hypertension, hyperglycemia, cancer, depression, inflammation, pain, and hyperlipidemia. Therefore, it is reasonable to consider BBR as a medication with a broad spectrum of activity that could emerge as a promising therapeutic agent.

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Data Availability Authors declared that data may be shared upon request.

Compliance with Ethical Standards

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