12-2022

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Pharmacological Research - Modern Chinese Medicine 5 (2022) 100184

Contents lists available at ScienceDirect

Pharmacological Research - Modern Chinese Medicine

journal homepage: www.elsevier.com/locate/prmcm

Review

Berberis aristata and its secondary metabolites: Insights into nutraceutical and therapeutical applications

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ARTICLE INFO

Keywords:
Berberis aristata
Ethnopharmacological relevance
Bioactive secondary metabolites
Toxicity
Nutraceutical applications
Molecular mechanisms

ABSTRACT

Considering the rising global health challenges and public expectations in terms of safety and cost effectiveness, it is necessary to promote effective, safer and cheaper alternative treatment options, particularly to benefit low- and middle-income countries (LMICs). Therapeutic regimens implying natural sources *i.e.*, plants and their secondary metabolites have been trusted by a large proportion of sufferers and extensively searched for their pharmacological actions. *Berberis aristata*, commonly known as Zarishk, Daruharidra and Indian barberry, is being used in traditional medicine systems across the globe, particularly Asian countries *i.e.*, India and China, and has also gained much attention in the current era of modern medicine. The protective effects of *B. aristata* against a number of diseases are attributed to its bioactive metabolites, mostly alkaloids, including berberine, berbamine, aromoline, jatrorrhizine, oxyberberine, palmatine, tetrahydropalmatine, and lupeol. However, a comprehensive report describing the ethnopharmacological relevance, important secondary metabolites, cytotoxicity, and recent advances in its therapeutic efficacy against various ailments is either outdated or still lacking. Therefore, the current review summarizes the recent updates regarding the implications of *B. aristata* and its potential bioactive secondary metabolites in targeting various acute and chronic diseases including diabetes, cardiovascular complications, cancer, hepatic dysfunction, infectious diseases, oxidative stress, inflammation, neurodegeneration, and ageing-associated symptoms with special emphasis on the biochemical and molecular mechanisms/pathways.

1. Introduction

The last three decades are considered a golden age of worldwide health as many advancements were achieved to combat various communicable diseases (CDs) and non-communicable diseases (NCDs). These advancements include excessive funding from distinct funding bodies which significantly improved the health qualities in low-and middle-income countries (LMICs). The major areas covered in such projects constituted the availability of clean-drinkable water, sanitization practices, immunization services, and pre-birth care leading to the protection against most of the lethal illnesses worldwide [1–4]. Recently, one of the most influential pandemics, namely, Covid-19 (caused by SARS-CoV-2), hit the China at first and transmitted at full pace to the entire world and caused around 4.77 million global casualties as of September 2021 and almost 10 percent of these deaths were documented in India only (0.448 million) [5,6]. The pandemics like Covid-19 exposed the inadequate medical facilities of the developed world. However, extensive preventive measures somehow restricted the spread of SARS-CoV-2and latter the development of distinct vaccines, after a couple of years of its first encounter, provided first line defense against SARS-CoV-2 to almost 70 % of the world's adult population [7].

On the other hand, NCDs like cancer, cardiovascular diseases (CVD) [8,9], particularly atherosclerosis [10], stroke, diabetes [11–13], and neurological disorders [14,15] have also established themselves to a more complicated level with time and most of the sufferers face drug-resistance or drug-intolerance-like conditions. In contrast, poverty [16], socioeconomic status [17], under-nutrition [17,18] and lack of awareness in LMICs worsen the health outcomes [19]. Therefore, the safety aspects of the available standard therapies and need for dropping down the expenditure on the effective modern medical facilities provoked majority of the researchers to shift their interests towards the alternative medicine. Various plants and their bioactive-metabolites have been extensively studied for the management of different CDs and NCDs in LMICs especially, atherosclerosis [20–22], diabetes [23–25], cancer [26], ageing [27] and neurodegenerative disorders [15].

Similarly, different *Berberis* Sp. including *B. aristate, B. vulgaris*, *B. croatica, B. lyceum*, *B. khorassanica* and *B. aquifolium* have also been studied for their traditional therapeutic implications [28,29]. Among these,

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https://doi.org/10.1016/j.prmcm.2022.100184
Received 4 August 2022; Received in revised form 14 October 2022; Accepted 20 October 2022
Available online 21 October 2022

B. aristata together with its bioactive metabolites has widely been investigated in the traditional Chinese medicine (TCM) as well as Indian herbal medicine system for its beneficial pharmacological effects against distinct acute as well as chronic illnesses *i.e.*, diabetes (both Type-I and II) [30–32], CVD [33,34], cancer [35], microbial diseases [36], gastroenterological abnormalities [37], and dysregulated redox [38] and inflammatory state [28,39]. A review on medicinal herbs belonging to the TCM summarized the mechanistic insights of the hypoglycemic potential of *B. arista* in experimental diabetic animals [40]. *B. aristata* and its metabolite *i.e.*, berberine are the best prescribed medications for gastrointestinal discomfort in the TCM [41]. Unlike allopathic regimens relying only on the solo constituent with pharmacological effects via distinct molecular mechanisms, TCM constitutes different metabolites with pleiotropic therapeutic benefits and lesser toxicity issues, thus being preferred for the management of disease conditions [42,43].

Different *in-vitro, in-silico,* cell culture, animal model and clinical interventional studies have validated the protective impact of *B. aristata* and its secondary metabolites. However, a comprehensive report describing the ethnopharmacological relevance, important secondary metabolites, cytotoxicity, and recent advances in its therapeutic efficacy against various CDs and NCDs is either outdated or still lacking. Therefore, the current review summarizes the recent updates regarding the ethnopharmacological implications of *B. aristata* and advancements in the discovery of potential bioactive secondary metabolites and their therapeutic properties in targeting various acute and chronic diseases with special emphasis on the biochemical and molecular mechanisms. A single line search strategy was implied using key words *i.e.*, *B. aristata,* secondary metabolites, ethnopharmacology, pharmacological effects, toxicity, *in-vitro*, *in-vivo*, *in-silico* studies and metabolic disorders on distinct scientific and biological repositories like PubMed/Medline, PMC, Google scholar, Scopus, and Web of science between a time frame of 2005 and 2022. However, we preferred to review the articles published in or after 2010 unless and until we were unable to find any recent article for a specific pharmacological effect.

2. *B. aristata*: ethnobotanical aspects and ethnopharmacological properties

B. aristata (Family: Berberidaceae) has traditionally been used for the treatment of various diseases by different ethnic communities from north India, particularly Himalayan regions, as well as other Asian countries like China, particularly in TCM [28,44,45]. It is well reckoned with distinct alternative names in different geographical areas and ethnicities like Daruharidra, peet, Zarishk, and Indian barberry. The therapeutic effects of *B. aristata* have been mentioned in traditional and religious scriptures including Ayurveda and named as Darunisha, Peeta, Daruharidra, Darvi, Peetadru, Peetachandana, Hemakanti, and Kashtarajani. In ancient Indian literature, the taste (Rasa) of *B. aristata* has been defined as Tikta that means bitter or astringent. The taste conversion after digestion (Vipaka) has been described as Katu *i.e.*, pungent, whereas, the mode of digestion has been categorized into Laghu *i.e.*, easy to digest [46]. The pharmacological effects of *B. aristata* extracts have been described in *Charaka Samhita*, Ayurveda's definitive treatise, which suggests that distinct aliments *i.e.*, hemorrhage, piles, abnormal functioning of liver and gall bladder, and pruritus can be cured by oral administration of *B. aristata* extract [44–46]. *Sushruta Samhita* also prescribed the implications of *B. aristata* for the treatment of digestive abnormalities, urinogenital disorders, and declined breast milk in lactating mothers [46].

Among various formulations of *B. aristata*, *Daarvaadi Kashyaaya* has been demonstrated to manage leucorrhoea and metrorrhagia, while another formulation named *Daarvaadi Churnam* has been widely used for piles and internal abscesses. Other potent formulations like *Daarvaadi Ghritam* and *Daarvaadi Tailam* have shown protective effects against bleeding piles and obesity, respectively [46]. Traditionally, *B. aristata* is also used as a concentrated liquor, reckoned as *Rasaut,* for the treatment of dermal diseases, diarrhoea, cholera, high bilirubin content, inflammatory diseases, and microbial infections. The root extract of this shrub is also used for the treatment of eye and dermal infections/disorders, piles and malaria in different states of the India [45,47]. Even an investigation by South African researchers evaluated the invasion and cultivation dynamics of *B. aristata* in Africa and posed serious concerns regarding the quick eradication from the African lands due to its impact on the Chinese economy [48]. The description of various formulations constituting *B. aristata* along with their pharmacological effects is mentioned in Supplementary Table S1.

3. Potential secondary metabolites/bioactive compounds of *B. aristata*

Different plant extracts, essentials oils and their bioactive secondary metabolites have been extensively used for the treatment and management of distinct metabolic diseases due to their safety and less or no toxicity [8,15,23]. A recent study demonstrated that *B. aristata* constitutes phytochemicals of different classes such as alkaloids, flavonoids, saponins, steroids, coumarins, glycosides, tri-terpenoids, polyphenols, tannins, reducing sugars, metal ions and, among these, the alkaloids are the most abundant phytoconstituents from *B. aristata* stem [45,49]. The potential beneficial effects of different parts of *B. aristata* have been attributed to the presence of secondary metabolites including berberine, berberamine, aromoline, jatrorrhizine, columbamine, oxyberberine, palmatine, tetrahydropalmatine, oxycanthine, lupeol, and oxycanthine [28]. Different studies have standardized the secondary metabolites form *B. aristata*, a key representative of TCM [50,51]. The structures of the major secondary metabolites from *B. aristata* are represented in Fig. 1.

4. Cytotoxicity studies: evidences from *in-vitro* and *in-vivo* studies

In a recent study, different extracts of *B. aristata* and diterpenes were assessed for their mutagenicity (using Ames test) as well as *in-vitro* cytotoxicity against blood cells, which concluded that aqueous and organic extracts did not show any mutagenicity or potential cytotoxicity against blood cells [36]. In addition, acute oral toxicity study of diterpenes isolated from *B. aristata* did not exhibit any undesirable changes in Swiss albino mice [36]. However, diterpenes from *B. aristata* exhibited potent cytotoxic effects against various cancer cell lines *i.e.*, L20B, RD and Hep 2 cells [36]. A study showed that the oral administration of different doses of jatrorrhizine caused death of the mice in a dose-dependent manner with an $LD_{50}$of 5500mg/kg. In contrast, the LD_{50} of jatrorrhizine was markedly greater than the LD_{50} of berberine (763 mg/kg) [52]. The same study also reported that the administration of jatrorrhizine at 70.05mg/kg/day for three months did not lead to any mortality, toxicity and drug associated abnormalities of urinary and haematological profiles in SD rats [52].

The LD_{50} value for berberine sulphate (isolated from *B. aristata*) in rats was 205 mg/kg. However, at 50 mg/kg, it caused diarrhoea in 4 out of 10 rats signifying its direct impact on the gastrointestinal tract [53]. The acute toxicity studies of berberine, palmatine and epiberberine showed that these alkaloids from *B. aristata* showed higher LD_{50} values (713.57, 1533.68, and 1360 mg/kg, respectively) [54]. These three alkaloids also affected the viability of HepG2 and 3T3-L1 cells [54]. These findings advocate that *B. aristata* and its secondary metabolites are safe for biological applications.

5. Pharmacological effects of *B. aristata* and its bioactive metabolites in targeting various diseases

5.1. Effects on redox state

Despite the major regulatory mechanisms, redox imbalance, particularly a rise in physiological oxidants, has been established as a

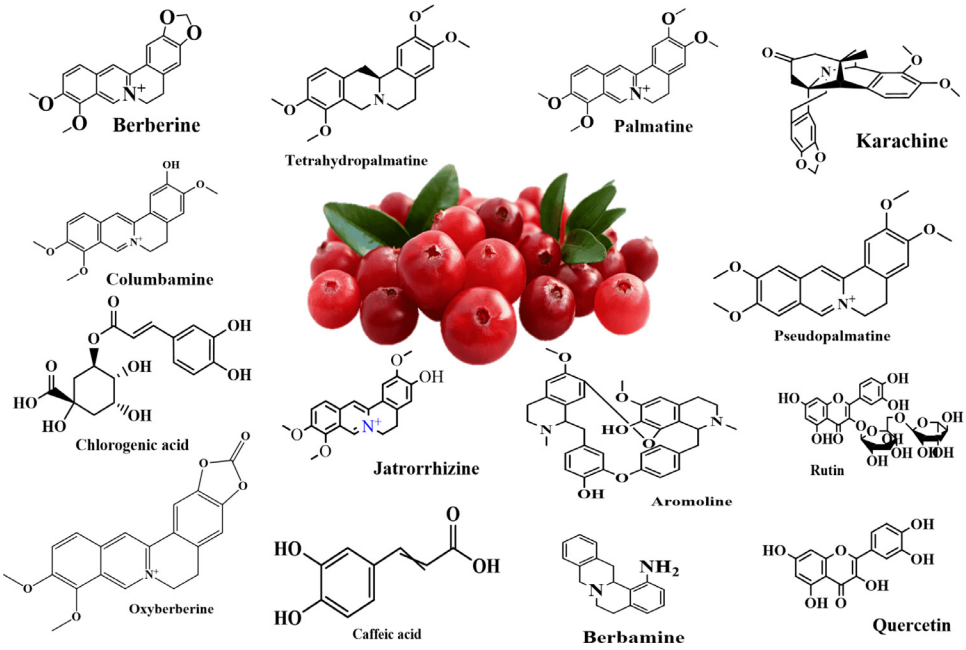

Fig. 1. Structural representation of potential bioactive secondary metabolites from *B. aristata*.

key mediator that facilitates the progression of distinct metabolic ailments via its ability to disrupt the membrane potential and perturbations in macromolecules like DNA, structural and functional proteins, and lipids [9,12,20,55,56]. Till date, various *in-vitro* methods have been used for the determination of antioxidant properties of different medicinal plants and their secondary metabolites *i.e.*, 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant potential (FRAP), hydroxyl radical and 2,2′-Azino-di-(3-ethylbenzothiazoline)-6-sulfonic acid assay along with other *in-vivo* biomarkers of oxidative homeostasis *i.e.*, catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), Glutathione peroxidase (GPx), and aryl esterase (PON-1) [9,10,20,23,24,57]. Gacche and Dhole assessed the redox modulatory role of *B. aristata* ethanolic extract and reported that it exerted potent *in-vitro* DPPH radical quenching (IC_{50}: 150 µg/ml) [38]. Further, they also analysed the hydroxyl radical scavenging activity of *B. aristata* ethanolic extract and demonstrated that it did not show hydroxyl radical quenching activity [38]. In a recent study, researchers assessed the level of the anti-oxidants and pro-oxidants in Complete Freund's adjuvant (CFA)-triggered arthritis and observed a diminished status/activity of GSH, CAT, and SOD and elevated level of thiobarbituric acid reactive substances (TBARS) and nitric oxide (NO). However, administration of 100 and 200 mg/km of hydroalcoholic extract of *B. aristata* markedly improved the level/activity of GSH, CAT, and SOD and declined the malondialdehyde (MDA) and NO contents [58]. Further, *B. aristata* also up-regulated the mRNA expression of heme oxygenase-1 (HO-1) in paw tissues of arthritic rats via up-regulation of nuclear factor erythroid 2 (NFE2)-related factor-2 (Nrf-2), which is known to regulate the expression of HO-1 [58].

Recently, berberine has been shown to exhibit potent antioxidant activities and it suppresses the mitochondrial ROS generation in spiral ganglion cells via targeting sNMDAR1/Nox3 pathway [59]. The detailed analysis of mechanisms for the antioxidant activities of berberine in diabetic state suggests the involvement of distinct pathways *i.e.*, AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPKs), Nrf2 pathway, and nuclear factor-κB (NF-κB) pathways [60]. Another *in-vivo* study demonstrated that treatment with berberine ameliorated the diazinon-induced damage in cerebellum tissues and oxidative imbalance in rats via diminishing the level of MDA and stimulating the activity of enzymatic antioxidants *i.e.*, SOD, GPx and CAT in a dose-dependent manner as well as under resistance training [61]. Berberine supplementation also normalized the indices of oxidative stress including GPx and SOD transcripts together with the level of GSH in diabetic mice model [62]. In addition, berberine significantly alleviated the oxidative stress in the lenses of diabetic rats via modulation of SOD, CAT, and GPx activities and the level of TBARS [63]. Berberine also protected against lead (Pb)-mediated oxidative imbalance and hepatotoxicity in rats by increasing SOD, CAT, and GPx activities along with GSH content, a non-enzymatic antioxidant. These beneficial effects of berberine against Pb-induced oxidative stress, hepatic necrosis and inflammatory response were comparable to the effects of reference standard silymarin [64].

Berbamine, another phytochemical from *B. aristata* with potent pharmacological effects, has shown protective effects against steatosis via regulating the lipid accumulation, inflammation, and oxidative imbalance as evident by the enhanced activities of CAT and SOD as well as GSH level in fatty acid-challenged HepG2 cells [65]. Another study showed that treatment of berbamine alleviated isoproterenol-mediated cardiac injury in rats through the modulation of enzymatic (*i.e.*, CAT, SOD, GPx, and GST) as well as non-enzymatic (GSH) antioxidant levels/activities. It also improved the mitochondrial dysfunction by controlling the activities of respiratory enzymes [66].

Similarly, palmatine, a protoberberine alkaloid, is isolated from different parts of *B. aristata* [45]. Treatment with palmatine also showed that it exhibited neuromodulatory potential in Aβ-induced *Caenorhabditis elegans* model of neurodegeneration via reducing the ROS-specific DCFDA fluorescence [67]. Moreover, palmatine supplementation regulates the activities of antioxidant enzymes in experimental diabetic rats [68]. On the other hand, two β-sitosterol's *i.e.*, β-sitosteryl-3β-glucopyranoside-6′-O-palmitate and 3-O-(6′-O-linoleoyl-β-D-glucosyl)-β-sitosterol from *B. aristata* showed protective effects against $FeCl_2$-triggered lipid peroxidation [69]. These findings strongly suggest that *B. aristata* as well as its secondary metabolites possess noticeable antioxidant effects and hence may be promoted to combat oxidative stress-associated complications.

5.2. Effects on inflammatory signaling cascades

The infection/inflammation fuels the development of various diseases including CVD, neurological disorders, cancer, and diabetes along with its complications [8,9,11,15,22,57]. Most importantly,

lipopolysaccharide (LPS), a potent immunogen from the Gram-negative bacteria, triggers a pro and systemic inflammatory state through enhanced generation of inflammatory cytokines/chemokines, thereby, facilitating the development of above-mentioned disorders [8–10]. Various plant extracts, essential oils and their bioactive metabolites have shown anti-inflammatory effects in cell culture and animal studies *i.e.*, flavonoids, carotenoids and plants such as *Rosmarinus officinalis* L.*, Allium sativum* Linn*, Curcuma longa*, and *Solanum lycopersicum* [8–10,15]. Similarly, administration of *B. aristata* extract markedly suppressed the protein expression of inflammatory markers *i.e.*, interleukin-1β (IL-1 β), IL-6, Tumor necrosis factor receptor 1 (TNF-R1) and cyclooxygenase-1 (COX-1) that are reckoned to trigger the inflammatory cascades, whereas, the expression of anti-inflammatory IL-10 was stimulated in peritoneal macrophages [39].

Further, *B. aristata* extract supplementation resulted in down-regulation of IL-1 β, IL-6, TNF-R1, NF-κB and vascular endothelial growth factor (VEGF) expression in an adjuvant-induced arthritis (AIA) model. In addition, the HO-1/Nrf-2 ratio was also improved and the protein level of matrix metalloproteinases (MMP)-3 and 9, known to degrade the extra cellular matrix, was also suppressed after *B. aristata* extract treatment [58]. Treatment with oxyberberine showed a noticeable alleviation in dextran sulfate sodium (DSS)-induced colitis via targeting tall like receptor-4 (TLR4)-MyD88-NF-κB signalling pathway and also blocked the translocation of NF-κB p65 to nucleus and subsequent signalling [70]. Palmatine also exhibited potent anti-inflammatory effects through modulation of IL-1β, IL-6, IL-8, nitric oxide (NO), TNF-α, TLR-4, CD-14, MMP-2 & MMP-9, IL-10 in LPS-challenged HT-29 cell line and goat endometrial epithelial cells [71–73].

On the other hand, berbamine diminished the inflammatory response in LPS-exposed macrophages and neutrophils [74]. Similarly, the treatment with berbamine also regulated the MAPK (JNK and ERK1/2) pathways and reduced the activation of NF-κB in LPS-stimulated macrophages [74]. Moreover, incubation with berbamine evidently combated the LPS or CH_3COOH-induced IL-1β and IL-6 mRNA expression and p65 and STAT3 phosphorylation in RAW264.7 macrophage cells and protected C57BL/6J mice against alcoholic liver disease [75]. Two sitosterol's namely β-sitosteryl-3β-glucopyranoside-6′-O-palmitate and 3-O-(6′-O-linoleoyl-β-D-glucosyl)-β-sitosterol isolated from *Berberis spp*. exhibited strong anti-inflammatory effects via inhibiting *in-vitro* activity of COX-1 and COX-2 [69]. In conclusion, *B. aristata* and its secondary metabolites exhibit promising anti-inflammatory effects and may be further evaluated for their therapeutic potential against various inflammatory diseases including atherosclerosis, diabetes and cancer.

5.3. Antidiabetic effects

Diabetes mellitus, a disorder associated with elevated blood glucose level due to abnormal insulin secretion or function, stands among the top causes of worldwide mortalities [11,24,57]. Epidemiological studies have confirmed that there are around 450 million live cases of DM across the world and these numbers are predicted to further increase up to 700 million till 2045 [76,77], wherein almost half of the population (49.70%) carrying the disease burden are undiagnosed [76]. The strategies for the management of this metabolic dysregulation aims to restrict the blood glucose and glycosylated hemoglobin (HbA1c) levels within predetermined and permissible levels [11,23,24]. Different strategies are being used to achieve desired glycaemic control, particularly, adjustment of life style, exercise, restricted diet, and dietary intake of antioxidants, if failed, medical diagnosis and prescriptions are opted. Major therapeutic regimens include compensation of deficient insulin secretion through insulin administration for type-1 DM (T1DM) and oral drug candidates for type-2 DM (T2DM) subjects [11]. Despite desirable therapeutic effects, these prescriptions have shown several undesired adverse effects, especially, inefficient/delayed absorption and robust glucose lowering in case of high dose insulin. Such adverse effects of synthetic drugs have called the discovery of alternative drugs from natural sources. Plants, their extracts, essential oils, and bioactive metabolites are getting more and more attention throughout the world [23,24]. Similarly, a clinical report on the antidiabetic effects of TCM revealed the beneficial antidiabetic potential of berberine via its ability to lower down the free fatty acid content in T2DM subjects [78].

In this regard, *B. aristata* has been correlated with improved glycaemic control, HbA1c, and basal insulin [79]. A randomized and placebo control clinical trial on 102 patients observed that treatment with *B. aristata* extract in combination with *Silybum marianum* improves the glycaemic control in diabetic dyslipidemic subjects via increasing the insulin C-peptide [80]. Another clinical trial with same combination showed the protective effects on T1DM as well as reduced the insulin doses required before meals [32]. The level of fasting blood glucose (FBG), PPG, HbA1c, total cholesterol (TC), triglyceride rich lipoproteins (TGRLs) and LDL-C were also reduced after the administration of *B. aristata/S. marianum* extracts [32]. Another interventional study concluded that *B. aristata* increased the level of insulin through its antioxidant mechanisms and ability to repair damaged pancreatic β-cells in T1DM and T2DM cases [81].

A study showed that *B. aristata* extract has strong potential to regulate glucose homeostasis via decreased blood glucose, increased glycogen content and decreased activity of glucose-6-phosphatase, increased glucokinase and glucose-6-phosphate dehydrogenase activity, when compared to untreated diabetic rat model [30]. Another study also demonstrated that, among different extracts, ethanolic extract of *B. aristata* exerts remarkable antidiabetic effects and lowered the blood glucose in oral glucose tolerance test (OGTT) in over-night fasted rats. It also decreased the serum glucose level (248±8.75 to 62±6.78) and increased the glycogen content (12.99±1.66 to 35.03±9.89) in an experimental diabetic rat model [82]. A two month randomized, double-blind, and placebo-controlled study in Iranian subjects with T2DM showed that berberis fruit extract markedly reduced the FBG and HbA1c levels [83].

In addition to antidiabetic effects of *B. aristata* extracts, berberine, the most abundant compound of *B. aristata* plant/extracts, also exerts anti-glycaemic effects as evident by different *in-vitro*, cell culture, *in-vivo* animal model studies and human clinical trials. A mechanistic report showed that this heteropentacyclic alkaloid exerted potent antidiabetic effects via enhancing the secretion of insulin through elevation of glucagon-like peptide-1(GLP-1) levels, stimulating the process of glycolysis by activation of AMPK pathway and amplified glucokinase activity, decreasing the mitochondrial functionality and the process of adipogenesis. It also increased glucose transporter-4 (GLUT-4) level which is well reckoned to facilitate the transport/diffusion of glucose, and showed strong antidiabetic effects via α-amylase inhibition in a non-competitive manner as evident by enzyme kinetics studies [84].

The same study also revealed that berberine inhibits the activity of α-amylase by interacting at two distinct sites S-1 and S-2 (9 Å apart) with binding energies (ΔG) -4.840 and -5.004 kcal/mol, respectively [84]. The interaction of berberine at S-1 was facilitated via by a number of charged and polar amino acid residues including Tyr82, Asp117, His122, Tyr155, Arg204, Asp206, Thr207, Lys209, His210, Glu230, Asp233, His296, Asp297, and Arg344,whereas, interaction at S-2 was mediated by hydrophobic residues that mostly belonged to N-terminal of the target protein [84]. A clinical study in newly diagnosed type-2 diabetic adults (n=36) demonstrated that berberine lowered the level of FBG (from 10.6 to 6.9 mmol/L), postprandial blood glucose (PP) (from 19.8 to 11.1mmol/L) and HbA1c (from 9.5% to 7.5%) [85]. The berbamine, a potent alkaloid from *B. aristata* roots, alleviates the high fat diet (HFD) and STZ induced T2DM in rats via decreasing the HbA1c level and improving the hepatic glycogen content as well as increased the mean percent insulin positive cells [86]. Further, the potent hypoglycaemic effect of berbamine was also corroborated with increased hexokinase and glucose 6-phosphate dehydrogenase activities as well as compromised glucose 6-phosphatase and fructose 1,6-bisphosphatase [86].

Other isoquinoline alkaloids that are the characteristic metabolites of *B. aristata*, palmatine and jatrorrhizine, also enhanced the insulin

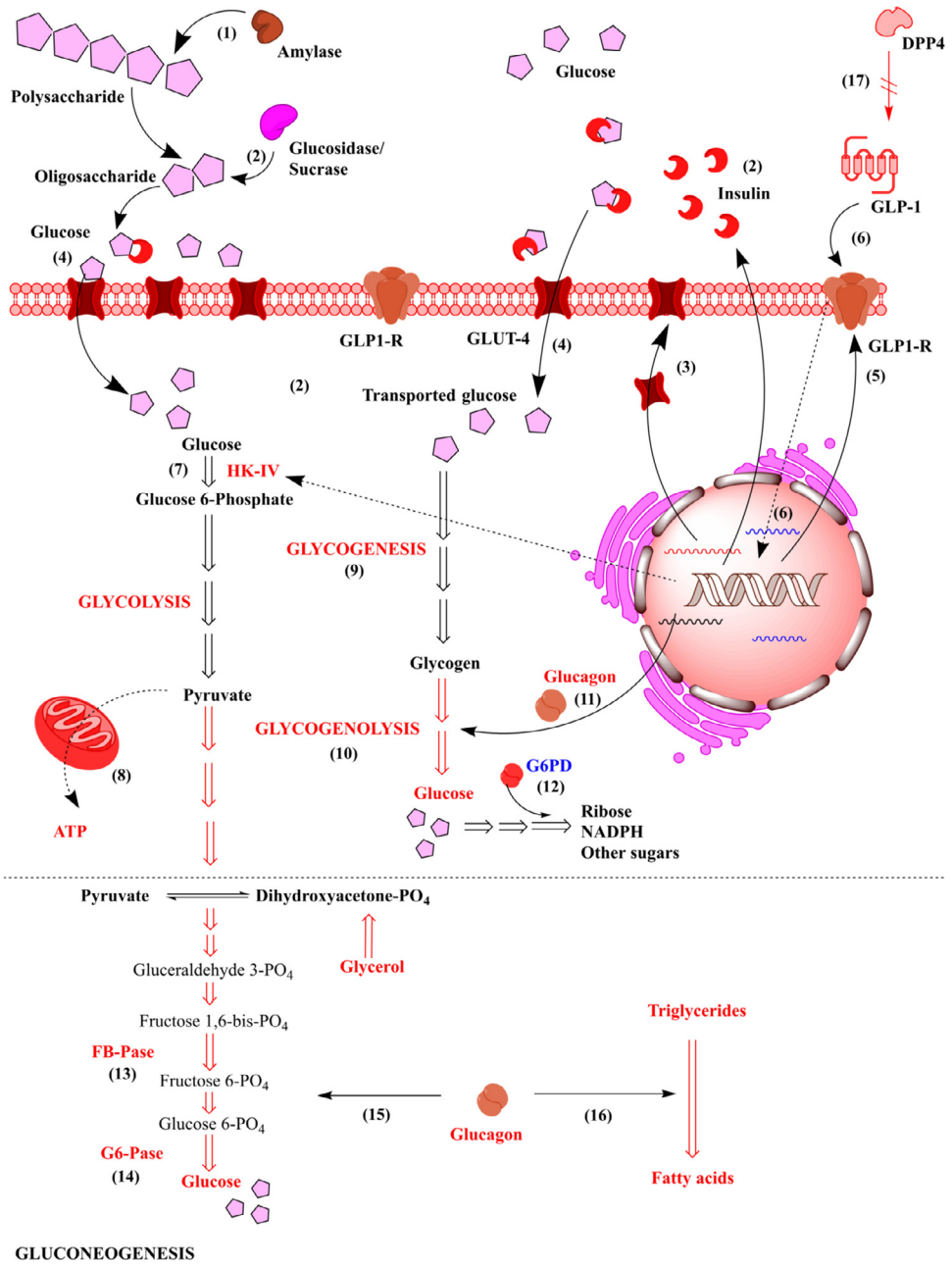

Fig. 2. Antidiabetic mechanism of *B. aristata* and its secondary metabolites. The *B. aristata* and its bioactive compounds inhibit the activity of carbohydrate metabolizing enzymes *i.e.*, amylase (1) and glucosidase (2) and prevent the conversion of complex polysaccharide into oligo and monosaccharides (particularly glucose) to combat hyperglycemia; stimulate the GLUT-4 expression (3) and GLUT-4-mdeiated glucose transport (4); up-regulate the expression of GLP1-R (5) to facilitate GLP-1/incretin-directed modulation of insulin and glucagon expression (6); stimulate the glycolysis via increasing the hexokinase-IV (HK-IV) activity (7) and subsequent energy production through respiration (8); regulate the glycogenesis (9) and glycogenolysis (10); modulate the GLP-1-dependent glucagon expression (11); stimulate the conversion of excess glucose into ribose and other metabolites/sugars via inhibition of glucose- 6-phosphate dehydrogenase (G6PD) (12); inhibit the process of gluconeogenesis from pyruvate and other precursors *i.e.*, glycerol via blocking the activities of fructose 1,6-bisphosphatase (FB-Pase) (13), glucose 6-phosphatase (G6-Pase) (14) and glucagon (15); inhibit the conversion of triglycerides into fatty acids (16) and inhibit the DPP4-mediated GLP-1 inactivation (17).

secretion in rat pancreatic β-cells (RINm5F) either in absence or presence of glucose [87]. Both these compounds also inhibited the activity of maltase with an IC_{50} of 38.42 μg/ml and 22.05 μg/ml, respectively. Palmatine and jatrorrhizine further inhibited the activities of sucrase and α-glucosidase [87]. These effects were further validated in *in-vivo* study, which also observed that the treatment with palmatine and jatrorrhizine stimulated the secretion of insulin and hence raised the serum level which ultimately resulted in diminished serum glucose level [87]. Another study showed that the berberine and palmatine exhibited strong *in-vitro* α-glucosidase inhibitory activity [88]. A study in myocytes L6 cells showed that the treatment with palmatine modulated the expression of genes responsible for the glucose homeostasis like GLUT-4, PPARα and PPARγ [89]. The above-mentioned findings strongly suggest that *B. aristata* and its bioactive compounds possess significant anti-diabetic effects via targeting distinct molecular mechanisms in *in-vitro, in-vivo*, and clinical settings (Fig. 2).

5.4. Anticancer effects

Sitting among the top of the mortality causes, the pathogenesis of cancer has called for the discovery and development of novel and effective therapeutic approaches at broad scale [90]. In this context, natural products/remedies have gain significant attention in recent decades and even a set of secondary metabolites reached to the clinical trials. In Indian and TCM, different plants from the genus *Berberis* with ethnic values are being used for their pharmacological, especially anticancer effects [91]. A recent report showed that methanolic extract of *B. aristata* exerted significant anticancer effects in human osteosarcoma cells (HOS) via induction of ROS generation, enhanced apoptosis, nuclear fragmentation, autophagy, and caspase-3 activity, as well as diminished cell viability (either alone or in combination) [35].

Another study with stem plus bark extract of *B. aristata* evident its anti-tumorigenesis potential in Ehrlich ascites carcinoma (EAC)-bearing

mice and it also increased the survival rate and declined the body weight due to the decreased tumor cell proliferation after receiving intraperitoneal injection of 100 mg/Kg B.W. and 6.5 mg/Kg B.W. of aqueous and ethanolic extracts, respectively [92]. Apart from the anticancer effects of *B. aristata* extracts, its bioactive ingredients like berberine, oxyberberine, berbamine and palmatine also showed remarkable antitumorigenic and antiproliferative efficacy in different *in-vitro* and animal model studies. In this context, berberine has been extensively investigated for its beneficial effects against the management of different cancers [93–95]. Moreover, berberine and its chemical analogues have shown to limit the proliferation of pancreatic adenocarcinoma cells (PDAC), PANC-1 and MIA-PaCa2 cells via induction of ROS generation, apoptosis and cell cycle arrest at G1 phase [96,97].

A recent study demonstrated that the supplementation of berberine in combination with galangin inhibits the growth of oesophageal carcinoma cell lines like human oesophageal carcinoma cell lines including Eca9706, TE-1, EC109 and HEEC [98]. Further, this combination induced the apoptosis in Eca9706 cells via regulating the expression of apoptosis related proteins Bcl2, Bax and caspase-3 and also resulted in cell cycle arrest at G2/M phase through down-regulation of distinct cell cycle related Cyclins and CDKs at post-transcriptional level [98]. Further, the co-delivery of these compounds also enhanced the ROS generation and down-regulated the m-RNA and protein expression of Wnt3a and β-catenin in Eca9706 cells [98]. The same combination also diminished the tumor growth in nude mice with xenograft tumors [98]. Another study showed that berberine limits the proliferation of human chondrosarcoma cell line (HTB-94) through G2/M phase arrest in PI3K/Akt and p38 kinase-dependent pathways [99].

In addition to berberine, another secondary metabolite from *Berberis spp.,* oxyberberine, exerted potent anticancer activities against human hepatic adenocarcinoma cells (SK-Hep-1), human liver cancer cells (Hep-G2) and human non-small cell lung cancer (NCI-H12997) cells. However, the anticancer effect of oxyberberine in SK-Hep-1 cells was highest, when compared to cytotoxic effects reported in Hep-G2 and NCI-H12997 cells as confirmed by MTT assay after 72 h of incubation [100]. Moreover, berbamine has also showed anticancer effects in HepG2 and SMMC-7721 hepatocellular carcinoma cells via p53-dependent induction of apoptosis and suppression of Bcl-2 and survivin expression [101,102]. Another study on various carcinoma cells demonstrated that berbamine loaded lipid nanoparticles (BBM-NPs) exhibited potent anti-metastatic and antitumorigenic effects by inhibiting the migration in human A549 (alveolar basal epithelial adenocarcinoma cells), MDA-MB-231 (Human triple-negative breast cancer cells) and B16F10 murine melanoma cells [103]. The invasion was also restricted in A549 and MDA-MB-231 cells via suppression of matrix metalloproteinase (MMP)-2, MMP-9, Bcl-2 and VEGF protein expression. In addition to induction of apoptosis in these cells, it also showed significant antitumorigenic efficacy in B16F10 melanoma cell injected C57Bl/6 mice tumor model [103,104]. These findings were further validated by the other researchers who also reported anticancer effect of berbamine on A549 cells through reduced Bcl-2/Bax ratio and diminished relative migration in a dose dependent manner [105].

Further, berbamine in combination with Detoxified Pneumolysin Derivative ΔA146Ply showed enhanced anticancer effects against different breast cancer cells, particularly, MDA-MB-231 cells via targeting p-Akt/T-Akt/p-Erk/T-ERK/Bcl-2/Bax signalling [106]. Another study showed that co-supplementation of berbamine and docetaxel through chitosan/Sulfobutyl ether-Cyclodextrin nanoparticles showed potent anticancer activities in MCF-7 breast cancer cells by promoting the apoptosis, inhibition of cell-proliferation and down-regulation of survivin mRNA expression [107]. Similarly, berbamine treatment induced the apoptosis and autophagy as well as inhibited the metastasis in human colon cancer cells lines like HT-29, HCT116 and SW480 through suppression of Bcl-2 and activation of Bax, Caspase-3, Caspase-9 (apoptosis-related proteins), and ATG-12, ATG-5 and beclin-1 (autophagy-related proteins) [108,109]. It also induced the cell cycle arrest at G_0/G_1 in HCT116 and SW480 cells [109]. On the other hand, glioblastoma (GBM) is the most common primary brain tumor that accounts for about forty percent of all neurological malignancies. However, a newly synthesized berbamine derivative negatively regulates cell viability and triggers apoptosis in cancer stem-like cells of human GBM through up-regulation of miRNA-4284 and JNK/AP-1 signaling [110]. In addition to the individual antitumor effects on GBM, a combination of berbamine with paclitaxel showed enhanced antitumor potential in GBM cells via targeting ROS/Akt signaling pathway [111]. Berbamine also improved the radio sensitization of head and neck squamous cell carcinoma via limiting the STAT3 phosphorylation and modulating the Bax/Bcl-2 ratio [112].

The treatment of SKOV3 and ES2 of ovarian cancer cells with berbamine limited the cell proliferation and induced apoptosis and cell cycle arrest at G0/G1 phase. These effects were attributed to the berbamine-mediated modulation of caspase-3/caspase-9/Bax/Bcl-2 and Wnt/β-catenin signaling [113]. Another study showed that berbamine enhanced the anticancer effects of gefitinib on pancreatic cancer cells (*i.e.*, Panc-1 and Miapaca-2) via inducing the cell cycle arrest at G0/G1 and G1 phase in Panc-1 and miapaca-2 cells, respectively, as well as their co-delivery also diminished the protein expression of cell cycle associated proteins like cyclin D1, Cdk-4 and Cdk-6 [114]. It also enhanced the apoptosis promoting ability of gefitinib via regulating the Bax and Bcl-2 protein expression and also targeted STAT3 signaling [114].

A novel berbamine derivative (BBMD3) negatively affected the viable cell count and triggered apoptosis in various human osteosarcoma cells (G292, KHOS, and MG-63) through down regulation of cyclin D-1 and D-2 expression. It also increased the cleavages of caspase-3 and PARP along with the regulation of Bcl-2, Bcl-xL, survivin, Jak-2 and p-STAT protein expression [115]. Recently, another derivative 2-methylbenzoyl berbamine (BBD24) has also showed the ability to suppress the growth of isolated human osteosarcoma cells in NF-κB, ERK and AKT-dependent signaling networks [116]. The above-mentioned evidences are strongly advocating the fact that *B. aristata* along with its bioactive principals exhibit significant anti-cancer potential via targeting different signaling pathways (*i.e.*, Jak/STAT, ROS/Akt, NF-κB, and p-Akt/T-Akt/p-Erk/T-ERK/Bcl-2/Bax signaling), autophagy, and ROS generation in *in-vitro* and *in-vivo* models.

5.5. Effects on lipid metabolism or atherosclerotic cardiovascular disease

Lipids are the essential constituents of the cells, organs, and the body which participate in various structural as well as functional aspects of life. Considering their ubiquitous occurrence and the inevitable role in animal physiology, it's important to understand the coordinated metabolism of lipids in the body. Excess of different lipids and lipoproteins in the circulation as a result of deregulation of cholesterol homeostasis has been associated with moderate to severe CVD [8–10,22] or systemic complications including diabetes and its associated illnesses, particularly nephropathy, neuropathy, and retinopathy [11–13]. The low-density lipoprotein (LDL), among different lipoproteins, plays a crucial role in the establishment of CVD including atherosclerosis, whereas, high-density lipoprotein (HDL) is believed to protect against these complications through its paraoxonase-dependent antioxidant activity [9,10,12]. The level of these lipoprotein particles in the cytoplasm is strictly sensed by sterol regulatory element binding protein-2 (SREBP-2) which ultimately controls the expression of different genes that function in cholesterol homeostasis [9,117].

The major regulators of the cellular cholesterol level are HMG-CoA reductase (HMG-R), known for intracellular cholesterol synthesis; LDL-receptor (LDL-R), responsible for LDL-uptake by the cells and proprotein convertase subtilisin/kexin-9 (PCSK-9), a lysosomal degrader of LDL-R, which reduces LDL-uptake through LDL-R [8,10,26,118]. Therefore, management of cholesterol homeostasis involves targeting of here-mentioned distinct biochemical as well as molecular markers including HMG-R, LDL-R, PCSK-9, and SREBP-2. Owing to the adverse effects associated with the commercially available drugs, particularly statins,

researches have shifted their attention towards the natural drug candidates due to their safety, bioavailability as well as desired efficacy [21,117].

In the same context, a study showed that the treatment with *B. aristata* extract plays a very important role in the prevention of CVD via decreasing the level of circulatory total cholesterol (TC), triglycerides (TGs), and LDL, whereas, it increasing the level of HDL in high cholesterol fed rats [119]. Recently, *B. aristata* cortex extract (BCE) down-regulated the expression of PCSK-9 both at transcription and translation level and also influenced the promoter activity [34]. The co-delivery of BCE with red yeast rice and *Morus alba* leaves extract also suppressed the PCSK-9 mRNA and protein level and PCSK-9 promoter activity in HepG2 and Huh7 cells [34]. The BCE alone as well as in the same combination also up-regulated the expression of LDL-R, which ultimately facilitated the LDL uptake in HepG2 cells [34].

A clinical study was performed to assess the impact of co-delivery of *B. aristata* extract and *Silybum marianum* on the subjects facing challenges associated with long lasting statin therapy, when consumed at very high doses. To achieve the target, they divided the patients on statin therapy into two groups both receiving half of their respective previous statin doses either in the presence or absences of *B. aristata* extract and *S. marianum* combination [120]. This study concluded that lowering the statin dose resulted in a marked deregulation of circulatory markers of cholesterol homeostasis in placebo group. In contrast, treatment with the here-mentioned combination of *B. aristata* compensated the effects of reduced statin dose efficiently, when compared to placebo group [120]. In addition, anti-hypercholesterolemic effect of berbamine isolated from *B. aristata* and other *Berberis spp*. were evaluated in high cholesterol fed zebra fish model and found that berbamine exhibited strong hypocholesterolemic properties by diminishing the cholesterol content in caudal artery, plasma TC, TGs, LDL-C and hepatic lipid content [121]. Berbamine also down-regulated the mRNA expression of HMG-R and protein levels of microsomal triglyceride transfer protein (MTP). In contrast, the mRNA expression of hepatic LDL-R was up-regulated, which ultimately resulted in enhanced clearance of circulatory LDL cholesterol in zebra fish model of hypercholesterolemia [121].

Similarly, a recent review concluded that berberine exhibited potent anti-atherosclerotic effects via targeting different biochemical and molecular mechanisms including the activity of PCSK-9 and LDL-R in different models [122]. Berberine was found to suppress the expression of PCSK-9 in HepG2 cells [123]. It also affected the expression and activity of hepatocyte nuclear factor-1α (HNF-1α) in HepG2 cells [124], which is a direct transcriptional activator of PCSK-9 expression [9].

Another study observed that treatment with berberine and palmatine exerted curative effects against HFD-induced experimental hypercholesterolemia in B6 mice model and reduced the hepatic triglyceride rich lipoprotein (TGRL) accumulations and also reduced the epididymal adipocyte size [125]. These beneficial effects after berberine and palmatine treatment were achieved through down-regulation of HMG-R and stimulation of LDL-R and cholesterol-7-α-hydroxylase (CYP7A1) mRNA expression. In addition to the effect on mRNA expression, the protein expression of HMG-R, LDL-R, CYP7A1, SREBP-2, farnesoid X receptor (FXR) and c-Jun N-terminal kinase (JNK) was also modulated by the treatment of these compounds [125]. The treatment with palmatine alone also showed the amelioration of these biomarkers in HFD-induced hamster model of hypercholesterolemia [126]. In conclusion, *B. aristata* and its bioactive metabolites exhibited promising anti-atherosclerotic effects through the regulation of PCSK-9/LDL-R/SREBP-2/HMG-R axis and subsequent lipid homeostasis (Fig. 3).

5.6. Hepatoprotective effects

Liver is the vital organ and is responsible for the adsorption, desorption, metabolism and excretion (ADME) of each and every metabolite, drug and toxic substances that are being ingested in the body. However, the drug-induced liver injury (DILI) is considered the major cause leading to the discontinuation of a clinical trial and withdrawal of a drug from pharmaceutical market. Despite the availability of various main stream therapeutic agents, finding a drug with the potential to cure against DILI is nowhere an easy task. Therefore, numerous herbs/plants, either alone or as polyherbal formulations, have been investigated for their hepatoprotective activity in different *in-vitro* (cell culture) and *in-vivo* settings. In the same context, the treatment with *B. aristata* root extract has been shown to prevent carbon tetrachloride (CCl_4)-induced hepatotoxicity in rats via modulating the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatise (ALP) as well as decreasing the level of total bilirubin in the serum [127]. Punarnavashtakkwath, a well-known Ayurvedic formulation consisting of eight plant species including *B. aristata*, has also been investigated for its hepatoprotective activity in CCl_4-induced hepatic injury in rats as well as HepG2 cells [128]. As a result of this study, the Punarnavashtakkwath was demonstrated to have protective effects via decreasing the activities of hepatic enzymes like ALT, ALP, AST as well as the level of TBARS and bilirubin in CCl_4-induced hepatic injury in rats [128]. It also stimulated the activities/level of hepatic SOD, CAT, and GSH in same model. The same formulation (15 μg/ml) also positively regulated the viability of CCl_4-exposed HepG2 cells and these effects on HepG2 cell viability were better than that of reference standard silymarin (50 μg/ml) [128]. Different herbal formulations from TCM constituting *B. aristata* have shown hepatoprotective effects [129].

In addition to the hepatoprotective effects of different formulations of *B. aristata*, berberine also showed ameliorative effects against acetaminophen-induced hepatotoxicity in mice via modulating the level of inflammatory markers, activities of hepatic ALT and AST, redox imbalance, lipid peroxidation, myeloperoxidase, preserving the cellular integrity, and restricting the monocyte migration into the arterial intima [130]. Berberine pre-treatment also showed the amelioration of the same biochemical, molecular, as well as histopathological parameters in methotrexate-induced hepatotoxicity in rats [131]. Like berberine itself, treatment with berberine nanoparticles (BBR-NPs) also alleviated the altered activity of hepatic enzymes in CCl_4-induced hepatotoxicity model [132]. Doxorubicin, one of the most efficient chemotherapeutic agents, is known to exhibit adverse effects on hepatic structure and function. The treatment with berberine showed protective effects against doxorubicin-induced hepatotoxicity through modulation of distinct cytochrome P450s and inflammatory cascades [133]. Another study showed that treatment with this compound significantly improves the paraquat-induced hepatic dysfunction through the modulation of ROS generation, GSH content, and ALT and AST activity [134].

A clinical study also evident the hepatoprotective effect of *Berberis Sp*. via alleviating lipid profile, hepatic ALT, AST and ALP activity, GPx activity as well as kidney associated biomarkers [135]. The results from another clinical trial revealed that berberine treatment significantly improved the nonalcoholic fatty liver disease (NAFLD) like symptoms by lowering TC, lipoproteins, FBG level, and activity of major hepatic enzymes, when compared to untreated subjects [136]. Moreover, berberine markedly lessened the CCl_4-induced hepatic dysfunction via activation of AMPK/transforming growth factor-β (TGF-β)/Akt signaling and regulation of hepatic enzymes in mice [137]. Further, this bioactive metabolite from *B. aristata* also showed hepatoprotective effects in $FeSO_4$-induced animals by improving the level of serum bilirubin, total protein, cholesterol and lipoproteins, lipid peroxidation markers, and rate of creatinine clearance [138]. A recent meta-analysis of clinical trials of berberine showed contradicting findings that it does not show significant effects on the hepatic functionality and the regulation of hepatic ALT and AST activity [139].

Another study in aflatoxin B1 and ochratoxin A-induced model of hepatotoxicity showed ameliorative effects of berberine through the modulation of activities of SOD, GPx, ALT, AST, gamma-glutamyl transferase (GGT), and LDH [140]. Another compound from *B. aristata*, palmatine, showed hepatoprotective activity in gentamicin-induced rat model of hepatic injury via improving the activities of ALT and AST

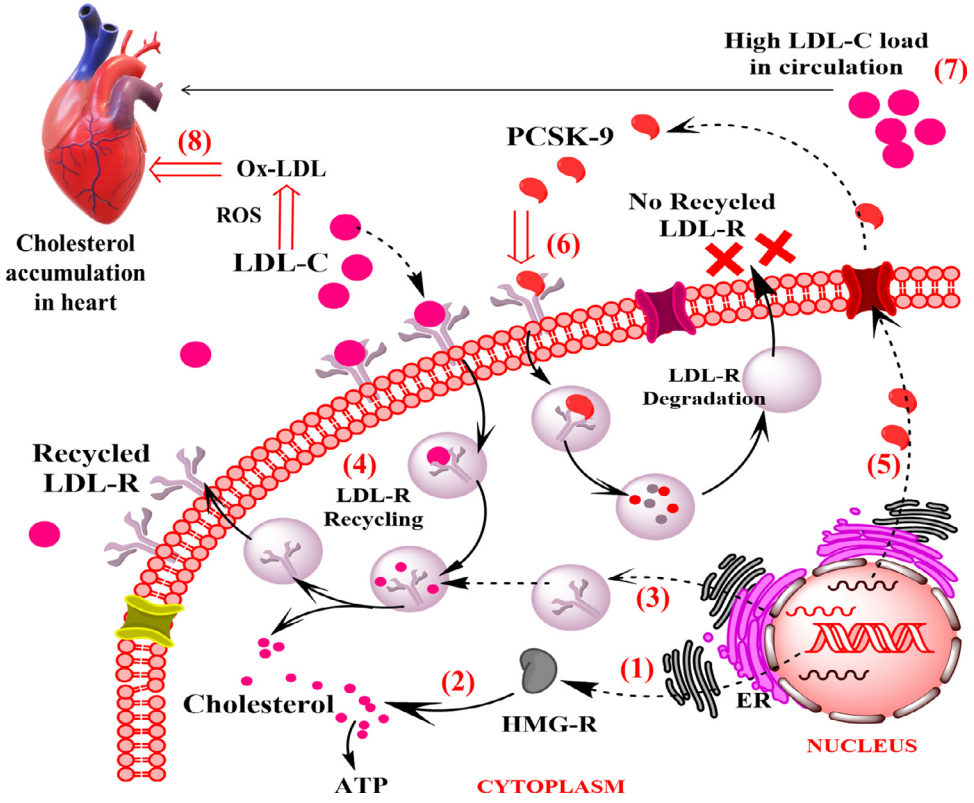

Fig. 3. Role of *B. aristata* and its bioactive metabolites in cholesterol homeostasis cardiovascular risk management. The cardioprotective mechanisms of *B. aristata* and its bioactive metabolites include: the suppression of HMG-R mRNA and protein expression (1) as well as subsequent activity to limit the cholesterol synthesis (2); the stimulation of LDL-R expression (3) and LDL-R recycling to hepatic cell surface to facilitate the LDL-C uptake and lower the circulatory atherogenic load (4); suppression of PCSK-9 expression (5) to restrict the interaction between PCSK-9 and EGF-A of LDL-R and subsequent lysosomal degradation of LDL-R (6); reduction of circulatory cholesterol and its accumulation in the arteries (7) and prevention of ROS-driven oxidative modification of LDL-C to generate Ox-LDL (8) which is more prone to be trapped in between the intima-media axis and elicits immunogenic as well as inflammatory cascades which further fuel the pace of atherosclerotic plaque formation.

as well as the level of MDA, GSH, and electrolytes [141]. In addition, palmatine also ameliorated the d-galactosamine/LPS-triggered hepatic-injury in mice via modulation of inflammatory cascades and apoptosis in hepatocytes [142]. These findings reported in different model systems of hepatotoxicity are strongly validating the hepatoprotective potential of *B. aristata* and its bioactive constituents.

5.7. Antimicrobial effects

Newly arising as well as previously identified infectious diseases are the major health concern and thus have gained much attention of the scientists across the globe. Among distinct infectious agents, bacteria are the major contributors to the pathophysiology of infectious diseases (around 55%) and majority of them are multi-drug resistant (MDR) [143]. Most of the synthetic antibiotics produce toxicity on different organs or tissues due to their chemical structure. Therefore, replacement of these toxic antibiotics with novel antimicrobial agents from natural sources is the demand of the time to meet the safety concerns. In this context, different plants and their metabolites have been investigated for their antimicrobial activity. A recent review by Neag *et al.*, [144] summarized the traditional uses and antimicrobial effects of berberine-containing plants and decoctions from *Berberis Sp.* in TCM [145]. Some berberine-containing decoctions have been shown to possess antibacterial activity in TCM [146,147]. Similarly, aq. extract of *B. aristata* showed potent bactericidal effects against a series of microbes with maximum antibacterial efficacy against *Klebsiella pneumoniae* 1, having a zone of inhibition (ZOI) of 25 mm. However, *K. pneumoniae*2 and some other bacteria showed a marked resistance against *B. aristata* extract. The same extract also exerted strong antimicrobial effects against *Candida albicans* (ZOI: around 23 mm) [36]. Berberine, a major constituent of *B. aristata*, showed potent inhibitory effects against various methicillin-resistant *Staphylococcus aureus* (MRSA) strains with minimum inhibitory concentrations (MICs) between 32 and 128 μg/mL and extended the antibacterial efficacy of commercially available beta-lactam antibiotics *i.e.*, ampicillin and oxacillin [148,149].

The incubation of berberine also potentiated the effects of fluconazole against the growth of yeast, hyphal growth and biofilm generation via regulation of relevant genes in *C. albicans* that were initially resistant to FLC [150]. The treatment of berberine in combination with a well-known antifungal agent amphotericin B showed potent antimicrobial effects against *C. albicans/S. aureus* biofilms. This combination also impacted the transformation of *C. albicans* hyphae and their interaction with *S. aureus*. These beneficial effects of berberine-amphotericin B co-administration against *C. albicans/S. aureus* biofilm were attributed to the regulation of genes responsible for quorum-sensing as well as biofilm formation [151]. Similarly, berberine protected against *E. coli*-induced septic mortality and also increased the survival of the mice. It also potentiated the bactericidal effects of standard antibiotic drug along with the regulation of inflammatory cytokines levels [152]. Treatment with berberine showed potent antimicrobial effects against the MRSA, particularly MRSA252, via disrupting the morphological features of this MRSA and altering the fatty acid composition of the bacterial membrane [153].

The extract of *B. aristata* also exhibited strong *in-vitro* antiparasitic effects against *Plasmodium berghei* NK65, a known malarial parasite of rodents. These effects of *B. aristata* were further validated in *in-vivo* studies in *P. berghei* NK65-challenged BALB/c mice model of malaria which showed its preventing effects against *P. berghei* NK65 infection and also increased the survival of mice model from 7.5 days to 12.8 days [154]. A traditional herbal formulation constituting berberine and matrine restricted the biofilm production and altered the cellular morphological features in a MDR strain of *E. coli*. The inhibitory effects of berberine on *E. coli* biofilm were attributed to the suppression of quorum sensing-associated genes *i.e.*, pfS, hflX, and fliA [155]. Another study reported that berberine chloride exerted antimicrobial activity against 14 species of *Staphylococccus* with maximum bactericidal effects observed in case of *S. haemolyticus* and *S. epidermidis*. These anti-staphylococcal effects were further enhanced when berberine chloride was synergistically applied with reference standard linezolid, cefoxitin and erythromycin [156].

Researchers synthesized various derivatives of berberine-specific imidazoles which showed strong bactericidal effects against Gram +ve and Gram -ve bacteria. The strongest antibacterial activity was reported

in case of imidazolyl-berberine 3a against *Eberthella typhosa* (MIC: 1 μg/mL). This berberine-imidazole analog showed mild cytotoxic effects as well as ROS generation and its antibacterial effects were attributed to its ability to intercalate between the DNA strands and thus limiting the replication and cell growth [157]. The antibacterial effects of berberine were markedly extended by encapsulating it into nanogels and further surface modifications using positively charged polyelectrolyte [158].

Similarly, conjugation of berberine with shellac nanoparticles along with Poloxamer 407-mediated surface modifications resulted in strong antimicrobial effects against *E. coli*, *C. reinhardtii* and *S. cerevisiae*, when compared with un-conjugated berberine. The enhanced efficacy of this berberine-conjugate was attributed to the presence of positively charged surfactant, which showed strong interaction with negatively charged membrane [159]. Other studies also reported the augmented antimicrobial action of berberine nanoparticles [160]. Moreover, benzyl derivatives of berberine exhibited potent antimicrobial efficacy against different Gram +ve and Gram-ve bacteria as well as fungal strains and these effects were better than that of ciprofloxacin and fluconazole [161]. Another study showed that berberine and palmatine extended the antibacterial efficacy of ciprofloxacin against sixty isolates of MDR *Pseudomonas aeruginosa* from burn infections via functioning as the inhibitors of efflux pumps [162]. Additionally, both these compounds showed protective effects against the gastric ulcers via regulating redox status and restricting the colonization of *Helicobacter pylori*, a well-established causative agent of peptic ulcer disease [163].

The above discussed findings are strongly supporting the potent antimicrobial effects of *B. aristata* extracts as well as its secondary metabolites. These findings suggest that supplementation of *B. aristata* extracts and its bioactive metabolites, alone or in combination with other antimicrobial agents, may be implied as promising therapeutic regimen in the management of different microbial diseases.

5.8. Antiglycation/anti-aging effects

Poorly managed and long lasting hyperglycaemic conditions facilitate the establishment of distinct secondary complications in DM patients and the glycation process has been stated as the major culprit [11,12,57]. Glycation proceeds in a sequential and non-enzymatic reaction of carbonyl species like sugars with other macromolecules, particularly, proteins, DNA and lipoproteins, which ultimately lead to the formation of advanced glycation end products (AGEs) [27,118]. These AGEs encounter with their receptors (RAGEs) that is followed by various signaling cascades leading to cellular disintegration [12,57]. These observations advocate the significance of discovery of antiglycation agents to block the glycation as well as diabetes-associated secondary complications. Considering the adverse effects of aminoguanidine, standard antiglycation agent, various plants and their lead metabolites (including iridin, carvacrol, tocotrienol, and glycyrrhizic acid) have been used to block the formation of AGEs both in *in-vitro* and *in-vivo* settings [12,27,55,56,118]. Berberine, a bioactive constituent of *B. aristata*, has showed protective effects against diabetic complications via targeting the formation of AGEs as well as advanced protein oxidation adducts in STZ-induced diabetic rat model [63].The findings from other studies also validated the efficacy of berberine in targeting AGEs-induced complications in diabetic rat models as well as mesangial cells and concluded that this bioactive metabolite exerts inhibitory effects against the generation of AGEs and subsequent RAGE/TGF-β1 signaling and aberrant proliferation of mesangial cells, a sign of the progression of renal failure [164,165]. A meta-analysis of effects of berberine on diabetic state also showed that this bioactive compound from *B. aristata* lowers the level of HbA1c, a marker of glycoxidative modification of circulatory haemoglobin [166].

In addition to the berberine, palmatine also showed the inhibitory effects against D-ribose and methylglyoxal (MGO)-induced BSA and hemoglobin-AGEs formation [167]. Similarly, quercetin also exerted beneficial effects against dietary AGEs-induced Alzheimer's like pathologies in mice via modulating the Aβ content, neurotransmitters, activation of tau, and inflammatory cascades in brain [168]. Other *in-vitro* and molecular modelling studies also confirmed the antiglycation effects of quercetin against glucose, ribose, MGO and fructose-induced protein AGEs formation [169,170]. Another recent study concluded that quercetin protects against the MGO-induced proliferation of cancerous MCF-7 cells via restricting the structural changes in HSA, particularly the formation of AGEs and aggregates [171]. Similarly, rutin and its derivatives have also showed *in-vitro* inhibitory effects against histone H1 and BSA-AGEs formation (induced through a number of potent glycating agents) [172,173]. Various *in-vivo* studies also confirmed the protective pharmacological role of this flavonoid in targeting AGEs-induced diabetic complications including diabetic cataract, characterized by opacification of the eye lenses [174–176]. Moreover, the administration of rutin also protected against AGEs-induced osteoarthritis in human chondrocytes as well as a surgically destabilized mice model via modulation of redox mediators, inflammatory markers (MMP-13, IL-6, TNF-α, and COX-2), and AGEs level [177].

Caffeic acid, another secondary metabolite from *B. aristata*, significantly ameliorated the epithelial to mesenchymal transition in AGEs-induced HK-2 cells via targeting β-catenin signaling [178]. It further showed its anti-ageing therapeutic potential against LDL-AGEs-triggered inflammatory response by interfering the RAGE transcription, AGEs-RAGE interaction and subsequent secretion of inflammatory cytokines including C-reactive protein (CRP) and chemokines *i.e.*, monocyte chemo attractant protein (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells [179]. Another similar study reported that caffeic acid exhibits inhibitory effects against D-glucose-induced protein AGEs formation and also protected the protein-AGEs-exposed HUVECs by the suppression of IL-1β, IL-18, VCAM-1, and CRP expression as well as ROS formation [180]. Chlorogenic acid, an esterified adduct of caffeic acid and commonly isolated from *B. aristata*, has showed potent antiglycation effects leading to the diminished level of BSA-AGEs as well as their cross-reactivity with collagen [181,182]. Chlorogenic acid was also found to inhibit the D-fructose-induced ovalbumin-AGEs formation after intestinal digestion [183]. It also protected the high glucose-exposed H9c2 cells via blocking the AGEs formation as well as redox regulation [184]. In conclusion, *B. aristata* and its secondary metabolites exhibited promising antiglycation and anti-aging effects and may be further evaluated for their therapeutic potential against various glycation and aging-induced diseases including diabetes using distinct preclinical and clinical studies.

5.9. Neuroprotective effects

Neurological ailments are one of the causes of disability adjusted life years across the globe and Alzheimer's disease (AD) is the most recognized pathology accounting for 60 to 80 % of the total cases of dementia [15]. The manifestations of AD are largely attributed to the formation and accumulation of amyloid-β (Aβ), redox imbalance, inflammatory cascades, neurotransmitters and the activities of acetylcholine esterase (AChE) as well as butyrylcholine esterase (BChE) [15]. Distinct strategies have been investigated for their neuroprotective effects since few decades *i.e.*, inhibitors of AChE, BChE, protein aggregation and Aβ formation, N-methyl-D-aspartate (NMDA) receptor, antioxidants and anti-inflammatory agents [15,185]. The drugs of choice in the current scenario for the management of neurological pathologies include the inhibitors of cholinergic mediators *i.e.*, AChE and NMDA [186–188].

Among these, tacrine, the 1st of its kind AChE inhibitors, was discontinued owing to the various adverse events including hepatotoxicity as well as drug intolerance after a long lasting or life-long prescriptions [15,189–191]. Therefore, different herbal formulations as well as their bioactive metabolites have gained worldwide attention to achieve desired therapeutic efficacy, safety and cost effectiveness in combating neurological disorders [15]. Similarly, *B. aristata* L. extracts have shown their neuro-modulatory effects in different experimental settings.

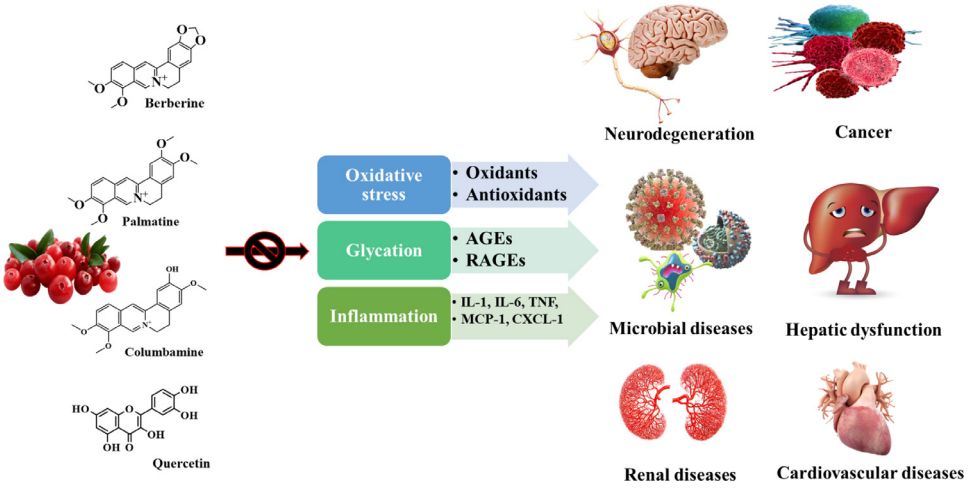

Fig. 4. Cartoon representation of overall pharmacological effects of *B. aristata* and its secondary metabolites.

Briefly, administration of *B. aristata* extract exhibited protective effects against 6-OHDA-mediated Parkinson's disease and ameliorated the behavioural pattern, increased the coordination of muscles, diminished rotation, lowered lipoperoxidative events, as well as augmented activities of enzymatic antioxidants like SOD and CAT along with the non-enzymatic antioxidant (GSH) [192]. Moreover, treatment with barberry extract elevated the outward potassium current in brain cells, which further signifies its neuroprotective activity [193]. In another study, berberine administration resulted in neuroprotective effects in a mice model of traumatic brain injury and improved the learning as well as memory skills via suppression of MMP-3 and MMP-9 expression and amelioration of redox imbalance and inflammatory cascades. Berberine also inhibited the activity of AChE while triggered the choline acetyltransferase functions [194]. In addition, a recent review summarized the neuromodulatory effects of berberine in different animal models and concluded that it protects against a wide range of neurological manifestations, particularly memory and learning impairments in case of AD, however, they do not found any clinical trial regarding the use of berberine in combating neurological disorders [195].

Administration of berberine showed ameliorative effects against diffuse axonal injury in rats and improved compromised learning and memory skills via targeting inflammatory markers *i.e.*, TNF-α, IL-1β, MCP-1 and the expression of NF-κB, Bax, and Cyt-C [196]. Apart from the role of distinct chemical entities in the progression of neurological ailments, heavy metals are also known to cause the onset of such disorders. Similarly, berberine significantly improved the cognitive behaviour in heavy metal-induced neurodegeneration rat model of AD as evident by Morris water maze test and improvement of memory deficits. Treatment of berberine for 30 days post-AD induction also improved the inflammatory markers like TNF-α, IL-12, IL-6, IL-1β, COX-2, and TNF-α converting enzyme. *In-silico* molecular modelling studies revealed that berberine strongly interacted within the active pocket of AChE and the activity and the tissue level expression of AChE was also suppressed in brain slices of rats. In addition, it also restricted the production of Aβ42 that is well reckoned to direct the accumulation of Aβ plaques and stimulated the generation of Aβ40 possessing antioxidant potential [197].

To uncover the neuromodulatory effects of palmatine on depression-like symptoms, researchers first developed a stress-induced mice model of depression-like pathology via exposing them to mild stress. Following the twenty-one days of stress-challenge, subsequent treatment with palmatine for the same duration resulted in a marked amelioration of oxidative stress, corticosterone levels and immobility periods in stressed model comparable to reference drug, fluoxetine. However, the locomotor activity was not affected by the administration of either of the drugs [198]. A recent study also evident the anti-depressive potential of palmatine in rats facing diabetic neuropathic pain and depression via down-regulation of hippocampal $P2X_7$ receptor and modulation of TNF-α and IL-1β secretion [199]. An analog of palmatine was shown to markedly restrict the aggregation of tau protein-derived aggregation-prone hexapeptide fragment (PHF6) via interacting its counterparts known for β-sheets conformation and also led to the disassembly of PHF6 aggregates and diminished amyloid levels [200].

Apart from the berberine and palmatine, jatrorrhizine also showed potent *in-vitro* AChE activity [201]. Furthermore, a report analysed the synergistic effects of berberine and palmatine against the AChE activity and suggested their potential benefit in targeting AD pathologies [202]. These findings suggest that supplementation of *B. aristata* extracts and its bioactive metabolites, alone or in combination with other neuroprotective agents, may be implied as promising therapeutic regimen in management of different neurological disorders, particularly, AD, Parkinson's, and migraine.

6. Conclusion

The rising health concerns and public expectations regarding the safety and cost effectiveness of the currently available modern medicine have demanded the discovery of effective, safer and cheaper alternative treatment options, particularly to benefit LMICs. *B. aristata* is being used in traditional medicine system of India and China and the existence of distinct bioactive metabolites is believed to be the driving force behind its potential therapeutic effects against various health issues. The current review uncovered the recent updates regarding the implications of *B. aristata* and its potential bioactive secondary metabolites in targeting various acute and chronic diseases. These beneficial effects were achieved through the modulation of distinct pathways like PCSK-9/LDL-R/HMG-R pathway, TGF-β/Akt signaling, AChE/BChE/Aβ-axis, inflammatory cascades, redox mediators (both enzymatic and non-enzymatic), Jak/STAT, ROS/Akt, NF-κB, and p-Akt/T-Akt/p-Erk/T-ERK/Bcl-2/Bax signaling in cancer (Fig. 4). Further clinical studies are required to reach a conclusion about its promotion for public use aiming the management of different CDs and NCDs.

Declaration of Competing Interest

Authors declare that there is no conflict of interest.

Acknowledgement

The support from the DST, India to the Department of Biosciences under the FIST program is highly acknowledged. Dr. SS Alvi is highly indebted to the DHR, MoHFW, GOI for providing him the prestigious

Young Scientist Fellowship (File No.: 12014/13/2019-HR). We also acknowledge the Integral University, Lucknow for providing the necessary research facilities. This article has acquired Integral University MCN (IU/R&D/2022-MCN0001697).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.prmcm.2022.100184.

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