The incidences of diabetic mellitus and other metabolic diseases such as hypertension and hyperlipidemia are increasing worldwide; however, the current treatment is not able to control the rapidly increasing trend in diabetes mortality and morbidity. Studies related to the effectiveness of extracts and pure compounds obtained from plants have shown promising responses in preclinical and clinical studies related to these metabolic diseases. Plants belonging to the genus Berberis (Family: Berberidaceae) are widely distributed with nearly 550 species worldwide. Extracts and compounds obtained from Berberis species, especially Berberine alkaloid, showed effectiveness in the management of diabetes and other metabolic diseases. Various pharmacological experiments have been performed to evaluate the effects of Berberis extracts, berberine, and its natural and chemically synthesized derivatives against various cell and animal disease models with promising results. Various clinical trials conducted so far also showed preventive effects of Berberis extracts and berberine against metabolic diseases. The present review focuses on i) research updates on traditional uses, ii) phytopharmacology and clinical studies on Berberis species, and iii) active metabolites in the prevention and treatment of diabetes and other metabolic diseases with a detailed mechanism of action. Furthermore, the review critically analyzes current research gaps in the therapeutic use of Berberis species and berberine and provides future recommendations.
INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that is characterized by an abnormal long-term increase in plasma glucose levels. Diabetes is mainly classified into four types, i.e., type I diabetes (T1DM), type II diabetes (T2DM), gestational diabetes, and specific types of diabetes due to other causes (American Diabetes Association, 2019). Many factors, such as insulin deficiency or resistance as well as altered carbohydrate, protein, and fat metabolisms, are usually the reasons for high blood glucose levels leading to DM. Chronic hyperglycemia related to diabetes is often associated with many other complications, such as cardiovascular, dermatological, neurological, renal, retinal, and nerve diseases. Diabetes is one of the most common chronic disease, and it has shown an increasing rate of occurrence over the past decade (Bullard et al., 2018). According to the World Health Organization (WHO), the total number of people with diabetes worldwide substantially increased from 108 million in 1980 to 422 million in 2014 (World Health Organization, 2016). Along with diabetes, the incidence of other metabolic diseases, such as hyperlipidemia, is also increasing rapidly (Karr, 2017).

Metabolic syndrome (MS) is associated with a group of disease conditions that occur together, and it is composed of central adiposity, hyperglycemia, hypertriglyceridemia, low high-density lipoproteins (HDL)-cholesterol, and hypertension. This disease cluster of diabetes and cardiovascular diseases is also known as “The Deadly Quartet”, “Syndrome X”, and “The Insulin Resistance Syndrome” (Alberti, 2005). Various treatment options are available to mitigate MS, including the diabetic condition and related disorders (Deedwania and Volkova, 2005). As MS is manifested by the cluster of diseases, use of a single drug candidate might not be able to provide necessary therapeutic effects. Plant extracts and isolated compounds can be possible options as adjuvants in such cases. Traditionally, various medicinal plants and their products (extracts and isolated compounds) have been used in the treatment of diabetes and hypertension (Oyedemi et al., 2009; Tabassum and Ahmad, 2011; Rizvi and Mishra, 2013; Ezuruike and Prieto, 2014). Various research showed the protective/curative effect of plant extracts as a whole and/or an individual bioactive compound against diabetes and other metabolic diseases (Tabatabaei-Malazy et al., 2015; Waltenberger et al., 2016).

Plants belonging to the genus Berberis (Family: Berberidaceae) are widely distributed worldwide with nearly 550 species. A decoction prepared from the roots of Berberis plants is one of the common traditional recipes for the treatment of diabetes (Neag et al., 2018). Various studies have reported the traditional uses Berberis plants for the treatment of metabolic diseases (e.g., diabetes and hyperlipidemia) in many countries, including India, Pakistan, China, and Iran (Hamayun et al., 2006; Uniyal et al., 2006; Rahimi Madiseh et al., 2014; Rana et al., 2019). Various bioactive compounds, such as alkaloids, polyphenols, flavonoids, anthocyanins, etc., have been found in Berberis species along with various vitamins and mineral components (Andola et al., 2010; Srivastava et al., 2015; Belwal et al., 2016; Rubio et al., 2013). Various research showed the protective/curative effect of plant extracts as a whole and/or an individual bioactive compound against diabetes and other metabolic diseases (Dong et al., 2012; Lan et al., 2015; Wang H. et al., 2018). BBR is also distributed in various plant species of other genera such as Coptis, Hydrastis, Mahonia, Tinospora, Xanthorrhiza, and many others (Neag et al., 2018). In the genus Berberis, the distribution of BBR and other alkaloids is mostly in its root part, followed by the stem bark and the stem itself (Andola et al., 2010). In addition, its presence in trace amounts has been reported from leaves and berries. Various studies have been conducted to evaluate the effectiveness of Berberis extract or bioactive alkaloidal compounds against diabetes and other MS with promising results (Gulfras et al., 2008; Meliani et al., 2011; Imenshahidi and Hosseinzadeh, 2016; Mirhadi et al., 2018). Moreover, various clinical trials were also conducted on testing their effectiveness against diabetes and other metabolic diseases and showed variable effects (Zhang et al., 2010; Pérez-Rubio et al., 2013). Considering the Berberis species and their active alkaloidal components, the present review specifically focuses on their
effectiveness against diabetes and other metabolic diseases. This review discusses various traditional uses of *Berberis* against metabolic diseases, along with its cell- and animal-model studies. The pharmacological effects of *Berberis* extracts and alkaloids against diabetes and other metabolic diseases are also discussed along with the molecular mechanism of action. Furthermore, based on the present studies of *Berberis* species against diabetes and metabolic diseases, research gaps were highlighted, and future recommendations were made.

**METHODOLOGY**

The scattered scientific information on *Berberis* species and isolated compounds used to counteract metabolic diseases was collected and documented. The synonyms of the various species were crosschecked with the plant name database The Plant List (www.theplantlist.org, Retrieved on November 22, 2019). Afterwards, the available articles on respective species were retrieved using popular search engines and various databases, such as SciFinder, ScienceDirect, PubMed, Scopus, Mendelej, JOAP, Microsoft academic, and Google Scholar. The keywords used were *Berberis*, berberine, diabetes, metabolic diseases, metabolic syndrome, ethnopharmacology, ethnobotany, chemical constituents, alkaloids, *in vitro*, *in vivo*, clinical study, and clinical trials. The data were congregated through the Boolean information retrieval method by using a plant name along with an “AND” operator followed by diabetes and metabolic syndrome. No prerequisite limitations on publications, i.e., language, year, and publication type (original contribution, review article, or key editorial note), were taken into consideration.

**TAXONOMY AND ECOLOGY OF GENUS BERBERIS**

According to The Plant List database (www.theplantlist.org, retrieved on September 20, 2019), the family Berberidaceae consists of a total of 19 genera. The members of the genus *Berberis* are reported to be difficult to identify taxonomically due to their extreme morphological variation in relation to the environmental factors and natural hybridization (Ahrendt, 1961; Rao et al., 1998). Various overlapping morphological characters, such as flowers, leaves, stems, and berries—which also depend upon the season—and plant age also make it difficult to identify during field tasks (Rao and Hajra, 1993; Rao et al., 1998; Tiwari and Singh Adhikari, 2011). *Berberis* species are widely cultivated around the world due to their high medicinal and ornamental value. Most members of the genus *Berberis* are reported to be tolerant to shade, resistant to drought, and widely distributed in open and wooded habitats and wetlands. These plants are also studied as indicators of habitat degradation in the temperate region due traditionally to their thorny stem and unpalatable shoots (Champion and Seth, 1968).

Representative photographs of some *Berberis* species from the Indian Himalayan Region (IHR) are shown in Figure 1, and their major plant parts used to extract berberine and other bioactive alkaloids are shown in Figure 2.

**ETHNOPHARMACOLOGY OF BERBERIS SPP. AGAINST DIABETES AND OTHER METABOLIC DISEASES**

A literature review revealed that the ethnopharmacological uses of *Berberis* species have been documented from different parts of the world for the treatment of diabetes, hypertension, and obesity, and some of them also revealed the formulation methods. A majority of *Berberis* species were found to be used in the Himalayan region of India and Pakistan.

*B. lycium* Royle has been used traditionally for the treatment of diabetes mellitus and other diseases, particularly by the local inhabitants of the Himalayan region (Hamayun et al., 2006). Apart from diabetes, *B. lycium* is also used to treat bone fractures, diarrhoea, fever, intestinal colic, internal wounds, jaundice, menorrhagia, opthalmic disorders, piles, rheumatism, sun blindness, and throat pain (Jabeen et al., 2015; Adhikari et al., 2019). Fruits and leaves of *B. lycium* are also reported to be used for the treatment of diabetes mellitus in south-west of Iran (Rahimi Madiseh et al., 2014) and Pakistan (Zain-UL-Abidin et al., 2018). The water extract obtained by soaking the root bark in water is used for the treatment of diabetes (Ahmed et al., 2004). The whole plant is used to treat diabetes in Chamba district of Himachal Pradesh, West Himalaya, India (Rana et al., 2019). The Bhotiya tribal community of the Central Himalayan region of India used *B. lycium* roots with water for the treatment of diabetes (Phondani et al., 2010).

The stem of *B. aristata* DC. is widely used in Indian traditional medicine for the treatment of diabetes (Upwar et al., 2011), which is also reported in Ayurvedic Pharmacopoeia. The decoction (5–10 mL) of roots or stems of this species prepared with water was taken twice a day for 1–2 weeks to treat diabetes in Uttarakhand region (Kumar et al., 2019). It is also used by Uttarakhand people for the treatment of hypertension (Singh et al., 2019). The root, stem, and fruit also have been used to treat obesity (Chandrasekaran et al., 2018). *B. asiatica* is also used for the treatment of diabetes by the tribal communities of Chhota Bhangal, Western Himalaya, India. The decoction prepared from the roots is concentrated and dried in shade and then used with the sap of bitter guard for the treatment of diabetes (Uniyal et al., 2006).

In Iranian traditional medicine, *B. vulgaris* L. is extensively used to treat diabetes and hypertension (Rahimi-Madiseh et al., 2017). Local people use a decoction from the fruits and roots of *B. vulgaris* to treat hypertension (Baharvand-Ahmadi et al., 2016). The fruits are most frequently used in traditional and modern medicine (Rahimi Madiseh et al., 2014). Dried roots of *B. crateagina* DC. were recorded to be used as anti-diabetic
agents locally in Turkey, and the decoction or infusion prepared from dried roots was taken orally one to two times a day for the treatment of diabetes (Durmuskahya and Öztürk, 2013). The anti-diabetic activity has also been reported for *B. brevissima* Jafri and *B. parkeriana* C.K.Schneid. (Alemardan et al., 2013). Bahmani et al. (2016) reported that the inhabitant of Urmia, Iran, use boiled and steamed *B. integerrima* Bunge extract for the treatment of diabetes.

**FIGURE 1** | Some Berberis species of Indian Himalayan Region (IHR). (A) *B. aristata* DC., (B) *B. asiatica* Roxb. ex DC., (C) *B. jaeschkeana* C.K.Schneid., (D) *B. lycium* Royle, (E) *B. pseudumbellata* R. Parker, (F) *B. thomsoniana* Schneider.

**FIGURE 2** | Various plant parts of (A) Berberis asiatica collected from Indian Himalayan Region (IHR), includes, (B) roots, (C) stems and (D) stem barks. These parts are the major sources to extract Berberine (yellow color) from Berberis species.
ALKALOIDS FROM BERBERIS SPECIES: POTENTIAL COMPOUNDS AGAINST METABOLIC DISEASES

A large number of studies have been conducted on the isolation and quantification of bioactive compounds from Berberis species. The phytochemical investigations of the genus Berberis have shown the presence of more than 105 compounds with varying structural confirmations. Most of the studies on Berberis species are focused on phytochemical screening; for the presence and estimation of different secondary metabolites, such as alkaloids, flavonoids, steroids, sugars, triterpenoids, tannins, and other preliminary assays such as total ash content, acid soluble ash content, and moisture content (Belwal et al., 2016; Belwal et al., 2017; Andola et al., 2018; Srivastava et al., 2006; Shahid et al., 2009). However, the isolation and characterization of alkaloids from genus Berberis is well documented. Alkaloids are one of the major bioactive chemical constituents of the Berberis species, and they are responsible for various pharmacological activities of either whole extract or isolated individual compounds. Berberine (BBR) is one of the most commonly reported alkaloids from various Berberis species along with palmatine, magnoflorine, and jatrorrhizine, etc. (Figure 3) (Bhardwaj and Kaushik, 2012; Feng et al., 2018). Simple isoquinolone alkaloids are mainly reported from these species; however, studies have also reported their dimmers or dimeric benzylisoquinoline alkaloids (Leet et al., 1983). The detailed list of different alkaloids isolated from various Berberis species are given in Table 1. Among other compounds, BBR and its various natural and synthetic derivatives have also been evaluated and found effective in prevention and treatment of MS (Pérez-Rubio et al., 2013; Li et al., 2015; Zhao et al., 2017).

The effect of different habitat conditions (altitudinal variations and edaphic factors) of Berberis species has been investigated. Chandra and Purohit (1980) investigated eight Berberis species from different altitudinal range for determining the BBR concentration in different parts. Among these, B. asiatica was found to contain higher content of BBR than other species. Lower altitudinal range was found to contain higher BBR content within a species as compared to high altitude habitat. Among plant parts, roots contained a higher concentration of BBR (Chandra and Purohit, 1980). Similarly, variations in the BBR content of five Berberis species (i.e., B. aristata, B. asiatica, B. jaeschkeana, B. lyctum, and B. pseudumbellata) depending upon the habitat have also studied. The presence of higher BBR content was recorded from rocky habitats in B. jaeschkeana (Andola et al., 2018). Both altitude and edaphic conditions were found to be responsible for the variation in BBR content in root and stem bark. Lower altitude populations showed significantly higher BBR content and positively correlated with moisture and potassium availability in soil species. Among these, B. asiatica contain significantly higher BBR content as compared to other species (Andola et al., 2010) Seasonal variations in the BBR content revealed higher percentage in summer and lower in rainy season (Andola et al., 2018). Low moisture and high soil potassium level is reported to be well correlated with high BBR content (Andola et al., 2011).

IN VITRO ACTIVITIES AGAINST DIABETES AND OTHER METABOLIC DISEASES

It has been suggested that physical exercise and a proper diet can act as controllers of the cause of T2DM and metabolic diseases. Currently available pharmacological interventions can control many aspects of diabetes and metabolic diseases, like microvascular and macrovascular complications, hypertension, dyslipidemia, and obesity. However, there is also a need for novel therapeutic agents that work alone or in combination with
TABLE 1 | List of alkaloids isolated from various Berberis species.

| Plant source | Plant parts | Alkaloids | References |
|--------------|-------------|-----------|------------|
| B. acanthifolium | Stem bark | Berberine, tetrahydropalmitate | (Tiwari and Masood, 1977) |
| B. aestrianea | Root | Berberine | (Alamzeb et al., 2015) |
| B. amurenensis | Stem | Berberine, palmatine, berberine | (Wu et al., 2015) |
| B. amurenensis | Young shoot | Berberine, oxyacanthine, pseudopalmitine, amurenine | (Yusupov et al., 1993b) |
| B. aristata | Root and stem bark | Berberine, berbamunine, jatrorrhizine, oxyacanthine, magnoberine | (Bajpai et al., 2015) |
| B. asiatica | Root | Berberine, oxyacanthine, berbamunine, palmatine, jatrorrhizine, oxyberberrine, tetrahydropalmitate, columbamine | (Bhakuri et al., 1968) |
| B. buxifolia | Root | Berberine, oxyacanthine, berbamunine, palmatine, jatrorrhizine, oxyberberrine, tetrahydropalmitate, columbamine | (Sharma et al., 1973; Shamma et al., 1974; Miana et al., 1979; Abu Zarga et al., 1982) |
| B. concinna | Stem bark | Berberine, tetrahydropalmitate | (Tiwari and Masood, 1977) |
| B. crataegina | Stem and root | Berberine, palmatine | (Petcu, 1968) |
| B. darwinii | Seed | Berbaine, oxyacanthine maganosine | (Valencia et al., 1985) |
| B. densiflora | Leaf | Berberine, β-acloxytopine, densinone, densinberine, glaucine, oxyacanthine, thalidimide, isocorydine, O-methylcorydine | (Khamidov et al., 1997c) |
| B. diaphana | Bark | Berberine, palmatine, magnoflorine, jatrorrhizine | (Feng et al., 2018) |
| B. dictyophylla | Bark | Berberine, palmatine, magnoflorine, jatrorrhizine | (Feng et al., 2018) |
| B. glaucomarica | Root | Oxyacanthine, tetrandrine | (Alamzeb et al., 2018) |

(Continued)
TABLE 1 | Continued

| Plant source | Plant parts | Alkaloids | References |
|--------------|-------------|-----------|------------|
| B. vulgaris | Leaves and shoots | Thalicmidine and in the shoots, berberin. Other alkaloids isolated included glucine, hydroxyacanthine, berberamine, isocordine | (Khamidov et al., 2003) |
| B. thunbergii | Aerial part | (-)-Tetrahydropseudocoptisine, pseudoprototone, (+)-chelidone, (+)-glazoinine, berberine, palmatine, columebamine, berberubine, oxyacanthine, berbamine, 8-oxoberberine, 8-oxoberberine, pakistinine, prunucoline, N-acetyltirhowenyveratrylamine | (Karimov et al., 1993f; Istatkova et al., 2007) |
| B. virgatum | Root | Berbamine, berberine chloride, palmatine | (Man and Ikram, 1970) |
| B. sibirica | Aerial part | Thalicmidine, oxyacanthine, isocordynine, thalicdimine, berberine | (Khamidov et al., 1997a) |
| B. tabiensis | Leaf | Oxyacanthine, isotetrandrine, thalicmidine | (Khamidov et al., 1993b; Khamidov et al., 1997a) |
| L.A. Camargo | Fruit | Oxyacanthine, palmatine, thalicmidine, isotetrandrine, berberine, berbamine, glaucine, isocordine, helamine | (Khamidov et al., 1993b) |
| B. thunbergii | Young shoots | Turcomidine, Turcubeine | (Khamov et al., 1993a) |
| L.A. Camargo | Leaf | Turcomidine, Turcubeine | (Khamov et al., 1993a) |
| B. virgatum | Bark | Berberine, palmatine, magnoflorine, jatrorrhizine | (Feng et al., 2018) |
| C.K. Schneid. | Whole plant | (-)-Berbervirine, berberine, jatrorrhizine, noroxyhydrastosine | (Lu et al., 1995) |
| B. vulgaris L. | Root bark | Berberine, palmatine, bersavine, muraricine | (Karimov et al., 1993i) |

Currently available drugs. Within the pharmacological options, phytochemicals have a great potential to act against T2DM, MS, and associated complications (Davi et al., 2010). Extracts of Berberis species and their components, especially alkaloids, have been documented for their potential activity against T2DM and MS in various in vitro studies (Table 2) (Potdar et al., 2012).

Studies in mouse 3T3-L1 cells suggested that BBR has a pivotal role in regulating adipose tissues (Kishimoto et al., 2015). Experiments in mitochondria isolated from the liver of high-fat-fed rats have shown that BBR exhibited protective effects against MS that was associated with the increased mitochondrial sirtuin-3 (SIRT3) activity, normalizing mitochondrial function, and preventing a state of impaired oxidative phosphorylation (OXPHOS) that caused energetic deficit (Teodoro et al., 2013). In the same way, the preventive effects of BBR on diet-induced insulin resistance (InsR) was suggested to be linked to sirtuin-1 (SIRT1) and mitochondrial biogenesis (Gomes et al., 2012). It has been suggested that BBR is a unique natural medicine against insulin resistance in T2DM and MS (Kong et al., 2009). Different investigations have concluded that BBR as a new hypolipidemic drug works by a different mechanism of action to that of statin drugs (Kong et al., 2004). BBR works on multiple molecular targets as an inhibitor of peroxisome proliferator-activated receptor (PPAR) γ and α and is a potential weight reducing, hypolipidemic, and hypoglycemic agent (Huang et al., 2006). Prolonged activation of AMP-activated protein kinase (AMPK) by BBR improved CD36 expression in hepatocytes and was evoked in fatty acid uptake via processes associated with hepatocellular lipid accumulation (Choi et al., 2017). Also, BBR improved insulin sensitivity (InsS) by inhibiting fat storage and adjusting the adipikope profile in human preadipocytes (Yang et al., 2012). The hypoglycemic effects of BBR have also been attributed to its acute activation of the transport activity of glucose transporter 1 (GLUT1) (Cok et al., 2011).

Numerous studies of BBR in in vitro models have shed light on its positive effect on T2DM. BBR promoted glucose uptake and inhibited gluconeogenesis by inhibiting SIRT3, and regulating the mitochondria-related pathways (Zhang et al., 2018). BBR treatment attenuated a palmitate-induced reduction in glucose uptake and consumption through a...
TABLE 2 | In vitro activity of extracts and/or isolated compounds from Berberis species against diabetes and metabolic diseases.

| Extracts from Berberis spp./isolated compounds | Model | Outcomes | References |
|-----------------------------------------------|-------|----------|------------|
| Berberine                                      | Mouse 3T3-L1 cells | Downregulated transcription factors (CCAAT/enhancer binding protein β, CCAAT/enhancer binding protein α) and PPARγ expression, suppress PI3K and inhibit 3T3-L1 fibroblast differentiation to adipocytes | (Kishimoto et al., 2015) |
| Berberine (BBR)                                | Mitochondria isolated from the liver of high-fat-fed rats | Reverted mitochondrial dysfunction induced by HFD and hyperglycemia in skeletal muscle, in part due to an upregulation of SIRT1 activity, normalizing mitochondrial function, and preventing a state of energetic deficit caused by impaired OXPHOS function | (Teodoro et al., 2013) |
| Berberine (BBR)                                | C2C12 cell line | ↑ InsR mRNA and ↑ protein expression in dose- and time-dependent results. InsR expression in the L6 rat skeletal muscle cells. BBR-enhanced InsR expression improved cellular glucose consumption only in the presence of insulin. Silencing InsR gene with small interfering RNA or blocking the p38 MAPK effect. BBR-induced InsR gene expression through a PKC-dependent activation of its promoter. Inhibition of PKC abolished BBR-caused InsR promoter activation and InsR mRNA transcription. | (Kong et al., 2009) |
| Berberine (BBR)                                | 3T3-L1 preadipocytes | Inhibitor of PPARγ and α | (Huang et al., 2006) |
| Berberine (BBR)                                | Human platelet | Inhibited platelet aggregation, superoxide production via modulating AR, NOX, and glutathione reductase activities in HG | (Paul et al., 2019) |

(Continued)
TABLE 2 | Continued

| Exports from Berberis spp./isolated compounds | Model | Outcomes | References |
|---------------------------------------------|-------|----------|------------|
| Berberine (BBR)                             | 3T3-L1 cells | ↑TG accumulation by tPpRS1-Pi3KpAkt, ↓GLUT4 translocation and insulinotropic action by pCREB-pIRS2-pAkt | (Ko et al., 2005) |
| Berberine (BBR)                             | L6 cells | ↑AMPK and tP38 MAPK phosphorylation | (Cheng et al., 2006) |
| Berberine (BBR)                             | 3T3-L1 cells | Regulation of PPARs and positive transcription elongation of factor b expression | (Zhou and Zhou, 2010) |
| Berberine (BBR)                             | HepG2 and C2O12 cells | ↑glucose metabolism by glycolysis stimulation and mitochondrial respiratory chain inhibition | (Xu et al., 2014) |
| Berberine (BBR)                             | HL-7702, normal human liver cell lines | LDLR up-regulation by AMPK-dependent Raf-1 activation | (Li et al., 2014) |

**Combination of berberine and/or derivatives**

| Exports from Berberis spp./isolated compounds | Model | Outcomes | References |
|---------------------------------------------|-------|----------|------------|
| Berberine (BBR) and dihydroberberine 9-O-lipophilic group substituted berberine (9-O-BBR) | L6 and LKB1 cells | AMPK activation, by complex I inhibition of the mitochondrial transport chain | (Turner et al., 2008) |
| 13-Methyberberine (13-Me-BBR) | Mouse 3T3-L1 cells | Downregulated the expression of adipocyte differentiation transcription factors (PPARY and C/EBPa), tPPARY, tC/EBPa, and ↓SREBP-1 protein levels. Effect require AMPK signaling pathway | (Chow et al., 2016) |
| Berberine (BBR) and metformin | HepG2 hepatocytes and C2O12 myotubes | Promotion of glucose metabolism via stimulation of glycosylation, not be related to AMPK activity. | (Xiao et al., 2018) |
| BBR derivatives: thalifendine | Human HepG2 liver cells | ↑LDLR or InsR protein expression. | (Wang et al., 2009) |
| BBR amide derivatives: Mannose modified berberine (m-BBR) | HL-7702 cells | ↑glucose-lowering efficacies | (Ren et al., 2017) |
| Pseudoberberine (pBBR) | HepG2 cells | AMPK activation and LDLR up-regulation. anti-diabetic activity may be mediated through insulin dependent pathway by the activation of IRTK and PI3K | (Wang et al., 2012) |
| Palmitine | Differentiated myocytes, L6 cells | | (Sangeetha et al., 2013) |

**Berberis extracts**

| Exports from Berberis spp./isolated compounds | Model | Outcomes | References |
|---------------------------------------------|-------|----------|------------|
| B. myrophylla roots ethanolic extract | non-resistant | hypoglycemic effects and ↑ glucose uptake by activating AMPK protein. | (Furianca et al., 2017) |
| B. vulgaris roots (ethanolic extract) and berberine (BBR) | α-Glucosidase | ↑α-glucosidase activity, extract > BBR | (Abd El-Wahab et al., 2013) |
| Jinqi Jiangtang tablet (berberine-contain) | α-Glucosidase, lipase and aldose | ↑α-glucosidase, lipase, and aldose reductase activities, | (Chang et al., 2015) |

The ↑ and ↓ signs shows significant increase and significant decrease of evaluated factors during mentioned studies. Reduction in cellular diacylglycerol (DAG) levels and the accumulation of triacylglycerol (TAG) in H9c2 cells (Chang et al., 2016). In addition, BBR displayed beneficial effects in the treatment of diabetes and obesity via stimulation of AMPK activity (Lee et al., 2006). The mechanisms of action of BBR in treatment of T2DM are suggested to be different than that of metformin and rosiglitazone (Zhang et al., 2010). BBR, as an insulin signal activator, had shown insulin-mimicry effects through the inhibition of protein tyrosine phosphatase 1B (PTP1B) activity on both adipocytes and myocytes (Chen et al., 2010) and acted as an effective insulin sensitizing and insulinotropic agent (Ko et al., 2005). Moreover, BBR and metformin promoted glucose metabolism by stimulating glycolysis through the inhibition of mitochondrial respiratory chain complex I and independent of AMPK activation (Xu et al., 2014). Besides, BBR circumvented the insulin signaling pathways and stimulated the glucose uptake through the AMP-AMPK-p38 MAPK pathway (Cheng et al., 2006). BBR modulated metabolism-related PPARs expression and differentiation-related positive transcription elongation factor b (P-TEFb) expression in adipocytes, which are associated with its hypoglycemic and hypolipidemic effects (Zhou and Zhou, 2010). In addition, BBR upregulated LDL receptor expression through Ras-independent (but AMPK-dependent) Raf-1 activation in liver cells (Li et al., 2014). BBR and metformin induced glycolysis and glucose consumption but are not related to the AMPK status (Xiao et al., 2018).

Different natural and synthetic derivatives of berberine are also evaluated for their in vitro activities. A BBR derivative, thalifendine, showed upregulatory activities for both LDLR and InsR, proving to be a potential treatment of both hyperlipidemia and hyperglycemia (Wang et al., 2009). Similarly, BBR amide derivatives improved the glucose-lowering effects (Ren et al., 2017). Mannose-modified BBR derivative exhibited high anti-diabetic activity at both high and low drug concentrations (Han et al., 2019). Palmitine showed anti-diabetic activity...
mediated through an insulin-dependent pathway by the activation of IRTK and PI3K (Sangeetha et al., 2013). Pseudoberberine (pBBR) has exhibited a potential effect on AMPK activation and LDLR upregulation as compared with BBR (Wang et al., 2012).

In the same way, the effects of species of the genus Berberis have been studied in several in vitro models and found effective. For instance, B. mycrophylla root extracts showed hypoglycemic effects and stimulated glucose uptake in HepG2 cells with and without resistance by activating AMPK protein (Furrianca et al., 2017). B. aristata bark methanolic extracts also inhibited the dipeptidyl peptidase-IV (DPP-IV) enzyme activity (Chakrabarti et al., 2011). B. vulgaris roots (ethanolic extract) and BBR showed α-glucosidase inhibition, where the inhibition caused by the extract was found to be higher than that of the BBR alone (Abd El-Wahab et al., 2013), and the extract also showed α-amylase inhibition activity (Boudjelthia et al., 2017).

Some of the mechanisms of Berberis species and BBR against diabetes and metabolic diseases are depicted in Figure 4.

**IN VIVO ACTIVITIES AGAINST DIABETES AND METABOLIC DISEASES**

Extracts of Berberis species and their components, especially alkaloids, have been documented for their potential activity against T2DM and MS in in vivo models (Table 3). In the MS condition, BBR improved vascular inflammation and remodeling that was found to be correlated with the ability to inhibit p38 MAPK activation, ATF-2 phosphorylation, and MMP-2 expression (Li et al., 2015). Long-term treatment with BBR diminished the adipose tissue weight and decreased the renal injury (MS related diseases) in spontaneously hypertensive rats (Kishimoto et al., 2015). In normal diet-fed mice treated with BBR, hepatic CD36 expression and TG levels were increased; however, these effects were prevented when hepatic CD36 was silenced with an adenovirus containing CD36-specific short hairpin RNAs (shRNA) (Choi et al., 2017). BBR also improved the insulin-mediated vasodilatation of mesenteric arteries in diabetic rats through upregulation of insulin receptor-mediated signaling and increasing vascular InsS (Geng et al., 2016). Similarly, BBR increased both InsR and the low-density lipoprotein receptor (LDLR) expression, which resulted in a cellular response against InsR (Kong et al., 2009). In hyperlipidemic hamsters, the cholesterol-lowering effect of BBR was found to be due to its activity on upregulation of hepatic LDLR (Kong et al., 2004). Administration of BBR in hyperlipidemic and InsR rats decreased blood free fatty acid levels and increased the activity of lipoprotein lipase, leading to the amelioration of blood lipid and glucose metabolism (He et al., 2004). BBR administration resulted in the decrease of fasting blood glucose (FBL) level and ameliorated glycogen structural fragility (Li et al., 2019). Furthermore, BBR displayed beneficial effects in the treatment of obesity, and this was in part via improvement of adipose tissue fibrosis (Wang L. et al., 2018). BBR was reported to act in the liver to regulate lipid utilization and to maintain whole-body energy metabolism by mediating autophagy and FGF21 activation (Sun Y. et al., 2018). Additionally, BBR is also reported to reduce the systemic low-grade inflammation of T2DM mice to alleviate disease, and this effect may be achieved through regulating the gut microbes or inhibiting the TLR4 signaling pathway (Cao et al., 2017). Other in vivo investigations also showed the hypoglycemic effects of BBR through the improvement in gut-derived hormones and the attenuation of both intestinal mucosal mechanic and immune.
| Extracts from *Berberis* spp./isolated compounds | Model | Outcomes | References |
|-----------------------------------------------|-------|----------|------------|
| Berberine | STZ-induced diabetic Sprague-Dawley rat | metabolic enzymes activities and preserved the glucose homeostasis | (Chandrasekaran et al., 2018) |
| Berberine | Specific pathogen-free male C57BL/6 mice | prolonged activation of AMPK BBR-induced tCD36 expression and fatty acid uptake | (Choi et al., 2017) |
| Berberine | male Sprague-Dawley diabetic rats | tDVS and tmesenteric vasoconstriction by insulin receptor-mediated signaling upregulation. tsecretion of inflammatory factors and tvascular remodeling. Inhibition of p38 MAPK activation, ATF-2 phosphorylation, and MMP-2 expression. | (Seng et al., 2016) |
| Berberine | male Wistar rats | BWG, tretroperitoneal adipose tissues, tmesenteric adipose tissues, and turinary albumin excretion. | (Li et al., 2015) |
| Berberine | T2DM STZ-induced Wistar rat | tPBGL, tFSIL, tInsS, tInsR-mRNA, and PKC activity in the liver. tsecretion of inflammatory factors, tmesenteric adipose tissue, and turinary albumin excretion. | (Kong et al., 2009) |
| Berberine | hyperlipidemic hamsters | tTC, tLDL-C, thepatic LDLR mRNA, and tliver HO-1 mRNA expression. | (Kong et al., 2004) |
| Berberine | Hyperlipidemic and IR rats | tTC, tTG, tApoB, tLDL-C, tFFA, tHDL-C, tIns, tApoAI, and t1p30 protein lipase activity. | (He et al., 2004) |
| Berberine | T2DM db/db mouse | tFBGL, tameliorated glycogen structural fragility, tBWG, tglucose tolerance, tcollagen deposition and reversed the upregulation of fibrosis related genes in the adipose tissue of HFD. tsecretion with AMPK activation, tJOCR and tATP production induced by high glucose, and tattenuation of glucose-stimulated expression of fatty acid synthase. | (Li et al., 2019) |
| Berberine | HFD Obese rats | tFBGL, tameliorated glycogen structural fragility, tBWG, tglucose tolerance, tcollagen deposition and reversed the upregulation of fibrosis related genes in the adipose tissue of HFD. tsecretion with AMPK activation, tJOCR and tATP production induced by high glucose, and tattenuation of glucose-stimulated expression of fatty acid synthase. | (Wang L, et al., 2018) |
| Berberine | Liver-specific SIRT1 knockout mouse | Regulation of lipid usage and preserved whole-body energy metabolism via autophagy and FGF21 activation. tsecretion with AMPK activation, tJOCR and tATP production induced by high glucose, and tattenuation of glucose-stimulated expression of fatty acid synthase. | (Sun Y, et al., 2018) |
| Berberine | Rat islets | Inhibition of glucose-stimulated insulin secretion with AMPK activation, JOCR and ATP production induced by high glucose, and attenuation of glucose-stimulated expression of fatty acid synthase. | (Bai et al., 2018) |
### TABLE 3 | Continued

| Extracts from *Berberis* spp./isolated compounds | Model | Outcomes | References |
|--------------------------------------------------|-------|----------|------------|
| Berberine (BBR) | db/db mice and high-fat-fed Wistar rats | ↓ GLWG, ↑ glucose tolerance, ↓ ITG, and ↓ insulin action | (Lee et al., 2006) |
| Berberine (BBR) | Diabetic rats | Direct inhibition of liver gluconeogenesis | (Xia et al., 2011) |
| Berberine (BBR) | Diabetic rats | Intestinal microbiome modulation | (Han et al., 2011) |
| Berberine (BBR) | Diabetic rats | Lipid metabolism regulation and ↓ elimination of free radicals | (Tang et al., 2008) |
| Berberine (BBR) | Diabetic rats | PPAR α/δ up-regulation and PPARα repression in liver | (Zhou et al., 2008) |
| Berberine (BBR) | Non-obese Diabetic rats | Regulation of MAPK activity to control the differentiation of Th17 and Th1 | (Cui et al., 2009) |
| Berberine (BBR) | Diabetic rats | Promotes secretion of glucagon-like peptide type 1 | (Lu et al., 2009) |
| Berberine (BBR) | Diabetic rats | Tyrosine phosphatase 1B activity inhibition and insulin-like effect | (Chen et al., 2010) |
| Berberine (BBR) | Diabetic hamster | Up-regulation of LXRα, PPARα, and down-regulation of SREBP1c | (Lu et al., 2010) |
| Berberine (BBR) | Diabetic rats | ↓ intestinal disaccharidases and β-glucuronidases activities | (Li et al., 2017) |
| Berberine (BBR) | Diabetic rats | Glucose metabolism modulation by GnRH-GLP-1 and MAPK pathway in the gut | (Zhang et al., 2014) |
| Berberine chloride (BC) | Diabetic rats | ↓ FBG, ↓ WBC, ↑ HbAc, ↑ plasma insulin, ↑ hemoglobin, ↑ FBG, ↑ HbA1c, ↑ TmCH, ↓ GC, ↓ TmCH, ↓ MCHC | (Chandrasegaran et al., 2017) |
| Berberine chloride (BC) | Diabetic rats | ↓ TC, ↓ TG, ↓ LDL-C, ↑ HDL-C, ↓ VLDL, ↑ HDL-C, ↓ TG, ↑ HDL-C, ↓ IL-1β, ↓ TNF-α, ↑ TGF-β, ↑ Akt and ↓ GLUT-4 | (Chandrasegaran et al., 2019) |
| Berberine fumarate (BF) | T2DM rats | ↑ metabolic disorder and ↓ inflammation by ↓ over-expression of TLR4 and p-JNK and ↓ PI3K and VGLUT2 expression | (Cui et al., 2018) |

### TABLE 3 | Continued

| Extracts from *Berberis* spp./isolated compounds | Model | Outcomes | References |
|--------------------------------------------------|-------|----------|------------|
| Berberine chloride (BC), oryzanol and vitamin B2 | Male Wistar hypobulimic rats | ↑ lipid effect without apparent adverse side effects | (Li et al., 2016) |
| Berberine (BBR), Orchisporin staminensis, policosanol, red yeast rice extract, folic acid and coenzyme Q10 | T2DM obese rats | ↑ maintaining glucose and ↑ lipid homeostasis, ↑ antihyperlipidemic activity | (Jia et al., 2019) |
| Berberine (BBR), and Timosaponin B2 (TB-2) and Glycyrrhizic acid | Goto-Kakizaki rats | ↑ anti-diabetic efficacy. | (Huang et al., 2019) |
| Berberine (BBR) with resveratrol | T2DM rats | ↓ FBG, ↑ insulin level | (Qiao et al., 2018) |
| Berberine (BBR) and Gelucire44/14 | High fat diet-induced mice | ↑ TC, ↓ TG, ↓ LDL-C | (Zhu et al., 2018) |
| Berberine organic acid salts (BOAs), including berberine citrate, berberine fumarate, berberine malate, and berberine succinate | T2DM rats | ↑ hypoglycemic effects | (Li et al., 2017) |
| Berberine (BBR) and Coptis chinensis extract (CCE) | T2DM rats | ↑ pancreatic insulin secretion via ↑ insulin β-cell proliferation and ↑ protein expression of PARP-1. | (Jiang et al., 2017) |
| Berberine (BBR) combined with Canagliflozin | Diabetic mice | ↑ FBG and ↓ insulin. Antidiabetic effect associated with ↑ pAMPK and ↓ TNFα in kidneys. | (Cai-Ming et al., 2016) |
| Berberine (BBR) and Ginsenoside Rb1 (Rb1) | Diabetic mice | Improved abnormal metabolism of glucose and lipid. | (Shang et al., 2015) |
| Berberine glycyrrhizinate complex salt (BGC) | GK rats | ↓ FBG, ↓ insulin level, ↓ GSP, ↓ LDL-C and ↓ MDA, and ↓ histopathological changes in kidney and pancreas. | (Wang et al., 2014) |

(Continued)
TABLE 3 | Continued

| Extracts from Berberis spp./isolated compounds | Model | Outcomes | References |
|-----------------------------------------------|-------|----------|------------|
| B. aristata roots (ethanolic extract)         | Diabetic rats | ↓ dose-dependent in hyperglycemia, ↓TC, ↓TG, ↓AST, and ↓ALT levels of serum, ↓serum creatinine and ↓blood urea. | (Mittal et al., 2012) |
| B. aristata stem (ethanolic extract)          | T1DM and T2DM abino rats | ↑ Liver glycogen and ↓FBG | (Rameshwar et al., 2009) |
| B. aristata roots (ethanolic extract)         | STZ-induced diabetic rats | ↓PBG | (Gupta et al., 2010) |
| B. aristata stem bark (aqueous extract)       | STZ-induced diabetic rats | ↓TC and ↓HDL-C | (Ahamad et al., 2012) |
| B. aristata bark (ethanolic extract)          | allophan-induced diabetic rats | ↓PBG | (Semwal et al., 2008) |
| B. aristata stem bark (methanolic extract)    | Alloxan-induced DiabeticRats | ↓PBG | (Akhtar et al., 2008) |
| B. aristata roots (methanolic-water extract)  | Diabetic rats | Regulated glucose homeostasis via ↑gluconeogenesis and ↓oxidative stress. | (Singh and Kakkar, 2009) |
| B. asiatica roots (water-ethanolic extract)   | Diabetic rats | ↓BW | (Singh and Jain, 2010) |
| B. dicyophylla roots (extract)                | Diabetic mice and normal mice | ↓FBG, ↓JCAM-1, ↓ANGII, and ↓SOD in serum expression | (Yue et al., 2013) |
| B. holsti roots (aqueous extract)             | Alloxan-induced diabetic male mice | ↓FBGL | (Kamani et al., 2017) |
| B. integerrima roots (aqueous extract)        | Diabetic male Wistar rats | ↑renal by control of blood glucose and renal protective effects. | (Ashraf et al., 2013) |
| B. integerrima fruits (anthocyanin fraction)  | Diabetic Male Sprague Dawley rats T2DM mice | ↑GLUT4 translocation, ↑oral glucose tolerance, ↑HDL-C, ↓BW, ↓blood glucose and ↓related blood-lipid contents. | (Yang et al., 2014) |
| B. julianae roots (methanolic extract)        | Diabetic rabbits | ↓FBG. | (Ahmad and Alamgeer, 2009) |
| B. lycium roots (aqueous extract)             | Diabetic rabbits | ↓TG, ↓TC, ↓LDL-C, and ↓HDL-C | (Ahmad et al., 2008) |
| B. lycium extract (BLE)                       | FEMALE diabetic rats | ↓FBG | (Hussain et al., 2017) |
| B. lycium leaves (methanolic extract)         | Alloxan treated rats | ↓FBG | (Gulfraz et al., 2007) |
| B. lycium roots (ethanolic extract)           | Alloxan treated rats | ↓FBG | (Gulfraz et al., 2007) |

(Continued)

TABLE 3 | Continued

| Extracts from Berberis spp./isolated compounds | Model | Outcomes | References |
|-----------------------------------------------|-------|----------|------------|
| B. lycium roots (powder)                      | Broilers | ↓TC and ↓TG. | (Mittal et al., 2012) |
| B. lycium roots (aqueous extract)             | Diabetic rats | ↓FBG, ↓TC, ↓TG, ↓LDL-C, ↓VLDL, ↓TG, ↓SOD, ↓TGOT, ↓SGPT, and ↓ALP | (Mustafa et al., 2011) |
| B. lycium fruits (aqueous extract)            | T1DM Rats | ↑ serum glucose levels, ↑serum alanine aminotransferase activities, ↓HbA1c. | (Karimi, 2016) |
| B. vulgaris roots (hydro-ethanolic extract)   | Diabetic rats | ↓ total antioxidant levels, ↓MDA and ↓FBG, and ↓mRNA level of GK | (Ismat et al., 2016) |
| B. vulgaris fruits (Hydro-ethanolic extract)  | Jatrophrinez Hyperglycemic mice | ↓ liver damage by influencing hepatic histopathological and biochemical markers | (Rahimi-Madiseh et al., 2017) |
| B. vulgaris fruits (hydro-ethanolic extract)  | Jatrophrinahine and berberine | ↓FBG, Berberine > Jatrophrinahine | (Fu et al., 2005) |
| B. vulgaris fruits (hydro-ethanolic extract)  | Palatin Normal rats | ↓FBG. | (Patel and Mishra, 2011) |

The ↑ and ↓ signs show significant increase and significant decrease, respectively, of evaluated factors during mentioned studies.

Berberis extracts

Barrier damages (Gong et al., 2017). In the same way, the gut microbiota modulation was also suggested to be an effective mechanism of the antidiabetic effect of BBR (Han et al., 2011). The lipid-lowering effect of BBR chloride treatment in hyperlipidemic rats was found to be associated with a global change in the metabolism of lipids, carbohydrates, and amino acids as well as the structure of microbiota (Li et al., 2016).

On the other hand, BBR protects against metformin-associated lactic acidosis (MALA) in streptozotocin (STZ)-induced T2DM (Almani et al., 2017). BBR attenuated hyperglycemia and its associated oxidative stress and inflammation through, possibly, the potentiation of the antioxidant defenses and upregulation of PPARγ expression (Mahmoud et al., 2017). BBR decreased 2-hour postprandial plasma glucose (2h-PPG) level in STZ-induced diabetic rats by locally inhibiting intestinal DPP-IV (Wang J. et al., 2016). Moreover, BBR also reduced the blood glucose level in diabetic
blood components (Chandirasegaran et al., 2017) and GnRH-GLP-1 and MAPK pathway in the gut (Zhang et al., 2008). BBR caused the glucose metabolism modulation by the ERK in Th17 differentiation through downregulation of STAT3 associated with its hypoglycemic effect, modulating lipids metabolic effects and its ability to scavenge free radicals (Tang et al., 2010). The inhibitory effect on intestinal disaccharidases and β-glucuronidase of BBR might be one of the mechanisms for BBR as an antihyperglycaemic agent (Li et al., 2008). BBR caused the glucose metabolism modulation by the GnRH-GLP-1 and MAPK pathway in the gut (Zhang et al., 2014). The treatment of BBR chloride notably protected the blood components (Chandirasegaran et al., 2017) and significantly reversed the abnormal levels of lipids, oxidant status, and insulin signaling molecules in the diabetic rat model (Chandirasegaran et al., 2019). BBR also reduced the release of lipopolysaccharides and ameliorated inflammation by reducing the level of lipopolysaccharide binding protein (LBP), thus alleviating intestinal injury and improving InsR (Cui et al., 2019).

The combination of Ortosiphon staminensis, policosanol, red yeast rice extract, BBR, folic acid, and coenzyme Q₁₀ provided an antihypertensive effect, which allowed for an effective control of blood pressure in patients with MS (Rozza et al., 2009). The berberine-metformin hybrid compound BMH473 was found to be beneficial for maintaining glucose and lipid homeostasis in T2DM rats, and it exhibited better antihyperlipidemic effects compared to metformin and BBR alone (Jia et al., 2019).

Combining timosaponin B₂ (TB-2) and BBR in a single formulation enhanced the anti-diabetic efficacy by improving the intestinal absorption (Huang et al., 2019). Glycerolrrhizic acid was also reported to improve the oral absorption of BBR by inhibiting P-gp, and it thus increased the anti-diabetic effects of BBR in db/db mice (Qiao et al., 2018). Lipid-lowering effects of BBR were also reported to be increased with resveratrol, which may be associated with upregulation of a low-density-lipoprotein (LDL) receptor (Zhu et al., 2018). Similarly, gelucire44/14 was found to enhance the oral absorption of BBR and thus improve the antidiabetic efficacy of BBR (Sun J. et al., 2018). Berberine organic acids (BOAs) were found to be comparable to berberine hydrochloride (BH) in terms of hypoglycaemic effects, they were but superior with regard to safety from hyperchloraemia in T2DM rats (Li et al., 2017). Coptis chinensis (containing berberine) and BBR exerted similar effects when used for the treatment of T2DM rats, mainly via the stimulation of the pancreatic secretion of insulin (Jiang et al., 2017). Berberine chloride was a stronger antiadipogenic agent than BBR or canagliflozin alone with fewer side effects on kidneys in the diabetic mice (Cai-Ming et al., 2016). BBR and ginsenoside Rb₁ (Rb₁) improve abnormal metabolism of glucose and lipid (Shang et al., 2015).

Extracts of Berberis plants have shown interesting results in in vivo models. The ethanolic extract of B. aristata showed antidiabetic activity due to its significant dose-dependent reduction effect on the blood glucose levels (Semwal et al., 2008; Mittal et al., 2012), which were also reported to be better than glibenclamide (Rameshwar et al., 2009) and comparable to metformin in diabetic rats (Pareek and Suthar, 2010). In addition, the aqueous extract of B. aristata showed significant antidiabetic activity, decreased total cholesterol, increased HDL-C levels, and prevented the body weight loss in diabetic rats (Ahamed et al., 2012).

The aqueous extract of B. lycium roots showed an antihyperlipidemic effect (Ahmed et al., 2008). B. lycium leaf extracts alleviated lipid profile levels and might be used efficiently in hyperglycemic and diabetic patients (Hussain et al., 2017). Also, the root extract of B. lycium reduced the serum glucose levels in normal and diabetic rats (Gulfraz et al., 2007). In chicken Broilers, the powder of B. lycium reduced the serum cholesterol (Chand et al., 2007). The oral administration of extracts of B. lycium showed hypoglycemic activity (Mustafa et al., 2011) and alleviated lipid profile levels (Rahimi Madiseh et al., 2014). Similarly, the methanolic extract of the B. lycium root and its main alkaloid BBR showed hypoglycemic activity (Gulfraz et al., 2008) and showed antiglycation activity (Khan et al., 2014).

On the other hand, in diabetic rats, the beneficial effects of B. vulgaris extracts showed positive effects in attenuating the side effects of T2DM (Karami et al., 2016), ameliorating oxidative stress (Hemmati et al., 2016), decreasing the liver damage by influencing hepatic histopathological and biochemical markers (Rahimi-Madiseh et al., 2017), and showed that the serum cholesterol and serum triglycerides levels were decreased (Meliani et al., 2011). Other species of Berberis have also been studied. For instance, B. asiatica hydro-ethanolic root extracts have shown to be a potent orally effective antidiabetic extract (Singh and Jain, 2010). Likewise, the B. dictyophylla cortex could significantly reduce the level of fasting blood glucose, ICAM-1, and ANG II expression (Yue et al., 2013). The B. holstii extract showed the reduction of blood glucose levels (Kimani et al., 2017). Furthermore, the aqueous extract of B. integrerrima roots improved renal dysfunction in STZ-induced diabetic rats through controlling blood glucose, and it also showed renal protective effects (Ashraf et al., 2017).
et al., 2013). The anthocyanin fraction of the fruits of B. integrerrima also showed hypoglycemic effects (Sabahi et al., 2016). Moreover, the methanolic extract of B. julianae roots was also reported to possess promising beneficial effects for the treatment of T2DM with the possible mechanism via stimulating AMPK activity (Yang et al., 2014).

Other alkaloids isolated from Berberis species have also shown promising activities against T2DM and MS. For example, berbamine increased the activity of metabolic enzymes and preserved the glucose homeostasis in HFD/STZ induced diabetic rats (Chandrasekaran et al., 2018). Jatrorihizine (JAT) induced an important decrease in FBG in normal and hyperglycemic mice, attributed to improve in aerobic glycolysis (Yan et al., 2005). JAT, BBR, and a combination of BBR and JAT decreased the FBG of diabetic and normal mice at different degrees. JAT also possessed the function of decreasing FBG, which was found less than that of BBR at the same dose level (Fu et al., 2005). Palmatine was also found to decrease FBG and suppressed the increase of blood glucose level in normal rats (Patel and Mishra, 2011).

STUDIES IN HUMANS

Several pilot studies as well as pre-clinical studies and clinical trials have evaluated the beneficial effects of Berberis extracts and isolated compounds on diabetes, metabolic syndrome, and other metabolic diseases (Table 4).

The administration of BBR in patients with MS was found to be effective in regulating the blood glucose and blood lipid levels, improving the InsR, and reducing the level of inflammatory responses in the body (Cao and Su, 2019). BBR also decreased the waist circumference, systolic blood pressure (SBP), triglycerides, and total insulin secretion along with an increase in InsS (Pérez-Rubio et al., 2013). BBR was suggested as a promising new hypolipidemic drug that acts through signaling pathways distinct from those of statins in the treatment of hyperlipidemia patients alone or in combination with other drugs for mild mixed hyperlipidemia patients (Kong et al., 2004). Besides, BBR has been shown to have a good potential as a drug to control lipid metabolism alone or in combination with other drugs for hyperlipidemic hepatitis or liver cirrhosis patients (Zhao et al., 2018). Moreover, BBR improved the InsS by limiting fat storage and adjusting adipokine profile in human preadipocytes and MS patients (Yang et al., 2012), and attenuated some of the metabolic and hormonal derangements in women with polycystic ovary syndrome (PCOS) (Wei et al., 2012). The administration of BBR was found to be effective in the regulation of blood glucose and blood lipid in T2DM patients (Ming et al., 2018) and in improving diabetic kidney disease by reducing UACR and serum Cys C (Li et al., 2018). On the other hand, BBR had also shown glucose-lowering activity with a mechanism different from metformin and rosiglitazone (Zhang et al., 2010). In pilot study, BBR demonstrated a potent oral hypoglycemic activity with positive effects on lipid metabolism (Yin et al., 2008). Also, the benefits of BBR in lowering blood glucose, lipids, body

| TABLE 4 | Studies in diabetic and/or metabolic syndrome patients using treatment with extract and/or isolated compounds of Berberis species. |
|---------------------------------------|-------------------------------------------------|-----------------------------------------------------------------|---------------------------------------|
| **Berberis spp./isolated compound** | **Study design/Model** | **Results** | **References** |
|---------------------------------------|-------------------------------------------------|-----------------------------------------------------------------|---------------------------------------|
| Berberine (BBR, 0.05g, 4 tablets/time, 3 times/day) | MS patients (n=80) RCT, 1 month | ↓FBG, ↓TBG, ↓InsR, ↓TG, ↓TC, ↓hs-CRP, and ↓IL-6 and ↓TNF-α | (Cao and Su, 2019) |
| Berberine (BBR, 0.5 g, 2 times/day) | T2DM patients (n = 300), double-blind, RCT, 16 weeks | ↓FPG | (Ming et al., 2018) |
| Berberine (BBR, 0.5 g, 3 times/day) | MS patients (n=24) double-blind, placebo-controlled, RCT, 3 months | ↓WC, ↓SBP, ↑TG, ↓AUC of glucose, ↑AUC of insulin, ↑insulinogenic index, and ↑Matsuda index | (Pérez-Rubio et al., 2013) |
| Berberine (BBR, 0.4 g, 3 times/day) | T2DM patients (n=114), RCT, 6 months | ↓WB, ↓AUC of insulin, ↑hs-CRP, ↑ESR, and ↑εGFR | (Li et al., 2018) |
| Berberine (BBR, 0.5 g, 2 times/day) | Mild mixed hyperlipidemia (n=32), double-blind, RCT, 12 weeks | ↓WC, ↓BMI, ↑leptin levels, ↑leptin/ adiponectin ratio, ↑HOMA-IR, and ↑HOMA-IR, ↑TG, ↑TC, ↑LDL-C, ↑hs-CRP, ↑hs-CRP, and ↑TSH | (Yin et al., 2008) |
| Berberine (BBR, 1 g, 1 time/day) | T2DM and mixed hyperlipidemia patients (n=116), double-blind, RCT, 3 months | ↓FBG, ↑HbA1c, ↑TG, ↑TC, ↓LDL-C, and ↓GDR | (Zhao et al., 2008) |
| Berberine (BBR, 0.5 g, 3 times/day) | Newly diagnosed T2DM patients (n=36) double-blind, RCT, 3 months | ↓FBG, ↓TP, ↓IR, and ↓LDL-C | (Zhang et al., 2008) |
| Berberine (BBR, 0.5 g, 2 times/day) | Hyperlipidemic patients (n =86), Open study, 3 months | ↓WC, ↓BMI, ↑leptin levels, ↑leptin/ adiponectin ratio, ↑HOMA-IR, and ↑HOMA-IR, ↑TG, ↑TC, ↑LDL-C, ↑hs-CRP, ↑hs-CRP, and ↑TSH | (Yin et al., 2012) |
| Berberine (BBR, 0.3g, 3 times/day) | MS patients (n=41) Double-blind, RCT, 3 months | ↓WC, ↓BMI, ↑leptin levels, ↑leptin/ adiponectin ratio, ↑HOMA-IR, and ↑HOMA-IR, ↑TG, ↑TC, ↑LDL-C, ↑hs-CRP, ↑hs-CRP, and ↑TSH | (Yin et al., 2012) |
| Berberine (BBR, 0.5 g, 3 times/day) | PCOS and IR patients (n=89) randomized, single center, placebo-controlled, 3 months | ↓FBG, ↓HbA1c, ↓TG, and ↓insulin levels | (Wei et al., 2012) |
| Berberine (BBR, 1.0 g, 1 time/day) | T2DM and dyslipidemic patients (n = 116) double-blind, placebo-controlled and multiple-center trial consisting of a screening visit, RCT, 2-week | ↓FBG, ↓HbA1c, ↓TG, and ↓insulin levels | (Zhang et al., 2010) |
| Berberine (BBR, 1.0 g, 1 time/day) | T2DM patients with fasting blood glucose (n = 96), 2 months | ↓FBG, ↓HbA1c, ↓TG, and ↓insulin levels | (Rashidi et al., 2018) |
| Berberine (BBR, 0.5 g, 2 times/day) | T2DM patients (n=228) double-blind | ↓FBG, ↓HbA1c, ↓TG, and ↓insulin levels | (Rashidi et al., 2018) |

(Continued)
TABLE 4 | Continued

| Berberis spp./isolated compound | Study design/Model | Results | References |
|-------------------------------|-------------------|---------|------------|
| Berberine (BBR, 0.5 g, 2 times/day) | randomized controlled, placebo, 4 weeks | aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (D'Addato et al., 2011) | |
| Berberine (BBR, 0.3 g, 3 times/day) | T2DM patients (n=30), open labelled, observational and single centre study, 12 weeks | Decreased C-reactive protein (CRP) (Cicero et al., 2014) | |
| Berberine (BBR, N.I., 2 times/day) | T2DM patients (n=41), open-label interventional RCT, 3 months | Reduced fasting glucose (FPG) and glycated haemoglobin (HbA1c) (Ferraretto et al., 2016) | |
| Berberine (BBR, 0.3 g, 3 times/day) | Mild hyperlipemic patients (n=97) Double-blind, RCT, 3 months | Increased high-density lipoprotein cholesterol (HDL-C) (Gonnelli et al., 2015) | |
| Berberine (BBR, 0.4 g, 1 time/day) | Hypercholesterolemia in tolerance to more than one statin (n=91), 3 months | Moderate dyslipidemic and MS patients (n=66), single-blind, placebo-controlled, RCT, 3 weeks | |
| Berberine combined with others compounds and extracts | hypercholesterolemic patients (n=63), double-blind, RCT, 2 months | LDL-C and TG (Kong et al., 2008) | |
| Berberine (BBR, 1.0 g, 1 time/day) and simvastatin (SIMVA) | Hypercholesterolemic patients (n=63), double-blind, RCT, 2 months | TC, LDLC, and TG (Kong et al., 2008) | |
| Berberine (BBR, 0.5 g; red yeast, 200 mg; and policosanol, 10 mg; 1 time/day) | Hypercholesterolemic patients (n=50), double-blind, single-centered, placebo-controlled, RCT, 6 weeks | TC, LDLC, TG, and FMD, and InsS (Affuso et al., 2010) | |
| Berberine (BBR, 0.5 g; policosanol, 10 mg; and red yeast rice, 200 mg; 1 time/day) | Hypercholesterolemic patients (n=135) randomized, double-blind, EZE-controlled, 6 months | LDL-C, and TG (Pisciotta et al., 2012) | |
| Armolipid Plus™ composed by (Berberine, BBR, 0.5 g; red yeast rice, 200 mg; policosanol, 10 mg; folic acid, 0.2 mg; coenzyme Q10, 2.0 mg; and astaxanthin, 0.5 mg; 1 time/day) | Hypercholesterolemic patients (n=102), double-blind, parallel controlled, Multiple centered, placebo-controlled, RCT, 12 weeks | LDL-C, and HbA1c (Sola et al., 2014) | |
| Armolipid Plus™ composed by (Berberine, BBR, 0.50g; red yeast rice, 200 mg; policosanol, 10 mg; folic acid, 0.2 mg; coenzyme Q10, 2.0 mg; and astaxanthin, 0.5 mg; 1 time/day) | Hypercholesterolemic patients (n=158) | TC and LDL-C (D’Addato et al., 2017) | |

(Continued)
TABLE 4 | Continued

| Berberis spp./iso-lated compound | Study design/Model | Results | References |
|---------------------------------|------------------|---------|------------|
| Berberine combined with others compounds and extracts | | | |
| 0.5 g; red yeast rice, 10 mg; coenzyme Q10, 2 mg; and hydroxytyrosol, 5 mg; 1 time/day) Berberine (BBR, 0.2g; monacolin K, 3 mg; chitosan, 10 mg; and coenzyme Q10, 10 mg; 1 time/day) | Double-blind, RCT, 4 weeks |  | |
| Estomineral lipid™ composed by (Berberine, BBR, 0.5 g; soy isolavones, 60 mg; Lactobacillus sporogenes, 1x10^6 spores; calcium phosphate dehydrate, 137 mg; vitamin D3, 5 μg; and folic acid, 0.2 mg; 1 time/day) Berberine (BBR, 1.0 g; phytoestrogens, 4 g; antioxidants, 2 capsules; probiotics, 12 billion colony forming units; fish oil, 2g; and soy, pea, and whey proteins, 40 g, 2-3 times/day) Berberine sulfate trihydrate (0.1 g, equiv. 69 mg berberine, BBR); Hop rho iso-alpha acids, 200 mg; vitamin D3, 500 IU; and vitamin K, 500 μg; 2 times/day) Berberine (BBR, 0.5 g, 3 times/day) and methylglyoxal (0.5 g x3 times/day) | CMS patients (n=44) open-label, 2-arm, RCT, 13 weeks | ↑body mass, ↑fat mass, ↑TC, ↑LDL-C, ↑HDL-C, ↑apoB, ↑HOMA-index, ↓HOMA-IR, ↓TC, ↓TG, ↓HDL-C, ↓LDL-C, and ↓cholesterol | |
| Berberine (BBR, 0.5 g; orthosiphon, 300 mg; red yeast rice, 80 mg; monacolin, 3 mg; policosanol, 10 mg; folic acid, 0.2 mg; and coenzyme Q10, 15mg; 1 time/day) | T2DM patient (n=200), case-control study, 3 months | ↑HOMA-IR, and ↑MGO | |
| | | | |

TABLE 4 | Continued

| Berberis spp./iso-lated compound | Study design/Model | Results | References |
|---------------------------------|------------------|---------|------------|
| Berberine extracts | | | |
| B. aristata stem powder (1.5 and 3 g in two divided doses daily) Berberol® compose by B. aristata (Berberine, BBR, 1.0 g) and S. marianum (silymarin, 210 mg) and only B. aristata extract (Berberine, BBR, 1.0 g) 2 time/day Berberol® compose by B. aristata (Berberine, BBR, 1.0 g) and S. marianum (silymarin, 210 mg) and vitamin K1, 500 μg; 1 time/day) | T2DM with dyslipidemic patients (n=90) open parallel, RCT, 9 months | ↓HbA1c, ↓TC, ↓TG, and ↓LDL | |
| | T2DM patients (n=69), single-blind, RCT, 120 days | ↓IFG, ↓HbA1c, ↓TC, ↓TG, ↓LDL (only Berberol®), ↓AST, and ↓ALT | |
| | T1DM patients (n=85) double-blind, randomized, placebo-controlled, 6 months | ↓TC, ↓HbA1c, ↓TG, ↓HDL-C, and ↓LDL-C | |
| | Dyslipidemic patients (n=105), Double-blind, RCT, 3 months | ↓TC, ↓LDL-C, ↓TC, ↓HDL-C, ↓apoB, and ↓HOMA-IR | |
| | T2DM and MS patients (n=50) double-blind, placebo-controlled, 6 months | ↓BMI, ↓HOMA-R, ↓TC, ↓HC, ↓HbA1c, and ↓T% | |
| | T2DM and MS patients (n=138), placebo RCT, 52 weeks | ↓TC, ↓HDL-C, ↓TG, ↓LDL-C, ↓HOMA-R, ↓WC, ↓T%, ↓VF%, ↓UA, ↓HbA1c, ↓SBP, and ↓DBP | |
| | T2DM patients (n = 26), 6 months | ↓TC, ↓HDL-C, ↓TG, ↓FFA, ↓WC, ↓HOMA-R, ↓ALT, and ↓AST | |
| | Dyslipidemic patients (n = 175), double blind, placebo-controlled, RCT, 6 months | ↓FPG, ↓IFG, ↓HOMA, and ↓dose of statin | |
| | Euglycemic, dyslipidemic subjects (n=137) double-blind,  | ↓FPG, ↓IFG, and ↓HOMA-index | |
| | | | |

(Continued)
TABLE 4 | Continued

| Berberis spp./isolated compound | Study design/Model | Results | References |
|--------------------------------|--------------------|---------|------------|
| **Berberis extracts**          |                    |         |            |
| marianum (silymarin, 210 mg)   | RCT, placebo-      | ↓TC, ↓LDL-C, | (Di Pierro et al., 2015) |
| 2 times/day                    | controlled, 6-months | ↓HDL-C (only Berberol ®), ↓FFP, and ↓HbA1c. | |
| Berberol ® K                  | T2DM and           | ↓TC, ↓LDL-C, | (Di Pierro et al., 2015) |
| compose by B. arista (Berberine, | hypercholesterolemic | ↓HDL-C, and ↓TG, and ↓CPK. | |
| BBR, 1.0 g) and S. marianum    | patients (n=45), 6- |          |            |
| (silymarin, 210 mg), Berberol    | months             |         |            |
| + statin, and Berberol ® +      |                    |         |            |
| + ezetimibe; 2 times/day        |                    |         |            |
| Berberol ® K                   | Dyslipidemic       | ↓TC, ↓LDL-C, | (Di Pierro et al., 2018) |
| compose by B. arista (Berberine, | patients (n=226),  | ↓HDL-C, and ↓TG, and ↓CPK. | |
| BBR, 1.0 g) and S. marianum    | non-blind non-     |          |            |
| (silymarin, 210 mg) and         | randomized, 6 months |         |            |
| Monakopure™. K20, 50 mg; 1     |                    |         |            |
| time/day                        |                    |         |            |
| Berberol ® K                   | Diabetic and       | ↓HbA1c, ↓TC, | (Di Pierro et al., 2017) |
| compose by B. arista (Berberine, | dyslipidemic       | ↓LDL-C, and ↓TG | |
| BBR, 1.0 g) and S. marianum    | patients (n = 59), 6 |          |            |
| (silymarin, 210 mg), and        | months             |         |            |
| Monakopure™. K20, 50 mg; 1 time/day |                |         |            |
| B. arista (83.3 mg), Cyperus    | T2DM patients (n=93) | ↓PBG, ↓FBG, | (Awasthi et al., 2015) |
| rotundus (83.3 mg), Cedrus       | Plot RCT, 24 weeks | ↓TC, and ↓HbA1c. | |
| deodara (83.3 mg), Emblica       |                     |         |            |
| officinalis (83.3 mg),           |                     |         |            |
| Terminalia chebula (83.3 mg)    |                     |         |            |
| and T. bellirica (83.3 mg)      |                     |         |            |
| 1-6 time/day                    |                     |         |            |
| B. vulgaris fruit (aqueous      | T2DM patients (n=31) | ↓TG, ↓TC, | (Shidfar et al., 2012) |
| extract, 3 g/day)               | Double-blind, RCT, 3 | ↓LDL-C, ↓apoB, | |
| months                          |                     | ↓glucose, ↓insulin, and ↓TAC. | |

The ↑ and ↓ signs show significant increase and significant decrease, respectively, of evaluated factors during mentioned studies. N.I., not informed.

weight, and blood pressure have been confirmed in T2DM and MS patients (Zhang et al., 2008). BBR played an important role in the treatment T2DM through downregulating the higher levels of free fatty acids (Gu et al., 2010). In another study, BBR reduced the fasting plasma glucose, post-meal blood glucose, and fructosamine; however, no signification changes were found in lipid profiles, fasting insulin, HOMA-IR, and HOMA-β% in T2DM patients (Rashidi et al., 2018).

In addition, BBR improved the glycemic parameters comparable to metformin in T2DM patients (Dange et al., 2016). BBR significantly ameliorated T2DM via modulation of *Bifidobacterium* species, TNF-α, and LPS (Chen et al., 2016). BBR improved the blood lipid level in mild hyperlipidemia patients (Wang L, et al., 2016). Likewise, it reduced the plasma LDL-C and TG in mixed hyperlipidaemic subjects (Cicero and Ertek, 2008).

The combination of BBR and simvastatin (SIMVA) in hypercholesterolemic patients significantly improved LDL-receptor upregulation and LDL-cholesterol downregulation compared to monotherapies, and the combined effect also reduce the statins dosage (Kong et al., 2008). The administration of BBR along with red yeast and policosanol on a daily basis was found to be effective in reducing cholesterol levels and was associated with the enhancement of endothelial function and InsS (Affuso et al., 2010). The administration of this supplementation in patients with familial hypercholesterolemia heterozygotes on stable treatment with LDL-C-lowering validated that the supplement reduced the LDL-C superior to that obtained by doubling the dose of statins (Pisciotto et al., 2012).

Also, the dietary supplement Armolipid Plus™ composed of BBR, red yeast rice, policosanol, folic acid, coenzyme Q10, and
astaxanthin showed significant reduction of cholesterolemia and positive plasma LDL-C levels in elderly (statin-intolerant) hypercholesterolemic patients (Marazzi et al., 2011). Moreover, it reduced LDL-C levels as well as total cholesterol/HDLc and ApoB/ApoA1 ratios, and it increased the Apo A1; tjos demonstrated the improvements in CVD risk indicators in patients with hypercholesterolemia (Sola et al., 2014) and amelioration of blood lipids and significant reduction of global CVD risk in dyslipidemic patients (Trimarco et al., 2011). In patients with low- to moderate-risk hypercholesterolemia, Armolipid Plus™ in association with a hypolipidic diet significantly reduced the total cholesterol and LDL-C levels (Gonnelli et al., 2015). In addition, Armolipid Plus™ improved the lipid profile similar to a low dose of a standard statin and also increased the HDL-C levels and improved the leptin-to-adiponectin ratio in patients with moderate dyslipidemia and MS (Ruscia et al., 2014). Armolipid Plus™ alone or in combination with ezetimibe enhanced the lipid profile in statin-intolerant patients with coronary heart disease (Marazzi et al., 2015). BBR and Armolipid Plus™ could be a useful alternative to correct dyslipidemias and to reduce CVD risk in subjects with moderate mixed dyslipidemias (Cicero et al., 2007).

Other food supplements containing BBR, including Body Lipid™, were suggested as an alternative to pharmaceutical treatment for patients with mild-to-moderate hypercholesterolemia (D’Addato et al., 2017). A new nutraceutical formulation containing BBR, monacolin K, chitosan, and coenzyme Q10 has proven effective in reducing non-HDL/LDL-C levels, representing an emergent therapeutic strategy in dyslipidemic patients (Spigoni et al., 2017). On the other hand, the combination of BBR and isoflavones was found to be effective in lowering CVD risk factors in menopausal women with moderate dyslipidaemia (Cianci et al., 2012).

Treatment with BBR and rho iso-alpha acids, vitamin D3, and vitamin K1 produced a more favorable bone biomarker profile, indicative of healthy bone metabolism in postmenopausal women with MS (Lamb et al., 2011). In a case–control study, BBR is more effective in decreasing the serum MGO levels and InsR through increasing the glycemic control in newly diagnosed T2DM patients (Memon et al., 2018). The intake of the natural formulation (containing BBR, orthosiphon, red yeast rice equivalent to monacolin, policosanol, folic acid, and coenzyme Q10) has evidenced the effective control of plasma lipids and keeps borderline high blood pressure within normal values compared with diet alone (Manzato and Benvenuti, 2014).

Stem powder of B. aristata was found to be effective in improving glycemic control and lipid profiles with no major adverse effects on T2DM patients (Sharma et al., 2017). The effect of B. vulgaris extract on T2DM and MS patients has been widely studied in humans. The intake of 3 g/d of B. vulgaris fruits aqueous extract for 3 months may have beneficial effects on lipoproteins, apoproteins, glycemic control, and TAC in T2DM patients (Shidfar et al., 2012). B. vulgaris juice reduced oxidative burden in patients with MS (Mohammadi et al., 2014). Other study showed the beneficial effects of processed B. vulgaris on certain atherosclerosis risk factors in T2DM patients (Ebrahimi-Mamaghani et al., 2009). B. vulgaris fruit extract showed beneficial metabolic effects in T2DM patients, improving the glucose catabolism via the glycolysis pathway, stimulating the insulin secretion or improving the insulin function, and later decreasing the glucose uptake (Moaeez and Quej, 2014). Another study demonstrated that the B. vulgaris juice evoked regulatory roles on HOMA-IR and improved HOMA-B with the metabolic controlling insulin-related indices in benign breast disease (Asemian et al., 2018). Also, B. vulgaris supplementation in patients with MS significantly diminished anti-HSPs 27 and 60 and hs-CRP levels and improved lipid profiles (Zilae et al., 2014). It is reported that the Hsp60 protein is able to induce the production of anti-Hsp60 antibodies, which leads to the destruction of β-islet cells. In the same way, Hsp60 acts as a proinflammatory signaling molecule, which plays a role in the non-resolved vascular inflammation, and this is recognized as one of the characteristic of T2DM (Juwono and Martinus, 2016). Others natural formulations containing Berberis have also been tested in humans. A clinical trial demonstrated that daily intake of polyherbal capsule by B. aristata and Cyperus rotundus, Cedrus deodara, Emblica officinalis, Terminalia chebula, and T. bellirica decreased the glucose level, enhanced lipid homeostasis, and maintained other serum biochemical levels to the normal in patients with T2DM (Awasthi et al., 2015).

The nutraceutical product Berberol®, containing a B. aristata extract (titrated in 85% BBR) plus a Silybum marianum extract (titrated in 60% silymarin), has been evaluated for its antidiabetic potential in humans. Berberol® was demonstrated to be more effective than BBR alone (administered at the same dose), reducing Hba1c in T2DM patients (Di Pierro et al., 2013). The incorporation of Berberol® into insulin therapy in patients with T1DM has the effect of a diminution of the insulin dose necessary for adequate glycemic control (Derosa et al., 2016). In dyslipidemic patients, Berberol® has proven to be safe and effective in improving lipid profile, InsR, and adipocytokines levels (Derosa et al., 2013). Berberol® also improved the cholesterol-lowering properties of statins and showed the positive effects on liver enzymes and glycemic control in patients with T2DM (Guarino et al., 2015). In addition, Berberol® significantly lowered abdominal adiposity and decreased the circulating uric acid level in overweight/obese patients with T2DM (Guarino et al., 2017). Berberol® was suggested as a good candidate for an adjunctive treatment option in diabetes, especially in patients with suboptimal glycemic control (Di Pierro et al., 2012). Berberol® administered as a single or add-on therapy in statin-intolerant subjects is an effective treatment to improve the lipidic and glycemic profiles in T2DM and hypercholesterolemia patients (Di Pierro et al., 2015). The combination of Berberol® and a reduced dosage of statin is found effective for the treatment of hyperlipidemia in patients intolerant to statins at high dosage (Derosa et al., 2015a) and in dyslipidemic euglycemic patients (Derosa et al., 2015b).

Berberol K®, was found to be a potentially good alternative in primary intervention in low cardiovascular-risk subjects with dyslipidemia, as an add-on therapy in mildly statin-intolerant patients, and as an alternative for dyslipidemic patients with a negative perception of statins (Di Pierro et al., 2017). Berberol K® reduced lipid profile effectively and improved the inflammatory...
parameters under a safe dose (Derosa et al., 2017). It was also found to be effective in diabetic subjects with dyslipidemia statin intolerant or with diarrhea caused by IBS or metformin (Di Pierro et al., 2018).

Few studies have also reported the effectiveness of BBR in non-alcoholic fatty liver disease (NAFLD). NAFLD is a result of abnormal fat accumulation in the liver due to the reasons other than alcohol, and it is considered to be a hepatic manifestation of MS. NAFLD results in the overproduction of sugars and triglycerides and plays a central role in the development of InsR and various other glucose- and lipid metabolism-related diseases (Yki-Järvinen, 2014). Recently, Yan et al. (2015) conducted a randomized, parallel controlled, open-label clinical trial in 188 NAFLD patients. Patients received lifestyle intervention (LSI) or LSI and 15 mg of pioglitazone qd or LSI and of BBR for 16 weeks. Parameters, including hepatic fat content, serum glucose level, serum lipid profiles, liver enzymes, and serum and urine BBR concentrations, were measured before and after treatment. LSI and BBR showed a reduction in hepatic fat content as compared to LSI and were better than pioglitazone in reducing body weight and resulted in better lipid profiles (Yan et al., 2015). Furthermore, a mechanism-based study revealed that BBR reduced hepatic TG accumulation and decreased the expressions of hepatic stearyl-coenzyme A desaturase 1 (SCD1) and other TG synthesis-related genes (Zhu et al., 2019). Berberine administration was also reported to recruit and activate BAT in both humans and mice (Wu et al., 2019).

CONCLUSION

Although there are many effective therapeutic drugs for the treatment of metabolic diseases, the current treatment did not control the rapid increasing trend in diabetes mortality and morbidity. Various therapeutic agents from both natural and synthetic sources are being investigated in patients with clinical signs of diabetic and other metabolic diseases. Formulations prepared from the various plant parts of Berberis species were found to be used traditionally in the treatment of diabetes and other metabolic diseases and related complications. A review of the scientific literature revealed that the extracts, isolated alkaloids from Berberis species including BBR and their derivatives, have shown promising effects in the studies related to diabetes and other metabolic diseases. The relatively low cost of BBR or supplements or extracts containing BBR, compared to other synthetic medications, will be of an advantage to the patients living in developing countries with poor socioeconomic circumstances. However, currently available scientific evidence is still not fully sufficient to prove their efficacy clinically. Further randomized double-blind clinical trials with a large number of patients and standardized clinical assessments are required to prove the effectiveness of the Berberis extracts and isolated compounds on metabolic diseases alone or in combinations. Novel pharmacological assessment techniques and analytical techniques will further provide additional opportunities for these agents. Moreover, the development of novel formulations of berberine could be an effective strategy for increasing its effectiveness against diabetes and other metabolic diseases.

AUTHOR CONTRIBUTIONS

TB, IB and JE conceptualized the manuscript. TB, AB, HD, HU, HK, IB and JE wrote the initial manuscript. TB, HD, HU, AP, IB and JE revised the manuscript. All authors agreed on the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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