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Review

The effect of Berberine on weight loss in order to prevent obesity: A systematic review

Zahra Ilyas[a], Simone Perna[a], Salwa Al-thawadi[a], Tariq A. Alalwan[a], Antonella Riva[b], Giovanna Petrangolini[b], Clara Gasparri[c,*], Vittoria Infantino[d], Gabriella Peroni[c], Mariangela Rondanelli[d,e]

[a] University of Bahrain, Department of Biology, College of Science, Sakhir Campus P. O. Box 32038, Bahrain
[b] Research and Development Unit, Indena, Milan, 20139, Italy
[c] Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona "Istituto Santa Margherita", University of Pavia, Pavia, 27100, Italy
[d] Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, 27100, Italy
[e] IRCCS Mondino Foundation, Pavia, 27100, Italy

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ABSTRACT

This study provides a critical overview of experimental studies in vitro, in humans, and in animals that evaluated the efficacy of Berberine and its effect on management of obesity and the related metabolic consequences. As a result of this review, we summarized the effects of Berberine in different models and the related mechanism of actions. In preclinical models, Berberine demonstrates that it affects gut microbiota by reducing diversity of microbes starting at a dosage of 100 mg/kg/day. Moreover, in animal models, Berberine explicates an action on glucose through the inhibition of α-glycosidase at a dose of 200 mh/kg/day. Berberine is also known to be effective against differentiation of adipocytes through a decrease in LXRs, PPARs, and SREBPs expression at 150 mg/kg/day. Other mechanism ascribed to Berberine are related to its inhibition of hepatic gluconeogenesis through the Phospheoenolpyruvate carboxykinase (PEPCK), Glucose-6-phosphate (G6Pase) and AMP-activated protein kinase (AMPK). Furthermore, Berberine (associated to Red Yeast Rice) is effective in decreasing lipid levels in rats, which consequently lowers the change of weight gain at dosage of 40 mg/kg to 380 mg/kg/day. All the above preclinical data are confirmed in human studies where Berberine can modulate the diversity of gut microbes at the dose of 500 mg/day. In addition, Berberine is found to have a beneficial impact on gene regulation for the absorption of cholesterol at a daily dose of 300 mg in humans, an amelioration on glucose accumulation at 1.0 g daily dose was also observed. For all these reasons, this review gives an important good account of the impact of Berberine in obesity treatment and prevention.

1. Introduction

Obesity is a chronic disease characterized by abnormal fat accumulation that may affect health adversely. The prevalence of obesity is rapidly accelerating [1]. The increase in prevalence of overweight and obese population has been of great concern globally, which has cost an estimate of 3.4 million deaths [2]. At least 4% of Years of Life Lost (YLL) and Disability- Adjusted Life Years (DALYs) are affected by obesity around the world [3]. The causes of obesity are multifactorial including genetic, hormonal and environmental. The increased risk of several comorbidities including Type 2 diabetes mellitus, cardiovascular disease, respiratory disorders, infertility, cancers, psychological and social disorder are associated with obesity [1,3].

Recently many active botanical ingredients have been used in obesity treatment and prevention such assaponins (e.g. glycyrrhizin and macrostemonoside A), polysaccharides (e.g. Lyciumbarbarum polysaccharide-4 and Schisandrachinesis polysaccharide), polyphenols (e.g. hawthorn leaves flavone and resveratrol), alkaloids (e.g. betania,

Abbreviations: A20-IEC-KO mice, A20 intestinal epithelial cell knock out mice; ACAT2, Acyl-coenzyme A: cholesterol acyltransferase-2; ApoB84, apolipoprotein B 84; ABCA1, ATP-binding cassette transporter; BMI, body mass index; BSH, bile salt hydrolase; BERBERINEPS, Berberine and plant sterols; CaCo-2 cells, Cancer coli-2; FBS, fasting blood sugar; HFD, high fat diet; HDL, high-density lipoproteins; LPS, lipopolysacchride; LDL, low-density lipoproteins; LXRalpha, liver X receptor alpha; NPC1L1, Niemaan-Pick C1-Like 1; PBS, postprandial blood sugar; SCFA, short-chain fatty acid; TCHL/TC, total cholesterol; TG, total glycosides; TLR4/TNF-α, toll-like receptor 4/tumor necrosis factor alpha

* Corresponding author.
E-mail address: clara.gasparri01@universitadipavia.it (C. Gasparri).

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Table 1
Studies on the effects of berberine on obesity through difference mechanism in Human subjects.

First Author, Year	Compound	Dosage	No.of subjects	Duration	Main outcomes/Results
Blood glucose and diabetes					
Zhang, 2008 [6]	Berberine	1.0 g/ day	n = 116 patients with type 2 diabetes and dyslipidemia. The patients were randomly assigned to receive double-blinded or placebo.	3 months	In Berberine group, fasting glucose decreased from 7.0 to 5.6 mM/liter and postprandial blood glucose decreased from 12.0 to 8.9 mM/liter. Decrease in TG from 2.51 to 1.61 mM/liter, TCHL from 5.31 to 4.35 mM/liter and LDL from 3.23 to 2.55 mM/liter.
Yin, 2008 [12]	Berberine or metformin	0.5 g t.i.d./ day	n = 84 subjects (49 women and 35 men) – 36 adults with newly diagnosed type 2 diabetes and 48 adults with poorly controlled type 2 diabetes	1 weeks	**For newly diagnosed group** - Significant decreases in hemoglobin A1c (HbA_{1c}; from 9.5% ± 0.5% to 7.5% ± 0.4%, $P < 0.01$), fasting blood glucose (FBG; from 10.6 ± 0.9 mmol/L to 6.9 ± 0.5 mmol/L, $P < 0.01$), postprandial blood glucose (PBG; from 19.8 ± 1.7 to 11.1 ± 0.9 mmol/L, $P < 0.01$) and plasma triglycerides (from 1.13 ± 0.13 mmol/L to 0.89 ± 0.03 mmol/L, $P < 0.05$) were observed. **For poorly controlled group** – It acted by lowering FBG and PBG, HbA1c from 8.1% to 7.35%.
Adipocytes and insulin resistance cells					
Yang 2012 [17]	Berberine	0 μM, 0.1 μM, 1 μM, and 10 μM	Preadipocytes of human omental fat and patients with metabolic syndrome. (n = 9; 3 females and 6 males)	3 months	Treatment was done using 10 μM Berberine. Results indicate that Berberine inhibit of human preadipocyte differentiation, leptin and adiponectin secretion by downregulating the expression of PPARγ2, C/EBPα, adiponectin, and leptin mRNA. For patients with metabolic syndrome, Berberine lowers the leptin level (8.01 versus 5.12 μg/L) and decrease their BMI (31.5 ± 3.6 versus 27.4 ± 2.4 kg/m^2)
Gene regulation					
Pei, 2018 [21]	Berberine	300-mg/ day	Human: n = 45 ACS (Acute Coronary Syndrome) patients at Xinhua Hospital affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China	3 months	Macrophages were pretreated with BERBERINE (5, 10, and 25 μM), rosuvastatin (5, 10, and 25 μM), and combination of BERBERINE and rosuvastatin for 1 h before stimulation with ox-LDL for 24 h. Galectin-3 protein and mRNA were upregulated by ox-LDL stimulation. BERBERINE and rosuvastatin at 25 μM (but not at 5 or 10 μM) abolished the effect of ox-LDL on galectin-3 gene and protein expression, whereas combination of rosuvastatin and BERBERINE (25 μM) further decreased galectin-3 expression compared with BERBERINE or rosuvastatin alone.
Lee, 2010 [22]	Berberine	50 μM / day	Foam cells by macrophages (n = 10)	4 weeks	Treatment resulted in accumulation of oxidized low-density lipoprotein (oxLDL)-mediated lipid due to increase in cholesterol efflux. Berberine enhances mRNA and protein expression of ATP-binding membrane cassette transport protein A1 (ABCA1). Berberine induces nuclear translocation and activation of liver X receptor alpha.
Breast cancer and menopause					
Cinanci, 2013 [31]	Estromineral lipid (EL)	soy isoflavones 60 mg; Ls 1. 109 spores + Berberine 500 mg + calcium phosphate dihydrate 137 mg + vitamin D3 5 μg + folic acid 0.2 mg of calcium 240 mg + vitamin D3 5 μg (CaD) / day	n = 120 women: enrolled for deficiency of calcium, vitamin and for menopause.	12 weeks	Estromineral lipid (EL) treatment lowered plasma cholesterol, LDL-c, and TG and improved menopausal symptoms compared with CaD treatment. The combination of isoflavones and Berberine was effective in significantly lowering cardiovascular risk factor in menopausal women.
Zanardi, 2012 [32]	Berberine and Red Yeast Rice	AP 1 tablet/day. AP tablets contain Berberine 500 mg, red yeast rice extract 200 mg (equivalent to 3 mg monacolins), policosanol 10 mg, folic acid 0.2 mg,	n = 21 HT-BC (Hormone-therapy following breast-cancer) patients	3 months	Treatment was done by AP tablets which contain Berberine 500 mg, red yeast rice extract 200 mg, policosanol 10 mg, folic acid 0.2 mg, coenzyme Q10 2 mg, and asthaxantin 0.5 mg. The lipid profile was significantly improved by AP vs. diet: 1.8

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Table 1 (*continued*)

First Author, Year	Compound	Dosage	No.of subjects	Duration	Main outcomes/Results
Blood glucose and diabetes					
		coenzyme Q10 2 mg, and asthaxantin 0.5 mg.)			% decrease in total cholesterol on diet and a further 15.3 % decrease with AP vs. diet, a 3.1 % decrease in LDL cholesterol after diet and an 18.9 % decrease after AP treatment vs diet alone and a 36.5 % decrease after AP vs. diet.
Intestinal permeability and epithetical junction					
Li, 2010 [41]	Berberine		Caco-2 monolayers (n = 123)		The distortion of tight junction morphology and redistribution of tight junction protein occludin was prevented by Berberine treatment. Berberine inhibits the dislocation of occludin from raft fractions to non-raft fractions in membrane microdomains of tight junctions.
Gu, 2009 [42]	Berberine		Caco-2 cells (n = 263)		Berberine reduces epithelial gut permeability and might help explain the possible mechanisms of anti-diarrhea activity of Berberine.
Wu, 2014 [43]	Berberine-Loaded Nanoparticles	1.0 mg/mL/day	Caco-2/RAW 264.7 cells co-culture (n = 110)		Berberine-loaded nanoparticles protects intestinal tight-junction barrier function against nitric oxide and inflammatory cytokines released from LPS-stimulated macrophage by determining the transepithelial electrical resistance (TEER) and paracellular permeability of a model macromolecule fluorescein isothiocyanate-dextran (FITC-dextran).
Amasheh, 2010 [44]	Berberine	50 μM/day	HT-29/B6 human colon cells (n = 212)		Using chamber experiments and two-path impedance spectroscopy revealed a decrease of paracellular resistance after TNFa to 11 ± 4%, whereas transcellular resistance was unchanged. The permeability of the paracellular marker fluorescein was increased fourfold.

matrina and Berberine) and other compounds like rhein and emodin [4]. Berberine, a naturally occurring alkaloid, is found in certain species of flowering plants like *Berberidaccae, Coptis rhizomes and Hydrastis Canadensis*. Traditionally, Berberine was used in Chinese medicine for the treatment of gastrointestinal infections [5]. Clinical research and animal studies have provided significant results showing that Berberine can regulate glucose, lipid metabolism and attenuate insulin resistance [4,6].

Many studies also suggested that Berberine could prevent obesity by down regulating expression of genes that promote the proliferation and differentiation of adipocyte [5,7,8]. Moreover, it could alleviate the growth of adipose tissue by inducing the enzymes that activate the glucose and fatty acids uptake. In addition, Berberine regulates the levels of gut hormones, subsequently, treating obesity and insulin resistance.

Other studies suggested that Berberine can enhance insulin resistance by modulating the gut microbiota [7–9]. Previous studies on Berberine suggest that it may help in the treatment of dyslipidemia, insulin resistance, and cardiovascular disease accompanying obesity by different molecular and cellular mechanisms [9,10].

The aim of this review is to summarize the previously published clinical studies in vitro, vivo and in humans where the efficacy of Berberine has been evaluated in terms of dosage and timing of administration regarding obesity.

2. Material and methods

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [11]. It was carried out through the following steps: (1) Formulation of review question: “What are the health benefits associated with the consumption of berberine?”; (2) Definition of subjects: Animals and humans; (3) search strategy for the identification of relevant intervention studies that included the effect of berberine on obesity; and (4) analysis of the data through the systematic review.

2.1. Search strategy

Articles written in English were identified by searching PubMed (https://www.ncbi.nlm.nih.gov/punmed/), Scopus (https://www.scopus.com/home.uri), and Google Scholar (https://scholar.google.it/). The search strategy was based on the following search terms: berberine [MeSH Terms]) OR obesity[MeSH Terms]) OR blood glucose [MeSH Terms]) OR diabetes [MeSH Terms]) OR adipocytes [MeSH Terms]) OR insulin resistance cells [MeSH Terms]) OR cholesterol metabolism [MeSH Terms]) OR gene regulation [MeSH Terms]) OR gut microbiota [MeSH Terms]) OR breast cancer [MeSH Terms]) OR menopause [MeSH Terms]) OR hepatic gluconeogenesis [MeSH Terms]) OR intestinal permeability [MeSH Terms]) OR epithelial junction [MeSH Terms]). This search strategy retrieved 50 studies, after screening based on titles and pertinence, we entered 35 studies in the flowchart process. These 35 studies were selected initially from Scopus and Google Scholar search engines.

Eligible studies were required to report baseline and follow-up values, the dosage given on daily or weekly bases for humans and animals subjects to determine the effect of berberine on obesity through difference mechanism for blood glucose, diabetes, adipocytes, insulin resistance cells, gut microbiota, cholesterol metabolism, gene regulation, breast cancer and menopause, hepatic gluconeogenesis, intestinal permeability and epithelial junction. Almost all studies were non-randomized with control group differentiating from dosage of berberine given.

2.2. Analysis of data and presentation of the outcomes

A total of 50 studies had been included from 2000 to 2019, out of which 35 (on human = 11, Animals = 22 and human-animal = 2) were accepted from 2006–2019. This is because that each study was selected based on the content required for description associated with the headings.

Clinical trials investigating the effectiveness of berberine on reduction of obesity through different mechanism and it outcomes were included. For human study, the following data were collected: first author, publication year, compound, dosage, number of subjects, duration and main outcomes/results. For animal study, same procedure was followed with the addition of research objectives. Thus, we summarize animal studies based on Cochrane methodology.

3. Results

3.1. Effect of Berberine on blood glucose and diabetes

Table 1 shows the effect of berberine supplements in human subjects, had a significant effect on blood glucose and provided a significant cure for diabetes demonstrated by the work Zhang et al. [6] on patients with type 2 diabetes, obesity and dyslipidemia showed that Berberine is an effective plant alkaloid that decreases the levels of total glycerides, Low-density lipoproteins and Total Cholesterol, which are the main factors contributing to obesity by the inhibition of α –glycosidase. Yin, Xing & Ye [12], reported the effect of Berberine in newly diagnosed and poorly controlled groups for type 2 diabetes. Berberine reduced obesity by lowering FBG and PBG through monotherapy study, thereby controlling diabetes.

In Table 2, studies done by Tang, Wei, Chen & Liu [13] on Wistar rats in which diabetes was induced through tail vein injection with alloxan and a high -fat diet, the Berberine treatment showed a significant decrease in lipid profile, through significantly blocking the increment of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-px).

Another study conducted by Zhang et al. [14] (Table 2), on the effect of Berberine on KKAy mice model showed a lowering of serum insulin and lipid metabolism, and leads to a lowering of glucose levels, which in turn reduce body weight. Berberine upregulated the expression of glucose transporter 4 (GLUT4), mitogen-activated protein kinase 14 (MAPK14), MAPK8(c-jun N-terminal kinase, JNK), peroxisome proliferator-activated receptor *α* (PPAR*α*), uncoupling protein 2 (UCP2), and hepatic nuclear factor 4*α*(HNF4*α*), whereas it down-regulated the expression of PPARγ, CCAAT/enhancer-binding protein (CEBP), PPARγ coactivator 1*α*(PGC 1*α*), and resistin.

3.2. Effective mechanism of Berberine on adipocytes and insulin resistance cells

Adipocytes are the main store house of lipids and fatty acids, which leads to obesity, diabetics and other associated disease. In Table 3 shows the effects of Berberine on adipocytes and on insulin resistance cells. A recent study done by Wu et al. [15], showed that Berberine tend to reduce weight by increasing brown adipose tissue (BAT). It also improves insulin sensitivity through stimulation of BAT genes, which play an important role in the regulation of energy balance.

Research done by Li et al. [16] on hamsters showed that Berberine opposes the effect of streptozotocin by decreasing alter visceral white adipose tissue LXRs, PPARs, and SREBPs transcriptional programs in visceral white adipose tissue and helps in reduction of body weight. Berberine increases liver X receptors (LXRs) and peroxisome proliferator-activated receptors (PPARs) expression (Table 2).

A study done on human fat in vitro and by Yang et al. [17] (Table 1), showed that the expression of PPARγ2, C/EBP*α*, adiponectin, and leptin mRNA is down regulated in preadipocytes upon treatment with Berberine.

Table 2
Studies on the effects of berberine on obesity through different mechanism in Animal subjects.

First Author, Year	Compound	Research objectives	Study design	No.of subjects	Duration	Main outcomes/ Results
Blood glucose and diabetes						
Tang, 2006 [13]	Berberine (100 and 200 mg/kg/day)	Inhibition of progression of diabetes induced by alloxan	Diabetes was induced by tail vein injection with alloxan in Wistar rats followed by feeding on high- cholesterol diet.	n = 15	3 weeks	Pancreatic sample withdrawn after 3-weeks of Berberine treatment showed a significant decrease in fasting blood glucose levels, serum content of TC, TG, LDL-c and effectively increased HDL-c. Also, Berberine treatment blocks the increase of MDA, SOD and GSH-px levels in diabetic rats.
Zhang, 2011 [14]	Berberine (250 mg/kg/day)	Explored the effects of berberine on the weight, glucose levels, lipid metabolism, and serum insulin of KKAy mice and investigated its possible glucose and lipid-regulating mechanism.	Randomly divided KKAy mice into two groups: berberine group and control group	2 groups (n = 8 per groups)	4 weeks	Mice fed with Berberine show significant decrease in FBS, area under the curve (AUC), fasting serum insulin (FINS), homeostasis model assessment insulin resistance (HOMA-IR) index, TC, and TG, compared with those of control group.
Adipocytes and insulin resistance cells						
Li, 2011 [16]	Berberine (150 mg/kg daily)	The therapeutic mechanisms of berberine on fat-induced visceral white adipose tissue insulin resistance in type 2 diabetic hamsters.	Type 2 diabetic hamsters were induced by high-fat diet with low-dose streptozotocin. Investigation was done by gene expression alterations.	Golden Syrian hamsters (n = 16)	9 weeks	The type 2 diabetes was induced into hamsters by high-fat diet and low-dose streptozotocin which increases the body weight and visceral white adipose tissue weight, insulin resistance, intra- adipocyte lipid accumulation. Significant increase in SREBPs expression, decrease in liver X receptors and peroxisome proliferator-activated receptors (PPARs) expression in visceral white adipose tissue were observed. Treatment with Berberine significantly altered visceral white adipose tissue LXRs, PPARs, and SREBPs transcriptional programs leading to decrease in body weight, intra-adipocyte lipid accumulation and increase insulin resistance.
Cholesterol metabolism						
Wang, 2014 [18]	Berberine (50, 100, and 150 mg/kg/d)	The mechanisms of action of berberine (BBR) on cholesterol homeostasis using in vivo and in vitro models	Cholesterol absorption rate was measured with the dual stable isotope ratio method, and plasma lipids were determined using the enzymatic methods	Male Sprague-Dawley rats (n = 20)	8 weeks	Treatment with Berberine in rats on atherogenic diet showed reduction in plasma T-CHL (29 %–33 %) and nonHDL cholesterol levels (31 %–41 %). It was found that BERBERINE interfered with cholesterol micellization, decreased cholesterol uptake by Caco-2 cells and permeability through Caco-2 monolayer.
Zhou, 2017 [19]	Berberine 72.6 mg/kg b.w.), and evodiamine 16.6 mg/kg b.w and Berberine and evodiamine (BB + EV) (89.2 mg/kg b.w.).	The objective was to investigate the lipid-lowering effect of berberine and evodiamine combination in hyperlipidemic rat	Hyperlipidemia was established by providing high-fat-diet (HFD)	n = 60	4 weeks	Results showed that by combination of Berberine and evodiamine – levels of serum cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C), as well as hepatic TC decreased. During the experiment period, liver weight index was remarkable reduce and Berberine combined with evodiamine remarkably decrease the expressions of intestine ACAT2, NPC1L1, and ApoB48 compared with HFD group, leading

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Table 2 (*continued*)

First Author, Year	Compound	Research objectives	Study design	No.of subjects	Duration	Main outcomes/ Results
Blood glucose and diabetes						
						to inhibition of intestinal cholesterol absorption.
Wang, 2010 [20]	Berberine, plant stanols (PS) and their combination (100 mg/kg/d)	To determine the efficacy and underlying mechanism of berberine (BBR), plant stanols (PS) and their combination on plasma lipids.	Male Golden Syrian hamsters were randomly divided and fed a cornstarch-casein-sucrose-based diet containing 0.15 % cholesterol and 5% fat.	Golden Syrian Hamsters divided into 4 groups (n = 15 per group)	4 weeks	BERBERINE and PS significantly lowered plasma total- and nonHDL-cholesterol levels, and BERBERINEPS markedly improved cholesterol-lowering efficacy compared to BERBERINE or PS alone. Thus, the combination inhibits cholesterol absorption. Berberine upregulated sterol 27-hydroxlase gene expression and BERBERINEPS increased both cholesterol-7α-hydroxylase and sterol 27-hydroxlase gene expressions. Therefore, it was suggested that cholesterol-lowering action of Berberine involve the inhibition of cholesterol synthesis and stimulation of bile acid synthesis.
Gene regulation						
Chow, 2016 [5]	11 protoBerberines (13- MethylBerberine, coptisine, palmatine, corydaline, dehydrocorydaline, dihydroBerberine, 13-methyldihydroBerberine, tetrahydroBerberine, demethyleneBerberine, berberrubine, and *N*-methyltetrahydroBerberine (5 μM of each)	To study the potential of 13-methylberberine as a candidate for metabolic syndrome treatment and its cytotoxicity.	3T3-L1 adipocytes from mouse	n = 3	1 month	The compound down-regulated the expression of main adipocytes differentiation transcription factors, peroxisome proliferator- activated receptor gamma (PPARγ) and CCAAT enhancer binding protein alpha (C/EBPα). It also targets their gene, causing reduction in levels and this lipid-reducing effect is attenuated by AMP-activated protein kinase.
Gut microbiota						
Liu, 2018 [23]	Berberine (200 mg/kg/day for 8 weeks)	Anti-obesity effects and prevents insulin resistance in high-fat diet (HFD)-fed obese rats by modulating the gut microbiota	The effects of berberine on obesity and insulin resistance by examining the lipopolysaccharide (LPS)/toll-like receptor 4 (TLR4)/tumor necrosis factor (TNF)-α signaling pathway in livers of HFD-fed obese rats	Wistar rats: n = 40 specific pathogens free (SPF)	8 weeks	Berberine (200 mg/kg) diet was fed which result in significant lowering fasting blood glucose, TG, LDL-c and insulin resistance. Berberine diet also reversed the effect and inhibited LPS-induced TLR4/TNF-α activation. Therefore, protecting gut microbiota by increasing protectivity of bacteria like Bifidobacterium and decreasing gram negative bacteria like E. coli.
Tian, 2018 [24]	Berberine (100 mg/kg/day)	The effect of berberine (BBR), a natural plant alkaloid, on intestinal bacteria using in vitro and in vivo models.	NMR-based metabolomics combined with flow cytometry was used to evaluate the direct physiologic and metabolic effect of BBR on the bacteria	Mouse: intestine (in vivo) and cecal bacteria (in vitro). (n = 6 per group)	5 days	**In Vivo:** Mouse intestinal bacterial communities when expose to short-term treatment altered intestinal bacteria by reducing *Clostridium* cluster XIVa and IV and their bile salt hydrolase (BSH) activity and resulting in accumulation of taurocholic acid (TCA). This accumulation was associated with activation of intestinal FXR, that mediate bile acid, lipid and glucose metabolism. **In Vitro:** Berberine exposure altered bacterial physiology, community composition and function of isolated mouse cecal bacteria which induce reducing BSH-expressing bacteria like *Clostridium* spp.

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Table 2 (*continued*)

First Author, Year	Compound	Research objectives	Study design	No.of subjects	Duration	Main outcomes/ Results
Blood glucose and diabetes						
Zhang, 2015 [25]	Berberine and Metformin (100 mg/ kg body weight/day)	To demonstrated that metformin and berberine similarly shifted the overall structure of the gut microbiota in rats	Reverting effects on the high-fat diet-induced structural changes of gut microbiota	Rats divided into 5 groups (n = 134 Operational Taxonomic Units)	10 weeks	Diet of bebeerine was reported in modulating the gut microbiota and enrichment of SCFA (Short-chain fatty acids) – producing bacteria - Allobaculum, *Bacteriodes*, *Blautia*, *Butyricoccus*, and *Phascolarctobacterium* and reducing microbial diversity, that may contribute to their beneficial effects to the host.
Zhang, 2012 [26]	Berberine (100 mg/kg/day)	To reveal that berberine effectively prevented the development of obesity and insulin resistance in high-fat diet (HFD)-fed rats, which showed decreased food intake	Bar-coded pyrosequencing of the V3 region of 16S rRNA genes	HFD – fed rats (n = 120)	8 weeks	A dose of 100 mg/kg body weight prevented the body weight increase Observed in HFD-fed rats and NCD-fed diet. It occurred due the regulation of gut microbiota, because of a shift towards the reduction of diversity of gut microbes and elevation of fecal SCFA concentrations.
Cao, 2016 [28]	Berberine (200 mg/kg/d)	To determine the effect of berberine on NASH induced by high-fat (HFD).	BALB/c mice were randomized into three groups, including: control, model, and berberine treatment. With the exception of the control group with the standard diet, the model, and the treatment groups were treated by HFD.	BALB/C mice: grouped → control, model and Berberine treatment (n = 10)	5 weeks	Berberine restores the relative levels of Bifidobacterium (2.16 ± 0.63 vs. 0.50 ± 0.08) and ratio of Bacteroidetes /Firmicutes (0.76 ± 0.26 vs. 0.39 ± 0.11). Microbiota restoration led to significant reduction in body weight, serum levels of lipids, glucose, insulin and homeostasis. Improvement was also observed in serum transaminase activity and nonalcoholic fatty liver disease activity score, thus attenuating NASH.
Li, 2016 [29]	Berberine compounds (BC), consisting of Berberine, oryzanol and Vitamin B6. Dose: 150 mg/kg of BERBERINE, 24 mg/kg of oryzanol and 10 mg/kg of vitamin B6	To determined anti-hyperlipidemia activity of berberine and underlying mechanisms.	Body weight and food intake were recorded weekly, and lipid profiles in serum were determined biochemically. Metabolites in serum, urine, liver and feces were analyzed by GC-MS, and the structure of microbiota was determined by 16S rDNA sequencing.	Male Wistar rats: chow diet (n = 10) and HFD (n = 20).	4 weeks	Lipid lowering was observed in the hyperlipidemic rats upon BC treatment without apparent adverse side effects. Metabolomics analysis indicated that the BC treatment resulted in increased pyruvic acid, serotonin, and ketogenic and glycogenic amino acid levels in the serum, increased pyridoxine and 4-pyridoxic acid in the urine, decreased hypotaurine and methionine in the liver, and increased putrescine and decreased deoxycholate and lithocholate in feces. The BC treatment also resulted in an enrichment of beneficial bacteria (e.g. *Bacteroides*, *Blautia*) and a decrease in *Escherichia*.
Sun, 2016 [30]	Berberine chloride (150 mg/kg/day)	To investigate whether or not berberine could improve metabolic status of high-fat-fed rats through modulation of microbiota-gut-brain axis	Berberine was administered on high-fat-fed Sprague-Dawley rats. Brain-gut hormones were detected, and changes of gut microbiota were analyzed by 16S rRNA gene sequencing	Sprague-Dawley rats: divided into 3 groups (n = 6 per group)	8 months	Reduces weight gain and lipolysis in the high-fat diet-fed group. It ameliorated Insulin resistance and decreased endogenous glucose production. Therefore, modulates microbiota-gut-brain axis including structural and diversity changes of microbiota, elevated serum glucagon-like peptide-1 and neuropeptide Y level, decreased orexin A level, up-regulated glucagon-like peptide-1 receptor mRNA level as well as ultra-structural.
Hepatic gluconeogenesis						
	Berberine (380 mg/kg/day)				7−8 weeks	

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Table 2 (*continued*)

First Author, Year	Compound	Research objectives	Study design	No.of subjects	Duration	Main outcomes/ Results
Blood glucose and diabetes						
Xia, 2011 [33]		To understand activation of adenosine monophosphate activated protein kinase (AMPK) and improvement of insulin sensitivity	The rats were fed on high fat diet (63.47 % calorie in fat) for 8 weeks, and then followed by a single low-dosage intraperitoneal injection of streptozotocin (STZ, 30 mg/kg, Sigma, St Louis, MO) after 12 -h fast.	Sprague- Dawley rats (n = 9)		Berberine is reported to decrease Gluconeogenesis gene, Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-Phosphatase (G6Pase) in liver which lowers the fasting glucose. Additionally, it also reduces hepatic steatosis and inhibit the expression of fatty acid synthase (FAS) in liver. It was concluded that the inhibition occurs likely as a result of mitochondria inhibition by Berberine, thereby improving glucose metabolism through an insulin-independent pathway.
Zhang, 2012 [34]	Berberine (50 mg/ kg/day and 100 mg/kg) and sodium caprate (50 mg/kg/day)	To demonstrated theco-administration of sodium caprate, an absorption enhancer, with BER could significantly increase the bioavailability of BER without any serious mucosal damage	Diabetic rat model induced by high-fat diet and low dose STZ (30 mg/kg)	n = 58	4 weeks	BERBERINE reduced body weight and caused a significant improvement in glucose tolerance without altering food intake in diabetic rats. BER reduced plasma triglycerides and improved insulin action
Jiang, 2015 [35]	Berberine (156 mg/kg per day) or metformin (184 mg/kg per day)	To investigate the molecular mechanisms of berberine inhibition of hepatic gluconeogenesis in a diabetic rat model.	One group was selected as the normal group. The rats were fed on a high-fat diet for 1 mo and received intravenous injection of streptozotocin for induction of the diabetic models.	40 Rats: 5 groups (n = 8 per group)	12 weeks	Berberine improved impaired glucose tolerance and decreased plasma hyperlipidemia. It also decreased fasting plasma insulin and homeostasis model assessment of insulin resistance (HOMA-IR)
Wei, 2016 [36]	Berberine: low oral dose 40 mg/kg/day BERBERINE (LB) and high oral dose 160 mg/kg/ day BERBERINE (HB).	Berberine modulates lipid metabolism and inhibits hepatic gluconeogenesis by decreasing expression of Hepatocyte Nuclear Factor-4α (HNF-4α)	Male C57BL/6 J mice: grouped into 2 - > control and high-fed diet group 4 groups with n = 12 in each group who receive and didn't receive Berberine treatment.	n = 12	4 weeks	Treatment of T2D mice for 4 weeks or treatment of PA-incubated HepG2 cells for 24 h with BERBERINE decreased expression of HNF-4α and the microRNA miR122. Expression of HNF-4α in HepG2 cells increased expression of gluconeogenic and lipid metabolism enzymes and BERBERINE treatment or knock down of miR122 attenuated the effect of HNF-4α expression.
Teodoro, 2013 [37]	Berberine (100 mg/kg/day)	To demonstrate berberine treatment to recovers mitochondrial efficiency when altered by a high-fat feeding.	Male Sprague–Dawley rats: control group and BERBERINE treated group	n = 20	8 weeks	Mitochondria isolated from the liver of high-fat fed rats exhibited decreased 28 capacity to accumulate calcium and impaired oxidative phosphorylation (OXPHOS) capacity, as shown by 29 impaired mitochondrial membrane potential, oxygen consumption and cellular ATP levels.
Intestinal permeability and epithetical junction						
Gong, 2017 [38]	Berberine	To explored whether the anti-diabetic effect of berberine was related to the intestine mucosal barrier.	Rat model of T2DM divided into 2 groups	N = 6 per group	9 weeks	The rat model was established by high glucose-fat diet and intravenous injection of streptozocin. Berberine was given at different concentrations which resulted in lowering levels of hyperglycemia and hyperlipidemia, additional with the 2.77-fold increase in intestinal permeability.
Hou, 2019 [39]	Berberine and rifaximin	To investigate effects of berberine exerts on A20 expression and regulation of intestinal epithelial tight junctions via the TNF-α-NF-κB-MLCK pathway in Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D).	C57BL/6 wild type (WT) and A20 IEC-KO mice	N = 48 per group	2−3 weeks	Mice model were divided into normal control (CN), model control (MC) and rifaximin and Berberine groups. Results showed that Intestinal epithelial space of WT Berberine mice improved more than A20 IEC-KO Berberine mice compared to MC mice. Further, WT Berberine mice exhibited greater expression of A20 compared with MC mice.

(*continued on next page*)

Table 2 (*continued*)

First Author, Year	Compound	Research objectives	Study design	No.of subjects	Duration	Main outcomes/ Results
Blood glucose and diabetes						
Gu, 2011 [40]	Berberine (200 mg/kg)	To examine the protective effect of berberine in endotoxin-induced intestinal tight-junction injury in a mice model of endotoxinemia.	Male C57BL/6 Mice	N = 8 per group (5 groups)	1 week	Ileal mucosal permeability to fluorescein isothiocyanate dextran assay indicated that Berberine reduced the permeability of the gut barrier in endotoxinemia. The results demonstrated that pretreatement with Berberine partially reversed the redistribution of tight-junction proteins in colon epithelium and in membrane microdomains.

3.3. Impact of Berberine on cholesterol metabolism

Cholesterol metabolism plays an important role in alleviating the level of lipid that is associated with obesity. Table 2, accounts for the effective role of Berberine on cholesterol metabolism. A study performed by Wang et al. [18] concluded that Berberine decreases the cholesterol uptake through Caco-2 cells and permeability through Caco-2 monolayer through the down regulation of Acyl-coenzyme A: cholesterol acyltransferase-2 expression.

Zhou et al. [19] also highlighted the effect of Berberine and evodiamine on hyperlipidemia by inhibiting the absorption of cholesterol in the intestine. However, Wang et al. [20], indicated that the combination of Berberine and plant stanols lowers the lipids accumulation by inhibiting cholesterol absorption through up regulating gene expression of sterol 27-hydroxlase, cholesterol-7α-hydroxylase and sterol 27-hydroxlase (Fig. 1).

3.4. Effect of Berberine on gene regulation

As shown in Table 2, Berberine is responsible for the regulation gene in animal subjects for synthesis of fatty acid and its associates. A study performed by Chow et al. [5] showed that 11 different type of proto-Berberine regulate specific gene of 3T3-L1 adipocytes in mice. It was deduced that Berberine down regulates different transcriptional factors, PPARγ and C/EBPα. Down regulation leads to switching off of genes causing lowering of lipid profile.

In Table 1, a study done by Pei et al. [21], demonstrated that Berberine alleviates the activation of ox-LDL-induced macrophages by down regulation of galectin-3 through NF-κB and AMPK signaling pathways in percutaneous coronary intervention (PCI).

Also, Lee et al., [22] reported that accrual of oxidized low-density lipoprotein (oxLDL) occur due to increase in cholesterol efflux. Berberine works best by inducing nuclear translocation and LXRalpha expression, which abrogates the formation of foam cells by macrophages by enhancing LXRα-ABCA1-dependent cholesterol efflux.

3.5. Effect of Berberine on regulation of gut microbiota

In Table 2, Gut microbiota is important for the microflora of the intestine; growth of other diversity of bacteria can cause harmful internal infection. Treatment with berberine in animal subjects provides the evidence on regulation of gut microbiota. Recent studies done by Liu et al. [23] on rats and Tian et al. [24], on mice, concluded that Berberine alter bacterial physiology, community composition and increase the growth of protecting bacteria like Bifidobacterium. It effects by inhibition of LPS-induced TLR4/TNF- α activation and BSH-expression.

Also, a study done by Zhang et al. [25] showed that Berberine modulates the production of bacterial diversity that are enriching with the production of SCFA and contribute to the benefit their host. Zhang et al. [26], gave evidence that Berberine promotes structural changes of gut microbiota. It was reported that by the pyrosequencing of the V3 region of 16S genes revealed a significant reduction in gut microbiota diversity. Lipopolysaccharide (LPS)-binding protein (LBP) is a biomarker of circulating exogenous antigen and was found in higher concentration in the serum that was essentially prevented by Berberine co-administration.

A study done by Han, Lin and Huang [27] (Table 3), concluded that Berberine has significant antimicrobial activity against several microbes. The prevention occurs by inhibiting the assembly function of FtsZ and halting the bacteria cell division. Therefore, the study suggested that the modulation of gut microbiota is one mechanism of the antidiabetic effect of Berberine.

In Table 2, a related study done by Cao et al. [28] demonstrated that Berberine alleviates NASH and its predisposing factors, normalizing gut microbiota by the mechanical down regulation of CD14, IL-1, IL-6 and

Table 3
Studies on effects of berberine on obesity through different mechanism in Human-Animal (combined) subjects.

First Author, Year	Compound	Dosage	No.of subjects	Duration	Main outcomes/Results
Adipocytes and insulin resistance cells					
Wu, 2019 [15]	Berberine	100 mg/day	Human (n = 10) and Mice (n = 10)	1 month	Treatment with Berberine results in increase in Brown adipose tissue (BAT) mass and activity. Thereby, reducing body weight with improve insulin sensitivity in mildly overweight patients with non-alcoholic fatty liver disease. On the other side, Berberine promotes BAT development by stimulating the expression of brown adipogenic genes which enhance BAT thermogenesis and global energy expenditure in diet-induced obese mice and chow-fed mice.
Gut Microbiota					
Han, 2011 [27]	Berberine	500 mg/day	Diabetic patients (n = 10) and Mice (n = 10)	10 weeks	Administration of Berberine to diabetic patient showed the proportions of Firmicutes and Clostridia were significantly reduced, while the relative abundance of Bacteroidetes and Betaproteobacteria was increased. Whereas, for the NOD mice which became diabetic due to the oral administration of probiotic. When treated with Berberine, modulate gut microbiota without systemic anti-infective activity.

TNF-α expression. Also Li et al. [29], reported the effect of Berberine compounds by the up regulation and downregulation of serum, liver and fecal metabolites through *R2X* and *Q*2 of PCA score and *R*2Y and *Q*2 of PLS-DA score. Sun et al. [30] analyzed the changing of gut microbiota by 16S gene sequencing. They suggested that Berberine improved metabolic disorders induced by a high-fat diet through modulation of the microbiota-gut-brain axis. Berberine led to marked changes of microbiota composition in majority genus, with significant enriching effects on Bacteriodes (Bacteriodetes phylum) ($p < 0.05$) and on Firmicutes, such as Dorea ($p < 0.05$), rc4–4 ($p < 0.05$), Roseburia ($p = 0.05$) and Blautia (p for ANOVA = 0.098).

3.6. Impact of Berberine on weight gain in breast cancer and menopause

Table 1 shows, the effect of Berberine on women's two major complications i.e. breast cancer and menopause. A study done by Cianci, Cicero, Colacurci, Matarazzo & De Leo [31] on women with a deficiency of calcium, vitamins and in menopause indicated that, a combination of Berberine with isoflavones lowers the TG, T-CHL, HDL, and LDL as well as cardiovascular factors to improve menopausal symptoms.

Another study was done by Zanardi et al. [32] on women using hormone-therapy following breast-cancer. AP tablets (Berberine + Red Yeast Rice) were used as a treatment that lowers the lipid profile, which in turn lowers the chance of weight gain. This indicates that AP, in combination with appropriate dietary management and moderate physical activity provides the excellent treatment for dyslipidemia.

3.7. Effect of Berberine on inhibition of hepatic Gluconeogenesis

Table 2 shows the effect of berberine on hepatic gluconeogenesis in animal subjects. One study done by Xia et al. [33] on inhibition of Hepatic Gluconeogenesis in Sprague-Dawley rats showed that Berberine targets the specific Gluconeogenesis gene, Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase) in the liver, causing the reduction in fasting glucose. Moreover, Berberine inhibits the FAS expression which accounts for less absorption of fatty acid by the liver and reduction of hepatic steatosis which occur as result of mitochondrial inhibition.

Research done by Zhang et al. [34], Jiang et al. [35], Wei et al. [36] and Teodoro et al. [37] on different rats models concluded that berberine is an effective alkaloid for the treatment of hepatic Gluconeogenesis in a high-fat fed diet. Berberine downregulated the elevated expressions of gluconeogenesis key enzymes PEPCK and G6Pase, inhibited the translocation of TORC2 from cytoplasm to nucleus and increased AMPK activity in liver tissues [34]. Another impact of berberine is its upregulated protein expression of liver kinase (LK)B1, AMP-activated protein kinase (AMPK) and phosphorylated AMPK (p-AMPK) [35].

On the other hand, miR122 is a critical regulator in the downstream pathway of HNF-4α in the regulation of hepatic gluconeogenesis and lipid metabolism in HepG2 cells. The effect of berberine on hepatic gluconeogenesis and lipid metabolism is mediated through HNF-4α and is regulated downstream of miR122 [36]. Lastly, Berberine treatment recovers mitochondrial efficiency when altered by a high-fat feeding. Berberine potent protective effects against metabolic syndrome may rely on increasing mitochondrial SirT3 activity, normalizing mitochondrial function and preventing a state of energetic 33 deficit caused by impaired OXPHOS.

3.8. Impact of Berberine on intestinal permeability and epithelial junction

Table 2 shows the variation regarding the intestine which is known as the first line of defense for the contact with dietary antigens. Work done by Gong et al. [38] on intestinal permeability and by Hou et al. [39], on intestine epithelial tight junction, indicates that berberine is

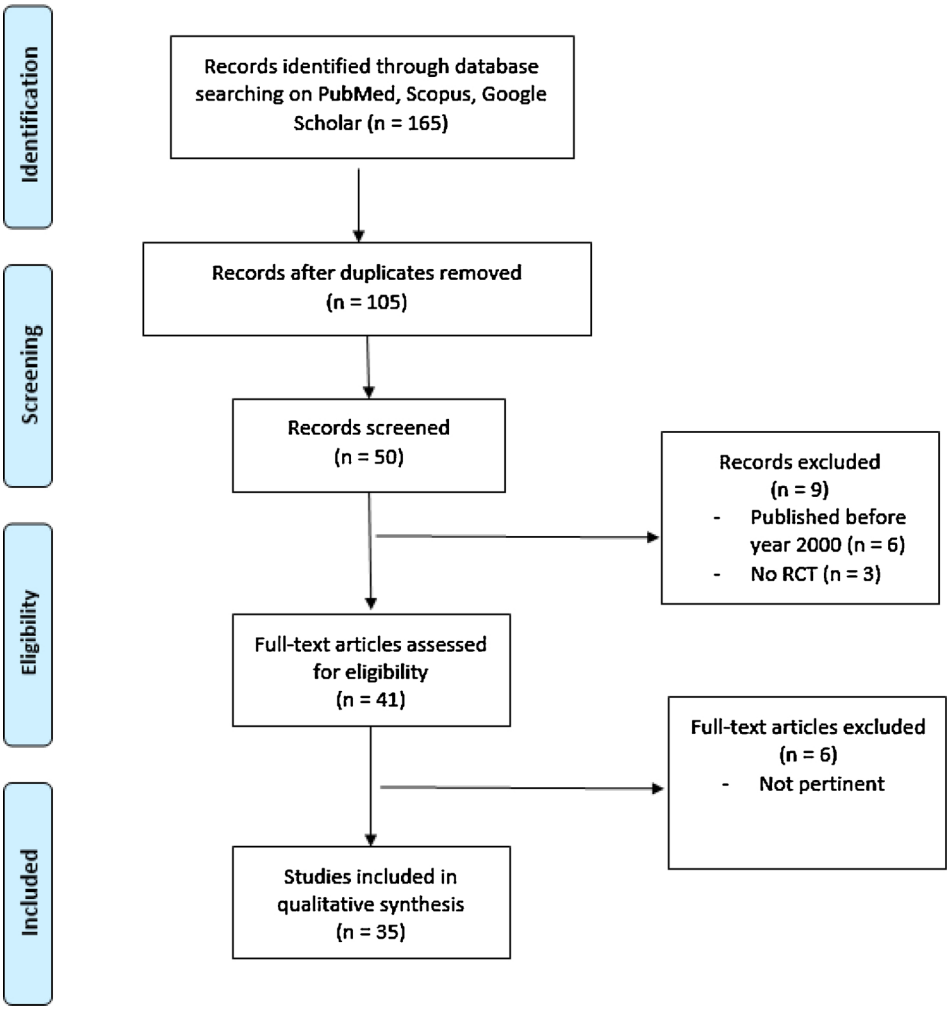

Fig. 1. Flow diagram of the study, RCT = randomized controlled trial.

not only effective against levels of glucose and lipids; it also produces effective impacts on the intestine by increasing it permeability by 2.77 folds and improving expression of A20. A study done by Gu et al. [40], indicated that pretreatment with Berberine attenuates disruption of tight junctions in intestinal epithelium in a mice model of endotoxinemia which is mediated through down regulation of the nuclear factor-jB and the myosin light chain kinase pathway.

Table 1 indicate the research done in vivo holds great importance on intestinal permeability in human subjects. Studies done by Li et al. [41], Gu et al. [42], and Wu et al. [43], on Caco-2 cells monolayer showed that Berberine protects the intestinal tight-junction by different pathways. The study suggested that the protective effect of Berberine on tight junctions was analyzed by measuring the trans-epithelial electrical resistance (TEER). It could reduce epithelial gut permeability and can restore barrier function in intestinal disease states [41–43]. However, NFa removed claudin-1 from the tight junction and increased claudin-2 expression. Berberine prevented TNFa-induced claudin-1 disassembly and upregulation of claudin-2. The effects of Berberine were mimicked by genistein plus BAY11-7082, indicating that they are mediated via tyrosine kinase, pAkt and NFkB pathways [44].

4. Discussion

This review highlighted that berberine effectively prevents the development of obesity through the modulation of gut microbiota, gene regulation, intestinal permeability and Hepatic Gluconeogenesis. In fact, obesity is always linked to high levels of lipids and lipid metabolism modulation is a focus of metabolic syndrome [45]. Berberine at a dosage from 200 mg/kg to 1.0 g daily is found to be effective for reducing blood glucose, as at this dosage it targets α-glycosidase and causes inhibition. The inhibition of this enzyme causes the limited amount of glucose absorption needed by the body. Therefore, berberine contributes to the prevention of being overweight.

One of the many mechanisms by which the fiber may protect against obesity is via the SCFA-mediated modulation of the secretion of gut hormones involved in the regulation of food intake and energy balance. Berberine at a dose of 100 mg/kg/day to 500 mg/kg/day chemically attenuates with the synthesis of enteroendocrine peptides involved in the glucose and energy homeostasis of obese people. It modulates gut microbiota by elevating intestinal peptides such as GLP-1, GLP-2 and peptide YY and decreasing gastric inhibitory polypeptides [46].

Regarding the differentiation of adipocytes, several studies have identified the mechanisms of action of berberine at the cellular level, particularly in hepatic cells, vascular smooth muscle cells, pancreatic β-cells, adipocytes and myocytes. AMP-activated protein kinase (AMPK) plays a critical role in modulating cellular processes and functions as a cellular energy sensor that involves the stimulation of catabolic processes (such as fatty acid oxidation, glucose uptake, lipolysis) while inhibiting anabolic processes (such as gluconeogenesis, fatty acid synthesis and cholesterol synthesis) [47]. Therefore, 150 mg/kg/day of berberine in a routine diet can mediate with the decreasing of LXRs, PPARs, and SREBPs expression and increase AMPK expression to use up stored energy in the form of adipocytes.

Regarding gene regulation, berberine can attenuates many gene

expression which lead to turning off genes such as LXRalpha expression and inhibit cholesterol absorption, by consuming 300 mg/day. Hence, berberine may inhibit protein synthesis, histone deacetylase (HDAC), or AKT/mammalian target of rapamycin (mTOR) pathways. Berberine also inhibits global protein synthesis, basal AKT activity and induced endoplasmic reticulum (ER) stress and autophagy, which is associated with the activation of AMP-activated protein kinase (AMPK). This helps in the inhibition of cholesterol, prevention in formation of adipocytes, lowering blood glucose and the reduction of the risk of obesity [48].

Berberine is known to attenuate hepatic gluconeogenesis and increase the permeability of intestine toward cholesterol absorption. A dose of 40 mg/kg to 380 mg/kg/day of Berberine is known to be effective for the inhibition of hepatic gluconeogenesis and 200 mg/kg dose is effective for intestine permeability and intestine epithelial junction. Lastly, this review showed the different impact of Berberine for the reduction of obesity. Berberine is not only effective for obesity, but also for other systems and consequences of obesity such as diabetes and cancer.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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