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Exploring the impact of mulberry fruits on metabolic syndrome: A systematic review of current evidence

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ABSTRACT

Background: Mulberries are rich in nutrients including a wide range of polyphenols that possess different bioactive properties. This systematic review illustrates mulberry's potential as a promising plant food for mitigating the perturbations associated with metabolic syndrome.
Methods: A systematic search was conducted on 1st March 2023 in Scopus and PubMed. A total of 15 eligible studies (in vitro and in vivo) studies evaluating the effect of mulberries on metabolic syndrome-related factors such as obesity, diabetes, high cholesterol and high blood pressure were included.
Results: Predominantly, the studies have centred around its anti-visceral-obesity and lipid-reducing effects. The interventions in these studies spanned 8–12 weeks, employing modest oral doses—ranging from 10 to 800 of mg/kg of body weight per day—of mulberry extracts, powders, or freeze-dried fruits. The favorable effects of mulberry are predominantly ascribed to its rich polyphenolic content, which interacts with diverse metabolic pathways. In terms of its anti-visceral-obesity effect, these polyphenolic compounds, particularly anthocyanins, exhibit the capacity to modulate fatty acid and triglyceride synthesis, enhance mitochondrial function, and attenuate reactive oxygen species accumulation. In vivo, constituents such as resveratrol, rutin, and anthocyanins demonstrate efficacy in inhibiting lipid synthesis, accumulation, and oxidation, leveraging their free radical scavenging ability, while concurrently orchestrating metabolic modulation in tandem with prebiotic agents.
Conclusions: Based on these data, it can be inferred that the utilization of white mulberry holds greater promise in the management of ailments like hypertension and dyslipidemia. Conversely, black mulberry displays efficacy in addressing diabetes and obesity.

Abbreviations: AMPK, adenosine monophosphate-activate protein kinase; BP_1, BP_2, BP_3, black mulberry polysaccharide fractions; C3G, cyaniding-3-O-glucoside; CAT, catalase; CE, catechin equivalent; CON, normal control group; CVD, cardiovascular disease; dMF, dried mulberry fruit powder; DW, dry weight; EMF, ethanoic extract of mulberry fruit; G6Pase, glucose-6-phosphatase; GAE, gallic acid equivalent; GPX, glutathione peroxidase; HCHF, high-carbohydrate high-fat; HF, high-fat; HFD, high-fat diet; HMB, high dose of MBEE; HMLE, high dose of MLE; HPD, high protein diet; LFD, low-fat diet; LMB, low dose of MBEE; LMLE, low dose of MLE; LPD, low protein diet; MAP, mean arterial pressure; MBEE, mulberry fruit ethanol extract; MC, mild high-fat diet; MEE, mulberry fruit ethanol extract.; MFE, mulberry fruit extract; MFP, mulberry fruit polysaccharide; MLE, mulberry leaf extract; MLFE, mulberry leaf and fruit extract; MPD, medium protein diet; MWEs, mulberry water extracts; NC or ND, normal diet; OVX, ovariectomy; PA, palmitic acid; PC, plain high-fat diet; PEPCK, Enzyme activities of phosphoenolpyruvate carboxykinase; PPAR, peroxisome proliferator-activated receptors; ROS, reactive oxygen species; SHRs, spontaneously hypertensive rats; SOD, superoxide dismutase; TG, triglyceride; WMFPs, white mulberry fruit polysaccharides.

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1. Introduction

Mulberry fruit belongs to the *Moraceae* family and more specifically to the genus *Morus* spp. This fruit originates from Asia, where the domestication of mulberry started as a requirement for silkworm (*Bombyx mori*) rearing thousands of years ago [1]. Afterwards, the mulberry has been diffusing in many other countries through the silk trade, this explains the reason why it is now easily found all around the world. The optimum temperature ranges of growth are from 24° to 29°C and humidity from 65 % to 80 % but mulberry can grow in both tropics and temperate regions [2], it could be cultivated in a wide variety of climatic, topographical and soil conditions [3]. Nowadays there are about 68 species of Morus and most of them are still cultivated in Asia, of each species there are several varieties, these are the results of intensive selection from open pollination, controlled hybridization and selection and mutation breeding [4]. White mulberry (*Morus alba*) and black mulberry (*Morus indica*) are two of the most common *Morus* species in the world [5]. The white mulberry is known as the main food source for silkworms, its color can vary between white and very light pink [6]. It is mainly cultivated in China, where has been used as an ingredient in Chinese medicine [7]. Black mulberry and red mulberry (*Morus rubra*) are molecularly different from white mulberries, they are respectively black-purple and purple-red fruits, and they can be easily found in northern India, Pakistan, and Iran [8].

Mulberries are primarily composed of water, followed by proteins, sugars, lipids, minerals, and vitamins at the chemical level [9,10]. The fruit's elevated moisture content results in its low-calorie profile. In terms of amino acids, mulberries encompass all nine essential amino acids that the human body cannot synthesize. The sugar content of mulberries varies based on their ripening stage, with glucose and fructose being the principal sugars [11]. These fruits exhibit minimal fat content, with linoleic acid being the dominant fatty acid across all mulberry species [12]. Other noteworthy fatty acids present include palmitic acid and oleic acid [13]. Furthermore, mulberries serve as a mineral source, predominantly containing potassium, phosphorus, and calcium [14]. In the realm of vitamins, mulberries are notably rich in thiamin, riboflavin, niacin, folate, vitamin A, vitamin E, and vitamin K [10].

Mulberry fruits, particularly those with deep coloring, exhibit a noteworthy abundance of polyphenolic compounds. Among these constituents, phenolic acids in mulberries are predominantly represented by hydroxycinnamic acid derivatives such as chlorogenic, cinnamic, and caffeic acids, as well as benzoic acid derivatives including gallic, vanillic, and hydroxybenzoic acids [15]. The cumulative content of these compounds in mulberry fruit ranges from 104.78 to 215.53 mg gallic acid equivalent (GAE) per 100 g of dry weight (DW). Furthermore, mulberries encompass a diverse array of flavonoids, including prominent flavanols such as rutin (the most abundant), quercetin, myricetin, and kaempferol, along with their respective derivatives. Additional flavanols present include catechin, epicatechin, and procyanidin B1 and B2. The combined content of flavonoids is recorded between 64.55 and 211.01 mg catechin equivalent (CE) per 100 g DW. Preeminent anthocyanins detected within mulberry fruits comprise cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3-glucoside, and pelargonidin-3-rutinoside. The concentration of these anthocyanins in mulberries ranges from 45 to 209 mg cyanidin-3-O-glucoside (C3G) equivalent per 100 g of frozen weight [10]. It is noteworthy that the phytochemical composition of mulberries is influenced by factors such as the specific cultivar, geographical region of cultivation, exposure to meteorological conditions, and the stage of ripening at harvest [16].

Both in vitro and in vivo investigations have revealed that the bioactive constituents of mulberry exhibit a spectrum of pharmacological properties, including but not limited to neuroprotection, anti-atherosclerotic, anti-inflammatory, immunomodulatory, antitumor, hypo-lipidic activities, along with anti-obesity effects and cardiovascular disease prevention [10,17,18]. These multifaceted effects stem from the potent antioxidant activity inherent in mulberry, predominantly attributed to its (poly)phenolic compounds (e.g., anthocyanins), which function as efficacious scavengers of oxygen radicals [10]. Anthocyanin intake has been associated with reduced risk of cardiovascular diseases (CVD), hypertension and type 2 diabetes [19]. In addition, results of a recent clinical trial have indicated that anthocyanins can improve sleep quality, stress levels, and depressive symptoms [20]. The cumulative impact of these activities renders mulberry a promising candidate for mitigating metabolic syndrome, as it effectively targets the fundamental etiologies underpinning the various disorders encompassed within this syndrome.

The metabolic syndrome is characterized by the concurrent presence of various pathologies, notably high blood pressure, hyperglycemia, and dyslipidemia [21]. These interconnected conditions collectively amplify the risk of cardiovascular disease (CVD); indeed, this syndrome confers a twofold increase in the susceptibility to both CVD and type 2 diabetes. A pivotal underlying factor is insulin resistance, intricately linked to all these components and seemingly underpinned by genetic determinants [22]. Significantly, obesity stands as a requisite criterion for diagnosing metabolic syndrome, as delineated by the International Diabetes Federation [23]. This body has also promulgated tailored diagnostic criteria, attuned to specific ethnicities, predicated upon assessments encompassing waist circumference, blood lipids (triglycerides and HDL), blood pressure, and fasting glucose. Presently, a definitive therapy for the metabolic syndrome remains elusive, necessitating the individual treatment of each constituent pathology to mitigate cardiovascular disease risk. Diverse strategies can be employed to address these maladies. Modest weight reduction has demonstrated the potential to curtail the onset of metabolic syndrome, complemented by an appropriate lifestyle and moderated physical activity [24]. Pharmacological interventions also feature prominently, encompassing agents such as sibutramine and orlistat for weight loss, metformin and thiazolidinediones for tackling and forestalling insulin resistance, statins, fibrates, omega-3 fatty acids, and niacin to mitigate dyslipidemia, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for hypertension management [25,26]. Notably, bariatric surgery, entailing adiposity redistribution, emerges as a promising avenue, exhibiting efficacy across multiple facets of the metabolic syndrome [27].

The aim of this review is to connect the effectiveness of bioactivities of different mulberry fruit species with metabolic syndrome prevention and management to find natural compounds that can be used in its treatment. Therefore, studies will be analyzed regarding the substances contained in mulberry fruits and their utilization in the prevention or treatment of the risk factors composing the metabolic syndrome.

2. Methods

This systematic review was conducted based on The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [28]. The protocol of this systematic review was registered at the Open Science Framework (https://doi.org/10.17605/OSF.IO/QAH7J).

2.1. Literature search

A systematic search was conducted by MT and SP in Scopus and PubMed on 1st March 2023 using the following search strategy: (mulberry OR Morus) AND (metabolic syndrome OR cholesterol OR insulin OR obesity OR high blood pressure). A manual search was conducted in Google Scholar to identify any relevant studies. The two reviewers (MT and SP) were responsible for screening each article's title, abstract, and full text. MR intervened where required.

2.2. Selection of studies

In vitro and in vivo studies considering cell lines, animal models, and human clinical trials were included. The included studies should have evaluated the effect of any type of mulberry (white, black, and red mulberries) on metabolic syndrome-related factors such as obesity, diabetes, high cholesterol and high blood pressure. Only complete original research articles published in English were considered. No date limit was considered in terms of the year of publication. Studies were excluded if they did not consider parameters not related to metabolic syndrome such as abdominal obesity, impaired fasting glucose, high triglyceride levels and low HDL (high-density lipoprotein) levels.

2.3. Data extraction

The reviewer MT extracted the data from the eligible studies. Firstly, the studies were divided into three categories: in vitro, in vivo (animal studies) and clinical trials (human studies) based on the level of evidence (type of study). The subject (area of research) of each study was identified. The following information was extracted from each study: mulberry type selected to be investigated, sample (or populations), posology/dosage, mechanism of action, and main results. A meta-analysis was not conducted due to the heterogeneity the eligible studies and outcomes measured.

2.4. Risk of bias assessment

The risk of bias assessment for the included studies was performed independently by MT and SP for the in vivo studies. The risk of bias assessment of the animal studies was performed according to the SYRCLE's risk of bias tool for animal studies [29]. This included assessing selection bias (sequence generation, baseline characteristics, and allocation concealment), performance bias (random housing and blinding), detection bias (random outcome assessment and blinding), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). The risk of bias assessment of the human studies was performed according to the revised Cochrane risk of bias tool for randomized trials (RoB 2) [30]. This includes assessing the bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in the measurement of outcome, and bias in the selection of the reported result.

3. Results

A total of 15 research articles were eligible to be considered for this systematic review as shown in the flowchart in Fig. 1. Out of the 15 studies, three studies were based on in vitro analysis, 11 studies were based on animal models and only one clinical study (in humans) was included. It is worth mentioning, that one study included both in vitro and in vivo (animal) experiments [31]. The type of mulberries used in

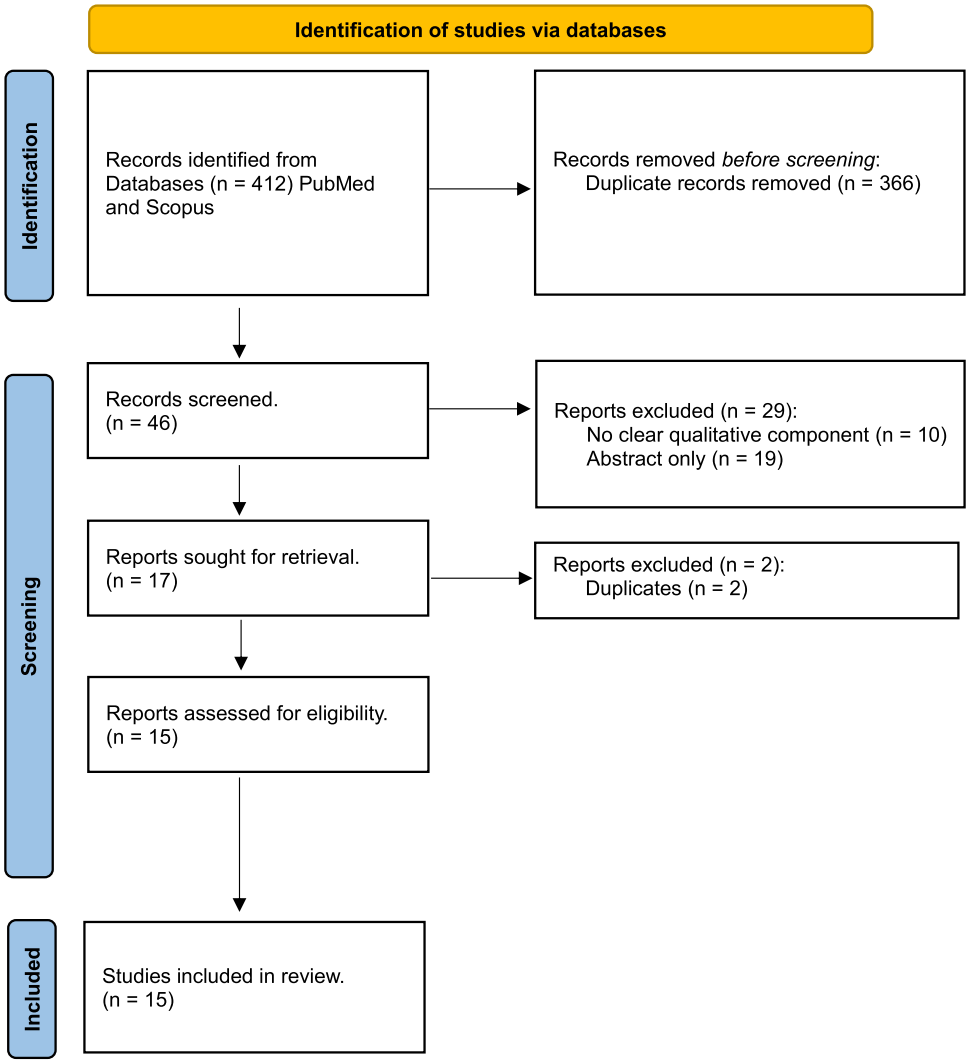

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

the studies differed. Two of the in vitro studies considered white mulberry [31,32], while one study evaluated the effect of black mulberry [33]. The majority of the in vivo animal studies considered investigating the effect of white mulberry [31,34–41], while two other studies considered black mulberry [42,43]. The only study conducted in humans to date used black mulberry [44]. None of the current studies have considered evaluating red mulberry. The summary of all the included studies has been outlined in Table 1 and the summary of the mechanisms of action reported in the included studies has been illustrated in Fig. 2.

3.1. Anti-visceral-obesity effect

Several investigations [32,33,35,37,38,42,43] have unveiled that the daily administration of mulberry fruit extract exhibits the capacity to reduce body weight as compared to animals subjected to a control diet. This effect has been observed over a variable period ranging from 8 to 12 weeks. For example, Chang et al. [32] conducted a study wherein treatment with mulberry anthocyanin extract at doses of 0.1, 0.3, and 0.5 mg/mL demonstrated a noteworthy reduction in lipid content in HepG2 cells, the levels of accumulation diminished to 22.1 %, 34.1 %, and 37.2 % respectively. Furthermore, the treatments with mulberry anthocyanin extract exhibited a decrease in triglyceride synthesis, resulting in a reduction in the expression of glycerol-3-phosphate acyltransferase in comparison to the group induced by oleic acid.

A study by Chen et al. [33] established a correlation between three fractions of black mulberry fruit polysaccharides and their protective effect against palmitic acid-induced lipotoxicity. Notably, BP1 (one of three polysaccharide fractions) treatment displayed a pronounced influence on cell viability and survival rate. BP1 also exhibited a remarkable ability to mitigate the accumulation of reactive oxygen species in HepG2 cells, a primary contributor to palmitic acid-induced lipotoxicity. Additionally, the treatment with BP1 led to an increase in the levels of antioxidant enzymes such as catalase and glutathione peroxidase, which play a pivotal role in maintaining balanced oxidative stress levels. In addition, Chen et al. demonstrated that mulberry fruit polysaccharides exert concentration-dependent effects on body weight increase in mice [42]. The extent of body weight augmentation varied according to the type of diet: NC (normal diet) showed a 7.9 % increase, MC (mild high-fat diet) exhibited a 41.1 % increase, PC (plain high-fat diet) demonstrated a 10.9 % increase, LPD (low-protein diet) displayed a 42.5 % increase, MPD (medium-protein diet) exhibited a 31.2 % increase, and HPD (high-protein diet) showcased a 17.2 % increase.

In a similar vein, Lim et al. explored the anti-obesity properties of mulberry leaves and fruits in obese mice [35]. Their study revealed that treatments with mulberry leaf and fruit extracts (MLFE) led to significant reductions in body weight as compared to mice fed a high-fat diet. Moreover, the MLFE regimen resulted in decreased fat droplet size, reduced crown-like structure count, and hindered hepatic fat deposition by inhibiting fat droplet accumulation. In addition, Peng et al. demonstrated that the administration of varying doses of mulberry water extracts impeded weight gain induced by a high-fat diet, particularly after 10 weeks [37]. Furthermore, mulberry water extracts were found to decrease body fat, reduce the gonadal fat ratio independent of dosage, and decrease the pararenal fat ratio in a dose-dependent manner.

Another in vivo study conducted by Song et al. illustrated that administering mulberry fruit ethanol extract led to a reduction in lipid droplet presence and white adipocyte size, thus thwarting lipid accumulation in the liver [43]. Additionally, mulberry fruit ethanol extract treatment significantly suppressed the expression of glycerol kinase and fatty acid desaturase. An investigation by Wattanathorn et al. established a connection between the reduction in body weight percentage induced by a high-carbohydrate and high-fat diet in ovariectomized rats and the consumption of encapsulated mulberry fruit extract [38]. Notably, the study found that low and medium doses of the extract were associated with an increase in adipocyte density in the gonadal and mesenteric regions. Conversely, a high dose of the extract resulted in a notable elevation of adipocyte density and a reduction in adipocyte size in gonadal, mesenteric, and subcutaneous areas.

3.2. Glycemic lowering effect

The existing body of literature presents a compendium of in vivo investigations that explain the impact of mulberry fruit on diabetes, as evidenced by various studies [31,35,38,42,43]. A study by Chen et al. unveiled that treatment with mulberry fruit polysaccharides yielded a concentration-dependent reduction in blood glucose levels, manifesting a notable decrease in hyperglycemic stress [42]. This reduction was demonstrated across different concentrations, with low (LPD) leading to a decrease of − 32.1 %, medium (MPD) eliciting a reduction of − 42.9 %, and high (HPD) showcasing a substantial decline of − 48.9 %. Furthermore, the study documented a decrease in the area under the curve of blood glucose response for MPD (−16.7 %) and HPD (−24.2 %), as well as diminished serum insulin levels for MPD (−32.9 %) and HPD (−48.8 %). A parallel study by Lim et al. exhibited a significant decrease of approximately 30 % in the area under the curve of the intraperitoneal glucose tolerance test among mice administered a high-fat diet along with mulberry leaves and fruit extract, as compared to those subjected solely to the high-fat diet regimen [35]. This combined intervention also induced reductions in fasting plasma glucose and insulin levels, thus ameliorating the homeostasis model assessment of insulin resistance.

Research by Song et al. corroborated these findings by demonstrating that mulberry ethanol extract treatment was instrumental in enhancing glucose tolerance, insulin resistance, and sensitivity [43]. The treatment was associated with reductions in serum glucose and insulin levels, thereby yielding a lower homeostasis model assessment of the insulin resistance index coupled with an elevated homeostasis model assessment of the insulin sensitivity index. Likewise, a subsequent investigation by Wattanathorn et al. reaffirmed the anti-diabetic potential of mulberry fruit. This study revealed that medium (50 mg/kg BW) and high (250 mg/kg BW) doses of encapsulated mulberry fruit extract exerted favorable effects on fasting blood sugar levels induced by a high-carbohydrate and high-fat diet [38]. Notably, after a four-week regimen, the medium dose of encapsulated mulberry fruit extract significantly curtailed the plasma glucose area under the curve, while at the eight-week mark, all doses of the extract evinced an increased plasma glucose area under the curve.

Furthermore, Yan et al. conducted both in vivo and in vitro investigations, elucidating a noteworthy augmentation in glucose consumption (18.8 %, 17.7 %, and 31.8 % at concentrations of 50, 100, and 250 μg/mL of mulberry anthocyanin extract, respectively) within HepG2 cells [31]. Additionally, the extract exhibited the ability to counteract the suppressed glucose uptake caused by elevated glucose and palmitic acid levels. In the context of db/db mice fed with mulberry anthocyanin extract, a conspicuous reduction (38.7 % and 41.3 %, respectively) in glucose levels was observed, as compared to the control group. Furthermore, the extract ameliorated glucose intolerance, as evidenced by reduced areas under the curve (17.7 % and 24.3 % lower for MAE-50 and MAE-125, respectively), alongside serum insulin concentrations and homeostatic model assessment of insulin resistance indexes.

3.3. Lipid-lowering effect targeting triglycerides and improving HDL cholesterol

Numerous investigations [31,34,36–38,42,44] have explored the lipid-lowering potential of mulberry, particularly in vivo settings involving murine, rodent, and hamster models. Chaiwong et al. recently conducted a randomized controlled trial on mice to elucidate the correlation between mulberry and its lipid-lowering effects [34]. Following a 3-month intervention with dried mulberry fruit powder, a notable reduction in triglyceride levels and an elevation in HDL cholesterol

Table 1
Summary of the current studies investigating the effect of mulberries on metabolic syndrome-related health factors.

Paper	Area of interest	Level of evidence	Mulberry sample	Sample	Posology/dosage	Mechanism of action	Main results
IN VITRO							
Chang et al., 2013	Visceral lipid accumulation	Foundational evidence	White mulberry anthocyanin extract	Human hepatoma cell HepG2, from American Type Culture Collection.	The cells were seeded in a 10 cm dish (1×10^6 cells/well) and treated with 500 mM oleic acid for 24 h. The proteins of the cells were harvested in a cold radioimmunoprecipitation assay (RIPA) buffer containing leupeptin (1.7 μg/mL) and sodium orthovanadate (10 μg/mL). The cell mixture was vortexed at 4 °C for 4 h, then centrifugated at 12000 rpm at 4 °C for 10 min	Mulberry anthocyanins attenuated oleic acid–induced lipid accumulation in HepG2 cells by regulating fatty acid and triglyceride synthesis and activating AMPK (adenosine monophosphate-activate protein kinase).	The treatment with extract showed high relevant expression of the lipogenic enzyme, cholesterol and TG biosynthesis, TG and fatty acid β-oxidation in HepG2 cells, proving his hepatic hypolipidemic effects. Furthermore, MWE reduced HepG2 cellular lipid accumulation by increasing AMPK phosphorylation.
Chen et al., 2021	Visceral lipid accumulation	Foundational evidence	Black mulberry polysaccharide fractions (BP_1, BP_2 and $BP_{3)}$	Human liver HepG2 cells, from the Cell Bank of Type Culture Collection of Chinese Academy of Sciences.	The cells were seeded in a 96-well culture plates at a density of 5×10^3/well then BPs were diluted to 0.05, 0.1 and 0.2 mg/mL with DMEM medium, added into the culture plates and exposed to PA (0.4 mmol/L) for 24 h. Then were added 5 mg/mL of MTT and cells were incubated for 4 h at 37 °C in the dark. The formazan crystals formed were, at the end of the culture period, dissolved in 150 μL DMSO.	BP_1 reduce PA-induced lipotoxicity by eliminating accumulation of ROS, improving mitochondrial function, reversing glutathione depletion and enhancing antioxidant enzyme activities.	BP_1 had the most significant protective effect on PA-induced lipotoxicity. This study showed that BP_1 significantly inhibits the accumulation of ROS and superoxide anion radical induced by PA and alleviate oxidative damage. The treatment with BP_1 also increased the enzyme activities of CAT and GPX to maintain normal metabolic function in HepG2 cells.
Yan et al., 2016	Impaired fasting blood glucose	Foundational evidence	White mulberry anthocyanin extract	HepG2 cells	The cells were cultured in Dulbecco's modified Eagle's medium with 10 % fetal bovine serum, 100 IU/mL penicillin and 100 μg/mL streptomycin at 37 °C and 5 % CO_2 atmosphere. Then were washed twice with PBS and incubated for 24 h with 5.5 mM of normal glucose (negative control) or 30 mM of high glucose plus 0.2 mM of palmitic acid in the absence or presence of extract with different concentrations.	The anti-diabetic effects of anthocyanins are due to the interaction of multiple signaling pathways, enzymes and transcription factors.	The treatment with extract reduced insulin resistance and enzyme activities (PEPCK and G6Pase), and increased glucose consumption, uptake, and content.
IN VIVO – ANIMAL STUDIES							
Chaiwong et al., 2021	Serum lipid levels	Randomized controlled trial (1B)	Dried mulberry fruit powder (dMF), from ripe mulberries (*M. alba*)	24 female C57BL/6 J mice (8 weeks old, weighing 18–20 g)	Mice were randomly divided into 4 groups fed with either control diet, HF diet, HF+ 100 mg/kg dMF or HF+ 300 mg/kg dMF. Duration: 3 months.	The polyphenolic compounds contained in dMF inhibited lipid accumulation and oxidation.	Both doses of dMF prevented the accumulation of visceral fat and the aortic wall-thickening (50 %) and raised HDL levels while reducing TGs levels.
Chen et al., 2018	Impaired fasting blood glucose and	Randomized controlled trial (1B)	Black mulberry (*M. nigra*) fruit polysaccharide (MFP)	50 male obese diabetic *db/db* mice and normal	Diabetic mice were divided into 5 groups, fed differently, MC group received only distilled water, PC group	The MFP (prebiotics) effect the gut microbiota, which plays a vital	The MFP treatment decreased the lipid accumulation and body weight

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Table 1 (*continued*)

Paper	Area of interest	Level of evidence	Mulberry sample	Sample	Posology/dosage	Mechanism of action	Main results
	visceral lipid accumulation			*db/m* mice (8 weeks old)	received 20 mg/kg BW of metformin, LPD group received 200 mg/kg BW of polysaccharides (low dose), MPD group received 500 mg/kg BW of polysaccharides (medium dose) and the HPD group received 800 mg/kg BW of polysaccharides (high dose). The db/m mice were regarded as the NC group and received distilled water only. Duration: 8 weeks.	role in modulating lipid metabolism.	increase, and the blood glucose and insulin levels (in a concentration-dependent manner).
Lim et al., 2013	Visceral lipid accumulation and impaired fasting blood glucose	Randomized controlled trial (1B)	Mulberry (*M. alba*) leaf and fruit extracts (MLE and MFE)	36 male C57BL/6 mice (4 weeks old)	The animals were divided into 6 groups with different diet: CON lean control mice with distilled water, HF high fat fed obese mice with distilled water, LMLE high-fat fed obese mice with low dose of MLE (133 mg/kg/day), HMLE high-fed obese mice with high dose of MLE (333 mg/kg/day), LMLFE high-fat fed obese mice with low dose of MLE and MFE (133 mg/kg/day MLE and 67 mg/kg/day MFE) and HMLFE high-fat fed obese mice with high dose of MLE and MFE (333 mg/kg/day MLE and 167 mg/kg/day MFE). Duration: 12 weeks.	The polyphenolic compounds contained in mulberry fruits and leaves have preventive effects against obesity by reducing proteins levels of oxidative stress and inflammatory markers.	The body weight gain, fasting plasma glucose and insulin levels were significantly reduced in combinational MLFE treatment groups compared with HF group regardless of doses. Moreover, the MLE and MLFE treatments decreased fat droplet accumulation by inhibiting hepatic fat deposition.
Noh et Yoon, 2022	Serum lipid levels	Randomized controlled trial (1B)	Mulberry fruit (*M. alba*) ethanol extract (MBEE)	24 male Sprague-Dawley rats (6 weeks old)	The animals were divided into 4 groups: CON received a normal control diet, HFD high-fat diet, LMB high-fat diet with low dose of MBEE (150 mg/kg/day) and HMB high-fat diet with high dose of MBEE (300 mg/kg/day). Duration: 6 weeks.	MBEE regulates the balance between pro-inflammatory and anti-inflammatory adipokines by reducing leptin and the leptin/adiponectin ratios.	The MBEE treatment did not markedly reduce the high-fat diet-induced weight gain and adipose tissue increase. HMB increased the levels of HDL cholesterol while LMB decreased the levels of plasma triglycerides.
Park et al., 2019	Blood pressure	Randomized controlled trial (1B)	Ethanolic extract of mulberry fruit (EMF) (*M. alba*)	Spontaneously hypertensive rats (SHRs)	The animals were divided into 4 groups: normotensive control, non-treated SHR, low dose (100 mg/kg) EMF-treated SHR and high dose (300 mg/kg) EMF-treated SHR. Duration: 6 weeks	Mulberry reduces blood pressure through its effects on smooth muscle proliferation and vascular contractility.	The treatment with EMF normalized hypertension in SHRs in a dose-dependent manner by preventing smooth muscle proliferation and vascular hyper-reactivity, but it didn't affect the endothelial functions.
Peng et al., 2011	Visceral lipid accumulation and serum lipid levels	Randomized controlled trial (1B)	Mulberry (*M. alba*) water extracts (MWEs)	40 male Syrian golden hamsters (6 weeks old)	The animals were divided into 5 groups: CON standard diet, HFD, HFD with 0,5 % MWEs, HFD with 1 % MWEs and HFD with 2 % MWEs. Duration: 12 weeks	The polyphenolic compounds of MWE have great ability in scavenging free radicals and inhibiting lipid oxidation and oxidative stress, improving the lipid metabolism.	The treatment with MWE lowered the body weight and body fat, the serum TG levels and raised the HDL cholesterol levels.
Song et al., 2016	Impaired fasting blood glucose and visceral lipid accumulation	Randomized controlled trial (1B)	Mulberry fruit (*M. nigra*) ethanol extract (MEE)	36 male C57BL/6 J mice (4 weeks old)	The animals were randomly divided into 3 groups: LFD low-fat diet, HFD high-fat diet, MEE high-fat diet with 100 mg/kg/day of MEE. Duration: 14 weeks.	Anthocyanins have a lipid-lowering effect, due to decreasing the fatty acid synthesis and	The MEE treatment significantly decreases HFD-induced body weight gain, improved hepatic

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Table 1 (*continued*)

Paper	Area of interest	Level of evidence	Mulberry sample	Sample	Posology/dosage	Mechanism of action	Main results
						enhancing the fatty acid oxidation.	lipid profile and attenuated insulin resistance.
Wang et al., 2019	Blood pressure	Randomized controlled trial (1B)	White mulberry (*M. alba*) fruit polysaccharides (WMFPs)	60 male Sprague-Dawley rats (250–300 g) and 10 male SHRs (250–300 g)	The animals were treated with 5 mg/kg w/w, intravenous injection of WMFPs.	Polysaccharides contained in mulberries are considered anti-hypertensive components as they have a direct vessel-relaxing effect, which is caused by direct action on vascular smooth muscle cells or stimulation of the endothelium to free relaxing factors.	The treatment with WMFPs induced endothelium-dependent vessel relaxation in rat mesenteric artery and decreased mean arterial pressure (MAP) in both normotensive rats and SHRs.
Wattanathorn et al., 2019	Visceral lipid accumulation, impaired fasting blood glucose and serum lipid levels	Randomized controlled trial (1B)	Encapsulated mulberry fruit (*M. alba*) extract (MME)	48 female Wistar rats (10 weeks old, weighing 200–250 g)	The animals were divided into 8 groups: Group I normal diet (ND) + vehicle, group II HCHF + vehicle, group II OXV-HCHF + vehicle, group IV OVX-HCHF + isoflavone (15 mg/kg BW), group V OVX-HCHF + L-carnitine (250 mg/kg BW) and group VI-VIII OVX-HCHF + MME (10, 50 and 250 mg/kg BW). Duration: 8 weeks.	The phenolic compounds possess numerous biological activities, such as the increase of HDL-C, the reduction of density and size of adipocyte cells and increase in SOD, CAT and GSH-Px.	The treatment with MME mitigates the increase of body weight, visceral fat mass and triglyceride levels. It also increases PPAR-γ expression, which plays a crucial role on glucose metabolism.
Yan et al., 2016	Impaired fasting blood glucose	Randomized controlled trial (1B)	Mulberry (*M. alba*) anthocyanin extract (MAE)	Male C57BL6/J db/db and m/m mice (4 weeks old)	The animals were randomly divided into 5 groups: 10 nondiabetic lean littermates (m/m), 12 db/db mice fed by gavage with water, and 3 groups of 12 db/db mice fed by gavage with metformin (200 mg/kg BW) and MAE (50 and 125 mg/kg BW). All groups were fed with the same standard diet. Duration: 8 weeks.	The antidiabetic effect of anthocyanins is due to interaction of multiple signaling pathways, enzymes and transcription factors.	The treatment with MAE reduced fasting blood glucose, serum insulin, leptin, triglyceride and cholesterol levels, and incremented adiponectin levels.
Yang et al., 2010	Serum lipid levels	Randomized controlled trial (1B)	Freeze-dried mulberry (*M. alba*) powder (MFP)	30 male Wistar rats (2-month-old)	The animals were divided into 6 groups: normal diet (ND) group, ND + 5 % MFP (NDM I), ND + 10 % MFP (NDM II), high-fat diet (HF) group, HF + 5 % MFP (HFM I) and HF + 10 % MFP (HFM II). Duration: 4 weeks.	Essential unsaturated fatty acids are effective hypolipidemic compounds, they promote the uptake of HDL in the liver and lower plasma lipids.	The treatment with mulberry didn't show significant differences in rats fed with normal diet, whereas remarkably improved the serum and liver lipid profile in subjects fed with high-fat diet.
IN VIVO – HUMAN STUDIES							
Sirikanchanarod et al., 2016	Serum lipid levels	Randomized controlled trial (1B)	Freeze-dried black mulberry fruit	60 hyper-cholesterolemic subjects (8 M and 52 W), aged 30–60 years (fasting total cholesterol level ≥ 200 mg/dL or LDL cholesterol ≥ 130 mg/dL).	The subjects were divided into 2 groups the mulberry group, which consumed 45 g/day of freeze–dried mulberry, and the control group. All the subjects maintained their usual diets, avoiding anthocyanins-rich foods. Duration: 6 weeks.	Natural bioactive compounds, such as anthocyanins, and fibre contained in mulberry fruits exhibit pharmacological and biological effects on human health, including lipid-lowering effects.	The treatment with mulberry remarkably reduced serum TC and LDL-C, but had no significant effect on TAG and HDL-C.

beyond control levels were observed. In a parallel attempt, Chen et al. substantiated the lipid-modulating impact of medium and high doses of mulberry fruit polysaccharides (500 mg/kg and 800 mg/kg) [42]. Following mulberry fruit polysaccharides administration, considerable reductions in lipid and lipoprotein levels were evident in mice, starkly contrasting the model control group, which exhibited significant increases in triacylglycerol levels alongside HDL cholesterol reductions when juxtaposed with the normal control group. Conversely, Noh and Yoon (2022) demonstrated that a 6-week treatment with mulberry fruit ethanol extract failed to elicit noteworthy variations in HDL cholesterol levels in a high-fat diet setting, even though discernible enhancements were observed in the lower mulberry extract dose group [36]. Plasma

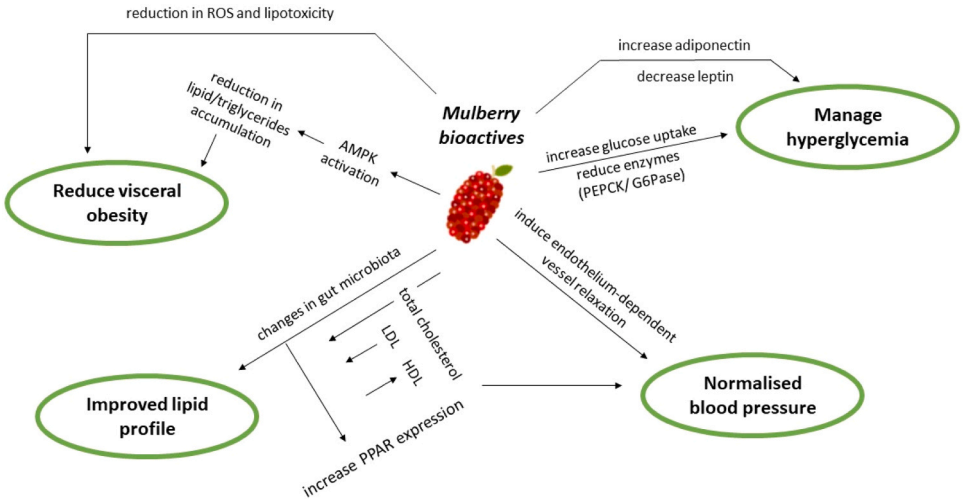

Fig. 2. The main mechanisms of action of mulberries towards reducing the risk of metabolic syndrome.

triglyceride levels remained relatively unaltered across the different treatment groups, with the high mulberry ethanol extract dose exhibiting lower levels in comparison to the high-fat diet group.

Peng et al. underscored the efficacy of mulberry water extracts (MWEs) in attenuating serum lipid levels through meticulous in vivo analysis [37]. Doses of 1 % and 2 % MWEs entirely counteracted the triglyceride elevation stemming from a high-fat diet, concurrently elevating HDL levels. Wattanathorn et al. corroborated these findings, documenting that varied doses of encapsulated mulberry fruit extract engendered significant reductions in triglyceride and cholesterol markers, while simultaneously augmenting HDL cholesterol levels vis-à-vis rats exclusively exposed to a high-carbohydrate and high-fat diet regimen [38]. Parallelly, Yan et al. scrutinized the influence of mulberry on the serum lipid profile [31]. Over a span of 4 weeks, discernible differences were not apparent in the groups subjected to a normal diet supplemented with freeze-dried mulberry powder, except for a noteworthy decline of 18.6 % in triglyceride levels within the high-fat diet group receiving 5 % MFP supplementation. Conversely, the high-fat diet group supplemented with 10 % MFP evidenced a marked reduction of 35.7 % in triglycerides alongside a notable 33.0 % increment in HDL cholesterol.

In a human study, Sirikanchanarod et al. affirmed the cholesterol-reducing influence of mulberry fruits, though HDL-cholesterol and triglyceride levels remained relatively consistent [44]. Noteworthy disparities emerged between the mulberry and control groups, particularly concerning LDL-C (lowered by 6.53 %) and TC (decreased by 3.73 %).

3.4. Blood pressure lowering effects

An in vivo investigation conducted by Wang et al. has documented the hypotensive properties of mulberry through the intravenous administration of white mulberry fruit polysaccharides (WMFPs) [41]. Notably, this intervention elicited a substantial reduction of approximately 10 mmHg in mean arterial pressure (MAP) in rats. Mechanistically, this effect was attributed to the mediation of nitric oxide (NO), as evidenced by a mitigated response in rats pre-treated with the NO synthase inhibitor L-NAME at a dosage of 30 mg/kg. Intriguingly, the hypotensive impact of WMFPs was even more pronounced in spontaneously hypertensive rats, where MAP was impressively lowered by approximately 40 mmHg, compared to its effects in the Sprague-Dawley rat population.

3.5. Risk of bias assessment

The results of the risk of bias assessment of the animal and human studies are presented in Tables 2 and 3, respectively. With respect to selection bias, in 4 out of 11 studies, the allocation sequence was randomly generated and applied. However, in eleven out of 11 studies, the investigators did not describe the sequence generation process such as the use of a random number table or a computer random number generation. For most of the studies, it is not clear how animals were allocated to different groups. In addition, for all studies, all groups had similar characteristics at baseline. Regarding allocation concealment, concealment with low risk for all studies. Indeed, no studies have explicated the concealed procedure when the investigators have allocated the animals to different groups. Moreover, all included studies have a low risk or unclear risk of performance bias. Indeed, the animals were not randomly housed during the experiment, and it is not clear whether the investigators were not blind from knowledge of which intervention each animal received during the experiment. Additionally, overall, it is not specified whether the investigators did not select animals at random for outcome assessment. However, the outcome assessment methods are the same in both groups for all studies. Regarding attrition and reporting bias, the risk is low for all studies since the outcome data reported in each study was completed for each outcome. All primary outcomes have been reported. Finally, the studies did not report other problems that could result in a high risk of bias. In a conclusion, according to SYRCLE's risk of bias tool, the quality of each study is debatable due to an inadequate or unclear randomization of allocation, housing and outcome assessment, and a lack of blinding. However, the studied population has similar characteristics at baseline making the sample homogenous and avoiding confounding bias. Moreover, regarding the reporting of outcomes (complete outcome data reporting, adequate outcome reporting), the risk of bias is low.

With respect to the only human study, it showed a low risk for all selected biases with unclear data on intervention and on reporting the results (Table 3).

4. Discussion

This systematic review has illustrated mulberry's potential as a promising plant food for mitigating the perturbations associated with metabolic syndrome. Predominantly, the studies have centered around its anti-visceral-obesity and lipid-reducing effects. Collectively, these investigations establish a tangible link between mulberry fruit consumption and the observed effects. This underscores the fruit's viability as a credible helpful option for ameliorating metabolic syndrome symptoms. The interventions in these studies spanned an average duration of 8–12 weeks, employing modest oral doses—typically ranging from tens to hundreds (10−800) of mg/kg of body weight per

Table 2
Risk of bias assessment of animal studies according to SYRCLE's risk of bias tool for animal studies.

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Chaiwong et al., 2021	Low risk	Low risk	Low risk	Low risk	Low risk
Chen et al., 2018	Low risk	Low risk	Low risk	Unclear	Low risk
Lim et al., 2013	Unclear	Unclear	Low risk	Unclear	Low risk
Noh et Yoon, 2022	Unclear	Low risk	Low risk	High risk	Low risk
Park et al., 2019	Low risk	Low risk	Low risk	Low risk	Low risk
Peng et al., 2011	Low risk	Unclear	Unclear	High risk	Unclear
Song et al., 2016	Low risk	Unclear	Low risk	Unclear	Unclear
Wang et al., 2019	Unclear	Low risk	Unclear	Unclear	Low risk
Wattanathorn et al., 2019	Low risk	Unclear	Unclear	Unclear	Unclear
Yan et al., 2016	Unclear	Unclear	High risk	Low risk	Low risk
Yang et al., 2010	Unclear	Unclear	Low risk	Low risk	Low risk

Table 3
Risk of bias assessment in human studies according to the revised Cochrane risk of bias tool for randomized trials (RoB 2).

Study	Bias arising from the randomization process	Bias due to deviations from the intended intervention	Bias due to missing outcome data	Bias in measurement of outcome	Bias in selection of the reported result
Sirikanchanarod et al., 2016	Low	Low	Unclear	Low	Unclear

day—of mulberry extracts, powders, or freeze-dried fruits (in the case of human subjects).

The favorable effects of mulberry are predominantly ascribed to its rich polyphenolic content, which interacts with diverse metabolic pathways. In terms of its anti-visceral-obesity effect, these polyphenolic compounds, particularly anthocyanins, exhibit the capacity to modulate fatty acid and triglyceride synthesis, enhance mitochondrial function, and attenuate reactive oxygen species accumulation in HepG2 cells [32]. In vivo, constituents such as resveratrol, rutin [35], and anthocyanins demonstrate efficacy in inhibiting lipid synthesis, accumulation, and oxidation [34], leveraging their free radical scavenging ability [37], while concurrently orchestrating metabolic modulation in tandem with prebiotic agents [42].

Polyphenols exert influence on the elevation of HDL-cholesterol levels and reduction of plasma lipids, notably triglycerides. This effect is manifested through the restraint of cholesterol and bile acid adsorption, alongside the inhibition of hepatic lipogenesis [39]. The antidiabetic impact of mulberry ensues from the intricate interaction between anthocyanins and various signaling pathways, enzymes, and transcription factors [31], culminating in improved glucose regulation and diminished insulin resistance [43].

Furthermore, the collaborative interplay of polyphenolic compounds and polysaccharides, denoted as anti-hypertensive constituents, elicits a direct vessel-relaxing response, attributed to their modulation of vascular smooth muscle proliferation and vascular contractility [40], alongside endothelial stimulation that potentiates the release of vasodilatory factors [41]. This concerted action culminates in the notable reduction of blood pressure.

Among the studied varieties, white mulberry emerges as the predominant subject, yielding the most profound outcomes. This is particularly evident in investigations scrutinizing its impact on serum lipid levels [34,36–39] and blood pressure- [40,41]. In these contexts, its composition rich in rutin, quercetin, gallic acid, chlorogenic acid, myricetin, caffeic acid, and polysaccharides assumes a pivotal role in mitigating the spectrum of maladies encompassing metabolic syndrome. Conversely, black mulberry demonstrates compelling findings, particularly in the reduction of visceral lipid accumulation [33,42,43] and the amelioration of impaired fasting blood glucose [42,43]. These effects are attributed to its bioactive constituents, notably cyanidin-3-glucoside, cyanidin-3-rutoside, and polysaccharides.

5. Conclusions

Based on these data, it can be inferred that the utilization of white mulberry holds greater promise in the management of ailments like hypertension and dyslipidemia. Conversely, black mulberry displays efficacy in addressing diabetes and obesity. This information holds significance for guiding future investigations, guiding the selection of the most appropriate mulberry variety for specific therapeutic purposes. This review serves as a reference point in the extant literature, consolidating studies that investigate the potential of mulberry as a mitigating factor for pathologies within the metabolic syndrome spectrum. It also serves as a foundation for expanding research into nascent areas, including human studies, the impact of mulberry fruit on blood pressure, and the effects of red mulberry, both in vitro and in vivo. The study's limitations encompass the omission of examinations involving mulberry leaves, which hold noteworthy medicinal properties and comparable potential within the medical domain.

CRediT authorship contribution statement

MT: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **AAR:** Visualization, Writing – original draft, Writing – review & editing. **MR**: Validation, Writing – review & editing. **SP**: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] K. Vijayan, B.N. Gnanesh, T. Amalendu, Botanical features and economic significance of mulberry. in: The Mulberry Genome, Springer International Publishing, Cham, 2023, pp. 1–11.

[2] E.D. Baciu, G.M. Baci, A.R. Moise, D.S. Dezmirean, A status review on the importance of mulberry (Morus spp.) and prospects towards its cultivation in a controlled environment, Horticulturae 9 (4) (2023) 444.

[3] P. Saini, G.K. Rohela, J.S. Kumar, A.A. Shabnam, A. Kumar, Cultivation, utilization, and economic benefits of mulberry. in: The Mulberry Genome, Springer International Publishing,, Cham, 2023, pp. 13–56.

[4] K. Vijayan, The emerging role of genomic tools in mulberry (Morus) genetic improvement, Tree Genet. Genomes 6 (4) (2010) 613–625.

[5] Y. Yang, Y.X. Tan, R.Y. Chen, J. Kang, The latest review on the polyphenols and their bioactivities of Chinese Morus plants, J. Asian Nat. Prod. Res. 16 (6) (2014) 690–702.

[6] B.K. Singhal, M.A. Khan, A. Dhar, F.M. Baqual, B.B. Bindroo,). Approaches to industrial exploitation of mulberry (Mulberry sp.) fruits, J. Fruit. Ornam. Plant Res. 18 (1) (2010) 83–99.

[7] Y. Jiang, W.J. Nie, Chemical properties in fruits of mulberry species from the Xinjiang province of China, Food Chem. 174 (2015) 460–466.

[8] M. Imran, H. Khan, M. Shah, R. Khan, F. Khan, Chemical composition and antioxidant activity of certain Morus species, J. Zhejiang Univ. Sci. B 11 (2010) 973–980.

[9] D. Bhattacharjya, A. Sadat, P. Dam, D.F. Buccini, R. Mondal, T. Biswas, A. K. Mandal, Current concepts and prospects of mulberry fruits for nutraceutical and medicinal benefits, Curr. Opin. Food Sci. 40 (2021) 121–135.

[10] Q. Yuan, L. Zhao, The mulberry (Morus alba L.) fruit-a review of characteristic components and health benefits, J. Agric. Food Chem. 65 (48) (2017) 10383–10394.

[11] T. Mahmood, F. Anwar, M. Abbas, M.C. Boyce, N. Saari, Compositional variation in sugars and organic acids at different maturity stages in selected small fruits from Pakistan, Int. J. Mol. Sci. 13 (2) (2012) 1380–1392.

[12] L. Liang, X. Wu, M. Zhu, W. Zhao, F. Li, Y. Zou, L. Yang, Chemical composition, nutritional value, and antioxidant activities of eight mulberry cultivars from China, Pharmacogn. Mag. 8 (31) (2012) 215–224.

[13] E.M. Sánchez-Salcedo, E. Sendra, Á.A. Carbonell-Barrachina, J.J. Martínez, F. Hernández, Fatty acids composition of Spanish black (Morus nigra L.) and white (Morus alba L.) mulberries, Food Chem. 190 (2016) 566–571.

[14] A. Ali Redha, A. Freije, C. Kodikara, M. Rondanelli, E. Aqeel, W. Zafar, H. Albunni, H. Merza, A. Khonji, M. Aljar, S. Perna, Comparison of fatty acid profile and mineral content of black mulberry (Morus nigra), white mulberry (Morus alba) and red mulberry (Morus rubra) grown in Bahrain, Appl. Food Res. 3 (2) (2023), 100358, https://doi.org/10.1016/j.afres.2023.100358.

[15] I. Khalifa, W. Zhu, K.K. Li, C.M. Li, Polyphenols of mulberry fruits as multifaceted compounds: compositions, metabolism, health benefits, and stability—a structural review, J. Funct. Foods 40 (2018) 28–43.

[16] A.R. Memete, A.V. Timar, A.N. Vuscan, F. Miere, A.C. Venter, S.I. Vicas, Phytochemical composition of different botanical parts of Morus species, health benefits and application in food industry, Plants 11 (2) (2022) 152.

[17] M.Y. Wani, N.A. Ganie, D.M. Wani, A.W. Wani, S.Q. Dar, A.H. Khan, M. H. Dehghani, The phenolic components extracted from mulberry fruits as bioactive compounds against cancer: a review, Phytother. Res. 37 (3) (2023) 1136–1152.

[18] V. Ipek, B.M. Balkan, M.E. Inanc, O. Kaplan, O. Corum, S. Gungor, A. Ata, Effects of mulberry extract on the liver pathology and serum biochemical parameters in carmustine administrated rats, J. Berry Res. 12 (1) (2022) 59–71.

[19] F. Giampieri, D. Cianciosi, J.M. Alvarez-Suarez, J.L. Quiles, T.Y. Forbes-Hernández, M.D. Navarro-Hortal, Y.A. Diaz, Anthocyanins: what do we know until now? J. Berry Res. 13 (1) (2023) 1–6.

[20] A. Micek, M. Owczarek, J. Jurek, I. Guerrera, S.A. Torrisi, G. Grosso, J. Godos, Anthocyanin-rich fruits and mental health outcomes in an Italian cohort, J. Berry Res. 12 (4) (2022) 551–564.

[21] M.E. Rubio-Ruiz, V. Guarner-Lans, I. Pérez-Torres, M.E. Soto, Mechanisms underlying metabolic syndrome-related sarcopenia and possible therapeutic measures, Int. J. Mol. Sci. 20 (3) (2019).

[22] D.E. James, J. Stöckli, M.J. Birnbaum, The aetiology and molecular landscape of insulin resistance, Nat. Rev. Mol. Cell Biol. 22 (11) (2021) 751–771.

[23] D. Nagayama, Y. Watanabe, T. Yamaguchi, K. Suzuki, A. Saiki, K. Fujishiro, K. Shirai, Issue of waist circumference for the diagnosis of metabolic syndrome regarding arterial stiffness: possible utility of a body shape index in middle-aged nonobese Japanese urban residents receiving health screening, Obes. Facts 15 (2) (2022) 160–169.

[24] J. Myers, P. Kokkinos, E. Nyelin, Physical activity, cardiorespiratory fitness, and the metabolic syndrome, Nutrients 11 (7) (2019).

[25] T.D. Müller, M. Blüher, M.H. Tschöp, R.D. DiMarchi, Anti-obesity drug discovery: advances and challenges, Nat. Rev. Drug Discov. 21 (3) (2022) 201–223.

[26] A.J. Garber, A.J. Garber, Y. Handelsman, G. Grunberger, D. Einhorn, M. J. Abrahamson, J.I. Barzilay, L. Blonde, M.A. Bush, R.A. DeFronzo, J.R. Garber, W. T. Garvey, et al., Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary, Endocr. Pract. 26 (1) (2020) 107–139.

[27] K.A. Martin, M.V. Mani, A. Mani, New targets to treat obesity and the metabolic syndrome, Eur. J. Pharmacol. 763 (2015) 64–74.

[28] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) 71.

[29] C.R. Hooijmans, M.M. Rovers, R.B. De Vries, M. Leenaars, M. Ritskes-Hoitinga, M. W. Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med. Res. Methodol. 14 (2014) 43.

[30] J.A. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, J. P. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) 14898.

[31] F. Yan, G. Dai, X. Zheng, Mulberry anthocyanin extract ameliorates insulin resistance by regulating PI3K/AKT pathway in HepG2 cells and db/db mice, J. Nutr. Biochem. 36 (2016) 68–80.

[32] J.J. Chang, M.J. Hsu, H.P. Huang, D.J. Chung, Y.C. Chang, C.J. Wang, Mulberry anthocyanins inhibit oleic acid induced lipid accumulation by reduction of lipogenesis and promotion of hepatic lipid clearance, J. Agric. Food Chem. 61 (25) (2013) 6069–6076.

[33] W. Chen, Y. Lu, D. Hu, J. Mo, J. Ni, Black mulberry (Morus nigra L.) polysaccharide ameliorates palmitate-induced lipotoxicity in hepatocytes by activating Nrf2 signaling pathway, Int. J. Biol. Macromol. 172 (2021) 394–407.

[34] S. Chaiwong, U. Chatturong, R. Chanasong, W. Deetud, K. To-On, S. Puntheeranurak, K. Chootip, Dried mulberry fruit ameliorates cardiovascular and liver histopathological changes in high-fat diet-induced hyperlipidemic mice, J. Tradit. Complement. Med. 11 (4) (2021) 356–368.

[35] H.H. Lim, S.O. Lee, S.Y. Kim, S.J. Yang, Y. Lim, Anti-inflammatory and antiobesity effects of mulberry leaf and fruit extract on high fat diet-induced obesity, Exp. Biol. Med. 238 (10) (2013) 1160–1169.

[36] D.J. Noh, G.A. Yoon, Mulberry (Morus alba L.) ethanol extract attenuates lipid metabolic disturbance and adipokine imbalance in high-fat fed rats, Nutr. Res. Pract. 16 (6) (2022) 716–728.

[37] C.H. Peng, L.K. Liu, C.M. Chuang, C.C. Chyau, C.N. Huang, C.J. Wang, Mulberry water extracts possess an anti-obesity effect and ability to inhibit hepatic lipogenesis and promote lipolysis, J. Agric. Food Chem. 59 (6) (2011) 2663–2671.

[38] J. Wattanathorn, S. Kawvised, W. Thukham-Mee, Encapsulated mulberry fruit extract alleviates changes in an animal model of menopause with metabolic syndrome, Oxid. Med. Cell. Longev. (2019) *2019*.

[39] X. Yang, L. Yang, H. Zheng, Hypolipidemic and antioxidant effects of mulberry (Morus alba L.) fruit in hyperlipidaemia rats, Food Chem. Toxicol. 48 (8–9) (2010) 2374–2379.

[40] S.W. Park, K.C. Shin, S.K. Yoou, H.J. Park, S.H. Eun, Y.M. Bae, B.H. Choi, Effects of an ethanolic extract of mulberry fruit on blood pressure and vascular remodeling in spontaneous hypertensive rats, Clin. Exp. Hypertens. 41 (3) (2019) 280–286.

[41] C. Wang, W. Cheng, S. Bai, L.I. Ye, J. Du, M. Zhong, B. Shen, White mulberry fruit polysaccharides enhance endothelial nitric oxide production to relax arteries in vitro and reduce blood pressure in vivo, Biomed. Pharmacother. 116 (2019), 109022.

[42] C. Chen, L.J. You, Q. Huang, X. Fu, B. Zhang, R.H. Liu, C. Li, Modulation of gut microbiota by mulberry fruit polysaccharide treatment of obese diabetic db/db mice, Food Funct. 9 (7) (2018) 3732–3742.

[43] H. Song, J. Lai, Q. Tang, X. Zheng, Mulberry ethanol extract attenuates hepatic steatosis and insulin resistance in high-fat diet–fed mice, Nutr. Res. 36 (7) (2016) 710–718.

[44] A. Sirikanchanarod, A. Bumrungpert, W. Kaewruang, T. Senawong, P. Pavadhgul, The effect of mulberry fruits consumption on lipid profiles in hypercholesterolemic subjects: a randomized controlled trial, J. Pharm. Nutr. Sci. 60 (2016) 7–14.