JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Review

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The Mulberry (*Morus alba* L.) Fruit—A Review of Characteristic Components and Health Benefits

Qingxia Yuan[†,‡] and Longyan Zhao*[,†,‡]

[†]School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan 430074, P. R. China

[‡]National Demonstration Center for Experimental Ethnopharmacology Education, South-Central University for Nationalities, Wuhan 430074, P. R. China

ABSTRACT: Mulberry (*Morus alba* L.) fruit has a high yield in one fruiting season in many countries, especially in Asia, and a long history of use as an edible fruit and traditional medicine. A great diversity of nutritive compounds such as fatty acids, amino acids, vitamins, minerals, and bioactive compounds, including anthocyanins, rutin, quercetin, chlorogenic acid, and polysaccharides have been found in mulberry fruit depending on the cultivars and maturity stages. Furthermore, the extracts and active components of mulberry fruit have demonstrated numerous biological activities, including antioxidant, neuroprotective, antiatherosclerosis, immunomodulative, antitumor, antihyperglycemic, and hypolipidemic activities in *in vitro* and *in vivo* studies, and they have received increasing interest from researchers and pharmaceutical companies. Although some mechanistic studies further substantiate these potential health benefits of mulberry fruit, a need exists to make a better understanding of the roles of these compounds in traditional medicine and the diet. This review provides recent findings regarding the chemical constituents and biological activities of mulberry fruit, which may be useful for stimulating deep research of mulberry fruit and for predicting their uses as important and safe contributors to benefit human health.

KEYWORDS: *Morus alba L., mulberry fruit, nutritive compounds, bioactive compounds, biological activities*

INTRODUCTION

Mulberry belongs to the genus *Morus* in the Moraceae family and is globally distributed under varied climatic conditions, ranging from tropical to temperate.[1,2] This plant contains 24 species and one subspecies, and *Morus alba* L. is a dominant species among them.[3,4] The origin of most cultivated mulberry varieties is traced back to the area of China/Japan and the Himalaya foothills. China is the country with the largest area of mulberry, which is above 626 000 ha, and then India nearly 280 000 ha.[5] The fruit of *Morus alba* L. is called mulberry in the English-speaking world and is also known as Sang Shen in China and Oddi in Korea, with high yield of more than 10 kg per tree from some cultivars in one fruiting season.[6]

In most mulberry-growing countries, mulberry fruit is commonly eaten fresh, dried, or processed into wine, fruit juice, and jam for its delicious taste, pleasing color, low calorie content, and high nutrient content.[7−9] In China, Korea, and Japan, mulberry fruit is also used in folk medicine for its pharmacological effects, including fever reduction, treatment of sore throat, liver and kidney protection, eyesight improvement, and ability to lower blood pressure.[10,11] The mulberry fruit was designated one of the first medicinal-and-edible plants by the Ministry of Health of China in 1985, and its medical use was recorded in the Chinese pharmacopoeia.[12] In support of these traditional properties, numerous studies have been conducted to confirm its chemical constituents, including amino acids, fatty acids, mineral, polyphenolics, and polysaccharides.[13−15] Previous studies have indicated that mulberry fruit extracts (MFE), such as anthocyanins, rutin, and polysaccharides, possess a range of biological activities, including neuroprotective, antioxidant, and antiobesity effects, as well as prevention of cardiovascular disease, immunomodulation, and antitumor activity.[16−20]

To our knowledge, a detailed compilation of research regarding the nutritional composition, phytochemicals, and bioactivities of mulberry fruit is lacking. To better utilize mulberry fruit, this paper aims to summarize recent knowledge regarding the composition and biological activities, among other perspectives, of mulberry fruit. This review may be useful for predicting other health benefits and potential drugs and may encourage new research and relevant industries to more deeply explore mulberry fruit in the future.

NUTRIENTS

Morus alba L. fruit contains abundant protein, lipid, carbohydrate, fiber, minerals, and vitamins but low calories (Table 1), which can be a healthy food choice for consumers. 100 g of the fresh mulberry fruit can produce 1.44 g of protein, which is higher than that of strawberries (0.67 g/100 g)[21] and raspberries (1.20 g/100 g)[22] and comparable to that of blackberries (1.39 g/100 g).[23] A total of 18 amino acids, including all nine essential amino acids required by humans, are found in mulberry fruit. The essential amino acid (EAA)/total amino acid (TAA) ratio is 42%, which is close to those of some high quality protein foods such as milk and fish.[13] The essential amino acid score (EAAS) of several EAA is more than 100, which meets the requirements of children or adults, according

Received: August 3, 2017
Revised: November 11, 2017
Accepted: November 12, 2017
Published: November 13, 2017

DOI: 10.1021/acs.jafc.7b03614
J. Agric. Food Chem. 2017, 65, 10383−10394

Table 1. Nutrient Composition of Fresh Mulberry Fruit[a]

Type	Unit	Content (per 100 g)	Type	Unit	Content (per 100 g)
Proximates			Vitamins		
Water	g	87.68	Vitamin C, total ascorbic acid	mg	36.4
Energy	kcal	43	Thiamin	mg	0.029
Protein	g	1.44	Riboflavin	mg	0.101
Total lipid	g	0.39	Niacin	mg	0.62
Carbohydrate	g	9.8	Vitamin B-6	mg	0.05
Fiber, total dietary	g	1.7	Folate, DFE	μg	6
Sugars, total	g	8.1	Vitamin A, RAE	μg	1
Minerals			Vitamin A, IU	IU	25
Calcium, Ca	mg	39	Vitamin E (alpha-tocopherol)	mg	0.87
Iron, Fe	mg	1.85	Vitamin K (phylloquinone)	μg	7.8
Magnesium, Mg	mg	18	Lipids		
Phosphorus, P	mg	38	Fatty acids, total saturated (SFA)	g	0.027
Potassium, K	mg	194	Fatty acids, total monounsaturated (MUFA)	g	0.041
Sodium, Na	mg	10	Fatty acids, total polyunsaturated (PUFA)	g	0.207
Zinc, Zn	mg	0.12			

[a](Adapted from USDA National Nutrient Database, 2011).

to the FAO/WHO/UNU reference.[24] Therefore, to a lesser extent, mulberry fruit could be a good protein source.

The order of abundance of fatty acids in mulberry fruit is polyunsaturated fatty acids (PUFA) > monounsaturated fatty acids (MUFA) > saturated fatty acids (SFA). PUFA were the major fraction of fatty acids, representing at least 76.68%,[25] which was determined to be higher than that of strawberries (~72%) and jujube (68.54−72.44%).[21,26] Ercisli and Orhan[3] and Sánchez-Salcedo et al.[25] both identified 14 fatty acids from mulberry fruit with different compositions and contents. The fatty acid profile can be affected by variables including environmental conditions and genetic factors.[25,27] In general, linoleic acid (C18:2), palmitic acid (C16:0), and oleic acid (C18:1) were the major fatty acids in mulberry fruit. The predominant fatty acid was linoleic acid (C18:2), which is necessary for human development, health promotion, and disease prevention, and it must be obtained from exogenous sources because humans cannot synthesize it.[28−30]

The sugar content in mulberry fruit increases during ripening.[31] The principal sugars are glucose and fructose.[32,33] Mulberry fruit is an outstanding source of minerals, particularly potassium, followed by calcium and phosphorus. High amounts of ascorbic acid are present, in the fresh fruit, at 36.4 mg/100 g of fresh weight (FW) mulberry fruit. In addition, mulberry fruit also provides other vitamins, such as thiamin, riboflavin, niacin, folate, vitamin A, vitamin B-6, vitamin E, and vitamin K. Four tocopherols were detected in mulberry fruit by Yang et al.[34] γ-Tocopherol (0.245 mg/g, including β-tocopherol) was present at the largest amount, followed by δ-tocopherol (0.074 mg/g) and α-tocopherol (0.004 mg/g). These reported nutrients in the mulberry fruit are beneficial for human health.

■ BIOACTIVE COMPOUNDS

Polyphenolics. Berry fruits are rich sources of polyphenolics. Polyphenolics represent a large family and are classified by their structural characteristics as flavonoids (anthocyanins, flavanols or catechins, flavonols, flavones, flavanones, isoflavonoids), phenolic acids, stilbenes, tannins, and lignans.[35,36] It is well established that intake of foods rich in polyphenols is associated with a reduced risk of cancer, cardiovascular diseases, and neurodegeneration.[36,37] Significant amounts and a wide diversity of phenolic compounds are present in mulberry fruit (Figure 1). The total phenolic, flavonoid, and anthocyanin

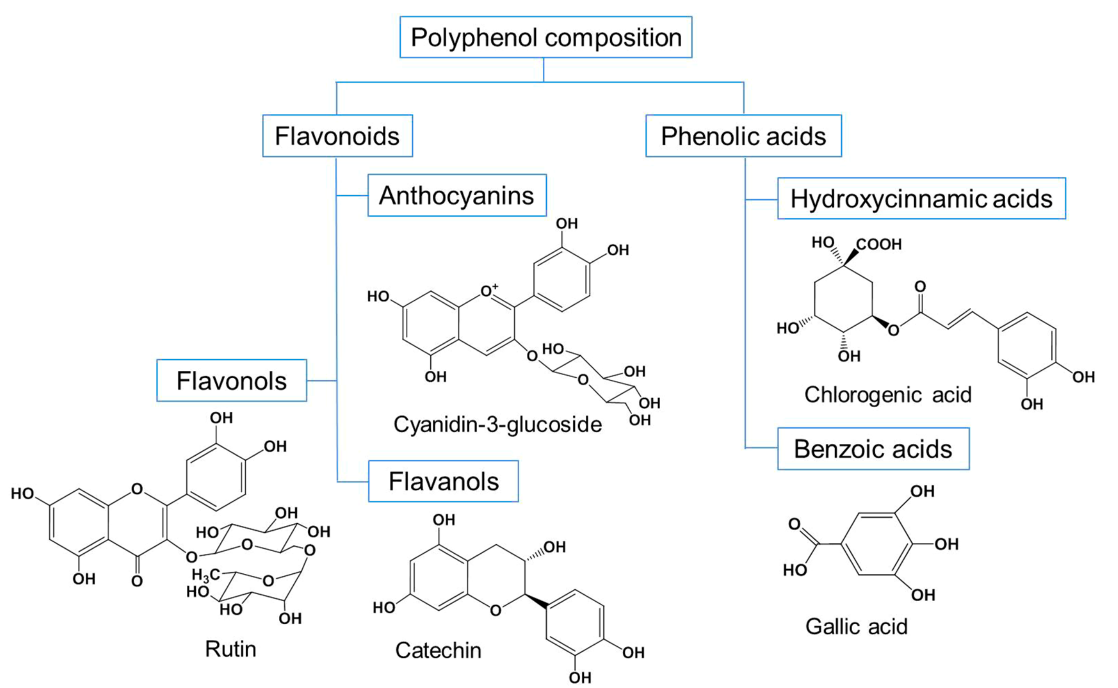

Figure 1. Chemical structures of the main polyphenol compounds in mulberry fruit.

DOI: 10.1021/acs.jafc.7b03614
J. Agric. Food Chem. 2017, 65, 10383−10394

Table 2. Polyphenol Composition in Mulberry Fruit

Class	Subclass	Compound	Content	References
Flavonoids	Anthocyanins	Cyanidin-3-glucoside	301.75 mg/g MAE[a]	42, 43
		Cyanidin-3-rutinoside	108.79 mg/g MAE	42, 43
		Pelargonidin-3-glucoside	NA[b]	95, 110
		Pelargonidin-3-rutinoside	NA	95, 110
		Cyanidin 3-O-(6″-O-α-rhamnopyranosyl-β-D-glucopyranoside)	270 mg/g CMA[c]	46
		Cyanidin 3-O-(6″-O-a-rhamnopyranosyl-β-D-galactopyranoside)	57 mg/g CMA	46
		Cyanidin 3-O-β-D-galactopyranoside	233 mg/g CMA	46
		Cyanidin 7-O-β-D-glucopyranoside	33 mg/g CMA	46
		Petunidin 3-O-β-glucopyranoside	5.1 mg/g CEE[d]	47
	Flavonols	Rutin	0.065−7.728 mg/100 g FW[e]	38
		Quercetin	31.88−58.42 mg/100 g DW[f]	39
		Quercetin 3-O-rutinoside	2.869 mg/100 g FW	48
		Quercetin 3-O-glucoside	1.069 mg/100 g FW	48
		Quercetin 3-O-galactoside	0.002 mg/100 g FW	48
		Myricetin	0.66−1.18 mg/100 g DW	39
		Kaempferol	0.24−1.61 mg/100 g DW	39
		Kaempferol 3-O-glucoside	1.623 mg/100 g FW	48
		Kaempferol 3-O-rutinoside	2.00−14.00 mg/100 g DW	14
	Flavanols	Catechin	309.26−750.01 mg/100 g DW	39
		Epigallocatechin Gallate	0.033−0.086 mg/100 g DW	38
		Epicatechin	8.47−17.12 mg/100 g DW	39
		Procyanidin B1	59.64−224.41 mg/100 g DW	39
		Procyanidin B2	1.02−5.66 mg/100 g DW	39
Phenolic acid	Hydroxycinnamic acid	Chlorogenic acid	5.3−17.3 mg/100 g DW	33
		Ferulic acid	0.057−2.949 mg/100 g DW	38
		p-Coumaric acid	0.024−0.142 mg/100 g DW	38
		o-Coumaric acid	0.015 mg/g FW	32
		Cinnamic acid	11.64−15.05 mg/100 g DW	39
		Caffeic acid	1.06−8.17 mg/100 g DW	39
	Benzoic acid	Gallic acid	7.33−23.34 mg/100 g DW	39
		p-Hydroxybenzoic acid	0.028−0.154 mg/100 g DW	38
		Syringic acid	0.049 mg/g FW	32
		Protocatechuic acid	0.264−0.794mg/ 100 g FW	38
		Vanillic acid	0.008 mg/g FW	32

[a]MAE, mulberry anthocyanin extract. [b]NA, not available. [c]CMA, crude mulberry anthocyanin. [d]CEE, crude ethanol extract. [e]FW, frozen weight. [f]DW, dry weight.

contents in mulberry fruit are 104.78−215.53 mg gallic acid equivalent (GAE)/100 g dry weight (DW), 64.55−211.01 mg catechin equivalent (CE)/100 g DW, and 45.42−208.74 mg cyanidin-3-*O*-glucoside (C3G) equivalent/100 g frozen weight, respectively.[38,39] The phenolic contents in mulberry fruit vary with different cultivars.[38,39] Besides the cultivars, maturity stages also exert significant influences on the phenolic content of mulberry fruit. The phenolic contents in mulberry fruit increase as the fruit progresses from unripened to fully ripened stages.[40] Lin and Tang[41] compared the total phenolic and flavonoid contents in four selected fruit species. The results showed that the total phenolic and flavonoid contents were significantly higher in mulberry fruit (1515.9 ± 5.7 mg GAE/100 g fresh matter (FM), 250.1 ± 6.3 mg quercetin equivalent (QE)/100 g FM) than other deep-colored fruits, such as strawberry (363.7 ± 6.7 mg GAE/100 g FM, 14.6 ± 3.0 mg QE/100 g FM), oriental plum (668.0 ± 8.0 mg GAE/100 g FM, 37.6 ± 7.0 mg QE/100 g FM), and loquat (199.4 ± 13.1 mg GAE/100 g FM, 14.2 ± 0.9 mg QE/100 g FM).

Anthocyanins. Anthocyanins are a subclass of flavonoids and a major contributor to flower and fruit colors ranging from red to blue and purple. Mulberry fruit anthocyanins have received a great amount of attention because of their multiple biological effects, including antitumor, antioxidant, and antidiabetic activities. Various anthocyanins have been identified and quantified in mulberry fruit (Table 2). The principal anthocyanin in mulberry fruit is C3G (Figure 1), followed by cyanidin-3-rutinoside (C3R).[42,43] A small amount of pelargonidin-3-glucoside and pelargonidin-3-rutinoside has been detected in mulberry fruit in addition to C3G and C3R in some reports.[44,45] Using high-speed counter-current chromatography, Du et al.[46] identified five anthocyanins in mulberry fruit: cyanidin 3-*O*-(6″-*O*-α-rhamnopyranosyl-β-D-glucopyranoside) (C3RG) (also known as keracyanin), cyanidin 3-*O*-(6″-*O*-a-rhamnopyranosyl-β-D-galactopyranoside) (C3RGa), C3G, cyanidin 3-O-β-D-galactopyranoside (C3Ga), and cyanidin 7-O-β-D-glucopyranoside (C7G). In another analytical study, the main anthocyanin was C3RGa, at 41.3% of mulberry anthocyanin extract (MAE), and other isolated pigments were C3RG and petunidin 3-O-β-glucopyranoside.[47]

Flavonols and Flavanols. Flavonols and flavanols are also the subgroups of flavonoids. Their structures are similar but slightly different in C-2, C-3, and C-4 positions. Compared to flavanols, flavonols have a double bond between C-2 and C-3 and a carbonyl group at C-4 of the C ring. Mulberry fruit contains many flavonols, including rutin (Figure 1), quercetin,

DOI: 10.1021/acs.jafc.7b03614
J. Agric. Food Chem. 2017, 65, 10383−10394

Table 3. Polysaccharides Isolated from the Fruit of *Morus alba* L

No.	Compound name	Molecular weight (kDa)	Monosaccharide Composition (molar ratio)	Structures	Bioactivities	References
1	FMAP	130	Gal, Man, Glc	Backbone composed of 1→3-*β*-D-Man*p*, branches composed of 1→6-*β*-D-Man*p* 1→3-*β*-D-Gal*p* and 1→4-*β*-D-Man*p*, terminated with Man residues		15
2	MFP		Ara:Gal:Glc = 13.4:8.32:78.47		Antioxidant and hypoglycemic activities	57
3	MFP-1		Ara:Gal:Glc = 7.19:6.33:86.48		Antioxidant and hypoglycemic activities	57
4	MFP-2		Ara:Gal:Glc = 36.01:34.12:29.87		Antioxidant and hypoglycemic activities	57
5	MP				Anti-inflammatory and antiapoptotic activities	59
6	PMF1	71.69	Xyl:Gal = 3.26:96.74	1→3, 1→6,1→2 linked Glc*p* and Xyl*p*		130
7	PMF2	84.33	Glc	1→3, 1→6,1→2 linked Glc*p*, *α*, *β*-Glycosidic bond		130
8	PMF3	103.17	Rha:Fuc:Xyl:Man:Glc:Gal = 9.31:1.76:13.09:14.18:25.49:36.17	1→3, 1→6,1→2 linked Glc*p*, (1→5)-Rha, *α*, *β*-Glycosidic bond		130
9	MFP-1	9.5,7.9,1.0,0.7	Ara:Gal:Glc:Xyl:Man = 19.2:31.4:26.3:5.98:7.12		Antioxidant and hypoglycemic activities	58
10	MFP-2	149,9.3,2.6,1.5	Ara:Gal = 44.9:55.2		Antioxidant and hypoglycemic activities	58
11	MFP-3	167,5.0,1.5	Ara:Gal = 55.3:44.7		Antioxidant and hypoglycemic activities	58
12	MFP-4	185,64.4,1.5,0.2	Ara:Gal:Glc = 59.9:27.2:13.0		Antioxidant and hypoglycemic activities	58
13	MFP3P	136.6	Rha:Ara:Gal:Glc:GalA = 25.98:21.51:23.1:13.06:16.35	Mainly composed of 1→6-linked glucose, T-arabinose, 1→2/1→3-linked rhamnose, and 1→3-linked galactose	Antioxidant and hypoglycemic activities	81
14	JS-MP-1	1639	Gal:Ara:Rha:Glc:Xyl:Man:Fuc = 37.6:36.3:18.4:3.1:1.7:1.6:1.3	Backbone composed of alternating sequences of (1→2)-*α*-L-Rha and (1→4)-*α*-D-GalA. Branches composed of (1→5)-*α*-L-Ara terminated with Ara residues, and (1→6)-*β*-D-Gal terminated with Ara residues.	Immunomodulation and antiobesity	60, 89

DOI: 10.1021/acs.jafc.7b03614
J. Agric. Food Chem. 2017, 65, 10383−10394

myricetin, and kaempferol (Table 2). Derivatives of quercetin and kaempferol are the major components of mulberry fruit flavonols. Glycosylated forms of quercetin and kaempferol, such as quercetin 3-*O*-rutinoside, quercetin 3-*O*-glucoside, quercetin 3-*O*-galactoside, kaempferol 3-*O*-glucoside, and kaempferol 3-*O*-rutinoside, have been found in some mulberry fruit cultivars.[14,48]

Generally, flavanols do not occur naturally as glycosides. Among them, catechin (Figure 1), epigallocatechin gallate, epicatechin, procyanidin B1, and procyanidin B2 have been found in mulberry fruit (Table 2). Natić et al.[38] stated that rutin was the most abundant phenolic compound, contributing 44.66% of the total phenolics in 11 mulberry samples. These results were consistent with previous findings.[32,49,50]

Phenolic Acids. Mulberry fruit also contains a variety of phenolic acids. The composition and contents of phenolic acids in mulberry fruit have been the subject of many studies. Phenolic acids in mulberry fruit are mainly represented by hydroxycinnamic acids and benzoic acid derivatives. Among hydroxycinnamic acid derivatives, chlorogenic acid (Figure 1), ferulic acid, *p*-coumaric acid, *o*-coumaric acid, cinnamic acid, and caffeic acid were found in mulberry fruit. In the group of benzoic acid derivatives, gallic acid (Figure 1), hydroxybenzoic acid, protocatechuic acid, and vanillic acid have also been reported. Mahmood et al.[33] and Gecer et al.[51] reported that chlorogenic acid was the most abundant phenolic acids in mulberry fruit, with contents of 5.3−17.3 mg/100 g DW and 2.4 mg/g, respectively. However, Butkhup et al.[39] reported that gallic acid (7.33−23.34 mg/100 g DW) and cinnamic acid (11.64−15.05 mg/100 g DW) were the major phenolic acids in mulberry fruit cultivars.

In general, there are discrepancies in the polyphenolic composition and content in mulberry fruit across studies. The differences depend not only on the cultivars used but also on the extraction and analytical methods, genetic differences, and growing conditions, including geographical and environmental conditions, such as temperature, humidity, light, and degree of maturity.[14,33,38,39]

Polysaccharides. A number of studies have shown that polysaccharides play important roles in physiological and pathological activities.[52−55] Mulberry fruit contains a significant amount of polysaccharides.[56] In recent years, increasing attention has focused on mulberry fruit polysaccharides (MFP), and some advances have been made to characterize these polysaccharides and their bioactivities. To date, several polysaccharides have been identified in mulberry fruit using various extraction methods and purification processes. Physicochemical properties and structural features, such as molecular weight and monosaccharide composition, have been studied using Fourier transform infrared spectra, high performance liquid chromatography, and methylation analysis, and they are summarized in Table 3. The names, biological activities and corresponding references are also included.

Several polysaccharide fractions with antioxidant and hypoglycemic activities were purified from mulberry fruit using various purification methods.[57,58] A glycoprotein with a carbohydrate content of 28.4% and protein content of 71.6% isolated from the lyophilized powder of mulberry fruit juice (yield 10.6%) showed better antiapoptotic activity than strawberry fruit polysaccharides.[59] Choi et al.[60] isolated and investigated the structural properties of a pectic-type MFP from mulberry fruit. The data obtained indicated that the polysaccharide has a rhamnogalacturonan type I (RG I) backbone composed of the repeating disaccharide fragments [4-*α*-D-Gal*p*A-1 → 2-*α*-L-Rha*p*-1 →]. The arabinan side chain is composed of (1 → 5)-*α*-L-Ara attached to the O-4 position of *α*-L-Rha*p*. The Arabinogalactan type II (AG II) side chain was found to have a (1 → 6)-*β*-D-galactan core branched at O-3 by *α*-L-Ara*f* (Figure 2). However, the connection patterns between

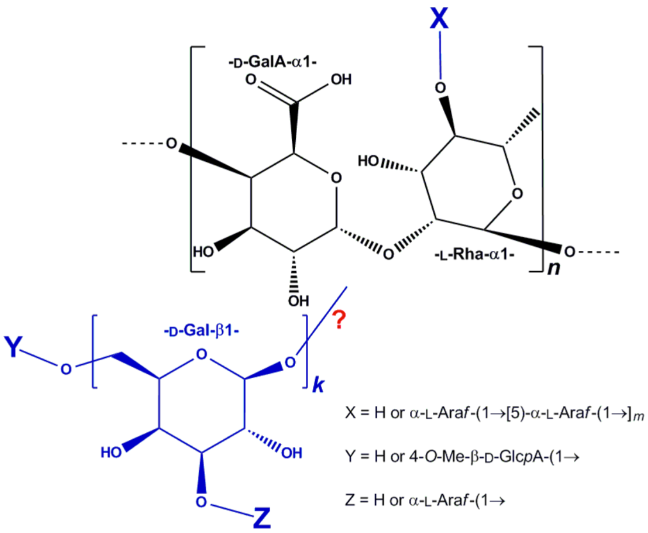

Figure 2. Structure of polysaccharide isolated from mulberry fruit.[60]

AG II and RG I are still unclear. In the future, structures of polysaccharides remain to be further determined to provide more information for elucidating the structure−activity relationship.

Melatonin. Melatonin (*N*-acetyl-5-methoxytryptamine) is a well-known neurohormone produced in the pineal gland and related structures that is involved in the regulation of circadian rhythms and sleep disorders.[61] It is also reported to possess a wide array of physiological activities, such as antioxidant and anti-inflammatory effects.[62,63] However, endogenous melatonin levels decrease with age and a multitude of pathophysiological changes of humans.[64,65] Deficiencies can be overcome by exogenous melatonin supplementation through food intake, which has been proven to raise circulating melatonin and boost human health.[66,67] High levels of melatonin have been detected in several plants, including mulberry fruit.[68] Wang et al.[68] studied dynamic changes in melatonin content during mulberry fruit development (from the fruit setting to ripening) and ethanol fermentation. High levels of melatonin (5.76 ng/g FW) were detected in stage I but then decreased in stage II and stage III. The melatonin level in mulberry wine was much higher than that in fruit. The melatonin content increased to 31.59 and 28.11 ng/mL during ethanol fermentation at 25 and 16 °C, respectively.

Other Bioactive Compounds. Deep-colored fruits are also good sources of carotenoids.[69] Aramwit et al.[70] compared the *β*-carotene content from different colored mulberry fruit. The *β*-carotene level in red fruits (23.7 *μ*g/100 g) was significantly higher than those in purple fruits (13.7 *μ*g/100 g) and purple-red fruits (14.0 *μ*g/100 g). Researchers also isolated many pyrrole alkaloids including some new compounds from mulberry fruit, among which some showed significant macrophage activating activity and inhibition of pancreatic lipase that is important in the regulation of obesity.[71,72] Recently, two naturally new compounds and 13 known compounds were

DOI: 10.1021/acs.jafc.7b03614
J. Agric. Food Chem. 2017, 65, 10383−10394

found, and moracin C with a benzofuran structure was responsible for lowering cholesterol levels. In the future, more compounds could be expected to be isolated from mulberry fruit and identified by researchers to further benefit human health.

■ BIOACTIVITIES

Antioxidant Activity. The antioxidant capacity of fruit is correlated well with the level of oxygen radical scavengers, such as phenolic compounds.[21,73,74] Research has shown that polyphenol-rich MFE can strongly inhibit lipid and linoleic acid oxidation and exhibit concentration-dependent free-radical scavenging activity against DPPH, hydroxyls, ABTS, and superoxide anion radicals, as well as reducing power.[46,75,76] Studies comparing the antioxidant activities of MFE from different cultivars and phenotypes found that antioxidant activity differed with cultivar and phenotype and demonstrated a correlation between the phenolic content and antioxidant capacity.[75,77] Similar results were obtained by Jiang et al.;[78] namely, a significant correlation ($P < 0.01$) was found between the total phenolic, flavonoid, and anthocyanin contents and antioxidant capacity of purified mulberry juice and purified mulberry marc. Nevertheless, the antioxidant activity was found to be dependent not only on the phenolic content but also on the identity of the phenolic compounds, other phytochemicals present, and synergistic effects among them.[79,80]

Mulberry fruit polysaccharides also showed good *in vitro* antioxidant activity. The antioxidant activities of four polysaccharide fractions (MFP-1, MFP-2, MFP-3, and MFP-4) from mulberry fruit were determined, and it was suggested that MFP-4, containing more galacturonic acid and a large part of low molecular weight fractions, had the greatest ability to scavenge DPPH and hydroxyl radicals.[58] The carboxyl or carbonyl groups of MFP may facilitate hydrogen atoms to bind to peroxy radicals and terminate the radical chain reactions. The selenide of the MFP showed higher peroxy radical-scavenging capacity than MFP *in vitro*, which may be due to the activation of the hydrogen atom of the anomeric carbon by the selenyl or seleno-acid ester groups.[81]

Lee et al.[82] focused on the protective effect of mulberry fruit in H_2O_2-induced oxidative injury of pancreatic MIN6N β-cells. In their study, 70% ethanol extracts of mulberry fruit rescued pancreatic MIN6N β-cell viability from 53.8% to 71.6% at a concentration of 400 μg/mL, and inhibited ROS accumulation and lipid peroxidation in a dose-dependent manner. Additionally, the extracts significantly inhibited H_2O_2-induced apoptotic cell death. Oxidative stress in HepG2 cells, induced by high glucose and palmitic acid, was established to explore the ameliorative effect of mulberry fruit *in vitro*.[83] Treatment with MAE decreased ROS and O_2^- accumulation, while it increased mitochondria numbers and mitochondrial membrane potential.

Antiatherosclerosis Activity. Atherosclerosis, a chronic inflammatory disease characterized by the accumulation of lipids in the arterial intima, is widely accepted as a main cause of cardiovascular disease.[84] Oxidative low-density lipoprotein (oxLDL) is an important atherogenic factor.[85] Consumption of a diet rich in natural antioxidants is associated with attenuation of the development of atherosclerosis.[86,87]

The antiatherosclerosis effect of mulberry water extracts (MWE) and MAE were investigated *in vitro* by Liu et al.[44] MWE and MAE scavenged DPPH radicals and inhibited relative electrophoretic mobility, formation of thiobarbituric acid reaction substances, and ApoB fragmentation in oxidation LDL induced by Cu^{2+} ($P < 0.05$). MWE and MAE also inhibited macrophage death induced by oxidative LDL and the formation of foam cells ($P < 0.05$). The efficacy of MAE was 10-fold higher than that of MWE, which indicated that mulberry anthocyanins could decrease atherogenesis. Chen et al.[20] reported that feeding 0.5% or 1.0% MWE (containing 2.5% anthocyanins and 4.6% total phenol) for 10 weeks significantly decreased plasma triglyceride levels in the cholesterol-fed rabbits. Atherosclerotic lesion was significantly reduced by 42%−63% in the aorta from rabbits fed with 0.5% or 1.0% of MWE compared to the control. Histological analysis revealed that MWE reduced the formation of foam cell and the migration of smooth muscle cells in blood vessel of rabbits. Chan et al.[49] investigated the antiatherosclerosis activity of mulberry polyphenol extracts (MPEs) and its underlying mechanism of action in vascular smooth muscle cells. They found that MPEs could arrest the A7r5 rat thoracic aorta smooth muscle cell cycle at the G0/G1 phase through induction of NO production and AMPK/p53 activation. The major active compounds were rutin, protocatechuic acid, and other polyphenols, such as EGCG, caffeic acid, and naringenin.

Immunomodulatory Activity. The immunomodulatory property of natural products has been widely investigated.[88] Several pyrrole alkaloids from mulberry fruit had significantly activated macrophage activity in RAW 264.7 cells by the enhancement of nitric oxide, TNF-α, and IL-12 production.[72] A glycoprotein (MP) isolated from mulberry fruit was also examined for its immunomodulatory effects in mouse primary macrophages by Liu and Lin.[56] MP markedly ($P < 0.05$) decreased pro-inflammatory cytokines including IL-1β and IL-6 and increased the anti-inflammatory cytokine IL-10. In addition, MP increased the ratio of Bcl-2/Bak protein expression, suggesting that MP enhanced cell viability via inhibition of apoptosis. In another recent study from Liu and Lin,[59] similar results were obtained in murine primary splenocytes. Lee et al.[89] tested the effect of a pectic polysaccharide (JS-MP-1) on immue function. The results indicated that JS-MP-1 could significantly stimulate the secretion of proinflammatory cytokines (TNF-α and IL-6) and chemokines (RANTES and MIP-1α) from murine RAW264.7 macrophage cells. The macrophages treated with JS-MP-1 also stimulated the expression of iNOS and cyclo-oxygenase-2. Chang et al.[90] indicated that MFE exerted its immunomodulatory activity by TLR4-mediated NF-κB and MAPK signaling pathways. In another study, Qian et al.[91] found that MFE was able to attenuate inflammatory responses by the NF-κB/p65 and pERK/MAPK pathways.

Antitumor Activity. To discover natural compounds with antitumor activities, a series of crude extracts and pure compounds from fruits have been obtained to investigate their antitumor activities.[92,93] Over the years, it has been reported that not only crude extracts but also compounds obtained from mulberry fruit exhibited antitumor activity through different pathways, which has been one of the most important biological activities of mulberry fruit. Chen et al.[94] indicated that mulberry anthocyanins inhibit the migration of A549 human lung carcinoma cells. Related literature has also demonstrated the antitumor activity of mulberry anthocyanins via inhibition of cell migration.[95] Chen et al.[96] investigated the synergistic effect of combined treatment with MWE and paclitaxel on human bladder cancer using TSGH 8301 cells and TSGH 8301 xenograft models. Paclitaxel/MWE can arrest TSGH 8301 cells at the G2/M phase during the cell cycle,

DOI: 10.1021/acs.jafc.7b03614
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inducing mitotic catastrophe and inhibiting the generation of early endosomes, which may be associated with expression of PTEN. Furthermore, animal experiments suggested that the combined treatment groups showed reduced tumor volume through activation of PTEN and Caspase 3 expression. The drug combination had a greater effect on cancer in almost all cases, than either drug alone. These results indicate that combinations of paclitaxel and MWE could provide a novel and effective therapeutic option in treating bladder cancer. Chang et al.[90] also explored the synergistic antitumor effect of MFE and another drug 5-fluorouracil in mice transplanted with CT26 cells. Leukocyte counts, spleen weight, NK cells, and CTL activity in the tumor xenograft mice were significantly increased in the MFE + 5-FU group. The antitumor activity was supposed to be the result of the immune-stimulatory effects.

Angiogenesis, the formation of new blood vessels from pre-existing ones, plays a crucial role in tumor progression,[97,98] and antiangiogenic agents have been approved for the treatment of cancer by this mechanism.[99] Lee et al.[100] reported that odisolane, a novel oxolane derivative (Figure 3) obtained from mulberry fruit, could significantly inhibit tube formation in human umbilical vein vascular endothelial cells (HUVECs). The molecular mechanism of its antiangiogenic effects is associated with inhibition of the expression of the vascular endothelial growth factor, p-Akt, and p-ERK protein in HUVECs. These results suggest that compounds isolated from mulberry fruit may be beneficial in antiangiogenesis therapy for cancer treatment. In the future, the mechanisms of antitumor activity of crude extracts and pure compounds from mulberry fruit need to be further elucidated.

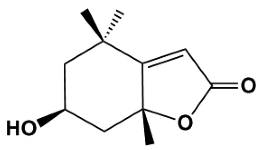

Figure 3. Structure of odisolane isolated from mulberry fruit.[100]

Antihyperglycemic Activity. Diabetes mellitus (DM), a chronic metabolic disorder characterized by hyperglycemia, has become the third most life-threatening disease worldwide.[101] The incidence of DM is constantly increasing, and it is estimated that there will be 300 million diabetes patients worldwide by the year 2025.[102] Many research groups have evaluated the hypoglycemic effects of natural products for the treatment of diabetes. Wang et al.[103] investigated the antidiabetic effect of MFE *in vitro* and *in vivo*. MFE rich in phenolics and flavonoids appeared to be a potent inhibitor of α-glucosidase, which was confirmed recently by Xiao et al.[104] The *in vivo* study showed that oral administration of MFE for 2 weeks significantly reduced fasting blood glucose and glycosylated serum protein in STZ-induced hyperglycemia mice. Polysaccharides obtained from mulberry fruit also have shown inhibitory effects on α-glucosidase, α-amylase, and the diffusion of glucose *in vitro*, and exhibited antidiabetic activity in Type 2 diabetes mellitus rats.[57,58,105]

Using HepG2 cells as a model, the mechanism behind the hypoglycemic activity induced by MAE was proposed. MAE may accelerate glycogen synthesis, promote gluconeogenesis, and ameliorate insulin resistance via the PI3K/AKT pathway. Furthermore, *in vivo* studies show MAE improved glucose metabolic disorders in db/db mice by activating protein kinase B phosphorylation and its downstream targets in insulin-sensitive tissues.[106,107] The hypoglycemic effects of MFE containing high levels of anthocyanins were studied in diabetic C57BL/KsJ-db/db mice.[108] The results revealed that MFE can enhance insulin sensitivity, reduce hepatic glucose production, increase glucose transporter 4 (GLUT4) levels in skeletal muscle, and decrease glucose 6-phosphatase and phosphoenolpyruvate carboxykinase levels in the liver. These effects are due to increased phosphorylation of AMP-activated protein kinase and the 160-kDa Akt substrate.

Hypolipidemic Activity. The hypolipidemic activity of mulberry fruit freeze-dried powder was tested in hyperlipidemia Wistar rats that were induced using a high-fat diet. The powder effectively reduced serum triglyceride (TG), total cholesterol (TC), serum low-density lipoprotein cholesterol, liver TG, liver TC, and atherogenic index but increased serum high-density lipoprotein cholesterol.[34] Furthermore, the effect of mulberry fruit consumption on lipid profiles in hypercholesterolemic subjects (aged 30−60 years) was studied. The level of TC and low-density lipoprotein cholesterol significantly decreased compared to the control group, indicating that mulberry fruit could improve lipid profiles in hypercholesterolemic patients.[109]

The hypolipidemic mechanism studies were carried out in hamsters with high-fat/cholesterol diets. Results indicated that MWE treatment increased low-density lipoprotein receptor expression and uptake of low-density lipoprotein (LDL) but decreased the expression of HMG-CoA reductase, fatty acid synthase, and glycerol-3-phosphate acyltransferase.[110] Using HepG2 cells, Chang et al.[43] investigated the protective effect of MAE and its underlying mechanisms. MAE reduced lipid accumulation induced by oleic acid. Triglyceride synthesis-related proteins and cholesterol biosynthesis related proteins were suppressed, while free fatty acid related proteins were elevated, indicating that MAE regulated lipid biosynthesis and lipolysis to exert hypolipidemic effects. There was also evidence to suggest that moracin C in mulberry fruit inhibits the proprotein convertase subtilisin-kexin type 9 (PCSK9) mRNA expression, and thereby decreases degradation of LDL receptor, which could lower cholesterol levels.[1] Thus, in addition to these compounds, other bioactive compounds such as polysaccharides could also be investigated to elucidate the hypolipidemic mechanism of mulberry fruit for many polysaccharides from natural products showing obvious hypolipidemic effects.[111,112]

Neuroprotective Activity. In an effort to reduce ROS-induced damage, Kang et al.[113] studied MFE and C3G to determine whether they were able to prevent ROS generation and reduce neuronal damage. In oxygen-glucose-deprived PC12 cells, C3G significantly increased cell viability. In middle cerebral artery-occluded animal models, C3G offered more neuroprotective effects against cerebral ischemia than MFE. C3G is a major neuroprotective constituent of MFE. Kim et al.[114] investigated the neuroprotection of mulberry fruit 70% ethanolic extract on Parkinsons's disease (PD) models. MFE significantly protected neurons from neurotoxins through antioxidant and antiapoptotic effects in *in vitro* and *in vivo* models. The protective effects of MFE against neurotoxicity is also supported by *in vivo* experimental models of early PD. MFE was able to inhibit olfactory dysfunction, ameliorate motor deficits and the degeneration of dopaminergic neurons, and inhibit the up-regulation of α-synuclein and ubiquitin, as part of Lewy bodies.[115] Kaewkaen et al.[116] found that dietary MFE supplementation could enhance memory, increase neuron

DOI: 10.1021/acs.jafc.7b03614
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density, and reduce AChE activity in rat models of middle cerebral artery occlusion. In addition, MFE-supplemented animals showed positive effects on Bcl-2-immunopositive neuron density and antioxidase activity. Artoindonesianin O (AIO) (Figure 4), a dietary phenolic compound from mulberry, was extracted and purified by Qiao et al.[117] AIO treatment lowered Aβ42- or *N*-methyl-D-aspartate (NMDA)-induced neurotoxicity and reduced okadamic acid-induced tau hyperphosphorylation in neuron cells. This mechanism is associated with inhibition of kinase p-ERK1/2 expression. In addition, the number of dendritic spines increased after AIO treatment. These results strongly suggest that AIO exerts significant neuroprotective effects on neurons.

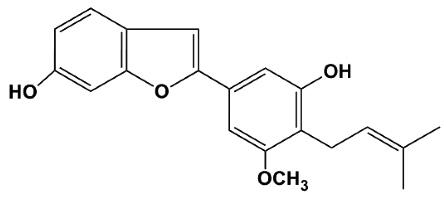

Figure 4. Chemical structure of AIO.[117]

Other Benefit Effects. In addition to the antioxidant, antiatherosclerosis, immunomodulative, anticancer, antihyperglycemic, hypolipidemic, and neuroprotective activities, other therapeutic uses of mulberry fruit have been found. The hepatoprotective effect of MWE was investigated in mice with induced liver injury. The results suggested that MWE effectively prevented liver injury, mainly via inhibition of lipogenesis, antioxidative stress, and anti-inflammation; increase of fatty acid transport; and stimulation of fatty acid oxidation.[118] The antifatigue activities of mulberry juice purification (MJP) and mulberry marc purification (MMP) were evaluated by the weight-loaded swimming test. MJP and MMP prolonged the weight-loaded swimming time; the antifatigue effects of MMP treatment were more obvious than those in MJP treatment.[78] The effect of the mulberry leaf and fruit extract mixture (MLFE) on early stage cutaneous wound healing in obese mice was examined. The results suggested that the MLFE can accelerate delayed wound closure in obese mice through activation of the NLRP3 inflammasome.[119] Khan and Jain[120] found that the ethanol extract of mulberry fruits exhibited significant antiulcerogenic effects in rats, and its mechanism may involve the antioxidant properties of the extract. The improvement of menopausal symptoms by astragalin (AST, also known as kaempferol-3-*O*-glucoside) isolated from mulberry fruit was studied *in vitro* and *in vivo*. The results showed that AST can inhibit granulosa cell (GC) apoptosis, promote serum 17β-estradiol and progesterone secretion, and increase follicle stimulating hormone and luteinizing hormone levels.[121]

TOXICITY AND SAFETY

Because herbal medicines are plants, they are often perceived as "natural" and therefore harmless and safe.[122−124] However, side effects associated with herb use have been reported.[125,126] Mulberry fruit has long been widely consumed as a fruit and in traditional medicine, and its biological activities have been studied. These beneficial properties recommend mulberry fruit for the development of novel functional foods or potential drugs as consumers' consciousness and demand for healthy food rise. Therefore, its safety needs to be evaluated. Peng et al.[127] studied the antiobesity effect and toxicity of MWE by examining the influence of oral administration of the extracts (0.5%−2%, w/w) for 12 weeks on hamsters. MWE showed both antiobesity effects and safety *in vivo*. Chang et al.[128] investigated the subchronic oral toxicity and genotoxicity of MFE. Sprague−Dawley (SD) rats were treated with MFE by daily oral dosing at 40, 200, and 1000 mg/kg for 90 days. No death, adverse reactions, or changes in food and water consumption, body weight, organ weight, or hematological or biochemical parameters were found. Moreover, the *Salmonella typhimurium* strains TA98, TA102, and TA1535 treated with MFE showed no genotoxicity in all of the test strains. Mulberry fruits were examined in health risk tests in adults, and the results showed no significant noncarcinogenic or carcinogenic health risks to consumers. Therefore, consumption of mulberry fruit is considered to be safe.[129]

PERSPECTIVES

Mulberry fruit contains abundant nutrients and bioactive compounds, and it possesses various pharmacological properties, indicating that it is a potential disease-fighting food for the prevention or treatment of chronic illness. However, there are still important gaps in our knowledge regarding the phytochemicals and biological activities of mulberry fruit. Based on the present encouraging findings, the following research work is recommended. The chemical constituents of mulberry fruit and their contents vary with the varieties, cultivars, environmental conditions, and stages of maturity. Although the chemical composition of mulberry fruit is already studied extensively, there may still be unknown compounds that contribute to its biological activities. Therefore, the unidentified compounds in mulberry fruit and their biological effects should be investigated deeply, and a consistent phytochemical profile should be developed for consumption and clinical trials. To date, there is little information regarding the metabolomics of phytochemicals such as phenolics and polysaccharides. Therefore, it is important to investigate the metabolites formed *in vivo* and how they exert their biological effects.

AUTHOR INFORMATION

Corresponding Author

*Phone: +86-15717157200; E-mail address: zhaolongyan@mail.scuec.edu.cn.

ORCID

Longyan Zhao: 0000-0001-9999-3433

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 31600649, 81373292) and Key Projects of Technological Innovation of Hubei Province (No. 2016ACA138).

Notes

The authors declare no competing financial interest.

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