Review

Phytochemicals, Pharmacological Effects and Molecular Mechanisms of Mulberry

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Abstract: There are numerous varieties of mulberry, and each has high medicinal value and is regarded as a promising source of traditional medicines and functional foods. Nevertheless, the nutrients and uses of mulberry differ from species (Morus alba L., Morus nigra L. and Morus rubra L.). Phenolic compounds are prominent among the biologically active ingredients in mulberry, especially flavonoids, anthocyanins and phenolic acids. Epidemiologic studies suggest that mulberry contains a rich, effective chemical composition and a wide range of biological activity, such as antioxidant, anti-inflammatory, anti-tumor and so on. However, compared with other berries, there has been a lack of systematic research on mulberry, and this hinders its further expansion as a functional fruit. The main purpose of this review is to provide the latest data regarding the effective chemical constituents and pharmacological effects of mulberry to support its further therapeutic potential and health functions.

Keywords: mulberry; composition; anthocyanins; flavonoids; biological activities

1. Introduction

Mulberry, which belongs to the genus Morus of the Moraceae family, is an aggregated berry that is oval-shaped, rich in nutrition, sweet and soft, with a unique flavor [1,2]. Mulberry is distributed in east, west and southeast Asia, southern Europe, southern North America, northwestern South America and some areas of Africa [3]. There are 24 species of Morus and one subspecies, with at least 100 known varieties [4]. Studies have shown that mulberry is beneficial for human health, which may be related to the compounds it contains, such as phenols, amino acids and sugars [5,6]. Since ancient times, mulberries have been used as fruits and herbs and have been listed by the Chinese Ministry of Health as one of the “food and medicine” agricultural products. The fruit is a high-quality natural raw material that is used for the production of modern food and diet regimens. It is commonly eaten, often dried, or processed into wine, syrups, canned food, fruit juice, jam and beverages [3,4,7–10]. The anthocyanin content in mulberry wine is much higher than that of red wine, and regular consumption can increase immunity.

There are many varieties of mulberry, with the most common species consisting of black mulberry (Morus nigra L.), white mulberry (Morus alba L.) and red mulberry (Morus rubra L.) [11]. Some studies have revealed that black mulberry has a higher content of total phenolics, total flavonoids, total anthocyanins and more antioxidant compounds than red...
mulberry or white mulberry [4,12,13]. Some authors point out that the nutrient and plant chemistry of mulberry are closely related to the area in which it was cultivated [14–16].

At present, a limited number of reviews on the phytochemical and pharmacological properties of mulberry have been published. The current review attempted to provide holistic insight into the composition of mulberry, which would promote human health, and to investigate biological activities against chronic diseases.

### 2. Composition of Mulberry

Mulberry is rich in nutrients, approximately 0.5–1.4% protein and about 7.8–9% carbohydrates [17]. Mulberry contains neutral sugars such as arabinose, galactose, glucose, rhamnose, xylose, mannose and also contains a large amount of uronic acid, namely in the form of galacturonic acid and glucuronic acid [18–21]. The most abundant amino acid in mulberry is glutamate, which accounts for approximately 20%, followed by glycine and aspartate [22]. It also contains lysine, leucine, isoleucine, histidine, threonine, tryptophan and glycine, among others. Among these amino acids, leucine, threonine, isoleucine, glycin, threonine, valine, tryptophan, arginine, aspartic acid and serine are found in a higher content in white mulberry when compared with black mulberry. In contrast, the content of lysine, histidine, and proline are higher in black mulberry and lower in white mulberry [23]. The fat content of mulberry is extremely low, and linoleic acid, oleic acid, palmitic acid and stearic acid make up 69.66–78.02% of the total fatty acids [24]. The vitamins in mulberry are mainly vitamin C, vitamin A and some B groups [16]. The organic acids of mulberry are succinic acid, acetic acid, malic acid, citric acid and tartaric acid [3]. The content of titrable acid is 0.20–2.65%, and the content in black mulberry is higher than that in white mulberry [4,23,25–27]. The minerals in mulberry are potassium, calcium, phosphorus, sodium, zinc, copper and selenium. Studies have shown that the content of potassium in black mulberry is much higher than that in other fruits [13]. Soluble solids mainly include sugar, acid, vitamins and minerals, and their content can directly affect the taste of fruits and vegetables. The total soluble solid content of mulberry is 6.2–25.8% [4,23,25,26].

Mulberry contains many phenolic compounds, and Table 1 contains the results of the determination of total phenol and total flavonoids from recent years. In addition to the above ingredients, mulberry also contains alkaloid compounds (quinine, 1-deoxyxojirimycin) and α-glucosidase inhibitors [28–30]. Different varieties of mulberry possess different chemical compositions and nutritional statuses, which are related to the climate, topography and soil conditions [7].

| Element | Mulberry | Origin | Concentration | Reference |
|---------|----------|--------|---------------|-----------|
| Total phenolic | M. alba, M. Nigra, M. rufra | Olor town, Erzurum, Turkey | 181–1422 mg GAE/100g FW | [4] |
| | M. nigra L. and M. alba L. | Jinhua, Zhejiang, China | 879–6585 mg GAE/kg FW | [12] |
| | 8 different varieties | Orihuela (latitude 38°04′08″ N × longitude 0°58′58″ W, 27 m above sea level) Alicante (South-Eastern Spain) | 6.98–13.59 mg GAE/g DW | [13] |
| | M. alba L. | Qinshui County, Shanxi province in China | 23.00 mg/g MFP | [15] |
| | 22 different varieties | Quanxi town, Wuyi county of Zhejiang Province, China | 199.45–2330.40 μg GAE/g FW | [25] |
| | 4 different varieties | northern regions of Pakistan | 880–1650 mg/100 g FW | [27] |
| | M. alba L. | Taichung, Taiwan | 1515.9 mg GAE/100 g FM | [31] |
| | different varieties | Yangpyeong, Korea | 7.0–2392.0 mg GAE/100 g | [32] |
| | Morus Microphylla Buckl | | 24.01 mg/g DW | [33] |
| Species          | Location                                      | Flavonoids Value                  | Reference |
|------------------|-----------------------------------------------|-----------------------------------|-----------|
| *M. nigra* L.    | Istanbul, Turkey                              | 1451.4 mg GAE/100 g DW            | [34]      |
| *M. alba* L.     | Mahasarakham University, Thailand             | 104.78–213.53 mg GAE/100 g DW     | [35]      |
| *M. nigra* L.    | Yesilyurt, Malatya (38.321059, 38.217478)     | 192.67 mg GAE/g                   | [41]      |
| *M. alba* L.     | Suncheon City, Korea                          | 524.06 mg/100 g DW                | [37]      |
| *M. nigra* L.    | Olur town, Erzurum, Turkey                   | 1375 mg GAE /100 g DW             | [51]      |
| *M. alba* L.     | Uncle and Fuyang, Zhejiang, China             | 11.67–690.83 mg GAE/g             | [43]      |
| 10 different     | Variety                                       | 670–7700 mg GAE/kg FW              | [38]      |
| *M. alba* L.     | National Institute of Agricultural Science and Technology, Suwon, Korea | 959.9–2570.4 μg GAE/g dried extracts | [39]      |
| *M. alba* L.     | Hangzhou, China                               | 547.60 mg GAE/MAE                 | [40]      |
| *M. nigra* L.    | Yesilyurt, Malatya (38.321059, 38.217478)     | 192.67 mg GAE/g                   | [41]      |
| *M. alba* L.     | Guanzhou, Guangdong, China                    | 35.53% in the proportion of dry matter | [42]      |
| *M. nigra* L.    | Puerto Real region (Spain)                    | 100.97–586.23 mg GAE/100 g FW     | [46]      |
| *M. alba* L.     | 11 different varieties                        | 2032.87 mg GAE/100 g DW           | [47]      |
| *M. nigra* L.    | Zhejiang province, China                      | 100.97–586.23 mg GAE/100 g FW     | [46]      |
| *M. alba* L.     | Ordu, Turkey                                  | 5.16 mg/100 g                     | [48]      |
| Mulberry fruit   | Mulberry fruit Sang-ju Silkworm Farming       | 185–344 mg 100/ g FW              | [49]      |
| *M. nigra* L.    | Jinhua, Zhejiang, China                       | 1005–3488 μGAE/ g FW              | [50]      |
| *M. alba* L.     | Jinhua, Zhejiang, China                       | 1375 mg GAE/100 g DW              | [51]      |
| *M. nigra* L.    | Anji and Fuyang, Zhejiang, China              | 11.67–690.83 mg GAE/g             | [43]      |
| Dried mulberry   | Dried mulberry fruits juice (Morus sp.)       | 3.21 mg GAE/g                     | [44]      |
| fruit            | *M. nigra* L.                                 | 1301.67 μg/g FW                   | [45]      |
| *M. nigra* L.    | Zhejiang province, China                      | 100.97–586.23 mg GAE/100 g FW     | [46]      |
| *M. alba* L.     | Taichung, Taiwan                              | 5.6–65.4 μg g DW                  | [39]      |
| *M. nigra* L.    | Qinshu County, Shaxi, China                   | 3.90 mg/g MFP                     | [15]      |
| *M. alba* L.     | Shaxi, China                                  | 250.1 mg QE/100 g FM              | [31]      |
| *M. nigra* and *M. rubra* L. | Olur town, Erzurum, Turkey | 29–276 mg QE/100 g FW | [4]      |
| *M. nigra* L.    | Jinhua, Zhejiang, China                       | 663–1292 mg QE/kg FW              | [12]      |
| *M. alba* L.     | Qinshui County, Shaxi, China                  | 3.90 mg/g MFP                     | [15]      |
| *M. alba* L.     | Taichung, Taiwan                              | 250.1 mg QE/100 g FM              | [31]      |
| *M. nigra* L.    | Shaanxi, China                                | 463.62 mg/100 g DW                | [36]      |
| *M. alba* L.     | Qinshui County, Shaxi, China                  | 1005–3488 μGAE/ g FW              | [50]      |
| *M. nigra* L.    | Taichung, Taiwan                              | 1375 mg GAE/100 g DW              | [51]      |
| *M. alba* L.     | Qinshu County, Shaxi, China                   | 5.6–65.4 μg g DW                  | [39]      |
| *M. alba* L.     | Shaxi, China                                  | 250.1 mg QE/100 g FM              | [31]      |
| *M. nigra* L.    | Shaanxi, China                                | 463.62 mg/100 g DW                | [36]      |
| *M. alba* L.     | Jinhua, Zhejiang, China                       | 1005–3488 μGAE/ g FW              | [50]      |
| *M. nigra* L.    | Taichung, Taiwan                              | 1375 mg GAE/100 g DW              | [51]      |
| *M. alba* L.     | National Institute of Agricultural Science and Technology, Suwon, Korea | 5.6–65.4 μg DW                | [39]      |
| *M. alba* L.     | Hangzhou, China                               | 893.73 mg RE/g mulberry anthocyanin extract | [40]      |
| *M. nigra* L.    | Yesilyurt, Malatya (38.321059, 38.217478)     | 125.86 mg QE/g                    | [41]      |
| *M. alba* L.     | Shanxi, China                                 | 7.53% in the proportion of dry matter | [42]      |
| *M. alba* L.     | Anji and Fuyang, Zhejiang, China              | 94.53–695.63 mg RE/g              | [43]      |
| ML juice         | Xinjiang, China                               | 53.85 mg QE/g                     | [44]      |

10 different varieties Yinchuan, Ningxia; Zaozhuang (Shandong); Jurong (Jiangsu); Guangzhou (Guangdong) 670–7700 mg GAE/kg FW [38]
11 different varieties | Zhejiang province, China | 16.38–368.16 mg RE/100g FW | [46]
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Mulberry fruit | Sang-ju Silkworm Farming Association, Sang-ju, Korea | 9.73 mg/100g | [48]
M. nigra L. | | 1473 mg RE/100g DW | [51]

FW: fresh weight; DW: dry weight; MAE: mulberry anthocyanin extract; RE: rutin equivalents; GAE: gallic acid equivalents; FAE: ferulic acid equivalents; FM: fresh matter; QE: equivalent of quercetin; MFP: powder of mulberry (Morus alba L.) fruit (MFP).

3. Content of Phenolic Compounds

Polyphenols play an important role in promoting human health and are the most relevant family of phytochemicals [53].

3.1. Flavonoids

Among them, flavonoids constitute a very wide range of groups and are distributed in a variety of vegetables and fruits. They have a common basic structure: C6–C3–C6, which usually forms an oxygen-containing heterocycle. Flavonoids are usually associated with sugars (glycosides), and therefore, they tend to be water-soluble.

3.2. Anthocyanins

Mulberries are especially rich in flavonoids, specifically anthocyanin [4,31,32,54,55]. Anthocyanin is the main active ingredient and chromogenic substance of mulberry, which is why mulberry is considered to be an important source of anthocyanin in the diet [33]. Its anthocyanin content is high, pigment is stable, can dissolve completely in water and has increased bioactive activity; therefore, it becomes a fruit pigment that cannot be replaced. Mulberry is an optimal source for extracting anthocyanin from pine bark, pine needles and grape seeds. Therefore, together with sea buckthorn, it is listed as a functional health food with the international development of the third generation of “fruit resources”. The most abundant anthocyanin in mulberry is cyanidin-3-glucoside (C3G), representing 53.94–78.23% of the total anthocyanins; cyanidin-3-rutinoside (C3R) accounts for 19–43.83%, and pelargonidin-3-glucoside (P3G) is measured in a proportion close to 5% [34,56–60]. The content of mulberry anthocyanins is shown in Table 2; white varieties do not contain any anthocyanins [24,25]. The content of anthocyanin in mulberry is related to mulberry variety, maturity, climate, soil, pruning of mulberry trees, pest control and other factors [3,7,61].

Table 2. Anthocyanin in mulberry.

| Mulberry | Anthocyanin | Origin | C3G | C3R | Reference |
|---|---|---|---|---|---|
| 4 different varieties | 184.3–227.0 mg/100g | Van province, Jinhua, Zhejiang, China | 1698 mg/kg FW | 693 mg/kg FW | [3] |
| M. alba L. | | Orihuela (latitude 38°04′08″ N × longitude 0°58′58″ W, 27 m above sea level) Alicante (South-Eastern Spain) | 0.004–1.26 mg/g DW | 0.004–0.08 mg/g DW | [13] |
| Species       | Concentration          | Location                          | Reference |
|--------------|------------------------|-----------------------------------|-----------|
| M. alba L.   | 0.87 mg/g              | Qinshui County, Shanxi, China     | [15]      |
| 22 different  | 306.91–1422.11 µg/g    | Quanxi town, Wuyi county of Zhejiang Province, China | [25]      |
| M. Microphylla Buckl. | 2.3 mg/g DW     | Yangpyeong, Korea                  | [33]      |
| 41 different  | 0.87–96.08 mg/g lyophilized mulberry fruit | all around China                 | [52]      |
| M. alba L.   | 137.3–2057.3 µg/g      | National Institute of Agricultural Science and Technology, Suwon, Korea | [39]      |
| M. alba L.   | 77.9% of the whole extract | Hangzhou, China                  | [40]      |
| M. alba L.   | 24.10–383.49 mg/g      | Anji and Fuyang, Zhejiang, China  | [43]      |
| 11 different  | 4.20–121.56 mg catechin equivalents/100 g FW | Zhejiang province, China       | [46]      |
| M. nigra L.  | 1572.41 mg/100 g DW    | Mulberry fruits Sang-ju Silkworm Farming Association, Sang-ju, Korea | [47]      |
| M. nigra L., M. rubra L. | 3–830 µg/g | Turkey                            | [50]      |
| M. alba L.   | 669 mg/100g DW         | São Paulo city, Brazil            | [51]      |
| M. alba L.   | 0.19–3.29 mg/g         | Quanxi town, Wuyi county of Zhejiang | [64]      |
| 31 kinds cultivated mulberry juices | 147.68–2725.46 mg/L |                                  |           |
3.3. Phenolic Acids

Mulberries contain phenolic acids (chlorogenic acid, gallic acid, protocatechuic acid, p-coumaric acid, O-coumaric acid, ferulic acid, caffeic acid, and vanillic acid), rutin, quercetin and resveratrol [3,15,56,66,67]. The main phenolic acids in mulberry are hydroxycinnamic acid derivatives [25]. Gallic acid and protocatechuic acid are the main derivatives of hydroxybenzoic acid in black mulberry [35,66]. The content of phenolic acids in mulberry is 0.02952–0.17564 mg/g fw [68]. Chlorogenic acid is the main phenolic component in black mulberry, while rutin is the dominant phenolic in white and red mulberry [3]. Chlorogenic acid is the main acid in the sugarless extract of black and white mulberry [36]. Gundogdu et al. described the concentration range of chloric acid in mulberry as 0.119–3.106 mg/g fw [3]. Butkhup et al. found that its concentration in white mulberry was 0.01 to 0.06 mg/g dw [35], and the concentration range of chlorogenic acid in white mulberry and black mulberry was reported by Sanchez-Salcedo et al. as 0.15–0.97 mg/g dw and 0.35–3.18 mg/g dw [13], respectively. The amount of chlorogenic acid in black mulberry was higher than that in white mulberry. As mulberry matures, the amount of chlorogenic acid and its isomers gradually decreases [69]. Song et al. detected resveratrol in 38 mulberry varieties from China at 0.0021–0.0053 mg/g [52]. Chon et al. found a significant difference in the total phenol content measured by different solvents [37]. The content of total phenolic compounds in mulberry is shown in Table 1, with black mulberry containing a higher amount than white mulberry [12,38].

4. Beneficial Effects of Mulberry

Recent studies have revealed that mulberries have positive biological activities against chronic diseases such as cancer, neurotoxicity, obesity, diabetes and memory degradation, among others. These protective properties are related to the potent antioxidant and anti-inflammatory activities of polysaccharides [70–74], carotenoids [75,76], rutin, resveratrol [77–79], anthocyanins [56,80], minerals (Se, Fe, Zn, Cr) [15], glutamate and other phenolic compounds [70,81]. Oxidative stress in the body produces free radicals, and phenolic compounds can protect the body from free radical-induced side effects [82,83]. Mulberry polysaccharide can regulate immune function, as it has excellent reducing power and hydroxyl radical scavenging capacity. The free radical clearance rate of mulberry polysaccharides is better than that of ascorbic acid and rutin, and the IC50 is 0.059–0.119 mg/mL [39,84]. The digestive rate of mulberry polysaccharides in gastric juice is the fastest and is second in intestinal fluid; saliva is not effective for breaking down these polysaccharides [25]. Vitamin A plays an important role in normal growth and tissue repair of the human body [14]. It is important to maintain the normal physiological function of the visual system and immune system. Carotenoid is an important dietary source of vitamin A [85]. Rutin is an antioxidant that has been shown to have anti-inflammatory properties and is essentially a flavonoid glycoside [86]. The content of rutin in mulberry is higher than in strawberry [67]. Rutin, morin, quercetin and myricetin are the main flavonols in mulberry [15], which are reported to be effective antioxidants [87]. Anthocyanin is a flavonoid that is found in large quantities in fruits and vegetables. However, the bioavailability of anthocyanin in the body is low. Studies have shown that anthocyanin absorbed into the plasma accounts for only 1% of the total intake, which may be low because
of limited intestinal absorption or due to the high cellular uptake and excretion rate of anthocyanin [88,89]. Some authors point out that the observed biological effect may not originate from the flavonoid itself, but rather, its secondary metabolites, because the flavonoid is detected in its original form in very low quantities [90].

4.1. Anti-Oxidant Activity

Oxidative stress reflects the imbalance of the body’s peroxidation and anti-oxidation. On the one hand, it is the systemic manifestation of reactive oxygen species (ROS). On the other hand, it involves the repair of the detoxification and oxidative stress damage caused by the organism’s peroxidation intermediates. The anti-oxidation ability of mulberry is particularly prominent [91-93]. This fact explains why it can slow down the aging process and prevent three primary human killers: cardiovascular disease, cancer and diabetes. The antioxidant capacity of mulberry has been repeatedly verified. Xu et al. used isolated compounds from mulberry to measure oxygen radical absorbance capacity (ORAC) and DPPH radical scavenging assay; all compounds showed potent ORAC with higher ORAC values than the positive control [5,94,95]. Zhang et al. used 700 μmol/L H₂O₂ to induce PC-12 cells for 8 h to establish a cell oxidative injury model. The high concentration of mulberry polysaccharide component T3-3 was found to have extremely strong cellular anti-oxidation effects, which resulted in an increase in cell viability of 41.81% [71]. Chang et al. found that mulberry extract and mulberry anthocyanin extract both scavenge free radicals, inhibit low-density lipoprotein oxidation and reduce atherosclerosis caused by macrophages. The latter was 10 times better than the former [96-98].

The molecular mechanism of this protection is not clear. However, it has been suggested that mulberry may participate in the insulin signaling pathway, regulate various transcription factors, improve the enzymatic activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) [21,99] and reduce the concentration of malondialdehyde (MDA), blood urea nitrogen (BUN), serum creatinine (Scr), nitric oxide (NO) and thiobarbituric acid-related substances (TBARS) [15,100]. Mulberry decreases the dysfunction of diabetic mice through the 5′ adenosine monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC)/mechanistic target of the rapamycin (mTOR) pathway. It promotes the phosphorylation of AMPK in insulin-sensitive tissues, inhibits the expression of ACC and mTOR, changes the expression of p38-mitogen-activated protein kinase (MAPK) and peroxisome proliferator-activated receptor gamma co-activator-1 alpha (PGC-1α) and protects hepatocytes against oxidative stress [40]. Luteolin hexoside and luteolin rutinoside clear 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2',2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) as well as inhibit α-glucosidase and show a significant positive correlation with each other [38]. Anthocyanins can inhibit lipid peroxidation, improve the thermal stability of DNA’s three-dimensional structure and form complexes to protect DNA from oxidative damage [101-103]. Following the most recent research, Table 3 describes the main biological effects attributed to anthocyanins. The specific antioxidant capacity of mulberry is shown in Table 4.
Table 3. The healthy effects of anthocyanins in mulberry.

| Mulberry | Anthocyanins | Duration of Study | Models | Method | Effect | Reference |
|----------|--------------|------------------|--------|--------|--------|-----------|
| 10 mulberry cultivars | C3G and P3G | 16-week | Human hepatoma cell HepG2 | HPLC-QTOF-MS | ↓α-glucosidase | [38] |
| Morus alba L. | C3G and C3R | 16-week | Male C57BL/6 mice 4 weeks old | HPL cytotoxicity assay C, Western blot analysis, Animal experiment with high-fat diet, Enzyme-linked immunosorbent assay (ELISA), RT-PCR, Histology and immunohistochemistry analysis, Western blot analysis, transmission electron microscopy | ↓acetyl coenzyme A carboxylase activities ↑the lipolytic enzyme expressions of PPARα and CPT1 | [96] |
| Fresh mulberry | | 16-week | HepG2 cells, Male db/db mice | Total reducing power assay (TRP assay), DPPH assay, ferric reducing antioxidant power (FRAP assay) | ↓MDA production ↑SOD and GP.sub.X activities | [99] |
| Morus alba L. | C3G, C3R and P3G | Animal experiments: 10-week | | | ↓islet degeneration, which may be due to autophagy stimulation ↓impaired mitochondria dysfunction ↓excessive free radical production | [40] |
| Morus alba L. | C3G | | | | ↓DPPH free radical ↓stress-induced oxidative damage | [43] |
| 11 mulberry cultivars | | | Human intestinal epithelial cell line Caco-2 | | ↑ROS scavenging activity | [46] |
| Morus alba L. | cyanidin 3-O-(6"-O-α-rhamnopyranosyl-β-d-glucopyranoside) (C3RG), cyanidin 3-O-(6"-O-α-rhamnopyranosyl-β-d-galactopyranoside) (C3R Ga), cyanidin 3-O-β-d-glucopyranoside | | | HPLC, ESI-MS, nuclear magnetic resonance (NMR) | ↓DPPH free radical | [104] |
| **Species** | **C3G (cyanidin 3-O-β-d-galactopyranoside)** | **C3Ga (Cyanidin 3-O-β-d-galactopyranoside)** | **C7G (Cyanidin 7-O-β-d-glucopyranoside)** |
|---|---|---|---|
| *Morus alba* L. | 2-week Male Kunming mice (18–20 g) | HPLC-PDA analysis, spectrophotography | ↓DPPH free radical and superoxide anion radicals, ↑antioxidant enzymatic activities (SOD, CAT, GSH-Px) |
| **Anti-diabetic** | | | [105] |
| **Morus alba** L. | C3G and C3R | 5-week Male C57BL/KsJ-db/db mice 5 weeks old | Insulin tolerance test, HPLC, the radioimmunoassay with an enzyme-linked immunosorbent assay (ELISA) with an enzyme-linked immunosorbent assay (ELISA), and HPLC-ESI-MS/MS, histology and immunohistochemistry analysis | ↑AMPK and AS160 in skeletal muscles, ↓gluconeogenesis in the liver, ↑phosphorylated (p)-AMP-activated protein kinase (pAMPK), p-Akt substrate of 160kDa (pAS160) and plasma membrane-glucose transporter 4 (GLUT4) in skeletal muscles, ↓the levels of glucose 6-phosphatase and phosphoenolpyruvate carboxykinase in the liver |
| **Morus alba** L. | C3G, C3R, P3G and pelargonidin 3-rutinoside | 6-week Murine macrophage-like cells and rat renal tubular epithelial cells, Five-week-old male ZDF (Lepr fa/CrlCrlj) and age-matched lean rats (Lepr fa/+) | Cell culture, MTT assay, HPLC-ESI-MS/MS, histology and immunohistochemistry analysis | ↓islet degeneration and the progressive decline in insulin secretion, ↓type 2 diabetes |
| *Mulberry* | C3G | Cell culture, MTT assay, immunofluorescent staining, flow intracellular reactive oxygen species, DNA fragmentation and the rate of apoptosis | ↓pancreatic β | [107] |
| Study                                                                 | Duration | Cell Type/Condition                                                                 | Methods                                                                 | Findings                                                                 |
|----------------------------------------------------------------------|----------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|
| **Morus alba L.**                                                     | 8-week   | Mouse pancreatic islet                                                               | Cytometric and Western blot analyses - cell apoptosis induced by high glucose conditions ↑insulin secretion | In vitro: ↓insulin resistance, ↓PGC-1α and forkhead box protein O1 (FOXO1), enzyme activities of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) ↑glucose consumption, glucose uptake and glycogen content In vivo: ↓fasting blood glucose, serum insulin, leptin, triglyceride and cholesterol levels ↑adiponectin levels ↑fasting blood glucose, glycosylated serum | [108] |
| **Morus alba L.**                                                     | 2-week   | Male Kunming mice (18–20 g)                                                          | HPLC-PDA analysis, spectrophotography Glucose consumption and uptake assays, ROS, O₂⁻, mitochondrial membrane potential (MMP) and mitochondrial numbers assays, Western blot, RNA isolation and qPCR analysis | Protein and anti-α-glucosidase alleviate cellular damage and this effect is related to Nrf2 ↑the life span of C. elegans ↑lipid peroxidation accumulation ↑SOD and GPx activity and PMK-1 expression | [105] |
| **Morus alba L.**                                                     |          | Human non-tumor hepatic cell line, LO2, C. elegans maintenance                       |                                                                        |                                                                        | [109] |
| **Anti-inflammatory**                                                 |          | Peritoneal macrophages (Female BALB/c strain mice (10 weeks old))                   | HPLC, ELISA, cell culture, ELISA, MTT                                   | ↓splenocytes’ (IFN-γ + IL-2 + IL-12)/IL-10 (Th1/Th2) cytokine secretion ratios and TNF-α/IL-10 (pro-/anti-inflammatory) cytokine secretion ratios | [67] |
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|------------------------|---------|
| **Fresh mulberry**     | 16-week weighting 20–25 g |
| **Morus alba L.**      | Male C57BL/6 mice at 4 weeks of age |
| Animal experiment with high-fat diet, ELISA, RT-PCR | ↓TNFα, IL-6, iNOS and NF-κB | [99] |
| **Morus alba**         | HepG2 cells, Male db/db mice (C57BL6/J genetic background, 4 weeks of age) and their nondiabetic lean littermates (m/m) |
| Histology and immunohistochemistry analysis, Western blot analysis, transmission electron microscopy | ↓the epididymal adipose mRNA expression of PPARγ, IL-6 and IL-1β |
| **Morus alba L.**      | ↑the expression of SREBP-1c and C/EBP | [40] |
| **Anti-cancer**        | Peritoneal macrophages, 6 weeks old female BALB/cByJNarl mice |
| Cell culture, MTT, ELISA | Mulberry juice (10–500 μg/mL): ↓pro-inflammatory cytokines |
| | TNF-a secretions by LPS-stimulated peritoneal macrophages |
| | ↑the secretion of anti-inflammatory cytokine IL-10 |
| | Mulberry juice (10μg/mL): ↑TNF-a |
| | Mulberry juice (500μg/mL): ↑IL-10 | [110] |
| **Morus alba L.**      | Seven-week-old male C57BL/6J mice weighing 20 g |
| HPLC, histology and immunohistochemistry analysis, Western blot analysis | ↓iNOS, COX2, NF-κB, TNF-a and IL-6 | [111] |
| **Morus alba L.**      | C3G and C3R |
| A549, a human lung cancer cell line obtained | MTT assay, cell migration and invasion assays | ↓matrix metalloproteinase-2 and urokinase-plasminogen activator (u-PA) | [93] |
| Plant                          | Tissue Inhibitor of Matrix Metalloproteinase-2 (TIMP-2) and Plasminogen Activator Inhibitor (PAI) | Tumor Cell Proliferation | Tumor Cell Apoptosis | Reference |
|-------------------------------|-------------------------------------------------------------------------------------------------|--------------------------|----------------------|------------|
| Mulberry Fruit (Moris fructus) |                                                                                                 | ↑                         | ↑                    | [112]      |
| Morus alba L.                 | Immunohistochemistry, Western blot analysis                                                      | ↓                         | ↑                    | [113]      |
| Morus alba L.                 | Western blot analysis, HPLC, MTT assay, Wound-healing assay, Boyden Chamber migration assay, Colony formation assay | ↑                         | ↑                    | [114]      |
| Morus alba L.                 | AGS cell line (obtained from the Bioresource Collection and Western blotting)                 | ↑                         | ↑                    | [115]      |

**Extraction Details:**

- **Mulberry Fruit (Moris fructus):**
  - From ATCC (Manassas, VA, USA)
  - A172 cells
  - RAW 264.7 macrophages, Six to eight-week-old BALB/c mice, and MUC2−/− mice with colorectal cancer
  - Dextran sulfate sodium (DSS)-induced acute colitis model: 19-day; MUC2−/− mouse model: 3-month

- **Morus alba L.:**
  - Cell culture, real-time quantitative PCR, Western blot analysis, ELISA, Animal disease models and diets
  - C57BL/6 mice, B16-F1 (a murine melanoma cell line)
  - SW1736 (BRAFV600E/wt) and HTh-7 (NRASQ61R) thyroid cancer cells

- **Lyophilized fruit of Mulberry:**
  - Western blot analysis
  - HPLC
  - AGS cell line (obtained from the Bioresource Collection and Western blotting analysis)
  - C3G and C3R

**References:**

- [112]
- [113]
- [114]
- [115]
- [116]
| Mulberry juice | 24-h | BALB/c mice | Animal experiment | ↓the growth of Porphyromonas gingivalis, Prevotella melaninogenica [117] |
|----------------|------|--------------|-------------------|-------------------------------------------------|
| **Anti-obesity** | 3T3-L1 preadipocyte cells (mouse embryonic fibroblast-adipose like cell line) | GC–MS, cell culture, Western blot analysis, TUNEL assay | ↑mitochondrial dysfunction, DNA fragmentation and cell apoptosis ↓the proliferation of 3T3-L1 preadipocyte cells |
| **Morus alba L.** | C3G and C3R | HPL cytotoxicity assay C, Western blot analysis | ↓fatty acid synthesis ↑fatty acid oxidation ↓the expression of sterol regulatory element-binding protein-1 and its target molecules [96] |
| Fresh mulberry | 16-week | The male C57BL/6 mice with 4 weeks of age | Animal experiment with high-fat diet, Enzyme-linked immunosorbent assay (ELISA), RT-PCR | ↓serum glucose and leptin levels [99] |
| **Morus australis Poir** | C3G, C3R and P3G | The male C57BL/6 mice with 4 weeks of age | Animal experiment with high-fat diet (HFD) | ↓insulin resistance, the size of adipocytes, lipid accumulation and leptin secretion [118] |
| **Morus alba L.** | C3G, C3R, P3G and pelargoni-dine-3-rutinoside | 6-week-old male hamsters | HPLC/ESI-MS-MS | ↓serum triacylglycerol, cholesterol, free fatty acid, the LDL/HDL ratio ↑the hepatic peroxisome proliferator-activated [119] |
| Mulberry fruit | C3G, C3R | Mouse 3T3-L1 cells, qRT-PCR, assay kit, cell culture | receptor R and carnitine palmitoyltransferase-1  
↓ fatty acid synthase and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase  
↓ the ratio of gonadal fat and pararenal fat  
↓ intracellular lipid content, TG, the expression of adipogenic genes in adipocytes which may be associated with AMPK activation | [48] |
| Dried mulberry fruit powder obtained from *M. alba* L. | Animal experiments: 3 months | 3T3-L1 preadipocytes; female C57BL/6j mice with 8 weeks of age  
Thirty male New Zealand white rabbits, weighing 2000–2200 g | LC-MS, Animal experiment with high-fat diet (HFD), histological analysis, biochemical analyses, ↓ TG, TC/HDLC, cell fat ↑ HDLC | [120] |
| *Morus alba* L. | 10-week | Animal experiment with high-cholesterol diet (HCD) | ↓ serum cholesterol and triglyceride and repress progression of atherosclerosis | [121] |
| *Morus alba* | 12-week | Male C57BL/6J mice (3 weeks of age) | Histological analysis, biochemical analyses, enzyme activity analyses, qRT-PCR  
↑ the activities of hepatic fatty acid β-oxidation enzymes (CPT and ACO), Ppara mRNA expression and plasma adiponectin level | [122] |

↑ : increase of substance;  ↓ : decrease of substance.
Table 4. Anti-oxidant activity of mulberry.

| Mulberry                  | Concentration           | Reference |
|--------------------------|-------------------------|-----------|
| DPPH M. alba L. and M. nigra L. | 0.52–6.43 mg VCE/g        | [12]      |
| 22 different varieties   | 0.0362–0.1291 mg TE/100 g | [13]      |
| M. nigra L.              | 4.41–508.08 mg TE/100 g  | [25]      |
| 22 different varieties   | 10.7–14.5 mg TE/100 g    | [26]      |
| M. alba L.               | 29.19–44.71 mg TE/100 g  | [68]      |
| M. alba L.               | 22.01–698.57 mg TE/g     | [43]      |
| M. nigra L.              | 946 mg TE/100 g          | [51]      |
| 8 different varieties    | 2.5–20.3 μmol TE/g       | [123]     |
| ABTS 22 different varieties | 4.41–508.08 mg TE/100 g  | [25]      |
| four different varieties | 0.0362–0.1291 mg TE/100 g | [13]      |
| M. nigra L.              | 2.5–20.3 μmol TE/g       | [123]     |
| 22 different varieties   | 33.57–438.25 mg Ascorbic acid/100 g | [25] |
| Eleven mulberry cultivars| 217.01–850.85 mg VCE/100 g FW | [45] |
| M. nigra L.              | 2788 mg TE/100 g         | [51]      |
| M. nigra L. and M. rubra L. | 0.51–1.44 mg TE/100 g    | [50]      |
| FRAP 22 different varieties | 0.26–4.87 mmol Fe2+/100 g | [25]      |
| Eleven mulberry cultivars| 11.92–319.40 mg VCE/100 g FW | [46] |
| M. nigra L.              | 0.37–1.69 mg TE/100 g    | [50]      |
| M. nigra L.              | 1836 mg TE/100 g         | [51]      |
| OH 22 different varieties | 33.57–438.25 mg Ascorbic acid/100 g | [25] |
| ORAC M. rubra            | 0.301–1.728 mmol TE/g    | [124]     |
| CUPRAC M. nigra L.       | 4046 mg TE/100 g         | [51]      |

DPPH: 1,1-diphenyl-2-picrylhydrazyl; ABTS: 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); FRAP: ferric reducing antioxidant power; OH: hydroxyl radicals; ORAC: oxygen radical absorbance capacity; CUPRAC: copper reducing antioxidant capacity; TE: Trolox equivalents; VCE: vitamin C equivalents; FW: fresh weight.

Studies have shown that the ability of mulberry to resist lipid oxidation increases with concentration, with 23.7–47.6% at 76 μg and 52.7–73.3% at 255 μg [39]. Studies have shown that the DPPH scavenging power of mulberry increased with maturity, according to the order of fully-ripened (49.83%) > semi-ripened (43.76%) > unripened (31.74%). The DPPH scavenging power of white mulberry is higher than that of other mulberry varieties [27,61]. However, generally speaking, the total antioxidant activity of black mulberry is stronger [125]. The total antioxidant activity of the sugar-free extracts of black mulberry ranged from 1.19 to 1.25 mmol Trolox/g, and white mulberry ranged from 0.75 to 0.78 mmol Trolox/g [126].

4.2. Hypoglycemic Activity and Hyperlipidemia Action

Mulberry can effectively regulate blood lipids and has certain protective effects on the cardiovascular and cerebrovascular systems [15]. Mulberry can improve the antioxidant status of the blood and liver and weaken lipid peroxidation. Mulberry polysaccharide significantly inhibits the content of low-density lipoprotein-C (LDL-C), decreases triglyceride and total cholesterol in the serum and liver of rats fed a high-fat diet, reduces the atherogenic index and increases serum high-density lipoprotein-C (HDL-C) levels [6]. In experiments simulating in vitro digestion, mulberry polysaccharide inhibits lipid digestion, and this effect is positively correlated. It is mainly related to gastric fluid and intestinal fluid, and saliva is not effective for the digestion of mulberry [18]. Choi et al. found that water-soluble polysaccharide JS-MP-1 in mulberry can reduce the number of
adipocytes by inhibiting the proliferation of preadipocytes [19]. Mulberry anthocyanin can reduce GLU, reduce leptin secretion, regulate fat production and lipolysis, decrease the size of fat cells and inhibit lipid accumulation [99,118,119,127]. Chang et al. found that mulberry anthocyanin was beneficial to the expression of PPARα and carnitine palmitoyl transferase 1 (CPT1), phosphorylation of AMPK and fatty acid oxidation and inhibited the synthesis of fatty acids and the accumulation of oleic acid-induced lipids in HepG2 human hepatoma cells [96,128]. Mulberry has a significant inhibitory effect on blood glucose in diabetic mice [36,106]. Mulberry anthocyanin prevents pancreatic islet degeneration and reduces insulin resistance in HepG2 cells [106,127]. C3G inhibits the apoptosis of pancreatic cells caused by glucose and oxidative stress [107]. Mulberry anthocyanin treats diabetes through AMPK, and its mechanism of action is similar to that of metformin, a drug for diabetes; its therapeutic effect is affected by PGC-1α [40].

4.3. Anti-Inflammatory Activity

Inflammatory disease is a complex process involving multiple cells, and its basic mechanism is the defense response of the body to protect and repair the damage of external inflammatory factors. Mulberry extract has good anti-inflammatory effects, although the mechanism is not particularly clear. It may have an important relationship with the promotion of the activation of murine macrophage RAW264.7 and the production of inflammatory factors [110]. JS-MP-1, a water-soluble polysaccharide isolated from Korean mulberry fruits, stimulates the RAW 264.7 cell to release RANTES, macrophage inflammatory protein-α (MIP-1α), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) [20,111]. The former two can attract leukocytes to the reaction site, and the latter two can mediate a variety of immune responses. Using lipopolysaccharide (LPS) to stimulate RAW264.7 cells to establish a model of inflammation, Zhu et al. found that mulberry could inhibit the secretion of nitric oxide (NO), prostaglandin E2 (PGE2), other inflammatory factors (in a dose-dependent manner) and the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), which may be related to the high resveratrol content in mulberry [129]. Wu et al. found that mulberry anthocyanin inhibited the expression of TNFα, IL-6, iNOS and nuclear factor-kappa light-chain-enhancer of activated B cells (NF-κB) and also inhibited the oxidative stress and inflammation caused by diet [99]. Mulberry is rich in rutin and quercetin, which have a strong immunoregulatory effect on spleen cells. They can reduce the secretion ratio of T-helper cells 1/2 (Th1/Th2) and pro-inflammatory/anti-inflammatory cytokines, which results in the anti-inflammatory effect of mulberry being preventive, not therapeutic [57,130]. Yan et al. found that the anti-inflammatory effect of mulberry was related to the improvement of metabolic disorders related to obesity, which was beneficial to messenger ribonucleic acid (mRNA), expression of insulin receptor substrate 1 (IRS1), sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) [40].

4.4. Anti-Tumor and Anti-Cancer Activity

In 1982, the U.S. National Academy of Sciences published “Diet, Nutrition, and Cancer”, which emphasized the importance of fruits and vegetables in the diet. In particular, citrus, crucifer and other fruits and vegetables rich in carotene have been shown to be effective in preventing cancer [131]. The U.S. National Research Council and the National Cancer Institute recommend eating more than five servings of fruits and vegetables per person per day to reduce the risk of cancer and heart disease [132,133]. The anticancer effect of mulberry has been confirmed in various cell lines, which have shown the inhibition of cancer cell growth and induction of apoptosis [112,134]. Cheng et al. found that mulberry polyphenol extracts (MPE) induce autophagy in Hep3B cells by inhibiting Akt and mTOR phosphorylation [135]. Zheng et al. confirmed that mulberry can indirectly enhance the immune function of mice to inhibit the formation of colon cancer [113]. Yan
et al. confirmed that mulberry anthocyanin can regulate glucose metabolism of hepatocellular carcinoma cells by promoting glycogen synthesis and reducing the production of glucose [108]. Liu et al. detected that anthocyanin in mulberry had a significant inhibitory effect on the development of gastric cancer. A possible mechanism is to increase the ratio of LC3-II/LC3-I and BAX/BCL-2 in gastric cancer SGC-7901 cells and promote the expression of Beclin1, Caspase-8. Huang and other researchers have shown that mulberry anthocyanin can effectively inhibit the metastasis of melanoma, which may be related to the Ras/PI3K signaling pathway [114]. Nie et al. found that mulberry anthocyanin can inhibit DNA synthesis by blocking the cell cycle in the S phase so that the tumor cells cannot undergo normal mitosis [136]. Long et al. discovered that mulberry anthocyanins could serve as a novel therapy method for thyroid cancer mainly by inducing apoptosis and autophagic-induced cell death [115]. Recent studies found that mulberry anthocyanins can induce apoptosis and enhance the autophagy of cancer cells; this can be used as a new treatment for cancer cells. Mulberry anthocyanin exhibits anticancer and anti-tumor effects in a dose-dependent manner [116,136].

4.5. Anti-Bacterial and Anti-Viral Activity

It is known that mulberry inhibits the proliferation and growth of many bacteria, including *Escherichia coli*, *Bacillus*, and *Staphylococcus aureus*. Mulberry red pigment has the dual function of pigmentation and bacteriostasis, which is an ideal functional for natural pigment. It has a strong inhibitory effect on *E. coli* and a weaker inhibitory effect on *S. aureus*, *Streptococcus mutans*, and *Bacillus subtilis*, while it has almost no inhibitory effect on molds and yeasts. Its antibacterial capacity is proportional to the concentration and inversely proportional to the pH of the environmental medium [98,137]. The flavonoids in mulberry have a greater inhibitory effect on bacteria (*E. coli* and *S. aureus*) than on molds (*Aspergillus niger* and *Penicillium citrinum*), and the antibacterial activity against *S. aureus* is slightly stronger in both bacteria [138]. Resveratrol exists in two forms: free form and glycoside binding state. Both forms exist in the cis and trans configuration and have neuroprotective and antioxidative effects, and therefore, have potential antiviral and immunomodulatory effects [77,78]. Anthocyanin may inhibit the activity of extracellular microbial enzymes, destabilize the plasma membrane and deprive the microbes of the substrates necessary for growth, thus affecting microbial metabolism [41,139]. Gram-positive bacteria are usually more susceptible to anthocyanin than Gram-negative bacteria [140].

Compared with other germicidal agents, mulberry has a great advantage and is safe for intestinal flora. The antiviral activity of mulberry shows that it is not only a promising fruit, but also a potential therapeutic drug.

4.6. Hepatoprotective and Renoprotective Activities

The liver is a giant “chemical plant” in the human body and plays an important role in the detoxification, storage of glycogen and secretion protein synthesis; it also assumes other functions. The kidney plays a role in maintaining environmental stability in the body. The liver and kidney are important to the human body. With the continuous improvement in living standards, excessive drinking, staying up late, eating food lacking nutrition and other acts detrimental to health are all increasingly common, causing adverse effects on the liver and kidney. Mulberry marc anthocyanins could decrease the contents of alanine aminotransferase, aspartate aminotransferase, hyaluronidase acid, hydroxyproline and collagen type-III in carbon tetrachloride (CCl4)-induced liver fibrosis rats [141]. Mulberry can activate AMPK and PPAR-α signals, reducing the levels of triglyceride (TG), total cholesterol (TC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), enhancing the activity of alcohol dehydrogenase in liver tissue and inhibiting the expression of lipid synthesis-related proteins, thereby preventing liver damage caused by alcohol [111,142]. Mulberry crude extract can promote the expression of Nrf2 in the liver. Nrf2 can induce the downstream phase II detoxification enzyme and phase III transporters, accelerating the metabolism of
nonylphenol [42]. Mulberry significantly inhibits blood urea nitrogen (BUN) and Scr and interferes with D-galactose-induced renal cell injury. It can also effectively improve renal function in rats with a certain dose-effect relationship. Mulberry polysaccharide also has a good effect on liver function, which activates alcohol dehydrogenase for subsequent detoxification [143].

### 4.7. Anti-Aging Activity

There are common causes and risk factors for the occurrence and development of human aging and many chronic degenerative diseases such as diabetes, hypertension, Alzheimer’s disease, atherosclerosis and various types of cancer. They are mainly caused by the harmful effects of free radicals (aging factors) on cell components and are the result of oxidation of the blood. The extract of mulberry is rich in phenolic substances and pigments that can significantly reduce the content of β-amloid protein, increase the activity of antioxidant enzymes and delay memory loss in the aging process [144,145].

### 4.8. Other Effects

Black mulberry extract can inhibit the induction of gamma irradiation and decrease the numbers of micronucleated polychromatic erythrocytes (MnPCEs) and micronucleated normochromatic erythrocytes (MnNCEs) in rat bone marrow cells and increase the ratio of PCE/PCE+NCE, thus reducing the toxic effects on bone marrow cells and the lethal effect of ionizing radiation [100]. Studies have shown that mulberry anthocyanin inhibits pancreatic islet degeneration, which may be associated with autophagy [40]. Jiang et al. found that mulberry can prolong the swimming time of mice and enhance their ability to ward off fatigue, laying an important foundation for mulberry to become a new type of anti-fatigue compound [43]. Mulberry extract is rich in flavonoids, which can lower the activity of tyrosinase, inhibit the production of melanin and treat skin pigmentation disease. This inhibitory effect is closely related to the antioxidant effect of mulberry [146,147]. In addition, mulberry extract can improve depression and relieve convulsions [148].

### 5. Conclusions

Mulberry is rich in nutrition and contains many functional components; it has high edible and medicinal value. The present review has highlighted the nutrients of mulberry fruits, particularly phenolic compounds, which show positive medicinal potential on health. Meanwhile, mulberry’s bioactive phytochemicals might help with a variety of chronic conditions.

Moreover, along with the advances in science and technology, great progress has been made in the study of the active ingredients of mulberry, but the research on the functional composition of mulberry is still insufficient, and it is the key to being able to complete future dietary intervention studies. Therefore, research on the functional components of mulberry should be intensified so that mulberry can be better integrated with industrialization. Additional data would enhance and promote the development and utilization of mulberry resources.

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References
1. He, Y.; Liu, G.; Xia, C.; Chen, J.; Zhao, J.; Li, X.; Deng, J.; Wang, X.; Xiang, Z.; Zeng, P. Laxative effect of mulberry ferment on two models of constipated mice. J. Funct. Foods 2022, 90, 104971. https://doi.org/10.1016/j.jff.2022.104971.
2. Sedjooa, R.-C.A.-A.; Ma, Y.; Xiong, M.; Yan, H. Fast monitoring total acids and total polyphenol contents in fermentation broth of mulberry vinegar using MEMS and optical fiber near-infrared spectrometers. Spectrochim. Acta A Mol. Biomol. Spectrosc. 2021, 260, 119938.
3. Gundogdu, M.; Muradoglu, F.; Sensoy, R.I.G.; Yilmaz, H. Determination of fruit chemical properties of Morus nigra L., Morus alba L. and Morus rubra L. by HPLC. Sci. Hortic. 2011, 132, 37–41.
4. Ercisli, S.; Orhan, E. Chemical composition of white (Morus alba), red (Morus rubra) and black (Morus nigra) mulberry fruits. Food Chem. 2007, 103, 1380–1384. https://doi.org/10.1016/j.foodchem.2006.10.054.
5. Xu, X.; Huang, Y.; Xu, J.; He, X.; Wang, Y. Anti-neuroinflammatory and antioxidant phenols from mulberry fruit (Morus alba L.). J. Funct. Foods 2020, 68, 103914.
6. Liu, Y.; Liu, Y.; Mu, D.; Yang, H.; Feng, Y.; Ji, R.; Wu, R.; Wu, J. Preparation, structural characterization and bioactivities of polysaccharides from mulberry (Mori Fructus). Food Biosci. 2022, 46, 101604. https://doi.org/10.1016/j.fbibio.2022.101604.
7. Huang, H.P.; Ou, T.T.; Wang, C.J. Mulberry (Sang Shen Zi) and its Bioactive Compounds, the Chemoprevention Effects and Molecular Mechanisms In Vitro and In Vivo. J. Tradit. Chin. Med. 2013, 3, 7–15.
8. Zhang, L.; Fan, G.; Khan, M.A.; Yan, Z.; Beta, T. Ultrasonic-assisted enzymatic extraction and identification of anthocyanin components from mulberry wine residues. Food Chem. 2020, 323, 126714. https://doi.org/10.1016/j.foodchem.2020.126714.
9. Mirzabe, A.H.; Hajjahmad, A. Filter press optimisation for black mulberry juice extraction. Biosyst. Eng. 2022, 215, 80–103. https://doi.org/10.1016/jbiosysteng.2022.01.001.
10. Tomas, M.; Toydemir, G.; Boyacioglu, D.; Hall, R.D.; Beekwilder, J.; Capanoglu, E. Processing black mulberry into jam: Effects on antioxidant potential and in vitro bioaccessibility. J. Sci. Food Agric. 2017, 97, 3106–3113. https://doi.org/10.1002/jsfa.8152.
11. Ma, G.; Chai, X.; Hou, G.; Zhao, F.; Meng, Q. Phytochemistry, bioactivities and future prospects of mulberry leaves: A review. Food Chem. 2022, 372, 131335.
12. Li, Y.; Bao, T.; Chen, W. Comparison of the protective effect of black and white mulberry against ethyl carbamate-induced cytotoxicity and oxidative damage. Food Chem. 2018, 243, 65–73.
13. Sánchez-Salcedo, E.M.; Mena, P.; García-Vigueras, C.; Martínez, J.J.; Hernández, F. Phytochemical evaluation of white (Morus alba L.) and black (Morus nigra L.) mulberry fruits, a starting point for the assessment of their beneficial properties. J. Funct. Foods 2015, 12, 399–408.
14. Liang, D.; Yang, Q.; Tan, B.; Dong, X.; Chi, S.; Liu, H.; Zhang, S. Dietary vitamin A deficiency reduces growth performance, immune function of intestine, and alters tight junction proteins of intestine for juvenile hybrid grouper (Epinephelus fuscoguttatus × Epinephelus lanceolatus). Fish Shellfish Immunol. 2020, 107, 346–356.
15. Yang, X.; Yang, L.; Zheng, H. Hypolipidemic and antioxidant effects of mulberry (Morus alba L.) fruit in hyperlipidaemia rats. Food Chem. Toxicol. 2010, 48, 2374–2379.
16. Paunović, S.M.; Mašković, P.; Milinković, M. Determination of Primary Metabolites, Vitamins and Minerals in Black Mulberry (Morus nigra) Berries Depending on Altitude. Erwerbs-Ostbau 2020, 62, 355–360. https://doi.org/10.1007/s10341-020-0509-7.
17. Singhal, B.K.; Khan, M.A.; Dhar, A.; Baqual, F.M.; Bindroo, B.B. Approaches to industrial exploitation of mulberry (Mulberry sp.) fruits. J. Fruit Ornam. Plant Res. 2010, 18, 83–99.
18. Chen, C.; Zhang, B.; Fu, X.; You, L.J.; Abbasi, A.M.; Liu, R.H. The digestibility of mulberry fruit polysaccharides and its impact on lipolysis under simulated saliva, gastric and intestinal conditions. Food Hydrocoll. 2016, 58, 171–178.
19. Choi, J.W.; Synytsya, A.; Capek, P.; Bleha, R.; Pohl, R.; Park, Y.I. Structural analysis and anti-obesity effect of a pectic polysaccharide isolated from Korean mulberry fruit Oddi (Morus alba L.). Carbohydr. Polym. 2016, 146, 187–196. https://doi.org/10.1016/j.carbpol.2016.03.043.
20. Lee, J.S.; Synytsya, A.; Kim, H.B.; Choi, D.J.; Lee, S.; Lee, J.; Kim, W.J.; Jang, S.; Park, Y.I. Purification, characterization and immunomodulating activity of a pectic polysaccharide isolated from Korean mulberry fruit Oddi (Morus alba L.). Int. Immunopharmacol. 2013, 17, 858–866.
21. Li, E.; Long, X.; Liao, S.; Pang, D.; Li, Q.; Zou, Y. Effect of mulberry galacto-oligosaccharide isolated from mulberry on glucose metabolism and gut microbiota in a type 2 diabetic mice. J. Funct. Foods 2021, 87, 104836. https://doi.org/10.1016/j.jff.2021.104836.
22. Lee, Y.; Hwang, K.T. Changes in physicochemical properties of mulberry fruits (Morus alba L.) during ripening. Sci. Hortic. 2017, 217, 189–196.
23. Jiang, Y.; Nie, W.J. Chemical properties in fruits of mulberry species from the Xinjiang province of China. Food Chem. 2015, 174, 460–466.
24. Sánchez-Salcedo, E.M.; Sendra, E.; Carbonell-Barrachina, A.A.; Martínez, J.J.; Hernández, F. Fatty acids composition of Spanish black (Morus nigra L.) and white (Morus alba L.) mulberries. Food Chem. 2016, 190, 566–571. https://doi.org/10.1016/j.foodchem.2015.06.008.
25. Chen, H.; Chen, J.; Yang, H.; Chen, W.; Gao, H.; Lu, W. Variation in total anthocyanin, phenolic contents, antioxidant enzyme and antioxidant capacity among different mulberry (Morus sp.) cultivars in China. Sci. Hortic. 2016, 213, 186–192. https://doi.org/10.1016/j.scienta.2016.10.036.

26. Calínansánchez, A.; Martíneznicolás, J.J.; Munerapicazo, S.; Carbonellbarrachina, A.A.; Legua, P.; Hernández, F. Bioactive Compounds and Sensory Quality of Black and White Mulberries Grown in Spain. Plant Foods Hum. Nutr. 2013, 68, 370–377.

27. Imran, M.; Khan, H.; Shah, M.; Khan, R.; Khan, F. Chemical composition and antioxidant activity of certain Morus species. J Zhejiang Univ. Sci. B. 2010, 11, 973–980. https://doi.org/10.1631/jzus.B1000173.

28. Zhao, X.L.; Fan, D.C. Review of physiological active components, extraction and detection methods and pharmacological bioactivities of mulberries. Chin. J. Pharm. Anal. 2017, 37, 378–385. https://doi.org/10.16155/j.issn.1004-1793.2017.03.02.

29. Junsong, P.; Hu, C.; Zhonghuai, X.; Guangwei, Y.; Ningjia, H. Determination of 1-Deoxynojirimycin in Black Mulberry Fruit by Ultra Performance Liquid Chromatography. Food Sci. 2015, 36, 207–210. https://doi.org/10.7506/spkx1002-6630-201520040.

30. Pérez-Gregorio, M.R.; Regueiro, J.; Alonso-González, E.; Pastrana-Castro, L.M.; Simal-Gándara, J. Influence of alcoholic fermentation process on antioxidant activity and phenolic levels from mulberries (Morus nigra L.). LWT Food Sci. Technol. 2011, 44, 1793–1801.

31. Lin, J.Y.; Tang, C.Y. Determination of total phenolic and flavonoid contents in selected fruits and vegetables, as well as their stimulatory effects on mouse splenocyte proliferation. Food Chem. 2007, 101, 140–147.

32. Khalifa, I.; Zhu, W.; Li, K.K.; Li, C.M. Polyphenols of mulberry fruits as multifaceted compounds: Compositions, metabolism, health benefits, and stability—A structural review. J. Funct. Foods. 2018, 40, 28–43.

33. Kim, I.; Moon, J.K.; Hur, S.I.; Lee, J. Structural changes in mulberry (Morus Microphylla. Buckl) and chokeberry (Aronia melano-carpus) anthocyanins during simulated in vitro human digestion. Food Chem. 2020, 318, 126449. https://doi.org/10.1016/j.foodchem.2020.126449.

34. Kamiloglu, S.; Capanoglu, E. Antioxidant activity and polyphenol composition of black mulberry (Morus nigra L.) products. J. Berry Res. 2013, 3, 41–51. https://doi.org/10.3233/BR-130045.

35. Butkhup, L.; Samappito, W.; Samappito, S. Phenolic composition and antioxidant activity of white mulberry (Morus alba L.) fruits. Int. J. Food Sci. Technol. 2013, 48, 934–940. https://doi.org/10.1111/ijfs.12044.

36. Wang, K.; Kang, S.; Li, F.; Wang, X.; Xiao, Y.; Wang, J.; Xu, H. Relationship between fruit density and physicochemical properties and bioactive composition of mulberry at harvest. J. Food Compos. Anal. 2022, 106, 104322.

37. Chen, S.U.; Kim, Y.M.; Park, Y.J.; Heo, B.G.; Park, Y.S.; Gorinstein, S. Antioxidant and anti-proliferative effects of methanol extracts from raw and fermented parts of mulberry plant (Morus alba L.). Eur. Food Res. Technol. 2009, 230, 231–237. https://doi.org/10.1007/s00217-009-1165-2.

38. Jin, Q.; Yang, J.; Ma, L.; Wen, D.; Chen, F.; Li, J. Identification of polyphenols in mulberry (genus Morus) cultivars by liquid chromatography with time-of-flight mass spectrometer. J. Food Compos. Anal. 2017, 63, 55–64.

39. Bae, S.-H.; Suh, H.-J. Antioxidant activities of five different mulberry cultivars in Korea. LWT Food Sci. Technol. 2007, 40, 955–962.

40. Yan, F.; Zheng, X. Anthocyanin-rich mulberry fruit improves insulin resistance and protects hepatocytes against oxidative stress during hyperglycemia by regulating AMPK/ACC/mTOR pathway. J. Funct. Foods. 2017, 30, 270–281.

41. Erden, Y. Sour black mulberry (Morus nigra L.) causes cell death by decreasing mutant p53 expression in HT-29 human colon cancer cells. Food Bioci. 2021, 42, 101113. https://doi.org/10.1016/j.fbio.2021.101113.

42. Liu, H.; Yang, J.; Huang, S.; Liu, R.; He, Y.; Zheng, D.; Liu, C. Mulberry crude extracts induce Nrf2 activation and expression of detoxifying enzymes in rat liver: Implication for its protection against NP-induced toxic effects. J. Funct. Foods. 2017, 32, 367–374. https://doi.org/10.1016/j等功能.2017.03.024.

43. Jiang, D.Q.; Guo, Y.; Xu, D.H.; Huang, Y.S.; Yuan, K.; Lv, Z.Q. Antioxidant and anti-fatigue effects of anthocyanins of mulberry juice purification (MJP) and mulberry marc purification (MMP) from different varieties mulberry fruit in China. Food Chem. Toxicol. 2013, 59, 1–7. https://doi.org/10.1016/j.fct.2013.05.023.

44. Chuah, H.Q.; Tang, P.L.; Ang, N.J.; Tan, H.Y. Submerged fermentation improves bioactivity of mulberry fruits and leaves. Chin. Herb. Med. 2021, 13, 565–572. https://doi.org/10.1016/j.chemed.2021.09.003.

45. Espada-Bellido, E.; Ferreiro-González, M.; Carrera, C.; Palma, M.; Barroso, C.G.; Barbero, G.F. Optimization of the ultrasound-assisted extraction of anthocyanins and total phenolic compounds in mulberry (Morus nigra) pulp. Food Chem. 2017, 219, 23–32. https://doi.org/10.1016/j.foodchem.2016.09.122.

46. Bao, T.; Li, Y.; Xie, J.; Jia, Z.; Chen, W. Systematic evaluation of polyphenols composition and antioxidant activity of mulberry cultivars subjected to gastrointestinal digestion and gut microbiota fermentation. J. Funct. Foods. 2019, 58, 338–349. https://doi.org/10.1016/j.jff.2019.05.017.

47. Turan, E.; Şimşek, A. Effects of lyophilized black mulberry water extract on lipid oxidation, metmyoglobin formation, color stability, microbial quality and sensory properties of beef patties stored under aerobic and vacuum packaging conditions. Meat Sci. 2021, 178, 108522. https://doi.org/10.1016/j.meatsci.2021.108522.

48. Lee, M.S.; Kim, Y. Mulberry Fruit Extract Ameliorates Adipogenesis via Increasing AMPK Activity and Downregulating MicroRNA-21/143 in 3T3-L1 Adipocytes. J. Med. Food 2020, 23, 266–272. https://doi.org/10.1089/jmf.2019.4654.

49. Lou, H.; Hu, Y.; Zhang, L.; Sun, P.; Lu, H. Nondestructive evaluation of the changes of total flavonoid, total phenols, ABTS and DPPH radical scavenging activities, and sugars during mulberry (Morus alba L.) fruits development by chlorophyll fluorescence and RGB intensity values. LWT Food Sci. Technol. 2012, 47, 19–24. https://doi.org/10.1016/j.lwt.2012.01.008.
50. Özgen, M.; Serçe, S.; Kaya, C. Phytochemical and antioxidant properties of anthocyanin-rich *Morus nigra* and *Morus rubra* fruits. *Sci. Hortic.* 2009, 119, 275–279.

51. Tomas, M.; Todyemir, G.; Boyacioglu, D.; Hall, R.; Beekwilder, J.; Capanoglu, E. The effects of juice processing on black mulberry antioxidants. *Food Chem.* 2015, 186, 277–284. https://doi.org/10.1016/j.foodchem.2008.08.007.

52. Song, W.; Wang, H.J.; Bucheli, P.; Zhang, P.F.; Wei, D.Z.; Lu, Y.H. Phytochemical Profiles of Different Mulberry (*Morus sp.*) Species from China. *J. Agric. Food Chem.* 2009, 57, 9133–9140.

53. Scuto, M.; Ontario, M.L.; Salinaro, A.T.; Caligirì, I.; Rampulla, F.; Zimbone, V.; Modafferi, S.; Rizzolio, F.; Canzonieri, V.; Calabrese, E.J.; et al. Redox modulation by plant polyphenols targeting vitagens for chemoprevention and therapy: Relevance to novel anti-cancer interventions and mini-brain organoid technology. *Free Radic. Biol. Med.* 2022, 179, 59–75. https://doi.org/10.1016/j.freeradbiomed.2021.12.267.

54. Wu, Y.; Zhang, C.; Huang, Z.; Lyu, L.; Li, W.; Wu, W. Integrative analysis of the metabolome and transcriptome provides insights into the mechanisms of flavonoid biosynthesis in blackberry. *Food Res. Int.* 2022, 153, 110948. https://doi.org/10.1016/j.foodres.2022.110948.

55. Wu, T.; Tang, Q.; Gao, Z.; Yu, Z.; Song, H.; Zheng, X.; Chen, W. Blueberry and mulberry juice prevent obesity development in C57BL/6 mice. *PloS ONE* 2013, 8, e77585. https://doi.org/10.1371/journal.pone.0077585.

56. Bao, T.; Xu, Y.; Gowd, V.; Zhao, J.; Xie, J.; Liang, W.; Chen, W. Systematic study on phytochemicals and antioxidant activity of some new and common mulberry cultivars in China. *J. Funct. Foods* 2016, 25, 537–547.

57. Hassimotto, N.M.A.; Genovese, M.I.; Lajolo, F.M. Identification and Characterisation of Anthocyanins from Wild Mulberry (*Morus nigra L.*) Growing in Brazil. *Food Sci. Technol. Int.* 2016, 13, 17–25. https://doi.org/10.1177/1920202705602.

58. Ştefănuţ, M.N.; Căta, A.; Pop, R.; Moşoara, C.; Zamfir, A.D. Anthocyanins HPLC-DAD and MS Characterization, Total Phenolics, and Antioxidant Activity of Some Berries Extracts. *Anal. Lett.* 2011, 44, 2843–2855.

59. Ştefănuţ, M.N.; Căta, A.; Pop, R.; Tanasie, C.; Boc, D.; Ienascu, I.; Ordodi, V. Anti-hyperglycemic effect of bilberry, blackberry and mulberry ultrasonic extracts on diabetic rats. *Plant Foods Hum. Nutr.* 2013, 68, 378–384. https://doi.org/10.1007/s11130-013-0380-y.

60. Qin, C.; Li, Y.; Niu, W.; Ding, Y.; Zhang, R.; Shang, X. Analysis and characterisation of anthocyanins in mulberry fruit. *Czech J. Food Sci.* 2010, 28, 117–126. https://doi.org/10.1080/19476330903450282.

61. Mahmood, T.; Anwar, F.; Afzal, N.; Kausar, R.; Ilyas, S.; Shoaib, M. Influence of ripening stages and drying methods on polyphenolic content and antioxidant activities of mulberry fruits. *J. Food Meas. Charact.* 2017, 11, 2171–2179. https://doi.org/10.1007/s11694-017-9602-6.

62. Hassimotto, N.M.A.; Genovese, M.I.; Lajolo, F.M. Absorption and metabolism of cyanidin-3-glucoside and cyanidin-3-rutinoside extracted from wild mulberry (*Morus nigra L.*) in rats. *Nutr. Res.* 2008, 28, 198–207. https://doi.org/10.1016/j.nutres.2007.12.012.

63. Park, S.W.; Jung, Y.S.; Ko, K.C. Quantitative analysis of anthocyanins among mulberry cultivars and their pharmacological screening. *J. Korean Soc. Hort. Sci.* 1997, 38, 722–724. https://doi.org/10.1002/jmir.24933.

64. Liu, X.; Xiao, G.; Chen, W.; Xu, Y.J.; Wu, J.J. Quantification and Purification of Mulberry Anthocyanins with Macroporous Resins. *J. Biomed. Biotechnol.* 2004, 2004, 713759. https://doi.org/10.1155/S111024304403052.

65. Huang, L.; Zhou, Y.; Meng, L.; Wu, D.; He, Y. Comparison of different CCD detectors and chemometrics for predicting total anthocyanin content and antioxidant activity of mulberry fruit using visible and near infrared hyperspectral imaging technique. *Food Chem.* 2017, 224, 1–10. https://doi.org/10.1016/j.foodchem.2016.12.037.

66. Zadernowski, R.; Naczk, M.; Nesterowicz, J. Phenolic Acid Profiles in Some Small Berries. *J. Agric. Food Chem.* 2005, 53, 2118–2124. https://doi.org/10.1021/jf040411p.

67. Liu, C.J.; Lin, J.Y. Anti-inflammatory effects of phenolic extracts from strawberry and mulberry fruits on cytokine secretion profiles using mouse primary splenocytes and peritoneal macrophages. *Int. Immunopharmacol.* 2013, 16, 165–170.

68. Zhang, W.; Han, F.; He, J.; Duan, C. HPLC-DAD-ESI-MS/MS analysis and antioxidant activities of nonanthocyanin phenolics in mulberry (*Morus alba L*). *J. Food Sci.* 2008, 73, 512–518. https://doi.org/10.1111/j.1750-3841.2008.00854.x.

69. Lee, K.M.; Oh, T.J.; Kim, S.H.; Kim, H.Y.; Chung, H.; Min, D.S.; Ahn, J.H.; Lee, H.J.; Lee, J.; Choi, H.K. Comprehensive metabolic profiles of mulberry fruit (*Morus alba Linnaceae*) according to maturation stage. *Food Sci. Biotechnol.* 2016, 25, 1035–1041. https://doi.org/10.1006/jfibo.2016.1017-167.

70. Jiang, S.; Qu, L.; Li, Y.; Li, L.; Wang, X.; Liu, Z.; Guo, Y.; Wang, H. Effects of Marsdenia tenacissima polysaccharide on the immune regulation and tumor growth in H22 tumor-bearing mice. *Carbohydr. Polym.* 2016, 137, 52–58.

71. Zhang, P.L.; Zhang, S.; Chen, X.X.; Liu, G.; Wang, Q.; Cao, Y.J.M.F.e.; Technology. Protective Effect of Mulberry Polysaccharides on H_2O_2-induced Oxidative Damage in PC-12 Cells. *Mod. Food Sci. Technol.* 2015, 31, 20–24.

72. Liu, F.; Zhu, Z.Y.; Sun, X.; Gao, H.; Zhang, Y.M. The preparation of three selenium-containing *Cordyceps militaris* polysaccharides: Characterization and anti-tumor activities. *Int. J. Biol. Macromol.* 2017, 99, 196–204.

73. Feng, H.; Fan, J.; Yang, S.; Zhao, X.; Yi, X. Antiviral activity of phosphorylated *Radix Cyathulae officinalis* polysaccharide against Canine Parvovirus in vitro. *Int. J. Biol. Macromol.* 2017, 99, 511–518.

74. Wang, Y.; Lin, D.; Wang, X.; Zhu, W.; Ye, J.; Li, G.; Ma, Z.; Deng, X. The impact of a novel peach gum-derived polysaccharide on postprandial blood glucose control in streptozotocin-induced diabetic mice. *Int. J. Biol. Macromol.* 2017, 98, 379–386. https://doi.org/10.1016/j.ijbiomac.2017.01.085.
Foods 2022, 11, 1170

75. Wojdylo, A.; Nowicka, P.; Bąbelewski, P. Phenolic and carotenoid profile of new goji cultivars and their anti-hyperglycemic, anti-aging and antioxidant properties. *J. Funct. Foods.* 2018, 48, 632–642. https://doi.org/10.1016/j.jff.2018.07.061.

76. Lee, S.A.; Lim, W.H.; Van Le, V.; Ko, S.R.; Kim, B.; Oh, H.M.; Ahn, C.Y. Lifespan extension and anti-oxidant effects of carotenoid pigments in Caenorhabditis elegans. *Bioresearch. Technol. Rep.* 2022, 17, 100962.

77. Kasselman, L.J.; Renna, H.A.; Voloshyna, I.; Pinkhasov, A.; Gomolin, I.H.; Teboul, I.; De Leon, J.; Carsons, S.E.; Reiss, A.B. Cognitive changes mediated by adenosine receptor blockade in a resveratrol-treated atherosclerosis-prone lupus mouse model. *J. Tradit. Chin. Med.* 2022, *In press.* https://doi.org/10.1016/j.jtcme.2022.01.006.

78. Tezerji, S.; Abdolazimi, H.; Fallah, A.; Talaei, B. The effect of resveratrol and quercetin intervention on azoxymethane-induced colon cancer in Rats model. *Clin. Nutr. Open Sci. 2022.* https://doi.org/10.1016/j.nutos.2022.01.008. In press.

79. Wang, S.; Gong, L.; Mo, Y.; Zhang, J.; Tian, Z.; Shao, C. Resveratrol attenuates inflammation and apoptosis through alleviating endoplasmic reticulum stress via Akt/mTOR pathway in fungus-induced allergic airways inflammation. *Int. Immunopharmacol.* 2022, 103, 108489. https://doi.org/10.1016/j.intimp.2021.108489.

80. Chen, K.; Wei, X.; Cortesniemi, M.; Pariyani, R.; Zhang, Y.; Yang, B. Effects of acetylated and nonacetylated anthocyanins extracts on gut metabolites and microbiota in diabetic Zucker rats: A metabolomic and metagenomic study. *Food Res. Int.* 2022, 153, 110978.

81. Yang, P.; Huang, K.; Zhang, Y.; Li, S.; Cao, H.; Song, H.; Zhang, Y.; Guan, X. Biotransformation of quinoa phenolic compounds with Monascus anka to enhance the antioxidant capacity and digestive enzyme inhibitory activity. *Food Bioci.* 2022, 46, 10156.

82. Aboonabi, A.; Singh, I.; Rose’Meyer, R. Cytoprotective effects of berry anthocyanins against induced oxidative stress and inflammation in primary human diabetic aortic endothelial cells. *Chem. Biol. Interact.* 2020, 317, 108940.

83. Oliveira, I.; Baptista, P.; Malheiro, R.; Casal, S.; Bento, A.; Pereira, J.A. Influence of strawberry tree (Arbutus unedo L.) fruit ripening stage on chemical composition and antioxidant activity. *Food Res. Int.* 2011, 44, 1401–1407.

84. Han, W.; Zhang, L.; Huang, X.; Qiu, S.; Jiankun, L. Flocculating purification and oxidation resistance of mulberry polysaccharides. *J. Nanjing Univ. Technol.* 2014, 36, 97–101.

85. Honarbaksh, M.; Malta, K.; Ericsson, A.; Holloway, C.; Kim, Y.K.; Hammerling, U.; Quadro, L. β-carotene improves fecal dysbiosis and intestinal dysfunctions in a mouse model of vitamin A deficiency. *Biochim. Biophys. Acta.* 2022, 1867, 159122. https://doi.org/10.1016/j.bbalip.2022.159122.

86. Semwal, R.; Joshi, S.K.; Semwal, R.B.; Semwal, D.K. Health benefits and limitations of rutin-A natural flavonoid with high nutraceutical value. *Phytochem. Lett.* 2021, 46, 119–128.

87. Lu, X.; Wang, L.; Wei, H.; Yang, Z.; Wang, W. Structure-activity relationship of flavonoids in antioxidant activity. *Food Sci.* 2006, 27, 233–237. https://doi.org/10.1016/S1872-2040(06)60045-5.

88. Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Remesy, C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* 2005, 81, 2305–2425.

89. Garcia-Alonso, M.; Minihane, A.M.; Rimbach, G.; Rivas-Gonzalo, J.C.; de Pascual-Teresa, S. Red wine anthocyanins are rapidly absorbed in humans and affect monocyte chemoattractant protein 1 levels and antioxidant capacity of plasma. *J. Nutr. Biochem.* 2009, 20, 521–529.

90. Di Gesso, J.L.; Kerr, J.S.; Zhang, Q.; Raheem, S.; Yalamanchili, S.K.; O’Hagan, D.; Kay, C.D.; O’Connell, M.A. Flavonoid metabolites reduce tumor necrosis factor-alpha secretion to a greater extent than their precursor compounds in human THP-1 monocytes. *Mol. Nutr. Food Res.* 2015, 59, 1143–1154. https://doi.org/10.1002/mnfr.201400799.

91. Natic, M.M.; Dabić, D.; Papetti, A.; Fotirić Akšić, M.M.; Ognjanov, V.; Ljubovjević, M.; Tešić, Ž.L. Analysis and characterisation of phytochemicals in mulberry (Morus alba L.) fruits grown in Vogdvina, North Serbia. *Food Chem.* 2015, 171, 128–136.

92. Liu, L.K.; Lee, H.J.; Shih, Y.W.; Chyau, C.C.; Wang, C.J. Mulberry anthocyanins extracts inhibit LDL oxidation and macrophage-derived foam cell formation induced by oxidative LDL. *J. Food Sci.* 2010, 73, H113–H211. https://doi.org/10.1111/j.1750-3841.2008.00801.x.

93. Chen, P.N.; Chu, S.C.; Chiou, H.L.; Kuo, W.H.; Chiang, C.L.; Hsieh, Y.S. Mulberry anthocyanins, cyanidin 3-rutinoside and cyanidin 3-glucoside, exhibited an inhibitory effect on the migration and invasion of a human lung cancer cell line. *Cancer Lett.* 2006, 235, 248–259.

94. Li, M.; Li, T.; Hu, X.; Ren, G.; Zhang, H.; Wang, Z.; Teng, Z.; Wu, R.; Wu, J. Structural, rheological properties and antioxidant activities of polysaccharides from mulberry fruits (Morus alba L.) based on different extraction techniques with superfine grinding pretreatment. *Int. J. Biol. Macromol.* 2021, 183, 1774–1783.

95. Li, F.; Zhang, B.; Chen, G.; Fu, X. The novel contributors of anti-diabetic potential in mulberry polyphenols revealed by UHPLC-HR-ESI-TOF-MS/MS. *Food Res. Int.* 2017, 100, 873–875.

96. Chang, J.J.; Hsu, M.J.; Huang, H.P.; Chung, D.J.; Chang, Y.C.; Wang, C.J. Mulberry anthocyanins inhibit oleic acid induced lipid accumulation by reduction of lipogenesis and promotion of hepatic lipid clearance. *J. Agric. Food Chem.* 2013, 61, 6069–6076. https://doi.org/10.1021/jf401171k.

97. Chen, Y.; Zhang, W.; Zhao, T.; Li, F.; Zhang, M.; Li, J.; Zou, Y.; Wang, W.; Cobbina, S.J.; Wu, X.; et al. Adsorption properties of macroporous adsorbent resins for separation of anthocyanins from mulberry. *Food Chem.* 2016, 194, 712–722.

98. Yang, J.Y.; Lee, H.S. Evaluation of antioxidant and antibacterial activities of morin isolated from mulberry fruits (Morus alba L.). *J. Korean Soc. Appl. Biol. Chem.* 2012, 55, 485–489. https://doi.org/10.1007/s13765-012-2110-9.

99. Wu, T.; Yin, J.; Zhang, G.; Long, H.; Zheng, X. Mulberry and cherry anthocyanin consumption prevents oxidative stress and inflammation in diet-induced obese mice. *Mol. Nutr. Food Res.* 2016, 60, 687–694. https://doi.org/10.1002/mnfr.201500734.
100. Ghasemnezhad Targhi, R.; Homayoun, M.; Mansouri, S.; Soukhantanlo, M.; Soleymanifard, S.; Seghatoleslam, M. Radio protective effect of black mulberry extract on radiation-induced damage in bone marrow cells and liver in the rat. *Radiat. Phys. Chem.* 2017, 130, 297–302.

101. Sarma, A.D.; Sharma, R. Anthocyanin-DNA copigmentation complex: Mutual protection against oxidative damage. *Phytochemistry* 1999, 52, 1313–1318.

102. Mas, T.; Susperregui, J.; Berke, B.; Chêze, C.; Moreau, S.; Nruhrich, A.; Vercauteren, J. DNA triplex stabilization property of natural anthocyanins. *Phytochemistry* 2000, 53, 679–687.

103. Wu, C.S.; Chung, T.J.; Lee, Y.J.; Hsu, J.D.; Lee, H.J. Mulberry supplementation reduces lipid deposition and protects hamster retina from oxLDL damage. *J. Funct. Foods* 2020, 71, 104007. https://doi.org/10.1016/j.jff.2020.104007.

104. Du, Q.; Zheng, J.; Xu, Y. Composition of anthocyanins in mulberry and their antioxidant activity. *J. Food Compos. Anal.* 2008, 21, 390–395. https://doi.org/10.1016/j.jfca.2008.02.007.

105. Wang, Y.; Xiang, L.; Wang, C.; Tang, C.; He, X. Antidiabetic and antioxidant effects and phytochemicals of mulberry fruit (*Morus alba L.*) polyphenol enhanced extract. *PLoS ONE* 2013, 8, e71144. https://doi.org/10.1371/journal.pone.0071144.

106. Sarikaphuti, A.; Nararatwanchai, T.; Hashiguchi, T.; Ito, T.; Thaworanunta, S.; Kikuchi, K.; Oyama, Y.; Maruyama, I.; Tancharoen, S. Preventive effects of *Morus alba* L. anthocyanins on diabetes in Zucker diabetic fatty rats. *Exp. Ther. Med.* 2013, 6, 689–695. https://doi.org/10.3892/etm.2013.1203.

107. Lee, J.S.; Kim, Y.R.; Song, I.G.; Ha, S.J.; Kim, Y.E.; Baek, N.I.; Hong, E.K. Cyanidin-3-glucoside isolated from mulberry fruit protects pancreatic β-cells against oxidative stress-induced apoptosis. *Int. J. Mol. Med.* 2015, 35, 405–412. https://doi.org/10.3892/ijmm.2014.2013.

108. Yan, F.; Zhang, J.; Zhang, L.; Zheng, X. Mulberry anthocyanin extract regulates glucose metabolism by promotion of glycolgen synthesis and reduction of gluconeogenesis in human HepG2 cells. *Food Funct.* 2016, 7, 425–433. https://doi.org/10.1039/c5fo00841g.

109. Yan, F.J.; Chen, X.A.; Zheng, X.D. Protective effect of mulberry fruit anthocyanin on human hepatocyte cells (LO2) and *Caenorhabditis elegans* under hyperglycemic conditions. *Food Res. Int.* 2017, 102, 213–224. https://doi.org/10.1016/j.foodres.2017.10.009.

110. Lin, J.Y.; Tang, C.Y. Strawberry, loquat, mulberry, and bitter melon juices exhibit prophylactic effects on LPS-induced inflammation using murine peritoneal macrophages. *Food Chem.* 2008, 107, 1587–1596.

111. Tang, C.C.; Huang, H.P.; Lee, Y.J.; Tang, Y.H.; Wang, C.J. Hepatoprotective effect of mulberry water extracts on ethanol-induced liver injury via anti-inflammation and inhibition of lipogenesis in C57BL/6j mice. *Food Chem. Toxicol.* 2013, 62, 786–796. https://doi.org/10.1016/j.fct.2013.10.011.

112. Jeong, J.C.; Jang, S.W.; Kim, T.H.; Kwon, C.H.; Kim, Y.K. Mulberry fruit (*Morus frutic) extracts induce human glioma cell death in vitro through ROS-dependent mitochondrial pathway and inhibits glioma tumor growth in vivo. *Nutr. Cancer* 2010, 62, 402–412. https://doi.org/10.1080/0163558903441287.

113. Qian, Z.; Wu, Z.; Huang, L.; Qiu, H.; Wang, L.; Li, L.; Yao, L.; Kang, K.; Qu, J.; Wu, Y.; et al. Mulberry fruit prevents LPS-induced NF-kappaB/pERK/MAPK signals in macrophages and suppresses acute colitis and colorectal tumorigenesis in mice. *Sci. Rep.* 2015, 5, 17348. https://doi.org/10.1038/srep17348.

114. Huang, H.P.; Shih, Y.W.; Chang, Y.C.; Hung, C.N.; Wang, C.J. Chemoinhibitory effect of mulberry anthocyanins on melanoma metastasis involved in the Ras/PI3K pathway. *J. Agric. Food Chem.* 2008, 56, 9296–9293. https://doi.org/10.1021/jf8013102.

115. Long, H.L.; Zhang, F.F.; Wang, H.L.; Yang, W.-S.; Hou, H.T.; Yu, J.K.; Liu, B. Mulberry anthocyanins improves thyroid cancer progression mainly by inducing apoptosis and autophagy cell death. *Kaohsiung J. Med. Sci.* 2018, 34, 255–262. https://doi.org/10.1016/j.kjms.2017.11.004.

116. Huang, H.P.; Chang, Y.C.; Wu, C.H.; Hung, C.N.; Wang, C.J. Anthocyanin-rich Mulberry extract inhibit the gastric cancer cell growth in vitro and xenograft mice by inducing signals of p38/p53 and c-Jun. *Food Chem.* 2011, 129, 1703–1709. https://doi.org/10.1016/j.foodchem.2011.06.035.

117. Sakagami, H.; Asano, K.; Satoh, K.; Takahashi, K.; Kobayashi, M.; Koga, N.; Takahashi, H.; Tachikawa, R.; Tashiro, T.; Hasegawa, A.; et al. Anti-stress, anti-HIV and vitamin C-synergized radical scavenging activity of mulberry juice fractions. *In Vivo* 2007, 21, 499–505.

118. Wu, T.; Qi, X.; Liu, Y.; Guo, J.; Zhu, R.; Chen, W.; Zheng, X.; Yu, T. Dietary supplementation with purified mulberry (*Morus australis* Poir) anthocyanins suppresses body weight gain in high-fat diet fed C57BL/6 mice. *Food Chem.* 2013, 141, 482–487. https://doi.org/10.1016/j.foodchem.2013.03.046.

119. Peng, C.H.; Liu, L.K.; Chuang, C.M.; Chyau, C.C.; Huang, C.N.; Wang, C.J. Mulberry water extracts possess an anti-obesity effect and ability to inhibit hepatic lipogenesis and promote lipolysis. *J. Agric. Food Chem.* 2011, 59, 2663–2671. https://doi.org/10.1021/jf1043508.

120. Chaiwong, S.; Chatturom, U.; Chanasong, R.; Deetud, W.; To-on, K.; Puntheeranurak, S.; Chulikorn, E.; Kajsongkram, T.; Sakanoah, V.; Chinda, K.; et al. Dried mulberry fruit ameliorates cardiovascular and liver histopathological changes in high-fat diet-induced hyperlipidemic mice. *J. Tradit. Chin. Med.* 2021, 11, 356–368. https://doi.org/10.1016/j.jtcm.2021.02.006.

121. Chen, C.C.; Liu, L.K.; Hsu, J.D.; Huang, H.P.; Yang, M.Y.; Wang, C.J. Mulberry extract inhibits the development of atherosclerosis in cholesterol-fed rabbits. *Food Chem.* 2005, 91, 601–607. https://doi.org/10.1016/j.foodchem.2004.06.039.

122. Tsuduki, T.; Kikuchi, I.; Kimura, T.; Nakagawa, K.; Miyazawa, T. Intake of mulberry 1-deoxynojirimycin prevents diet-induced obesity through increases in adiponecin in mice. *Food Chem.* 2013, 139, 16–23. https://doi.org/10.1016/j.foodchem.2013.02.025.
123. Srilhari, T.; Satyanarayana, U. Changes in free radical scavenging activity of Kombucha during fermentation. *J. Pharm. Sci. Res.* 2012, 4, 1978–1981.

124. Isabelle, M.; Lee, B.L.; Ong, C.N.; Liu, X.; Huang, D. Peroxyl radical scavenging capacity, polyphenolics, and lipophlic antioxidant profiles of mulberry fruits cultivated in southern China. *J. Agric. Food Chem.* 2008, 56, 9410–9416. https://doi.org/10.1021/jf801527a.

125. D’Urso, G.; Mes, J.J.; Monforto, P.; Hall, R.D.; de Vos, R.C.H. Identification of Bioactive Phytochemicals in Mulberries. *Metabolites* 2019, 10, 7. https://doi.org/10.3390/metabo10010007.

126. Arfan, M.; Khan, R.; Rybarczyk, A.; Amarowicz, R. Antioxidant Activity of Mulberry Fruit Extracts. *Int. J. Mol. Sci.* 2012, 13, 2472–2480. https://doi.org/10.3390/ijms13022472.

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

128. Takikawa, M.; Inoue, S.; Horio, F.; Tsuda, T. Dietary Anthocyanin-Rich Bilberry Extract Ameliorates Hyperglycemia and Insulin Sensitivity via Activation of AMP-Activated Protein Kinase in Diabetic Mice. *J. Nutr.* 2010, 140, 527–533. https://doi.org/10.3945/jn.109.118216.

129. Zhu, C.L.; Chen, M.; Wang, M.H.; Shen, T.; Qiang, Q.; Wang, X.F.; Ji, L.L.; Feng, Z.S.; Tao, Y.X.; Bai, Y.J.; et al. In vitro Characterization of the Anti-inflammatory Effect of Mulberry Extract and the Molecular Mechanisms. *Mod. Food Sci. Technol.* 2017, 33, 61–66.

130. Liu, C.J.; Lin, J.Y. Anti-inflammatory and anti-apoptotic effects of strawberry and mulberry fruit polysaccharides on lipopolysaccharide-stimulated macrophages through modulating pro-/anti-inflammatory cytokines secretion and Bcl-2/Bak protein ratio. *Food Chem. Toxicol.* 2012, 50, 3032–3039.

131. Liu, R.H. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am. J. Clin. Nutr.* 2003, 78, 517S–520S. https://doi.org/10.1093/ajcn/78.3.517S.

132. Criqui, M.H.; Ringel, B.L. Does diet or alcohol explain the French paradox? *Lancet* 1994, 344, 1719–1723.

133. Ness, A.R.; Powles, J.W. Fruit and vegetables, and cardiovascular disease: A review. *Int. J. Epidemiol.* 1997, 26, 1–13. https://doi.org/10.1093/ije/26.1.1.

134. Fairby, S.A.; Singab, A.N.B.; Agwa, S.A.; Abd El Hamid, D.M.; Zabra, F.A.; Abd El Moneim, S.M. The antiproliferative effect of mulberry (*Morus alba*) plant on hepatocarcinoma cell line HepG2. *Egypt. J. Med. Genet.* 2013, 14, 375–382.

135. Cheng, K.C.; Wang, C.J.; Chang, Y.C.; Hung, T.W.; Lai, C.J.; Kuo, C.W.; Huang, H.P. Mulberry fruits extracts induce apoptosis and autophagy of liver cancer cell and prevent hepatocarcinogenesis in vivo. *J. Food Drug Anal.* 2020, 28, 84–93. https://doi.org/10.1016/jjfda.2019.06.002.

136. Nie, C.; Zeng, Q.Q.; Zhang, X.F.; Wang, Q. Preliminary Study of Mulberry Anthocyanins on S180 Transplanted Tumorinhibitory Effect and Apoptosis Effect on Cells of Value-added. *Res. Pract. Chin. Med.* 2014, 28, 44–48. https://doi.org/10.13728/j.1673-6427.2014.06013.

137. Jiang-Lian, D.; Jian-Guo, X. Study on Antimicrobial Effects of Mulberry Red Pigment. *J. Food Sci.* 2007, 28, 87–89. https://doi.org/10.1016/S1872-583X(07)60014-4.

138. Li, G.Z.; Yu, H.Z.; Bu, X.Y.; Cao, Y.; Rao, L.Q. Extraction of Flavone Glycosides from the Seed of *Morus alba* L. by CO2 Supercritical Fluid and its Antimicrobial Effect. *Mod. Food Sci. Technol.* 2006, 22, 86–88.

139. Kim, B.S.; Kim, H.; Kang, S.S. In vitro anti-bacterial and anti-inflammatory activities of lactic acid bacteria-biotransformed mulberry (*Morus alba* Linnaeus) fruit extract against *Salmonella Typhimurium*. *Food Control* 2019, 106, 106758. https://doi.org/10.1016/j.foodcont.2019.106758.

140. Cisowska, A.; Wojnick, D.; Hendrich, A.B. Anthocyanins as Antimicrobial Agents of Natural Plant Origin. *Nat. Prod. Commun.* 2011, 6, 149–156. https://doi.org/10.1039/i1np00116f.

141. Li, Y.; Yang, Z.; Jia, S.; Yuan, K. Protective effect and mechanism of action of mulberry marc anthocyanins on carbon tetrachloride-induced liver fibrosis in rats. *J. Funct. Foods* 2016, 24, 599–601. https://doi.org/10.1016/j.jff.2016.05.001.

142. Gao, L.H.; Liu, S.N.; Liu, Q.; Li, C.N.; Li, L.Y.; Shen, Z.F. The ameliorative effects of mulberry nectar on alcoholism. *Food Mach.* 2010, 26, 83–85. https://doi.org/10.13652/j.issn.1003-5788.2010.01.047.

143. Wang, X.; Deng, Q.F.; Chen, H.G.; Zhou, X. Characterization and activity effect on ADH of polysaccharides from *Mori Fructus*.* Chin. J. Chin. Mater. Med.* 2017, 42, 2329–2333. https://doi.org/10.19540/j.cnki.cjcm.20170316.002.

144. Xia, C.L.; Tang, G.H.; Guo, Y.Q.; Xu, Y.K.; Huang, Z.S.; Yin, S. Mulberry Diels-Alder-type adducts from *Morus alba* as multi-targeted agents for Alzheimer’s disease. *Phytochemistry* 2019, 157, 82–91. https://doi.org/10.1016/j.phytochem.2018.10.028.

145. Liu, D.; Du, D. Mulberry Fruit Extract Alleviates Cognitive Impairment by Promoting the Clearance of Amyloid-β and Inhibiting Neuroinflammation in Alzheimer’s Disease Mice. *Neurochem. Res.* 2020, 45, 2009–2019. https://doi.org/10.1007/s11064-020-03062-7.

146. Kim, J.H.; Kim, T.I.; Ma, J.Y. Synergistic effects of novel herbal decoctions from *Panax ginseng* and *Morus alba* on tyrosinase activity and melanogenesis in vitro. *Heliyon* 2022, 8, e08866. https://doi.org/10.1016/j.heliyon.2022.e08866.

147. Zheng, S.; Zhu, Y.; Liu, C.; Fan, W.; Xiang, Z.; Zhao, A. Genome-wide identification and characterization of genes involved in melatonin biosynthesis in *Morus notabilis* (wild mulberry). *Phytochemistry* 2021, 189, 112819. https://doi.org/10.1016/j.phytochem.2021.112819.

148. Rebai, O.; Belkhir, M.; Fatouch, S.; Amri, M. Phytochemicals from mulberry extract (*Morus sp.): Antioxidant and neuroprotective potentials. *J. Appl. Phys.* 2017, 7, 217–222. https://doi.org/10.7324/japs.2017.70133.