Review of bioactive compounds from root barks of *Morus* plants (Sang-Bai-Pi) and their pharmacological effects

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**Abstract:** *Morus*, a plant genus from the family of Moraceae, most plants of which are used as traditional medicines in Asian counties. The root barks of *Morus* plants are normally called as Sang-Bai-Pi (SBP) in Chinese and used for the treatment of inflammatory and respiratory diseases. Decades of research on phytochemistry of SBP have led to the identification of various compounds, such as Diels–Alder-type adducts, flavonoids, benzofurans, stilbenes, polyhydroxylated alkaloids, etc. These compounds have showed a wide range of bioactive features including anti-inflammatory, anti-oxidative, anti-microbic, etc. This review focus on the bioactive compounds and their pharmacological effects of SBP which will help us fully understand the effective substances of SBP, and pave our way to further explore medicinal uses of SBP and comprehensive utilization of *Morus* species.

**Subjects:** Drug Discovery; Natural Products; Pharmacology

**Keywords:** *Morus*; Sang-Bai-Pi; root barks; bioactive compounds; pharmacological effects

1. Introduction

*Morus* Linn, a plant genus from family Moraceae, consists of 10–16 species recognized by botanists including *Morus alba* L., *Morus nigra* L., *Morus cathayana* Hemsl., *Morus wittiorum* Hand.-Mazz., *Morus mongolica* (Bur.) Schneid., *Morus australis* Poir., etc. (Datwyler & Weiblen, 2004). *M. alba*, a perennial herb, is the dominant specie among the genus *Morus*. It is distributed throughout Asia, Africa, Europe and South and North America, and found in wide range of areas (Zafar et al., 2013). The main use of *M. alba* is as the feed for silk worms, and it is also appreciated as medicines, fruits, vegetables,
animal feed, and landscaping (Kumar & Chauhan, 2008). In Asian countries, *M. alba* plays a key role in agriculture and traditional medicine. Besides its uses in agriculture, different parts of *M. alba* (i.e. fruits, leaves, twigs, and root barks) with abundant resources are commonly used as traditional medicines.

Root barks of *M. alba* (Sang-Bai-Pi or Mori Cortex) have been recorded in Chinese Pharmacopoeia and widely applied in traditional Chinese medicine since 500 BC for the treatment of lung heat, cough, edema, and oliguria (Pharmacopoeia Committee of P. R. China., 2010). In fact, original plants of ancient Chinese Sang-Bai-Pi (SBP) originated from more than one species of *Morus* by textual research. Thus, SBP include the root barks of most *Morus* plants in China (Yang & Wan, 2008). There are several reviews on the chemical and pharmacological advances of species in the genus *Morus* (Zafar et al., 2013). However, no detailed reports have been made on SBP of what bioactive compounds it contained and what are their pharmacological effects. Decades of research on phytochemistry of SBP have led to the identification of various compounds, which showed a wide range of biological properties. These studies prompted us to compile the progress. The current review is intended to focus on the bioactive compounds of SBP and their pharmacological effects from 1976 to 2015. There over 110 compounds, mostly Diels–Alder-type adducts, flavonoids, 2-Arylbenzofurans, and stilbenes, with anti-inflammatory, anti-oxidative, anti-microbial, anti-diabetic, anti-tumor, and other pharmacological effects are summarized in this paper. This will help us fully understand the effective substances of SBP, and pave our way to further explore medicinal uses of SBP and comprehensive utilization of *Morus* plants.

2. Ethnomedicinal and traditional uses

The root barks of *Morus* plants are called SBP in Chinese and Sōhakuhi in Japanese (Figure 1). In China, SBP was first recorded in Shennong’s Herbal—one of the world’s earliest pharmacopoeia. It is suggested that the roots of *Morus* plants are collected between late autumn and early spring. Brown layer is removed from fresh roots by copper knife without discarding the surface juice, then the white root barks are dried or fried with honey to make SBP. It is slightly sweet and contains lots of fiber, and much powder appears when it is torn open. SBP of good quality is usually white, thick, and flexible (Chinese Herbalism Editorial Board, 1999). SBP is used as dietary Chinese herbs (Yanze, Zhimin, & Junzeng, 2015), and in traditional Chinese medicine (TCM), it has been used in doses 9–15 g by decocting method for the treatment of cough, yellow sputum, bronchitis, xerophthalmia, nephritis, pulmonary diseases, incised wound, and so on (Chinese Herbalism Editorial Board, 1999; Li & Xu, 2012; Ma & Cai, 2013; Zhao, Yan, & Xiong, 2003).

Figure 1. Commercially available Sang-Bai-Pi (without removal of brown layer).
Figure 2. Bioactive Diels–Alder-type adducts from Sang-Bai-Pi.
3. Bioactive compounds

3.1. Diels–Alder-type adducts
Diels–Alder-type adducts, which formed by a Diels–Alder reaction between the α, β-olefinic moiety of a chalcone and an isoprene moiety, are the most representative compounds in the genus Morus. Nearly 90 Diels–Alder-type adducts have been isolated from Morus plants so far (Yang, Tan, Chen, & Kang, 2014). We summarized and updated the structures of some bioactive Diels–Alder-type adducts [1–38] from SBP are shown in Figure 2.

3.2. Flavonoids
The genus Morus is a rich source of flavonoids, and most flavonoids are substituted by prenyl and geranyl groups (Yang et al., 2014). Diverse flavonoids are resulted by different positions of substituents or cyclization. We summarized and updated the structures; some bioactive flavonoids [39–73] from SBP are shown in Figure 3.

3.3. 2-Arylbenzofurans and stilbenes
Morus plants are also rich sources of 2-arylbenzofurans and stilbenes, among which, 2-arylbenzofurans are commonly substituted by prenyl and geranyl groups. Diverse 2-arylbenzofurans are
resulted by different positions of substituents or cyclization (Yang et al., 2014). We summarized and updated the structures some bioactive 2-arylbenzofurans [74–101] and stilbenes [102–106] from SBP are shown in Figure 4.

3.4. Polyhydroxylated alkaloids

Polyhydroxylated alkaloids (alkaloidal iminosugars) are considered as analogs of saccharides in which the ring oxygen is replaced by nitrogen, and they are considered to have therapeutic potentials (Watson, Fleet, Asano, Molyneux, & Nash, 2001). The genus Morus has attracted much attention...
for its polyhydroxylated alkaloids, especially the principal \( \alpha \)-glycoside inhibitor—1-deoxyjirimycin (1-DNJ) [111] (Zhang, Li, et al., 2013). SBP contains 1-DNJ with high content and the structure is shown in Figure 5.
3.5. Other bioactive compounds
Triterpenoids [107–109] are seldom found in Morus plants. To the best of our knowledge, not more than 10 triterpenoids have been identified from SBP up to date. Besides the compounds mentioned above, there are also other types of bioactive compounds [110, 112–117] isolated from SBP (Figure 5).

4. Pharmacological effects

4.1. Anti-inflammatory effects
Kimura, Okuda, Nomura, Fukai, & Arichi (1986a, 1986b) firstly reported the inhibitory effects of SBP on arachidonate metabolism in rat platelets. Extracts of SBP showed inhibitory effects on cyclooxygenase (COX) isoenzymes (Rollinger et al., 2005). Total flavonoids of SBP (400 mg/kg) could obviously inhibit the xylene-induced ear swelling and the capillary permeability resulted from inflammation by acetic acid (Feng, Xie, Lin, Zhao, & Zhou, 2013). Studies reported that SBP extracts suppressed the production of nitric oxide (NO), prostaglandin E2 (PGE2), and mRNA expression of COX-2 in RAW 264.7 cells (Seo, Lim, Jeong, Ha, & Shin, 2013), and inhibited nuclear factor kappa B (NF-κB) activation (Eo et al., 2014).

A large number of anti-inflammatory compounds were found from SBP. Morusin [46], oxydihydromorusin (morusinol) [48], kuwanon C [39], mulberrofuran A [79], kuwanon G (moracenin B or albanin F) [1], kuwanon H (moracenin A or albanin G) [2], sanggenon D [10], and mulberrofuran G (albanol A) [29], J [31], O [32] were found to affect on arachidonate metabolism in rat platelets (Kimura et al., 1986a, 1986b). Morusin [46], kuwanon C [39], sanggenons B [24], C [7], D [10], E [11], O [8] inhibited COX activity (Cheon et al., 2000; Chi et al., 2001; Rollinger et al., 2005). Oxyresveratrol [102] inhibited the LPS-stimulated increase of inducible nitric oxide synthase (iNOS) expression (Chung et al., 2003).

Mornigrol D [94] and norartocarpetin [41] showed inhibition on release of β-glucuronidase (Wang, Yang, Liu, & Chen, 2010). Moracins C [74], D [87], O [89], P [90], R [78], artoidonesinonin O [84], alabafuran A [85], mulberrofurans J [31], L [81], Y [83], kuwanons A [53], C [39], E [55], T [40], sanggenon F [65], sanggenol L [69] and morusin [46] showed inhibitory effects on NO production (Qin et al., 2015; Yang, Matsuzaki, Takamatsu, & Kitanaka, 2011). Kuwanon J 2,4,10''-trimethyl ether [19], kuwanon R [20] inhibited NF-κB activity (Phung et al., 2012). Cudraflavone B [51] inhibited Tumor Necrosis Factor (TNF-α) gene expression and secretion by blocking the translocation of NF-κB (Hošek et al. 2011; Kollar et al., 2013). Kuwanon E [55], kuwanon G [1] and norartocarpone [58] significantly inhibited IL-6 production in lung epithelial cells (A549) and NO production in lung macrophages (MH-S) (Lim, Jin, Woo, Lee, & Kim, 2013). Caffeic acid [116] and p-coumaric acid [117] inhibited the production of PGE2 and mRNA expression of COX-2 in RAW 264.7 cells (Seo et al., 2013). Moracin C [74], mulberrofuran Y [83], mulberrofuran H [30], kuwanons C [39], E [55], oxydihydromorusin [48],...
Hot-water extract of SBP inhibited anti-chicken gamma globulin IgE-induced mast cell activation and histamine release which is important to allergic reactions (Chai, Lee, Han, Kim, & Song, 2005). The anti-allergenic activities of SBP may be related to the regulation of NF-κB and inhibition of Th2 cytokines IL-5 and IL-13 (Lee, Kim, & Kil, 2013). Hot-water extract also exerted antiasthmatic effects via enhancement of CD4+CD25+Foxp3+ regulatory T cells and inhibition of Th2 cytokines (Kim, Lee, Jeong, et al., 2011). While ethanol extract of SBP inhibited IL-6 production and bronchitis-like symptoms of lipopolysaccharide (LPS)-induced airway inflammation in mice (Lim et al., 2013). Moracin M [77] was found to be an effective phosphodiesterase-4 inhibitor (PDE4) (Chen, Zhao, et al., 2012).

4.2. Antioxidative effects
SBP extract showed strong free radical scavenging effect and inhibitory effect of xanthine oxidase and lipid peroxidation (Choi et al., 2002). Water extract of SBP showed antioxidant effects in assays FeCl2-ascorbic acid-induced lipid peroxidation in rats (Jin, Sa, Shim, Rhee, & Wang, 2005), and methanolic extract showed strong free radical scavenging effect and inhibitory effect of xanthine oxidase (Choi et al., 2002). Mulberroside A [103] showed liver protective action against CCL-induced hepatotoxicity (Jin, Kim, Heo, Han, & Wang, 2007; Jin et al., 2006). Moracins C [74] and M [77] inhibited malondialdehyde produced during microsomal lipid peroxidation induced by ferrous/cysteine (Tan, Liu, & Chen, 2008). Albanol B [34], moracin M [77], 2-methylene-3-methoxy-2,5-dihydrofuran-4-O-β-D-glucopyranoside [110], mulberrofuran G [29] showed potential activities on 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) (Cui, Wang, Liu, & Chen, 2008; Fu, Lei, Cai, Zhou, & Ruan, 2010). Mornigrol D [94] and alabafuran C [38] inhibited release of β-glucoronidase from rat polymorphonuclear leucocytes induced by platelet activating factor (Wang et al., 2010). Oxyresveratrol [102], moracin M [77], morusin [46] showed moderate DPPH radical scavenging activity (Mazimba, Majinda, & Motlhanka, 2011). Besides, SBP contained many phenolic compounds (Diels–Alder-type adducts, flavonoids, 2-arylbenzofuran, and stilbenes), which were highly correlated with antioxidant potentials of SBP (Chon et al., 2009; Cui, Li, & Jiang, 2011; Khan et al., 2013).

4.3. Antimicrobial effects
Nomura (Nomura, Fukai, Uno, & Arai, 1978) firstly tested antimicrobial activity of SBP. The methanolic extract of SBP has potent antimicrobial activities (Park, Lee, & Yang, 1990; Rollinger et al., 2006), and extracts of SBP also have inhibitory activity against respiratory viruses (Zhang, Li, Ye, Zhang, & Li, 2005). Bioassay-guided and phytochemical research resulted in the isolation of many antimicrobial and parasitic compounds. Mulberrofuran A [79] showed antimicrobial activity against Staphylococcus aureus and Fusarium roseum (Nomura et al., 1978). Ethyl β-resorcylate (ethyl 2,4-dihydroxybenzoate) [115] and 5,7-dihydroxychromone [113] exhibited antimicrobial activities against plant pathogenic fungi and bacteria (Uno, Isogai, Suzuki, & Shirata, 1981). 1-DNJ [111] may be effective in the treatment of AIDS infection (Sergio, 1989). Morusin [46], morusin 4′-glucoside [47], and kuwanon H [2] showed positive activities on HIV (Luo, Nemec, & Ning, 1995). Kuwanon G [1] and sanggenon C [7] inhibited the growth of oral pathogenic bacteria such as Streptococcus mutans, Streptococcus sobrinus, Streptococcus sanguis, and Porphyromonas gingivalis (Park, You, Lee, Baek, & Hwang, 2003; Park et al., 1990). Leachianone G [70] showed potent antiviral activity against herpes simplex type 1 virus (HSV-1) (Du et al., 2003). Kuwanon C [39], mulberrofuran G [29], albanol B [34], morusin [46], sorocereal [22], and sanggenons E [11], H [66] inhibited the secretion of TNF-α, IL-1/β and NF-κB nuclear translocation in LPS-stimulated macrophages (Zelová et al., 2014).
sanggenons B [24], D [10] were effective to pathogenic bacteria and fungi include Candida albicans, Saccharomyces cerevisiae, Salmonella typhimurium, Staphylococcus epidermidis, and S. aureus (Sohn, Son, Kwon, Kwon, & Kang, 2004). Both 2',4',5-trihydroxy-3-(γ,γ,γ-hydroxydimethyl)propyl-2',2'-dimethylpyrano(5",6"-6,7)-flavone [52] and 7-methoxy-5,4'-dihydroxyflavanonol [59] had significant antiviral effects against influenza viruses, respiratory syncytial viruses, and adenoviruses (Zhang et al., 2005). Kuwanon L [13], sanggenons B [24], C [7], D [10], E [11], G [15], O [8] revealed inhibition against Venturia inaequalis (Rollinger et al., 2006). Mulberroside C [95], moracin P [90], moracin O [89], moracin M [77] showed significant inhibitory activities against hepatitis C virus (Lee et al., 2007). Moracins C [74], Q [91], M [77] inhibited the growth of S. aureus, Streptococcus faecalis, Bacillus cereus, Escherichia coli, Klebsiella pneumoniae, Shigella dysenteriae, Pseudomonas aeruginosa, Salmonella typhi, Citrobacter freundii, Candida albicans, Microsporum audouinii (Kuete et al., 2009). Oxyresveratrol [102], moracin M [77], morusin [46], and kuwanon C [39] showed inhibitory activities against S. aureus, Bacillus subtilis, Micrococcus flavus, S. faecalis, Salmonella abony, P. aeruginosa (Mazimba et al., 2011). Mulberrofuran G [29] showed moderate inhibitory activity on hepatitis B virus DNA replication (Geng et al., 2012). Kuwanons G [1], O [14] were effective to control Ichthyophthirius multifiliis (Liang et al., 2015).

4.4. Antidiabetic effects
Aqueous extract of SBP significantly lowered the elevated blood glucose level with improvement in the serum lipid profile of streptozotocin (STZ)-induced diabetic rats (Ali, Ali, Mir, & Ali, 2011). Ethanolic extract of SBP reduced the amount of the glucose, increased insulin production, protected pancreatic β cells from degeneration, diminished lipid peroxidation, inhibited low density lipoprotein (LDL) atherogenic modification and lipid peroxides formation, and increased the expression of adipogenic maker proteins, such as peroxisome proliferator-activated receptors γ (PPARγ), adipocyte-specific fatty acid binding protein 4 (aP2), and GLUT4 (glucose transporter 4) (El-Beshbishy, Singab, Sinkkonen, & Pihlaja, 2006; Oh, Choi, & Yun, 2011; Singab, El-Beshbishy, Yonekawa, Nomura, & Fukai, 2005).

Much of anti-hyperglycemic activities attributed to some functional components such as moran A (Hikino, Mizuna, Oshima, & Konno, 1985), moran 20 K (Kim et al., 1999), morusin [46], cyclomorusin [49], neo-cyclomorusin [50], kuwanon E [55], moracin M [77], betulinic acid [109] (Singab et al., 2005), steppogenin-4'-O-β-D-glucoside [60], mulberroside A [103] (Heo, Jin, Jung, & Wang, 2007; Zhang, Chen, et al., 2009). Inhibitors for protein tyrosine phosphatase 1B (PTP1B) include sanggenons C [7], G [15], mulberroside C [27], kuwanon L [13] (Cui et al., 2006), albanafuran A [85], mulberrofuran W [82], mulberrofuran D [80], kuwanon J [18], kuwanon R [20], kuwanon V [21] (Hoang et al., 2009), albanafuran A [85], B [86], mulberrofuran A [79], and moracin I [75], 4'-(6,6-dimethyl-5-hydroxy-2-methylenecyclohexymethyl)-3',5',6-trihydroxy-2-arylbenezofuran [92], 2'-%-[3-methyl-3-(4-methyl-3penten-1-yl)-2-oxiranyl]methyl]-3',5',6-trihydroxy-2-arylbenezofuran [97] (Zhang, Luo, Wan, Zhou, & Kong, 2014). α-glucosidase inhibitors include 4'-(6,6-dimethyl-5-hydroxy-2-methylenecyclohexymethyl)-3',5',6-trihydroxy-2-arylbenezofuran [92], 2'-(1,3,3-trimethyl-7-oxabicyclo[2.2.1]hept-2-ylmethyl)-3'-methoxy-5',6-dihydroxy-2-arylbenezofuran [92], 2'-(6-hydroxy-3,7-dimethyl-2,7-octadien-1-yl)-3'-methoxy-5',6-dihydroxy-2-arylbenezofuran [96], 4'-(6-hydroxy-3,7-di-methyl-2,7-octadien-1-yl)-3',5',6-trihydroxy-2-arylbenezofuran [99], 2'-(6,7-dihydroxy-3,7-dimethyl-2-oxetan-1-yl)-3',5',6-trihydroxy-2-arylbenezofuran [98], 4'-(6,7-dihydroxy-3,7-dimethyl-2-oxetan-1-yl)-3',5',6-trihydroxy-2-arylbenezofuran [100], 2'-(6,7-dihydroxy-3,7-dimethyl-2-oxetan-1-yl)-3',5',6-dihydroxy-2-arylbenezofuran [101], albanafuran B [86], moracin I [75], and 1-DNJ [111] (Zhang, Li, et al., 2013; Zhang et al., 2014).

Anti-hyperlipidemic compounds include mulberrofuran G [29], albanol B [34], 5,7,2'-trihydroxyflavanone-4'-O-β-D-glucoside [57] (El-Beshbishy et al., 2006), kuwanons A [53], C [39], T [40], morusin [46], sanggenon F [65], uvaol [108], betulinic acid [109] (Yang et al., 2011), mulberroside A [103], and oxyresveratrol [102] (Jo, Kim, & Lim, 2014).
Nomura (Yamatake, Shibata, & Nagai, 1976) reported the anti-hypertensive effects of SBP in Japanese, and it was found that both the water-soluble and butanol-soluble fractions of SBP had hypotensive activity in rodents and dogs. Anti-hypertensive compounds include kuwanon G [1] (Nomura & Fukai, 1980; Oshima, Konno, Hikino, & Matsushita, 1980a), kuwanon H [2] (Nomura, Fukai, & Narita, 1980; Oshima, Konno, Hikino, & Matsushita, 1980b), moracenins C [5], D [6] (Oshima, Konno, Hikino, & Matsushita, 1980b), sanggenon C [7] (Nomura, Fukai, Hano, & Uzawa, 1981a), mulberrofuran C [27] (Nomura, Fukai, Matsumoto, Fukushima, & Momose, 1981b), sanggenon D [10] (Nomura, Fukai, Hano, & Uzawa, 1982), kuwanon M [3] (Nomura, Fukai, Hano, & Ikuta, 1983), mulberrofuran F [28], G [29] (Fukai et al., 1983). Moracenins C [5], and oxyresveratrol [49, 50], and neocyclomorusin [51], oxydihydromorusin [52], morusin [53, 54], and moracenins C [5], D [6] (Oshima, Konno, Hikino, & Matsushita, 1981), sanggenon C [7] (Nomura, Fukai, Hano, & Uzawa, 1981a), mulberrofuran C [27] (Nomura, Fukai, Matsumoto, Fukushima, & Momose, 1981b), sanggenon D [10] (Nomura, Fukai, Hano, & Uzawa, 1982), kuwanon M [3] (Nomura, Fukai, Hano, & Ikuta, 1983), mulberrofuran F [28], G [29] (Fukai et al., 1984).

4.5. Antitumor effects

Extract of SBP exhibited cytotoxic activity on human leukemia cells (K-562, B380) and mouse melanoma cells (B16) by inhibiting microtubule assembly (Nam et al., 2002), and induced cell growth arrest and apoptosis in human colorectal cancer cells (SW480) by activating ATF3 expression and down-regulated cyclin D1 level (Eo et al., 2014). Besides, SBP may be useful for treating multidrug-resistant cancer cells (Choi et al., 2013).

Compounds from SBP exhibited cytotoxic activities against various cancer cell lines. Cytotoxic compounds include sanggenol M [17], sanggenon C [7] (Shi et al., 2001), 7,2′,4′,6′-tetrahydroxy-6-geranylflavanone [112] (Kofujita, Yaguchi, Doi, & Suzuki, 2004), australisines A [4], B [36], C [37], mulberrofuran G [29], mongolicin C [33], chalcomoracin [35] (Zhang, Tang, Chen, & Yu, 2007), moracin C [74], morusin [46] (Ferlinahayati et al., 2007; Mei, Li, Zhang, Zuo, & Dai, 2011), steppogenin-7,4′-di-O-β-D-glucoside [62] (Zhang, Wang, et al., 2009), CMA-b1–1 (RG-1 type pectic polysaccharide) (Zhang, Liao, et al., 2013), cyclomorusin [49], cyclomulberrin [54] (Dat et al., 2010), soroceal B [23], mongolicin, sanggenon L [69], licoflavone C [42], oxydihydromorusin [48], 3′-geranyl-3-prenyl-2′,4′,5,7-tetrahydroxyflavone [43], etc. (Qin et al., 2015).

Lots of compounds with different antitumor mechanisms have been isolated from SBP. Morusin [46] inhibited induction of ornithine decarboxylase by teleocidin in mouse skin (Yoshizawa et al., 1989). Kuwanons G [1], H [2] were found to be specific antagonists for gastrin-releasing peptide (GRP)-preferring receptor (Mihara et al., 1995). Oxyresveratrol [102] and kuwanon Y [26] were shown to inhibit protein kinase C (PKC) (Hu, Chen, Yao, & Xu, 1996). Cathayanons A [12], B [9] exhibited potent activities on the inhibition of HL-60 cell adhesion to Bovine Arterial Endothelial cells (BAEC) (Shen & Lin, 2001). Sanggenon C [7] inhibited tumor cellular proteasomal activity and cell viability (Huang et al., 2012). Mulberrofuran G [29], H [30], D [80], W [82], moracins O [89], P [90], Q [91], sanggenon O [8], albafuran A [85], and kuwanon J [18] were found to inhibit Hypoxia-inducible factor-1 (HIF-1) accumulation (Dat et al., 2009). Mulberrofuran G [29] induced apoptotic cell death via both the cell death receptor pathway and the mitochondrial pathway (Kikuchi et al., 2010). Cudraflavone B [51], kuwanon E [55] and 4′-O-methylkuwanon E (kuwanon U) [56] exerted anti-proliferative and anti-inflammatory activities (Kollar et al., 2013).

4.6. Other pharmacological effects

There are also other bioactive compounds from SBP. For example, cyclomorusin [49] (Lin, Shieh, Ko, & Teng, 1993), morusin [46], kuwanon C [39] (Ko, Yu, Ko, Teng, & Lin, 1997), australone B [73] (Ko et al., 1999) have anti-platelet effects. Morusin [46] has anti-nociceptive effect (De et al., 2000). Mulberroside A [103] showed liver protective and P-Glycoprotein inhibitory effects (Jin et al., 2006; Li et al., 2014). Sanggenons C [7], D [10], G [15] and morusin [46] are positive GABAA receptor modulators (Gupta, Dua, Kazmi, & Anwar, 2014; Kim, Baburin, et al., 2012). Kuwanons C [39], E [55], U [56], 5′-geranyl-4′-methoxy-5,7,2′-trihydroxyflavone [44], morusin [46], oxydihydromorusin [48], cyclomorusin [49], and neocyclomorusin [50] exhibited cholinesterase inhibitory effects (Kim, Lee, Kim, et al., 2011). Sanggenol Q [64], kuwanon T [40], sanggenon N [68], mulberrofuran C [27], G [29], cudraflavone B [51], and oxyresveratrol [102] have hepatoprotective effects (Jung et al., 2015; Oh et al., 2002). Moracins C [74], M [77], oxyresveratrol [102] (He et al., 2014), cyclomulberrin [54], neocyclomorusin [50], sanggenon I [67], morusin [46], kuwanons E [55], U [56] (Lee et al., 2012),
morusalbanol A [25], sanggenols A [63], Q [64], mulberrofuran G [29], mulberrofuran C [27], moracin E [88] (Chen, Ding, et al., 2012; Jung et al., 2015), mulberroside A [103] (Wang et al., 2014), and kuwanon V [21] (Kong et al., 2015) have neuroprotective effects. While, kuwanon C [39], sanggenon D [10] (Lee et al., 2004), α-aminic acid [107], betulinic acid [109] (Pianwianpong, Pongpan, Suntornsk, & Luanrattan, 2007), 5'-geranyl-5,7,2',4'-tetrahydroxyflavone [45], steppogenin-7-O-β-D-glucoside [61], 2,4',2',4'-tetrahydroxychalcone [71], moracin N [76], kuwanon H [2], mulberrofuran G [29], morachalcone A [72], oxresveratrol-2-O-β-D-glucopyranoside [104], oxresveratrol-3′-O-β-D-glucopyranoside [106] (Zheng et al., 2010), mulberroside A [103], oxresveratrol-3-O-β-glucoside [105], oxresveratrol [102] (Kim et al., 2010; Kim, Park, et al., 2012; Park, Kim, Hwang, You, & Lim, 2011), moracenic D [6], sanggenon T [16], and kuwanon O [14] exhibited tyrosinase inhibitory activities (Zheng, Tan, & Wang, 2012).

5. Conclusion

In TCM, SBP was used to treat inflammatory diseases like incised wound, nephritis, arthritis, swelling, and so on. It is also used to treat respiratory disorders like cough, asthma, yellow sputum, bronchitis, and pulmonary diseases. Pharmacological studies over the past 80 years indicate that SBP have anti-inflammatory, antioxidative, antimicrobial, antidiabetic, anti-tumor, and other pharmacological effects. The findings that SBP can in vitro or in vivo inhibit inflammatory mediators and inflammations, at least in part, explains the folk use of SBP in diverse inflammatory diseases. While the antimicrobial effects on influenza and respiratory viruses, in part, proves the use of SBP in respiratory disorders.

Inflammation and oxidations play important roles in several conditions including asthma, allergy, cancer, bacterial and viral infections, diabetes mellitus, cardiovascular diseases, Alzheimer's disease, rheumatoid arthritis, bronchitis, osteoarthritis, etc. As a result, SBP extracts and its bioactive compounds with anti-inflammatory and antioxidative effects play positive role on these diseases.

Phytochemical investigation revealed that SBP contains several classes of compounds, such as Diels–Alder-type adducts, flavonoids, 2-arylfuran, stilbenes, polyhydroxylated alkaloids, etc. A variety of bioactive compounds were detected, and they showed effects on inflammatory mediators, free radicals, specific pathogenic microbes (influenza and respiratory viruses) and therapeutic targets (PDE4, PTP1B, α-glucosidase, PPARγ, HIF-1, PKC, GABA). The main and promising compounds of SBP such as kuwanons G [1], H [2], E [55], morusin [46], moracin M [77], mulberrofuran G [29], sanggenons C [7], D [10], mulberroside A [103], and 1-DNJ [111], showed excellent pharmacological effects.

Funding

This work was supported by Central Public Welfare Research Institutes [grant number Z070838]; National Natural Science Foundation of China [grant number 81403088]; Quality Guarantee System of Chinese Herbal Medicines [grant number 201507002]; China Postdoctoral Science Foundation [grant number 2013MS41160] for financial supports.

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References

Ali, A., Ali, M., Mir, S., & Ali, B. (2011). Phytochemical and biological screening of Morus alba (L) Bark. Planta Medica, 77, 14.
Chai, O. H., Lee, M. S., Han, E. H., Kim, H. T., & Song, C. H. (2003). Inhibitory effects of Morus alba on compound 48/80-induced anaphylactic reactions and anti-chicken gamma globulin IgE-Mediated mast cell activation. Biological and Pharmaceutical Bulletin, 26, 1852–1858. http://dx.doi.org/10.1248/bpb.28.1852
Huang, H. B., Liu, N. N., Zhao, K., Zhu, C. C., Lu, X. Y., Li, S. J., ... Hu, C., Chen, Z., Yao, R., & Xu, G. (1996). Inhibition of protein kinase C by stilbene derivatives from Morus alba L. Tianran Yaji Yu Kaifa, 8, 13–16. 

Huang, H. B., Liu, N. N., Zhao, K., Zhu, C. C., Lu, X. Y., Li, S. J., ... (2012). Sanggenon C decreases tumor cell viability associated with proteasome inhibition. Frontiers in bioscience (Elite edition), 3, 1315–1325.

Jin, Y. S., So, J. H., Shim, T. H., Rhee, H. I., & Wang, M. H. (2005). Hepatoprotective and antioxidative effects of Morus bombycis Koidzumi on CCl4-induced liver damage. Biochemical and Biophysical Research Communications, 339, 991–995. http://dx.doi.org/10.1016/j.bbrc.2005.02.076

Jin, Y. S., Lee, M. J., Han, W., Heo, S. I., Sohn, S. I., & Wang, M. H. (2006). Antioxidant effects and hepatoprotective activity of 2,5-dihydroxy-4,3′-dihydroxy-glycosyl-stilbene from Morus bombycis Koidzumi roots on CCl4-induced liver damage. Free Radical Research, 40, 986–992. http://dx.doi.org/10.1080/1071576060083823

Kim, J. K., Park, K. T., Lee, H. S., Kim, M., & Lim, Y. H. (2012). Evaluation of the inhibition of mushroom tyrosinase and cellular tyrosinase activities of oxayresveratrol: comparison with mulberroside A. Journal of Enzyme Inhibition and Medicinal Chemistry, 27, 455–503. http://dx.doi.org/10.3109/14756366.2011.59886

Kimura, Y., Okuda, H., Nomura, T., Fukai, T., & Arichi, S. (1986a). Effects of flavonoids and related compounds from mulberry tree on arachidonate metabolism in rat platelet homogenates. Chemical & pharmaceutical bulletin, 34, 1223–1227.

Kimura, Y., Okuda, H., Nomura, T., Fukai, T., & Arichi, S. (1986b). Effects of phenolic constituents from the Mulberry tree on Arachidonate metabolism in Rat platelets. Journal of Natural Products, 49, 639–644. http://dx.doi.org/10.1021/np500460s

Ko, H. H., Yu, S. M., Ko, F. N., Teng, C. M., & Lin, C. N. (1997). Bioactive constituents of Morus australis and Broussonetia papyrifera. Journal of Natural Products, 60, 1008–1011. http://dx.doi.org/10.1021/np970186o

Ko, H. H., Wang, J. J., Lin, H. W., Wang, J. P., & Lin, C. N. (1999). Chemistry and biological activities of constituents from Morus australis. Biochimica et Biophysica Acta (BBA) - General Subjects, 1434, 293–299. http://dx.doi.org/10.1016/S0304-4165(99)00084-7

Kofujita, H., Yaguchi, M., Doi, N., & Suzuki, K. (2004). A novel cytoxicyclic prenylated flavonoid from the root of Morus alba. Journal of Insect Biotechnology and Sericology, 73, 113–116.

Kollar, P., Barta, T., Holek, J., Soucek, K., Zavolod, V. M., Artinian, S., ... Tolnoukh, Rabih (2013). Prenylated flavonoids from Morus alba L. Cause inhibition of G1/S transition in THP-1 human leukemia cells and prevent the Lipopolysaccharide-Induced inflammatory response. Evidence-Based Complementary and Alternative Medicine, 2013, 1–13. http://dx.doi.org/10.1155/2013/350519

Kong, S. Y., Park, M. H., Lee, M., Kim, J. O., Lee, H. R., Han, B. W., ... Kim, H. J. (2015). Kuwannon V inhibits proliferation, promotes cell survival and increases Neurogenesis of neural stem cells. PLOS ONE, 10, e0118188. http://dx.doi.org/10.1371/journal.pone.0118188

Kuete, V., Fozing, D. C., Kapche, W. F. G. D., Mbaveng, A., T., Kuiate, J. R., Ngadjui, B. T., & Abegaz, B. M. (2009). Antimicrobial activity of the methanolic extract and compounds from Morus mesozygia stem bark. Journal of Ethnopharmacology, 124, 551–555. http://dx.doi.org/10.1016/j.jep.2009.05.004

Kumar, R. V., & Chauhan, S. (2006). Mulberry: Life enhancer. Journal of Medicinal Plants Research, 2, 271–278.

Lee, N. K., Son, K. H., Chang, H. W., Kang, S. S., Park, H., Heo, M. Y., & Kim, H. P. (2004). Prenylated flavonoids as tyrosinase inhibitors. Archives of Pharmacal Research, 27, 1132–1135. http://dx.doi.org/10.1007/BF02975118

Lee, H. Y., Yurn, J. H., Rho, Y. K., Oh, J. S., Choi, H. S., Chang, H. B., ... Talhouk, Rabih (2013). Inhibition of HCV replicon cell growth by 2-Arylbenzofuran derivatives isolated from Mori Cortex Radicis. Planta Medica, 73, 1481–1485. http://dx.doi.org/10.1055/s-2007-990249

Lee, H. J., Lyu, D. H., Koo, U., Nam, K. W., Hong, S. S., ... Kim, K. O., ... Mar, W. (2012). Protection of prenylated flavonoids from mori cortex radicis (Moraceae) against nitric oxide-induced cell death in neuroblastoma SH-SYSY cells. Archives of Pharmacal Research, 35, 163–170. http://dx.doi.org/10.1007/s12272-012-0118-7

Lee, K. J., Kim, B. K., & Kil, K. J. (2013). Suppressive effects of Morus alba Linne root bark (MRAL) on activation of MC9 mast cells. The Korea Journal of Herbolgy, 28, 33–42. http://dx.doi.org/10.6116/kjherb.2013.28.1.131

Li, Y. C., & Xu, X. R. (2012). Clinical observation on treating dry eye with the Sangbaipi decoction. Clinical Journal of Chinese Medicine, 4, 107–108.
Nomura, T., Fukai, T., Hano, Y., & Uzawa, J. (1982). Structure of Sanggenon D, a natural hypotensive Diels-Alder adduct from Chinese crude drug “Sang-Bai-Pi” (Morus Root Barks). Heterocycles, 17, 381–389.
http://dx.doi.org/10.3987/HET-1982-01-0381

Nomura, T., Fukai, T., Hano, Y., & Ikutou, H. (1983). Kuwanon M, a new Diels-Alder adduct from the root barks of the cultivated Mulberry tree (Morus lhou (ser.) Koidz.). HETEROCYCLES, 20, 585–591.
http://dx.doi.org/10.3987/H-1983-04-0585

Oh, H., Ko, E. K., Jun, J. Y., Oh, M. H., Park, S. U., Kang, K. H., Lee, H. S., & Kim, Y. C. (2002). Hepatoprotective and free radical scavenging activities of Prenylflavonoids, Coumarin, and Stilbene from Morus alba. Planta Medica, 68, 932–934.
http://dx.doi.org/10.1055/s-2002-34340

Oh, T. S., Choi, D. K., & Yun, J. W. (2011). Morus alba L. root bark stimulates adipocyte differentiation in 3T3-L1 cells. Biotechnol. & Bioengineering, 16, 978–986.
http://dx.doi.org/10.1002/bbrc.112257-011-0174-8

Oshima, Y., Konno, C., Hikino, H., & Matsushita, K. (1980a). Structure of moracenin B, a hypotensive principle of Morus root barks. Tetrahedron Letters, 21, 3381–3384.
http://dx.doi.org/10.1016/0040-4039(80)87694-1

Oshima, Y., Konno, C., Hikino, H., & Matsushita, K. (1980b). Structure of moracenin C, a hypotensive principle of Morus root barks. Heterocycles, 14, 1461–1464.

Oshima, Y., Konno, C., Hikino, H., & Matsushita, K. (1980c). The validity of oriental medicines. Part 24. Structure of moracenin A, a hypotensive principle of Morus root barks. Heterocycles, 14, 1287–1290.

Oshima, Y., Konno, C., & Hikino, H. (1981). Validity of oriental medicines. Part 28. Structure of moracenin D, a hypotensive principle of Morus root barks. Heterocycles, 16, 979–982.

Park, W. J., Lee, H. J., & Yang, S. G. (1990). The inhibitory effect of songgenin C from the root-bark of Morus alba L. on the growth and the cellular adherence of Streptococcus mutans. Yakshok Hoechi, 34, 434–438.

Park, K. M., Yao, J. S., Lee, H. Y., Boek, N. I., & Hwang, J. K. (2003). Kuwanon G: An antibacterial agent from the root bark of Morus alba L. against oral pathogen. Journal of Ethnopharmacology, 84, 181–185.
http://dx.doi.org/10.1016/S0378-8749(02)00318-5

Park, K. T., Kim, J. K., Hwang, D., Yoo, Y. M., & Lim, Y. H. (2011). Inhibitory effect of mulberroside A and its derivatives on melanogenesis induced by ultraviolet B irradiation. Food and Chemical Toxicology, 49, 3038–3045.
http://dx.doi.org/10.1016/j.fct.2011.09.008

Pharmacopoeia Committee of P.R. China. (2011). Pharmacopoeia of people’s republic of China. Beijing: Chemical Industry Publishers.

Phung, T. X. B., Tran, T. H. H., Dan, T. T. H., Chau, V. M., Hoang, T. H., & Nguyen, T. D. (2012). Chalcone-derived Diels-Alder adducts as NF-kB inhibitors from Morus alba. Journal of Asian Natural Products Research, 14, 596–600.
http://dx.doi.org/10.1080/10286020.2012.670221

Pianwijanonpong, N., Pongpan, N., Suntronsuk, L., & Luanratana, O. (2007). The triterpene constituents of the root bark of a hybrid between Morus alba L. and M. rotundifolia Koiz.: and its antifungal activities. Natural Product Communications, 2, 381–384.

Qiu, J., Fan, M., He, J., Wu, X. D., Peng, L. Y., Su, J., ... Zhao, Q. S. (2015). New cytotoxic and anti-inflammatory compounds isolated from Morus alba L. Natural Product Research, 29, 1711–1718.
http://dx.doi.org/10.1080/14786419.2014.995333

Rollinger, J. M., Bodensiek, A., Seiger, C., Ellmerer, E. P., Bauer, R., Langer, T., & Stupperich, H. (2003). Discovering COX-Inhibiting constituents of Morus root bark: activity-guided versus computer-aided methods. Planta Medica, 71, 399–405.
http://dx.doi.org/10.1055/s-2005-864132
Rollinger, J. M., Spitaler, R., Menz, M., Marschall, K., Zeiger, R., Ellmerer, E. P., ... Stupnner, H. (2006). Venturia inequalis -Inhibiting Diels–Alder adducts from Morus root bark. Journal of Agricultural and Food Chemistry, 54, 8432–8436. http://dx.doi.org/10.1021/jf061871g

Sergio, W. (1989). Mulberry roots and seeds may be effective in occurrence and therapeutic applications. Phytochemistry, 29, 75–76. http://dx.doi.org/10.1016/0031-9422(89)90172-2

Sharma, R., Sharma, A., Shono, T., Takesaki, M., Shirata, A., Fujimura, T., & Machi, H. (2001). Mulberry Moracins: Scavengers of UV stress-generated free radicals. Bioscience, Biotechnology, and Biochemistry, 65, 1402–1405. http://dx.doi.org/10.1271/bbb.65.1402

Shen, R. C., & Lin, M. (2000). Diels-Alder type adducts from Morus cathayana. Phytochemistry, 57, 1231–1235. http://dx.doi.org/10.1016/S0031-9422(00)00451-9

Singab, A. N. B., Ayoub, N. A., Ali, E. N., & Mostafa, N. M. (2010). Antioxidant and hepatoprotective activities of Egyptian moraceous plants against carbon tetrachloride-induced oxidative stress and liver damage in rats. Pharmaceutical Biology, 48, 1255–1264. http://dx.doi.org/10.3109/13880200903730659

Sohn, H. Y., Son, K. H., Kwon, C. S., & Kang, S. S. (2004). Antimicrobial and cytotoxic activity of 18 prenylated flavonoids isolated from medicinal plants: Morus alba L., Morus mongolica Schneider, Broussonetia papyrifera (L.) Vent., Sophora flavescens Ait and Echinopsorhiza koreensis Nakai. Phytomedicine, 11, 666–672. http://dx.doi.org/10.1016/j.phymed.2003.09.005

Tan, Y. X., Liu, C., & Chen, R. Y. (2008). 2-Arylbenzofuran derivatives from Morus rutifolia. Phytomedicine, 15, 1297–1303. http://dx.doi.org/10.1016/j.phymed.2006.11.009

Uno, N., Nakajig, A., Suzuki, A., & Shirata, A. (1981). Isolation and identification of ethyl 2,4-dihydroxybenzoate and 5,7-dihydroxychromone from the root bark of mulberry tree (Morus alba) and their biological activity. Nippon Sangeikaku Zasshi, 50, 422–427.

Wang, L., Yang, Y., Liu, C., & Chen, R. (2008). Studies on the extraction and isolation and antivirus effect of chemical constituents in Morus alba. Shenyang Yaoke Daxue Xuebao, 22, 207–209.

Zafar, M. S., Muhammad, F., Javed, I., Akhtar, M., Khaliq, T., Aslam, B., ... Zafar, H. (2013). White mulberry (Morus alba): A brief phytochemical and pharmacological evaluations account. International journal of agriculture and biology, 15, 612–620.

Zelova, H., Hanokova, Z., Cermaková, Z., Sméjkal, K., Dalí Akča, S., Babuška, P., ... Vacek, J. (2014). Evaluation of anti-inflammatory activity of prenylated substances isolated from Morus alba and Morus nigra. Journal of Natural Products, 77, 1297–1303. http://dx.doi.org/10.1021/nl4001025

Zhang, G. G., Li, Q. H., Ye, Y. Z., Zhang, H. X., & Li, F. (2005). Studies on the extraction and isolation and antiviral effect of chemical constituents in Morus alba. Shenyang Yaoke Daxue Xuebao, 22, 207–209.

Zhang, Q. J., Tang, Y. B., Chen, R. Y., & Yu, D. Q. (2007). Three new cytotoxic Diels-Alder-type adducts from Morus auriculata. Chemistry & Biodiversity, 4, 1533–1540.

Zhang, M., Chen, M., Zhang, H. Q., Sun, S., Xiao, B., & Wu, F. H. (2009). In vivo hypoglycemic effects of phenolics from the root bark of Morus alba. Fitoterapia, 80, 475–477. http://dx.doi.org/10.1016/j.fitote.2009.06.009

Zhang, M., Wang, R. R., Chen, M., Zhang, H. Q., Sun, S., & Zhang, L. Y. (2009). A new flavonane glycoside with anti-proliferation activity from the root bark of Morus alba. Zhongguo Tiannan Yaoxue, 7, 105–107.

Zhang, N., Li, Y. F., Zhou, Y. M., Hou, J., He, Q., Hu, X. G., ... Nie, Z. X. (2013). Rapid detection of polyhydroxylated alkaloids in mulberry using leaf spray mass spectrometry. Analytical Methods, 5, 2455–2460. http://dx.doi.org/10.1039/c3ay00118d

Zhang, X. M., Liao, W. F., Cong, Q. F., Dong, Q., & Ding, K. (2013). Isolation and structural characterization of the polysaccharides of Cortex Mori radicis. Huaxue Xuebao, 71, 722–728.

Zhang, Y. L., Luo, J. G., Wang, C. X., Zhou, Z. B., & Kong, L. Y. (2014). Geranylated 2-arylbenzofurans from Morus alba var. tatarica and their α-glucosidase and protein tyrosine phosphatase 1B inhibitory activities. Fitoterapia, 92, 116–126. http://dx.doi.org/10.1016/j.fitote.2013.10.017
Zhao, M., Yan, H. P., & Xiong, X. D. (2003). Clinical observation of effect of Jiawei Sangbaipi Decoction in treating severe pulmonary disease. *Chinese Journal of Experimental Traditional Medical Formulae*, 9, 52–54.
Zheng, Z. P., Cheng, K. W., Zhu, Q., Wang, X. C., Lin, Z. X., & Wang, M. F. (2010). Tyrosinase inhibitory constituents from the roots of Morus nigra: A structure–activity relationship study. *Journal of Agricultural and Food Chemistry*, 58, 5368–5373.
Zheng, Z. P., Tan, H.-Y., & Wang, M. (2012). Tyrosinase inhibition constituents from the roots of Morus australis. *Fitoterapia*, 83, 1008–1013.
http://dx.doi.org/10.1016/j.fitote.2012.06.001