WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 3, 349-399. Review Article ISSN 2277–7105

ANTI-INFLAMMATORY ACTIVITY OF *MORUS* (MULBERRY) SPECIES

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Article Received on 27 Dec 2025,
Article Revised on 16 January. 2026,
Article Published on 1 February 2026,

https://doi.org/10.5281/zenodo.18428141

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How to cite this Article: Abdullatif Azab*. (2026) Anti-Inflammatory Activity of Morus (Mulberry) Species. "World Journal of Pharmaceutical Research, 15(3), 342–399.

ABSTRACT

In our two previous review articles about the *Morus* (mulberry) plant genus, we presented the antidiabetic and brain-related properties-activities of its trees. In this article, anti-inflammatory and related activities of this genus will be reviewed. Inflammation is involved in many health disorders and this will be briefly presented in the introduction. Special attention will be drawn to active natural products, if published, and the structures of these compounds will be presented in clear figures. Additional properties of some of these compounds will be discussed in the discussion part. Since many articles indicate the active natural products responsible for anti-inflammatory activity, some of these compounds will be discussed in the discussion section. Finally, it is important to mention two important points. First, like in our previous publication in particular, and all publications in general, *Morus alba* is notably dominating. Second, when the cited article presents other properties in addition to anti-inflammatory, these will be mentioned but will not be discussed.

KEYWORDS: Anti-inflammatory, *Morus*, *Morus alba*, *Morus nigra*, LPS-induced, NO-inhibition, Oxyresveratrol, Moracin, DNJ, Mechanism of action.

Abbreviations: ahc and her/his colleagues, COX cyclooxygenase, DCM dichloromethane, DEE diethyl ether, DSS dextran sulfate sodium, EtOAc ethyl acetate GC-MS gas chromatography mass spectrometry, HPLC high performance liquid chromatography, IL-(number) interleukin, LC-MS liquid chromatography mass spectrometry, LPS

lipopolysaccharide, PD Parkinson's disease, PE petroleum ether, STZ streptozotocin, TFC total flavonoid content, TLC thin layer chromatography, TPC total phenolic content.

1. INTRODUCTION

Inflammation is health disorder that was defined in several close ways. Numerous review articles were published about this topic, and here very selected ones will be cited. According to L. Chen ahc: "Inflammation is a biological response of the immune system that can be triggered by a variety of factors, including pathogens, damaged cells and toxic compounds".[1] C.L. Rodrigues Soares ahc focused in their review article on biochemical aspects of inflammation: chemical and biochemical causes but mainly affected biomarkers.[2] In addition to chemical-biochemical causes of inflammation, N. Jameel ahc present in depth inflammations caused by physical factors (wounds), and they aimed to "demystify" inflammation.[3] V.P. Chavda ahc stated that "Inflammation: The Cause of All Diseases", and in depth test, this statement summarizes it all.[4]

Thousands of natural products were published for anti-inflammatory activity in research articles and consequently, these publications were summarized and discussed in dozens of review articles. Part of these review were general like Azab ahc.[5] F. Alam ahc.[6] and S. Saha.[7] But most of these review articles were more specific: Y.E. Joo, natural products derived drugs for treatment of inflammatory bowl diseases.[8] C-S. Yoon, treatment of neuroinflammation.[9] and drugs derived from Leonurine (**Figure 1**) and its laboratory synthesis.[10]

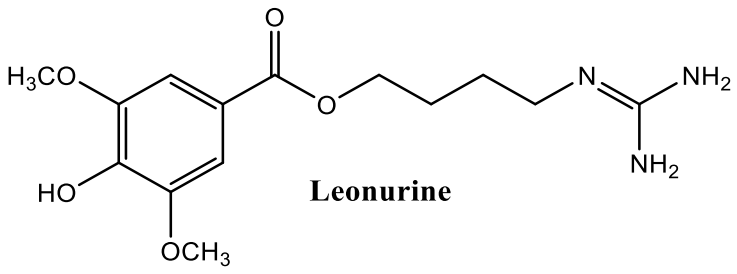

Figure 1. The Structure of Leonurine.

In our two previous review articles about *Morus* plant genus we presented and discussed its antidiabetic and nutritional properties.[11] and its brain-related protective activities.[12] In these articles we briefly presented the archaeological evidence of use of these plants by early humans, ethnobotany and ethnomedicine uses and domestication. We also discussed the complex taxonomy of this genus since there are hundreds of varieties, hybrids, cultivars and

recognized species. However, we accept the determination of the number of species of the *Morus* plant genus as 25, that can be seen below in **Table 1**.

2. Published Anti-inflammatory Activity of *Morus* Species

The anti-inflammatory property of the *Morus* plant genus is well recognized by many cultures and nations, and it was documented and published in many articles. The publications of S. Yadav ahc,[13] R. Dadhwal and R. Banerjee.[14] and M. Ezairjawi ahc.[15] are selected examples. Modern science has extensively investigated the medicinal-biological and other properties-activities of these plants and thousands of articles were published. As for anti-inflammatory activity, a summary of these findings is presented in **Table 1**.

Table 1. **Published Anti-inflammatory Activity of *Morus* Species.**

***Morus* Species**	**Anti-inflammatory & Other Activities, Method, Results, Reference**
M. alba	Root bark was separately extracted with *n*-hexane, DCM, EtOAc, acetone, ethanol, methanol and water, and each extract was analyzed for TFC and TPC. The extracts were tested for anti-inflammatory activity (NO inhibition in RAW 264.7 cells, EtOAc extract was most active), and antioxidant, antidiabetic and tyrosinase inhibition. Methanolic extract was chromatographed for active compounds resulting Kuwanon G, Kuwanon H, Morin, Morusin, Oxyresveratrol and Umbelliferone (**Figure 2A**). These compounds were also tested for the mentioned activity where Morusin was most anti-inflammatory active.[16] Commercial flavonoid-rich leaves extract was supplemented to high-carbohydrate-induced liver oxidative stress in *Monopterus albus*, resulting decrease of the expression of inflammatory and oxidative genes, as well as improvement of intestinal microbiota.[17] Leaves 70% aqueous ethanolic extract had analgesic and anti-inflammatory (carrageenan-induced paw edema in rats and mice) effects, with Ibuprofen and Pentazocine as reference drugs.[18] Leaves aqueous extract of *Uncaria gambir* and roots bark 70% aqueous ethanolic extract of *Morus alba* were mixed (1:1) to prepare a formulation named UP3005. This was tested for anti-inflammatory activity (carrageenan-induced paw edema in rats) and analgesic activity (acetic acid-induced writhing test). Effect was also tested with COX-2 inhibition method.[19] Follow up of previous study with UP1306, a mixture (1:1) of 70% aqueous ethanolic extracts of heartwood of *Acacia catechu* and the root bark of *Morus alba*.[20] Another follow ups of the study cited in reference 19: UP1304, a mixture of ethanolic extracts of rhizome of *Curcuma longa* and root bark of *Morus alba*.[21,22] Literature research that analyzed reports of the influences of different extracts in many aspects of patients with vascular dementia. The anti-inflammatory effect was evaluated mainly by tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) biomarkers.[23]

	Stems 80% aqueous ethanolic extract ameliorated the anterior cruciate ligament transection-induced rat model of osteoarthritis.[24] Commercial alkaloid extract (SZ-A powder) had positive effect on renal inflammation, through partial inhibition of cytokine-NO and TGF-β1 signaling in rats, HPLC analysis of SZ-A powder resulted the following alkaloids (**Figure 2A**): Fagomine 1,4-Dideoxy-1,4-imino-D-arabinitol and 1-Deoxynojirimycin (DNJ).[25] Stem bark (*Mori cortex*) 70% aqueous ethanolic extract had ameliorative activity on renal inflammation in STZ-induced diabetic rats. Effect was measured with several biomarkers.[26] Root bark aqueous and 70% aqueous ethanolic extracts were active against LPS-induced inflammation in RAW 264.7 cells. Effect was measured with five biomarkers.[27] Leaves 70% aqueous ethanolic extracts were active against LPS-induced inflammation in RAW 264.7 cells. Effect was measured with four biomarkers.[28] Leaves aqueous extract inhibited interleukin-1β-induced expression of inflammatory mediators by suppressing the activation of inflammation biomarkers in SW1353 human chondrocytes.[29] Twigs (*Ramulus mori*) ethanolic extract inhibited LPS-induced production of the pro-inflammatory cytokine interleukin-6 in Raw264.7 cells. A detailed mechanism of action is proposed.[30] Stem 80% aqueous ethanolic extract inhibited LPS-induced inflammation in RAW 264.7 cells. The extract was chromatographed (TLC) showing it had high content of Oxyresveratrol, that the authors refer the anti-inflammatory activity to.[31] Aqueous extract of sapwood inhibited LPS-induced inflammation in RAW 264.7 cells. Effect was measured with six biomarkers.[32] Roots methanolic extract had protective effect against Ethanol and Cerulein-induced model of pancreatitis in rats. HPLC analysis of the extract resulted significant amount of Cudraflavone B (**Figure 2A**).[33] Leaves of four genotypes were extracted with 50% aqueous ethanol and these extracts had anti-inflammatory and antioxidant activities in high fat-induced obese mice. Ant-inflammatory effect was measured with four biomarkers. HPLC analysis of the extracts afforded known compounds: 6 benzoic acids (like Parishin E, **Figure 2A**), 8 cinnamic acids, 15 flavonoids, 13 fatty acids, 4 saccharides or derivatives (like Picrasinoside F, **Figure 2A**) and 10 compounds that the researchers could not identify.[34] Bark methanolic extract had activity against imiquimod-induced inflammation in RAW 264.7 cells and in ear edema in mice. The extract was chromatographed affording Moracin O and Moracin P (**Figure 2B**), which were tested for the same activities and showed same effects as the crude extract. The effects of both test were measured using several inflammatory biomarkers.[35] Commercial aqueous fruits extract was supplemented to high-fat-diet-fed-rats, and it had ameliorative anti-inflammatory activity. Effect was tested with four biomarkers.[36] Fruits aqueous extract was chromatographed affording 22 compounds, where one of them, Oddioside A (**Figure 2B**), is a new natural product. The other 21 compounds were previously known, and they included Sargentodoside E

	(Oddioside A without the rhamnosyl moiety) and Pinellic acid (**Figure 2B**). The crude extract had anti-inflammatory activity against TNF-α-induced human dermal fibroblast damage. Effect was tested with several biomarkers.[37] Leaves powder was included in diet of healthy old overweight dogs for 12 weeks, resulting reduction of proinflammatory biomarkers and increase of anti-inflammatory biomarkers.[38] Resveratrol was isolated from leaves aqueous extract and used to prepare nanoparticles. These were tested for anti-inflammatory activity in LPS-induced RAW 264.7 cells and in DSS-induced ulcerative colitis in mice.[39] Leaves 95% aqueous ethanolic extract had anti-inflammatory activity in Paraquat-induced RAW 264.7 cells. Effect was measured using three biomarkers.[40] Fruits 70% aqueous ethanolic extract had activity against IL-1β-induced inflammation in human retinal pigment epithelial cells.[41] Commercial alkaloid extract (*Ramulus Mori* alkaloids) was used to prepare water-soluble complex as improved drug delivery method. It had anti-inflammatory activity in LPS-induced RAW 264.7 cells and in DSS-induced ulcerative colitis in mice.[42] Three commercial compounds that were originally isolated from this species, Kuwanon E, 4'-*O*-methylkuwanon E (**Figure 2B**) and Cudraflavone B, were active against LPS-induced inflammation in THP-1 human leukemia cells. The anticancer activity of these compounds in several cell lines is also reported.[43] Root bark 80% aqueous methanolic extract had anti-inflammatory activity in LPS-induced RAW 264.7 cells. Effect was measured with three biomarkers.[44] Fruits 80% aqueous ethanolic extract had anti-inflammatory activity in LPS-induced RAW 264.7 cells and anti-colitis effect in DSS-induced mice. Effects were measured with several biomarkers. Anticancer activity is also reported. Analysis of the extract showed that the active compounds were Ethyl linolenate, Linoleic acid and Hydroxyl methylfurfural (**Figure 2B**). These compounds were active in anti-inflammatory and anti-colitis tests.[45] Root bark methanolic extract was fractionized with water and EtOAc, and the EtOAc fraction was chromatographed affording 15 compounds, two of them were new: Soroceal B and Sanggenol Q (**Figure 2B**). All 15 compounds were tested for anti-inflammatory (and anticancer) activity but only four of them inhibited NO production in LPS-induced RAW 264.7 cells.[46] Stem bark 80% aqueous ethanolic extract had anti-inflammatory activity in LPS-induced *Porphyromonas gingivalis*. Effect was verified by suppression of inflammatory cytokines. Antibacterial activity is also published.[47] Leaves ethanolic extract had anti-inflammatory activity in LPS-stimulated THP-1 cells, which was measured with several biomarkers. Antibacterial activity is also published.[48] Root bark 80% aqueous methanolic extract was partitioned with chloroform, EtOAc, *n*-butanol and water. The EtOAc fraction was chromatographed yielding 26 compounds: 3',5'-Dihydroxy-6-methoxy-7-prenyl-2-arylbenzofuran (new compound), Moracin R (**Figure 2B**), Moracin C, Artoindonesianin O, Moracin D, Alabafuran A, Mulberrofuran L,

	Mulberrofuran Y, Kuwanon A, Kuwanon C, Kuwanon T, Sanggenon F (**Figure 2C**), Mulberroside A, Mulberroside B (**Figure 2D**), in addition to Moracin O, Moracin P, Morusin, Kuwanon E, Betulinic acid, Uvaol, Ursolic acid, *β*-Sitosterol, Oxyresveratrol 2-*O*-*β*-D-glucopyranoside, Adinosine, 5,7-dihydroxycoumarin 7-*O*-*β*-D-glucopyranoside and 5,7-dihydroxycoumarin-7-*O*-*β*-D-apiofuranosyl-(1→6)-*O*-*β*-D-glucopyranoside. Most of these compounds inhibited NO production in LPS- or Interferon gamma (IFN-γ)-induced inflammation in RAW 264.7 cells. Antiobesity activity is also reported.[49] Fruits and leaves were separately extracted with 70% aqueous methanol. Both extracts, separately or combined, had anti-inflammatory activity in high-fat-diet-induced mice. Effect was measured with six biomarkers. Antidiabetic and antiobesity activities are also reported.[50] Fruits aqueous extracts of four Korean cultivars were tested for phospholipase A and COX III inhibition activity. Antioxidant activity is also reported.[51] Fruits ethanolic extract was partitioned with three solvents and the chloroform fraction was chromatographed affording fifty compounds, three of them were new (**Figure 2D**). The isolated compounds were tested for anti-neuroinflammatory activity (NO production inhibition) in LPS-induced BV-2 microglia cells. Some of the compounds were active. Antidiabetic and antioxidant activities are also presented.[52] Fruits ethanolic extract had anti-inflammatory activity in LPS-induced RAW264.7 macrophages, where the effect was measured with three biomarkers. The extract was fractionized with *n*-hexane, DCM, EtOAc and *n*-butanol. Each one of the fractions was chromatographed and in **Figure 2D** some of the isolated compounds are shown: Ar-Turmerone, Odisolane and Morrole A. Antioxidant activity is also published.[53] Leaves 95% aqueous ethanolic extract and two of its components, resveratrol (**Figure 2D**) and oxyresveratrol, had anti-inflammatory activity in LPS-induced RAW 264.7 cells. Effect was measured with five biomarkers and a mechanism of action is proposed. Antioxidant activity is also reported.[54] Fruits, leaves, mistletoe and twigs were separately extracted with EtOAc. The extracts had anti-inflammatory activity in LPS-induced RAW 264.7 microphages. NO production inhibition was also measured. Leaves extract was most active. Antioxidant and cytotoxicity activities are also reported.[55,56] Juice of callus cells had anti-inflammatory activity in LPS-induced Caco-2 cells. Effect was measured with several biomarkers. TPC, TFC and antioxidant activity of the juice are reported. In addition, juice was analyzed for chemical composition indicating the presence of: Mulberroside F, Moracin M (**Figure 2D**) and some of its glycosides, in addition to Resveratrol and some of its glycosides, Oxyresveratrol and some of its glycosides, Mulberroside A.[57] Leaves 70% aqueous acetone alleviated inflammation caused by glyphosate in rats liver. The effect was measured with three biomarkers. Antioxidant activity, TFC and TPC are also reported.[58] Leaves were separately extracted with water and 80% aqueous ethanol, and both extracts had anti-inflammatory activity against D-galactosamine and LPS-induced acute liver injury in rats. Treatment also ameliorated oxidative

	stress. Analysis of both extracts for active compounds yielded known phenolics and DNJ.[59] Branches 70% aqueous ethanolic extract was chromatographed affording *cis*-Mulberroside A. This compound had anti-inflammatory activity in mice (carrageenan-induced) and in RAW 264.7 cells, where effect was measured with several biomarkers in both tests. Analgesic activity in mice is also reported.[60] Root bark was separately extracted with 70% aqueous ethanol and methanol. The methanolic extract was analyzed yielding Norartocarpanone (**Figure 2D**), Kuwanon E and Kuwanon G. The ethanolic extract and the three isolated compounds had anti-inflammatory activity in LPS-induced mice and in IL-1β treated A549 cells. In the first test, major effect was tested by NO production inhibition and in the second test by IL-6 production inhibition.[61] Root bark was separately extracted with 70% aqueous ethanol. The resulting extracts along with commercial Mulberrofuran G (**Figure 2D**), Kuwanon E, Kuwanon G and Morusin, had ameliorative effect in SO_2-induced acute bronchitis in rats and phorbol 12-myristate 13-acetate-induced inflammation in NCI-H292 cells.[62] Twigs methanolic extract was partitioned with several solvents including EtOAc, and this fraction was chromatographed affording five new compounds, 10-Oxomornigrol F, Ramumorin A, Ramumorin B (**Figure 2E**), (7″R)-(−)-6-(7″-hydroxy-3″,8″-dimethyl-2″,8″-octadien-1″-yl) apigenin and (4S,7S,8R)-trihydroxyoctadeca-5Z-enoic acid. In addition, 31 known compounds were also isolated. All isolated compounds were tested for anti-inflammatory activity in LPS-induced RAW 264.7 cells, where nine of them showed significant effect. This was measured with NO and COX-2 production.[63] Root bark chloroform extract was chromatographed affording Morusin, which was tested against 2,4,6-trinitrobenzensulfonic-induced colitis in rats, with sulfasalazine as a reference drug. Results were measured with several parameters indicating significant positive effects.[64] Root bark was separately extracted with *n*-hexane, DCM, EtOAc, *n*-butanol and water, and resulting extracts were tested against LPS-induced inflammation in RAW 264.7 cells. EtOAc fraction was most potent, so it was chromatographed affording Albanol B, Sanggenon B and Sanggenon D (**Figure 2E**). These compounds were also tested for the same activity and Albanol B was most potent. Effect was measured with three biomarkers, and a mechanism of action is proposed.[65] Root bark methanolic extract was partitioned with several solvents and the DCM fraction was chromatographed yielding Sanggenon A, Sanggenon M, Sanggenol A, Mulberofuran A, Mulberofuran B and Mulberofuran G (**Figure 2F**), in addition to Kuwanon G, Kuwanon E, Kuwanon T, Morusin and Moracin R. These compounds were tested against IL-6 production in TNF-α (Tumor Necrosis Factor-alpha)-induced MG-63 cells, and six of them were significantly active.[66] Bark methanolic extract and its component Moracin O and Moracin P, inhibited NF-κB (Nuclear Factor kappa B) in several cell lines. A mechanism of action is proposed.[67] Root bark 96% aqueous ethanolic extract was analyzed affording 24 compounds: Sanggenon H, Morusinol, Cyclomorusin (**Figure 2F**), Kuwanon

	K, Kuwanon S, Kuwanon U, Mulberrofuran A, Mulberrofuran B, Moracin G (**Figure 2G**), along with Kuwanon C, Kuwanon T, Morusin, Kuwanon E, Kuwanon H, Methyl 2,4-dihydroxybenzoate, Ethyl 2,4-dihydroxybenzoate, Moracin M, Moracin C, Oxyresveratrol, Mulberrofuran and Mulberrofuran Y. These compounds were tested for anti-inflammatory activity (COX inhibition) but only Oxyresveratrol showed significant activity. Anticancer and antiviral activities are also reported.[68] A follow up of the work cited in reference 25, but in this research activity was tested in LPS-induced inflammation in bone marrow-derived macrophage (BMDM) and RAW264.7 cells.[69] Follow up of studies cited in references 61-63 and 66, where the anti-inflammatory activity and mechanism of action of eleven previously isolated compounds are reported. In this study LPS-stimulated BV2 and RAW 264.7 cells were used, and the effects were measured using several biomarkers. Only Kuwanon T and Sanggenon A showed significant activity.[70] Fruits 70% aqueous ethanolic extract was fractionized with several solvents including DCM. This fraction was chromatographed affording 22 previously known compounds, even though some of them were isolated from this species for the first time. Among these compounds was Cyclo(L-Pro-L-Val) (**Figure 2G**) which had significant activity against LPS-induced RAW 264.7 cells. Effect was measured with several biomarkers, mainly NO production inhibition.[71] Fruits 80% aqueous ethanolic extract reduced pro-inflammatory and increased anti-inflammatory biomarkers, and attenuated adipokine imbalance in high-fat fed rats.[72] Alkaloid extract (SZ-A) had anti-atherosclerosis in apolipoprotein E-deficient mice through a high-fat and high-choline diet.[73] Morusin was isolated from root bark 70% aqueous ethanolic extract, and in combination with Docetaxel had anti-inflammatory activity in PC3 human prostate cancer cells. Effect was measured with four biomarkers Anticancer activity is also published.[74] Branch bark 95% aqueous ethanolic extract was partitioned with several solvents including EtOAc. Fractions were tested for anti-inflammatory activity in LPS-induces RAW 264.7 cells, and the EtOAc fraction was most potent. So, it was chromatographed to determine the active components, and they were identified as Isobavachalcone, Cudraflavone C (**Figure 2G**), Morusin, Quercetin, Kaempferol, Cudraflavone B, Umbelliferone, Oxyresveratrol and diglucosyl derivative.[75] Commercial Mulberroside A alleviated Ovalbumin or LPS-induced asthma or inflammation in mice. Effect was measured with several pro/anti-inflammatory and pro/antioxidant biomarkers. A mechanism of action is proposed.[76] Commercial Mulberroside A suppressed pro-inflammation and increased anti-inflammation biomarkers in aging mice model and human derived endothelial cells.[77] Leaves aqueous and methanolic extracts suppressed the tumor necrosis factor (TNF)-α-induced adhesion of monocytes to human aortic endothelial cells. Cytoprotective effect is also presented.[78] Twigs aqueous extract ameliorated DSS-induced colitis in mice, where effect was measured using for biomarkers.[79]

	Freeze-dried fruit juice was supplemented to mice with DSS-induced colitis resulting ameliorative effect that was measured with four biomarkers. Positive effect on gut microbiota is presented.[80] Anthocyanin-rich fruit ethanolic extract was supplemented to mice with DSS-induced colitis resulting ameliorative effect that was measured with several biomarkers. Analysis of the extract afforded mainly Cyanidin-3-*O*-glucoside and Cyanidin-3-*O*-rutinoside. Positive effect on gut microbiota is presented.[81] A combination of fruit powder, probiotic biomass and inulin had positive effect against DSS-induced colitis in rats.[82] Phytoformula containing the root barks of *Morus alba* (70% aqueous ethanolic extract), the fruits of *Schizandra sinensis* (70% aqueous ethanolic extract) and the roots of *Asparagus cochinchinensis* (methanolic extract) was prepared. It had anti-inflammatory activity in LPS-induced acute lung injury in mice and in lung epithelial cells and alveolar macrophages. Effects were measured using several biomarkers, especially NO production inhibition.[83] Special method was applied to extract polysaccharides from twigs (*Ramulus mori*) which contained seven monosaccharides. The extract had activity against LPS-induced inflammation in RAW 264.7 cells. Antioxidant and antibacterial are also presented.[84] Inflammation was induced in rats by cigarettes smoke and LPS and they were treated with Lianhua Qingke, a Chinese Traditional Medicine formulation. Results showed positive effect.[85] Leaves aqueous extract was active against glucolipotoxicity-induced hepatic lipid accumulation and inflammation in HepG2 cells. Effect was measured with several biomarkers. Analysis of the extract afforded Chlorogenic acid and two of its isomers as active components: Neochlorogenic and Cryptochlorogenic acids (**Figure 2G**).[86] High hydrostatic pressure fruits aqueous extract was active against LPS-induced inflammation in RAW 264.7 cells. Effect was verified using several biomarkers. The phenolics composition of the extract is published.[87] Leaves 50% aqueous ethanolic extract was analyzed affording Neochlorogenic acid (among other compounds), which was active against LPS-induced inflammation in A549 cells. Effect was measured with seven biomarkers.[88] Root bark (Mori Cortex Radicis) 70% aqueous ethanolic extract and its active components (five compounds including chlorogenic and neochlorogenic acid) were active against LPS-stimulated inflammation in RAW 264.7 cells.[89] Fruits, leaves and twigs were separately extracted with methanol and the three extracts were tested against LPS-stimulated inflammation in RAW 264.7 cells. Effect was measured with COX-2 inhibition and NO production inhibition. Fruits extract was practically inactive, leaves extract activity was weak (COX-2) and moderate (NO), while twigs extract was very weak to high, respectively.[90] Leaves 70% aqueous methanolic extract was partitioned with chloroform, *n*-butanol and water. Crude extract and fractions had inhibitory effects in LPS-induced RAW 264.7 cells. Effect was measured mainly with NO and prostaglandin E2 (PGE_2).[91] Leaves 95% aqueous ethanolic extract was fractionized by *n*-hexane, EtOAc

	and water. The EtOAc fraction had anti-inflammatory activity in LPS or interferon-γ-induced RAW 264.7 cells. Effect was measured mainly with NO and prostaglandin E2.[92] Stems 60% aqueous acetone extract was analyzed affording eight phenolics that were active against LPS-induced inflammation in BV-2 microglial cells. Effect was measured mainly by NO production inhibition. The isolated phenolics were: Isoscopoletin 6-(6-*O*-β-apiofuranosyl-β-glucopyranoside) (new, **Figure 2G**), Mulberroside A, 2,3-trans-Dihydromorin-7-*O*-β-glucoside, *E*-Resveratrol, Moracin M, Steppogenin, *E*-Oxyresveratrol and Dihydromorin.[93] Molecular docking of several active components that inhibit NO production.[94] Enzymatic hydrolysis of Mulberroside A that was isolated from root bark afforded Oxyresveratrol. This compound had anti-inflammatory activity against carrageenan-induced paw edema in rats and against LPS-induced inflammation in RAW 264.7 cells. Effect was measured mainly by NO production and COX-2 inhibition. A mechanism of action is proposed.[95] Branches methanolic extract was fractionized with EtOAc, *n*-butanol and water. The three fractions were analyzed and the EtOAc fraction yielded highest amount of Oxyresveratrol. Crude extract, EtOAc fraction and isolated Oxyresveratrol had anti-inflammatory activity by suppressing cell migration of Jurkat T cells in response to SDF-1 (Stromal cell Derived Factor-1).[96] Stems 80% aqueous ethanolic extract was chromatographed affording Oxyresveratrol. Both crude extract and isolated active compound inhibited three inflammatory mediators and metalloproteinase in LPS-induced RAW 264.7 macrophages and IL-1β-induced C28/I2 human chondrocyte cell line.[97] Twigs aqueous extract was analyzed yielding Oxyresveratrol. Both crude extract and isolated active compound ameliorated DSS-induced colitis in mice. Effect was tested with three biomarkers.[98] Bark was separately extracted with *n*-hexane, EtOAc and 70% aqueous ethanol. The three extracted were tested against carrageenan-induced paw edema in mice, and the EtOAc was most active. Wound healing activity is also reported. Effect was measured with several biomarkers including oxidant-antioxidant.[99] Leaves were separately extracted with chloroform, DEE and methanol. The three extracts were tested against carrageenan-induced paw edema in rats. Analgesic activity (mice) is also reported.[100] Roots methanolic extract was chromatographed affording Mulberrofuran H (**Figure 2H**), in addition to Moracin C, Mulberrofuran Y, Kuwanon C, Sanggenon H, Cudraflavone B and Morusinol. All these compounds were tested for anti-inflammatory activity in THP-1 cells. Sanggenon H was most active.[101] Leaves aqueous (40 °C) extract had activity against carrageenan-induced paw edema in rats. Analgesic activity is also reported.[102] Callus was cultured from leaves and extracted with 70% aqueous ethanol. The extract was active against human NF-κB reporter cells. Chromatography of the extract for active compounds revealed the presence of Ferulic acid, Kuwanon J, Mulberrin and Sanggenon F (**Figure 2H**).[103]

	Leaves 60% aqueous ethanolic extract had anti-inflammatory activity in unilateral ureter obstruction-induced mice. Effect was measured with several parameters including oxidant-antioxidant biomarkers. The extract was analyzed with HPLC affording Chlorogenic acid as the major active component. A mechanism of action is proposed.[153] Wood 50% aqueous ethanolic extract had anti-inflammatory activity in LPS-induced RAW 264.7 cells. Effect was measured with several parameters, mainly by NO production inhibition, and including oxidant-antioxidant biomarkers. The extract was tested in combination with extract of *Pinus densiflora* and with Methyl gallate. The extract was analyzed (GC-MS) resulting 36 known compounds, where molecular docking was performed to ten of them. Antibacterial and antioxidant activities are also published.[154] Roots bark ethanolic extract was analyzed affording Sanggenon C and Sanggenon O (**Figure 2H**), and both compounds inhibited NO production in LPS-induced RAW 264.7 cells.[208]
M. atropurpurea	Whole plant 85% aqueous ethanolic extract ameliorated inflammation in LPS-induced RAW 264.7 cells and in DSS-induced ulcerative colitis in mice. Effect was measured with several biomarkers including oxidant-antioxidant. The extract was analyzed for phenolics resulting 24 known compounds: Butin, Loureirin B (**Figure 3**), Kaempferol and 12 of its glycosides, and Quercetin and 8 of its glycosides.[104] a Heat stress-induced inflammation in rats was attenuated after treatment with commercial enzymatically treated leaf protein that was supplemented in food.[106] Leaf proteins were obtained by acidic extraction and were enzymatically hydrolysed. The product was active against LPS-induced inflammation in RAW 264.7 cells. Effect was measured with several biomarkers. Antioxidant activity is reported.[107] Leaf proteins were obtained by acidic extraction and were enzymatically hydrolysed. The product was active against DSS-induced ulcerative colitis in rats. Effect was measured with four biomarkers. Treatment improved gut microbiota.[108] a) Interestingly, the title, abstract and introduction of this article describe the activity “Leaf Flavonoids” and *Morus alba* is presented, whole in the experimental section it is stated that “whole plant” of *Morus atropurpurea* was used. It is well known that this name can or can not be synonym of *Morus alba*,[105] but this must clearly stated.
M. australis	Leaves methanolic extract ameliorated acetaminophen-induced liver inflammation in rats, where effect was measured with several parameters, including oxidant-antioxidant biomarkers. HPLC analysis of the extract yielded (major components) Naringenin, Protocatechuic acid (**Figure 4**), in addition to Gallic acid, Catechin, Gallocatechin gallate, Caffeic acid, Epicatechin, Rutin and Quercetin. Mechanism of action is proposed.[109] Roots ethanolic extract was prepared by microwave-assisted extraction. It had anti-inflammatory activity *in vitro* (LPS-induced RAW 264.7 cells) and *in vivo* (Carbon tetrachloride-induced hepatic damage in mice). Effect was measured mainly by COX-2 and NO production inhibition. HPLC analysis of the extract showed that Morusin was the major active component.[110]
M. bombycis	Stems methanolic extract alleviated collagen-induced arthritis in mice. A mechanism of action is proposed that includes inhibition of nuclear factor-κB

	and activator protein-1.[111] Stems methanolic extract had anti-inflammatory activity *in vitro* (LPS-induced RAW 264.7 cells, effect was measured with three biomarkers) and *in vivo* (monosodium urate-induced murine macrophages). HPLC analysis showed that Oxyresveratrol was major active component.[112] Cortex 80% aqueous methanolic extract was analyzed affording Moracinoside M, Mulberrofuran K, Kuwanon V, Kuwanon R (**Figure 5**), in addition to Moracin 3'-*O*-β-D-glucopyranoside, Mulberrofuran G, Kuwanon J, 5,7,2',4'-Tetrahydroxyflavanone, Oxyreveratrol, 7,2',4'–Trihydroxyflavanone and 2,4,2',4'-Tetrahydroxychalcone. These compounds were tested for anti-inflammatory activity in LPS-induced murine macrophages showing that Mulberrofuran K was most active component. Effect was measured with four biomarkers, mainly by NO production inhibition.[113]
M. cathayana	**No reported anti-inflammatory activity of this species**
M. celtidifolia	**No reported anti-inflammatory activity of this species**
M. ihou	Fruits 85% (w/v) aqueous methanolic extract ameliorated carrageenan-induced paw edema in rats. Effect was measured with nine parameters, mainly uric acid production inhibition.[114]
M. indica	Leaves were continuously (Soxhlet) extracted with PE chloroform, acetone, ethanol and chloroform-water. The ethanolic extract was active against carrageenan-induced paw edema and cotton pellet-induced granuloma in rats.[115] Roots methanolic extract was active against carrageenan-induced paw edema and cotton pellet-induced granuloma in rats. Antipyretic activity is also published.[116] Leaves were chromatographed affording DNJ which was active against stable angina pectoris in patients with coronary heart disease. Effect was measured with five parameters including oxidant-antioxidant biomarkers.[117]
M. isingnis	**No reported anti-inflammatory activity of this species**
M. japonica	**No reported anti-inflammatory activity of this species**
M. laevigata	Leaves were separately extracted with chloroform, DEE and methanol. The three extracts were tested against carrageenan-induced paw edema in rats. Analgesic activity (mice) is also reported.[100]
M. liboensis	**No reported anti-inflammatory activity of this species**
M. macroura	Fruits 70% aqueous ethanolic extract alleviated against acetic acid-induced ulcerative colitis in rats. Effect was measured with four biomarkers. Mechanism of action is proposed. Antioxidant activity is also presented.[118,119] Tree bark 90% ethanolic extract had anti-inflammatory activity in alloxan-induced diabetic rats. Effect was measured mainly with IL-1β. Antidiabetic activity is also published.[120] Stem bark ethanolic extract was partitioned with several solvents including EtOAc. This fraction was chromatographed affording Guangsangons F, G, H, I, J, Mulberrofuran J (**Figure 6A**) and Kuwanon J. The isolated compounds were tested for anti-inflammatory activity (release of β-glucuronidase in rats) resulting significant effect for Guangsangons H, I, J. Antioxidant activity is also published.[121] Branches and leaves were combinedly extracted with methanol and the extract was fractionized with several solvents, including EtOAc. This

	fraction was chromatographed affording (+)-Laricilinol, Balanophonin, (7*S*,8*R*)-5-Methoxyl balanophonin, (−)-(7*R*,8*S*)-Dihydroniconiferol alcohol, Hedyotisol A (**Figure 6B**), in addition to Moracin O, Moracin P, Moracin M and Moracin R. The isolated compounds were tested for anti-inflammatory activity (Lactate dehydrogenase release inhibition in LPS-induced J774A.1 cells) resulting no effect or weak effect (one compound).[122] b b- In this article, authors name some of the isolated compounds Moricin. But viewing the structures that they presented and comparing them with literature data reveals that fact that these are Moracins.
M. mesozygia	Leaves acetone extract inhibited NO production in LPS-activated RAW 264.7 cells. Anti-arthritic and antioxidant activities are published.[123] Leaves 50% aqueous ethanolic extract was partitioned with several solvents including EtOAc, and this fraction was active against complete Freund's adjuvant (CFA)-induced joint inflammation in rats. Anti-arthritic and antioxidant activities are published.[124] Leaves 50% aqueous ethanolic extract was partitioned with several solvents including EtOAc, and this fraction was active against carrageenan-induced paw edema in rats. Antinociceptive activity is also published.[125] Stem bark was extracted with 50% methanol:DCM and the extract was chromatographed yielding 14 compounds: Moracin N, Moracin S, Moracin L, Artopithecin A, Morachalcone A (**Figure 7**), in addition to Moracin C, Moracin M, Moracin D, Mulberrofuran L, Isobavachalcone, 2,2′,4,4′-Tetrahydroxychalcone, Betulinic acid, 3*β*-Acetoxy-urs-12-en-11-one and 4,4'-Diphenylmethane-bis(methyl) carbamate. The isolated compounds were tested for anti-inflammatory activity (LPS-induced HEKa skin cells, IMR-90 lung cells, HPrEC prostate cells) resulting effects from zero to very high. Antibacterial and anticancer activities are also published.[126] Stem bark 80% aqueous methanolic extract was active against carrageenan-induced paw edema in rats and using membrane stability of red blood cells. Acute toxicity studies are also published.[127]
M. mongolica	Stem and root bark 95% aqueous ethanolic extract was partitioned with several solvents including EtOAc, and this fraction was analyzed yielding 14 compounds: Mongolicin A, Mongolicin B, Mongolicin C, Mongolicin D, Mongolicin E, Mongolicin F (**Figure 8A**), Chalcomoracin, Mulberrofuran T, Mulberrofuran F, Kuwanon O (**Figure 8B**), in addition to Albanol B, Mulberrofuran G, Mulberrofuran H and Kuwanon H. The isolated compounds were tested for anti-inflammatory activity (inhibition of β-glucuronidase release in Platelet-Activating Factor-induced white blood cells), where three compounds had moderate to high effect. Antioxidant activity is also published.[128]
M. multicaulis	Branches methanolic extract had ameliorating activity of oxidized low-density lipoprotein-induced injury in human umbilical vein endothelial cells. The extract was analyzed resulting the isolation of Oxyresveratrol as major active component. Study of the mechanism of action revealed Nrf2 (Nuclear factor erythroid 2-related factor 2) activation. Molecular docking was conducted.[129]
M. nigra	Roots methanolic extract was chromatographed affording Sanggenon E (**Figure 9**), in addition to Mulberrofuran H, Kuwanon E, Kuwanon C, Sanggenon H and Soroceal. All these compounds were tested for anti-inflammatory activity in THP-1 cells. Sanggenon H was most active

	compound.[101] Leaves aqueous (40 °C) extract had activity against carrageenan-induced paw edema in rats. Analgesic activity is also reported.[102] Callus was cultured from leaves and extracted with 70% aqueous ethanol. The extract was active against human NF-κB reporter cells. Chromatography of the extract for active compounds revealed the presence of Ferulic acid, Kuwanon J, Mulberrin and Sanggenon F.[103] Leaves 50% aqueous ethanolic extract had anti-inflammatory activity tested with carrageenan-induced paw edema and cotton pellet-induced fibrovascular tissue growth in rats. The extract was analyzed for active phytosterols resulting the isolation of Germanicol (**Figure 9**), Betulinic acid and β-Sitosterol.[130] Roots lectin (no method of isolation, no structure) had activity against LPS-induced inflammation in rats. Effect was measured using several parameters including oxidant-antioxidant biomarkers.[131] Fresh fruits aqueous extract ameliorated Xylazine hydrochloride-induced periodontitis in rats. Effect was measured with several biomarkers where some indicated positive results and others showed no effect.[132] Fruits were separately extracted with acetone and EtOAc containing 5% HC*l* $_{(aq)}$. The extracts had anti-inflammatory activity in 5-fluorouracil-induced mucositis of digestive system in rats. Effect was measured using several parameters including oxidant-antioxidant biomarkers.[133] Leaves 95% aqueous ethanolic extract was active against LPS-induced RAW 264.7 cells. Effect was measured with several biomarkers especially NO production inhibition.[134] Leaves 70% aqueous ethanolic extract had alleviative activity on cardiovascular inflammatory process and insulin resistance of dyslipidemic mice. Effect was measured with several biomarkers especially blood lipid concentrations.[135] Concentrated fruits juice and gel that contained it, had ameliorated carrageenan-induced paw edema in rats. Effect was measured mainly by paw edema volume. Antioxidant activity is also published.[136] Leaves 70% aqueous methanolic extract had alleviative effect against paracetamol hepatotoxicity (inflammation) in mice.[137] Fruits polysaccharides attenuated DSS-induced colitis in mice. Effect was measured with several biomarkers and mechanism of action is proposed.[138] Leaves methanolic extract had positive activity against carrageenan-induced paw edema in rats. Effect was measured mainly by paw edema volume. Antimicrobial and wound healing activities are published.[139] Fruits were defatted with PE and ultrasonically extracted with ethanol affording anthocyanin-rich extract. The major components of this extract were Cyanidin-3-*O*-glucoside, Cyanidin-3-*O*-rutinoside and Rutin. The anti-inflammatory activity was tested *in vivo* by Xylene-induced ear edema in mice (volume of the edema) and *in vitro* by LPS-induced RAW 264.7 cells (mainly NO production inhibition). Antioxidant and antinociceptive activities are also published. [140] Fruits 70% aqueous ethanolic extract was supplemented to high fat diet fed-mice, separately or in combination with DNJ, Cyanidin-3-*O*-glucoside and Resveratrol. In all cases, concentrations of pro-inflammatory were reduced. Antiobesity activity is also published.[141]

	Fruits 50% aqueous ethanolic extract attenuated inflammation in LPS-induced mice. Effect was measured using several parameters including oxidant-antioxidant biomarkers. LC-MS analysis of the extract yielded 12 known phenolics. Antioxidant activity is also published.[142] Fruits ultrasonically-assisted 70% aqueous ethanolic extract had anti-inflammatory activity in cholesterol-fed and cigarette smoke-exposed hypertensive rats. Effect was measured with several parameters including oxidant-antioxidant biomarkers.[143] New roots lectin had activity against LPS-induced inflammation in rats. Effect was measured using several parameters including oxidant-antioxidant biomarkers.[144] Ripe and unripe fruits aqueous extracts were used to prepare ointments, and these had anti-inflammatory in skin wounds of rats. Effect was measured with several biomarkers. Unripe fruits extract was more potent. Anticancer and antimicrobial activities are also published.[145] Leaves aqueous extract had anti-inflammatory activity: *in vitro* (fibroblast cultures) and *in vivo* (dorsal wounds in mice).[146] Fermentation of plant residues increased the content of Cyanidin-3-*O*-glucoside in methanolic extract, which was active against LPS-induced human foreskin fibroblasts. Molecular docking of Cyanidin-3-*O*-glucoside was conducted.[147]
M. notabilis	**No reported anti-inflammatory activity of this species**
M. papyrifera	**No reported anti-inflammatory activity of this species**
M. rotundiloba	Hybrid of *M. Alba* and *M. Rotundiloba* parts (root bark, root wood, stem bark, stem wood) were separately extracted with *n*-hexane, EtOAc and ethanol. The extracts were tested for mushroom tyrosinase inhibition, which authors consider whitening and anti-inflammatory activity. They refer these activities to Betulinic acid (**Figure 10**) contained in these extracts.[148]
M. rubra	Fruits juice attenuated cigarette smoke-induced inflammation in rats. Effect was measured using several parameters including oxidant-antioxidant biomarkers.[149]
M. serrata	Leaves were separately extracted with chloroform, DEE and methanol. The three extracts were tested against carrageenan-induced paw edema in rats. Analgesic activity (mice) is also reported.[100]
M. trilobata	**No reported anti-inflammatory activity of this species**
M. wittiorum	Stem bark 95% aqueous ethanolic extract was partitioned with several solvents including EtOAc and this fraction was chromatographed yielding nine compounds: 4'-Prenyloxyresveratrol, Euchrenone a7 (**Figure 11**), in addition to Quercetin, Norartocarpanone, Resveratrol, Morachalcone A, Dihydrokaempferol, Morachalcone A, Oxyresveratrol and 5, 7, 3', 4'-Tetrahydroxy-3-methoxyflavone. These compounds were tested for anti-inflammatory activity (β-glucuronidase release inhibition, rat polymorphonuclear leukocyte induced by platelet activating factor), where Quercetin and Oxyresveratrol were active. Anticancer activity is also published.[150] Stem bark 95% aqueous ethanolic extract was partitioned with several solvents including EtOAc and this fraction was chromatographed yielding five new compounds: Wittifuran A, Wittifuran B, Wittifuran C, Wittifuran F, and Wittifuran G (**Figure 11**). The isolated compounds were tested for anti-inflammatory activity (β-glucuronidase release inhibition, rat

	polymorphonuclear leukocyte induced by platelet activating factor) resulting moderate activity. Antioxidant activity was also published.[151] Follow up of previous study using same methods afforded three new compounds: Wittifuran H, Wittifuran I and Wittifuran U (**Figure 11**). Wittifuran I was tested for anti-inflammatory activity. Anticancer activity was also published.[152]
M. yunnanensis	**No reported anti-inflammatory activity of this species**

* Unless stated otherwise, percentages of solvent mixtures are V/V.

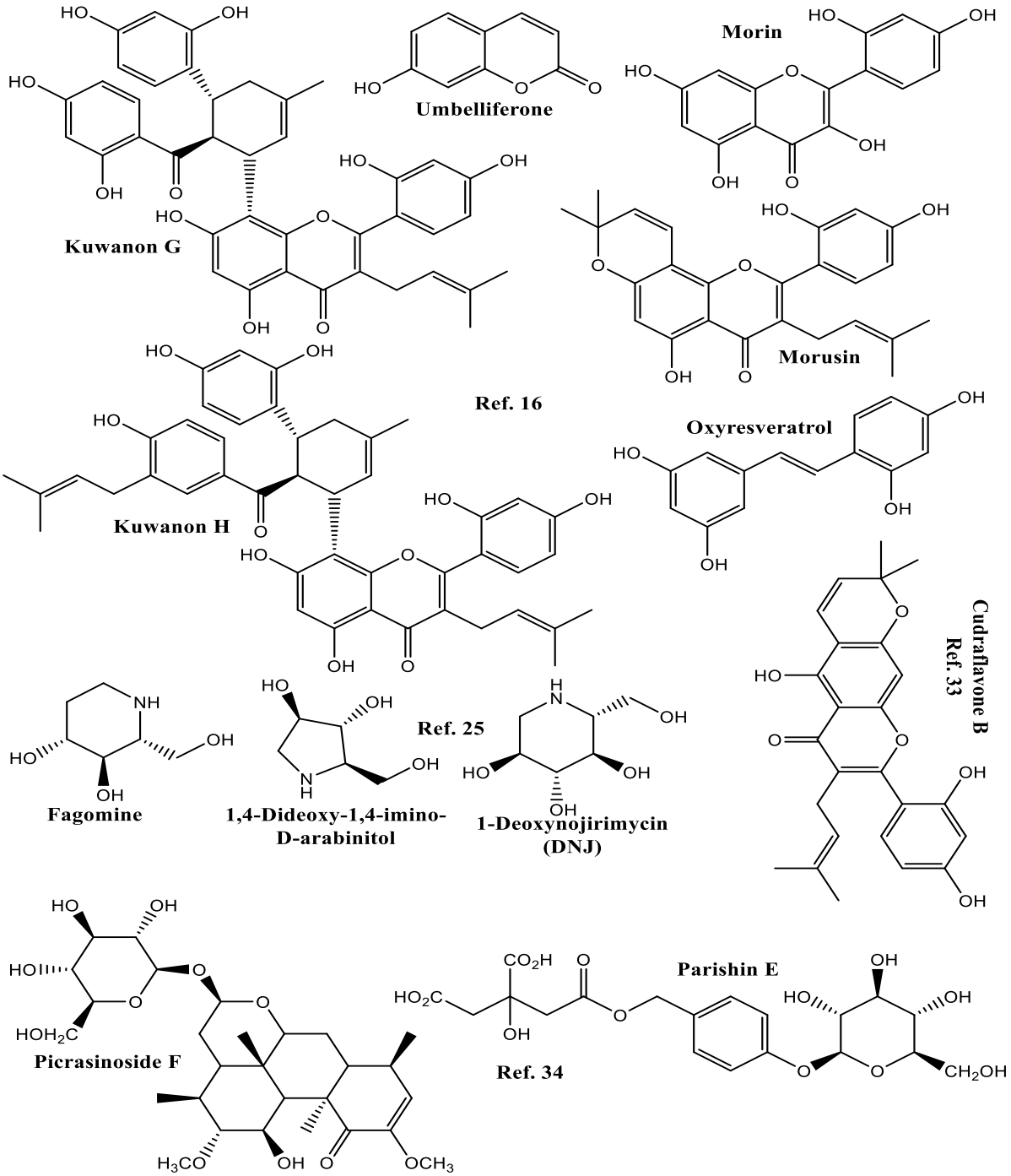

Figure 2: A. Natural products isolated from *Morus alba*.

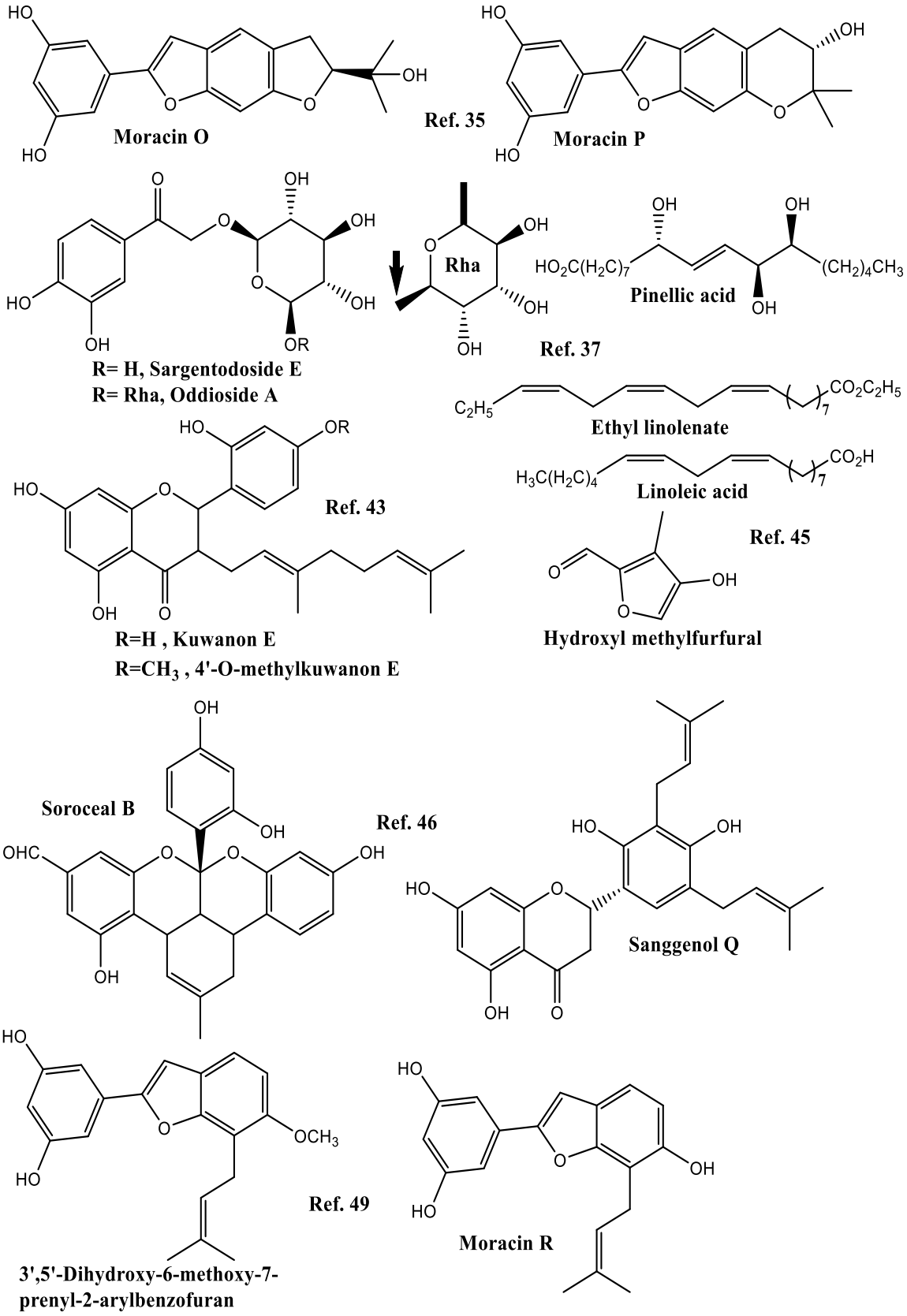

Figure 2B: Natural products isolated from *Morus alba.*

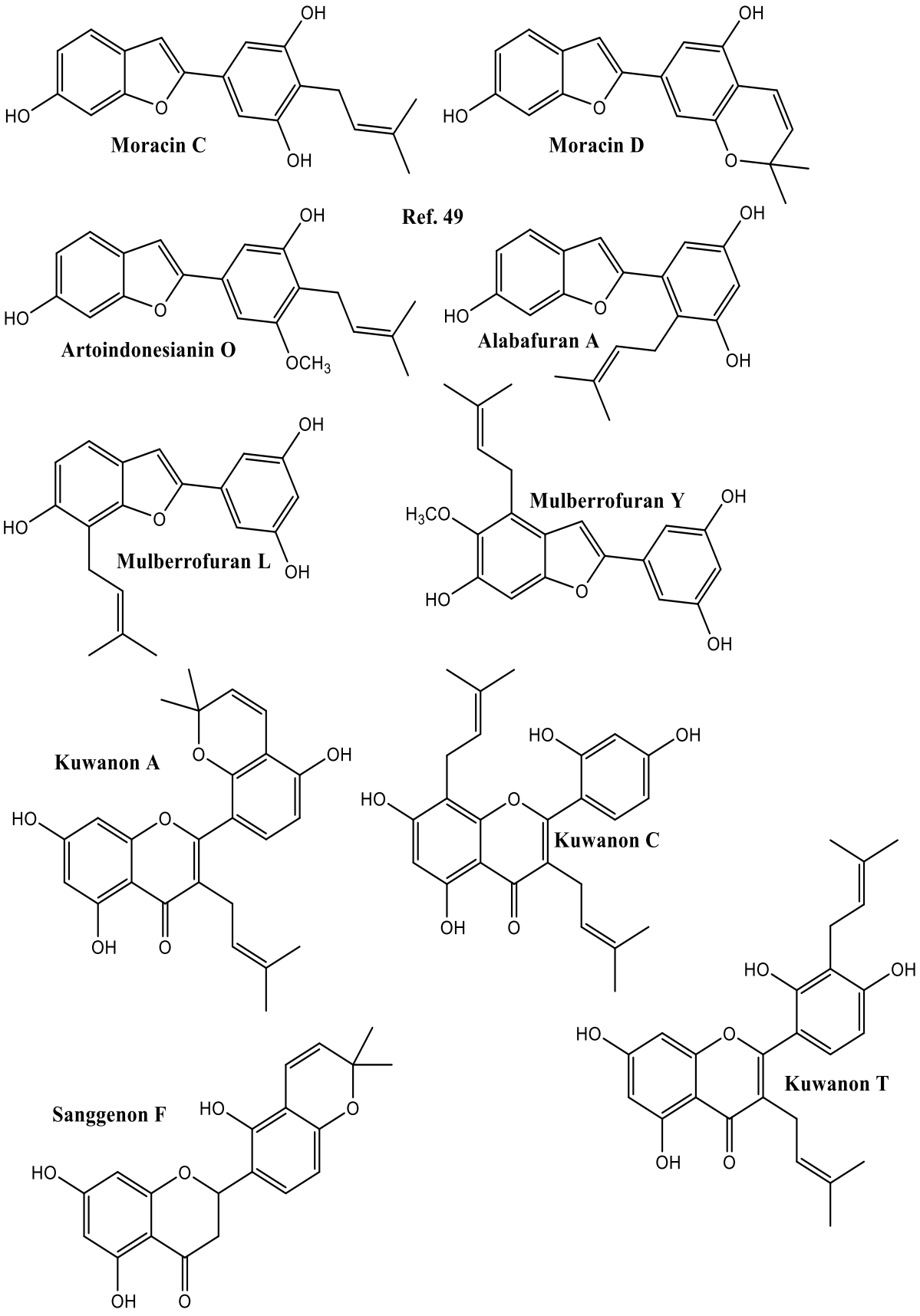

Figure 2C: Natural products isolated from *Morus alba.*

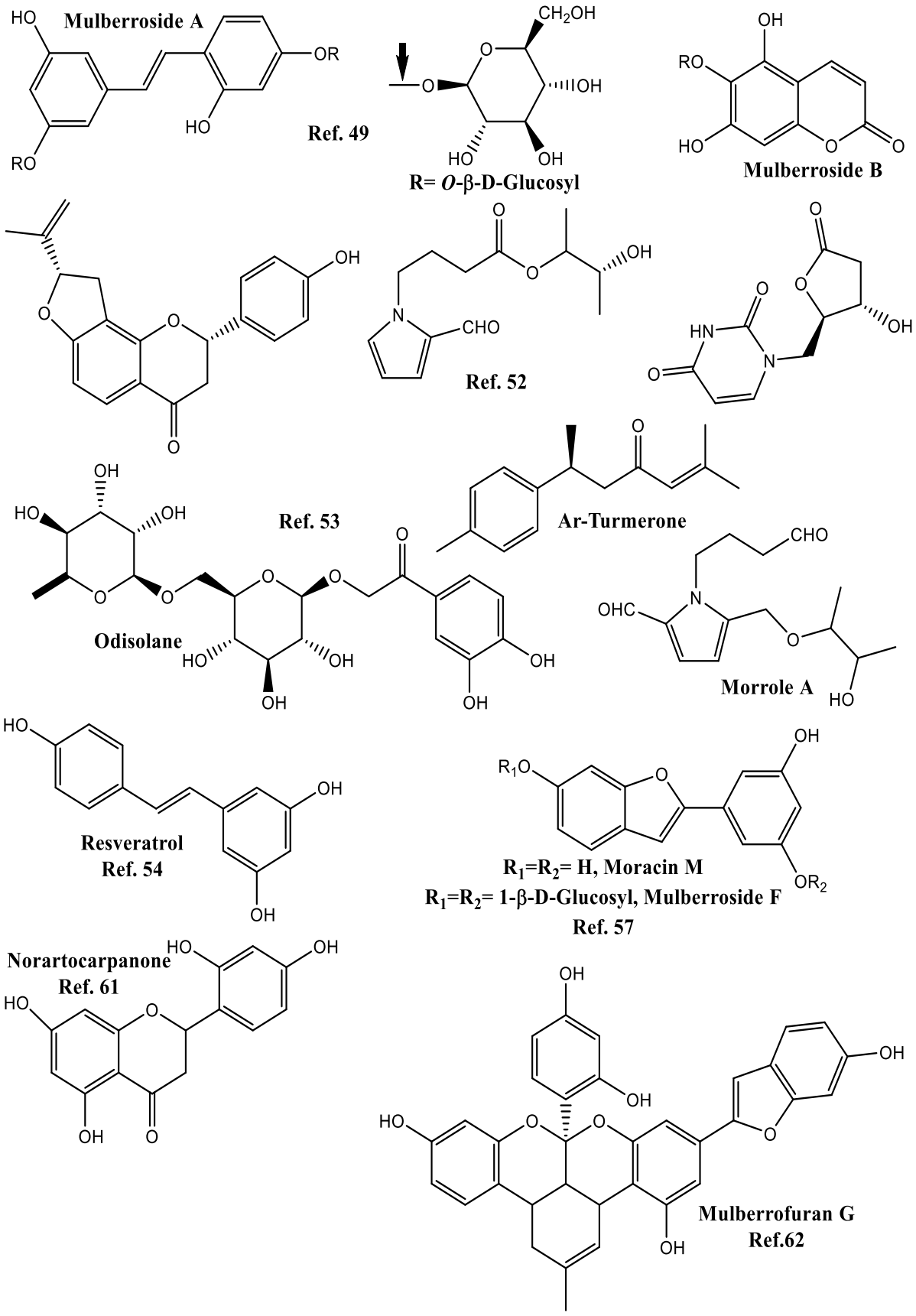

Figure 2D: Natural products isolated from *Morus alba.*

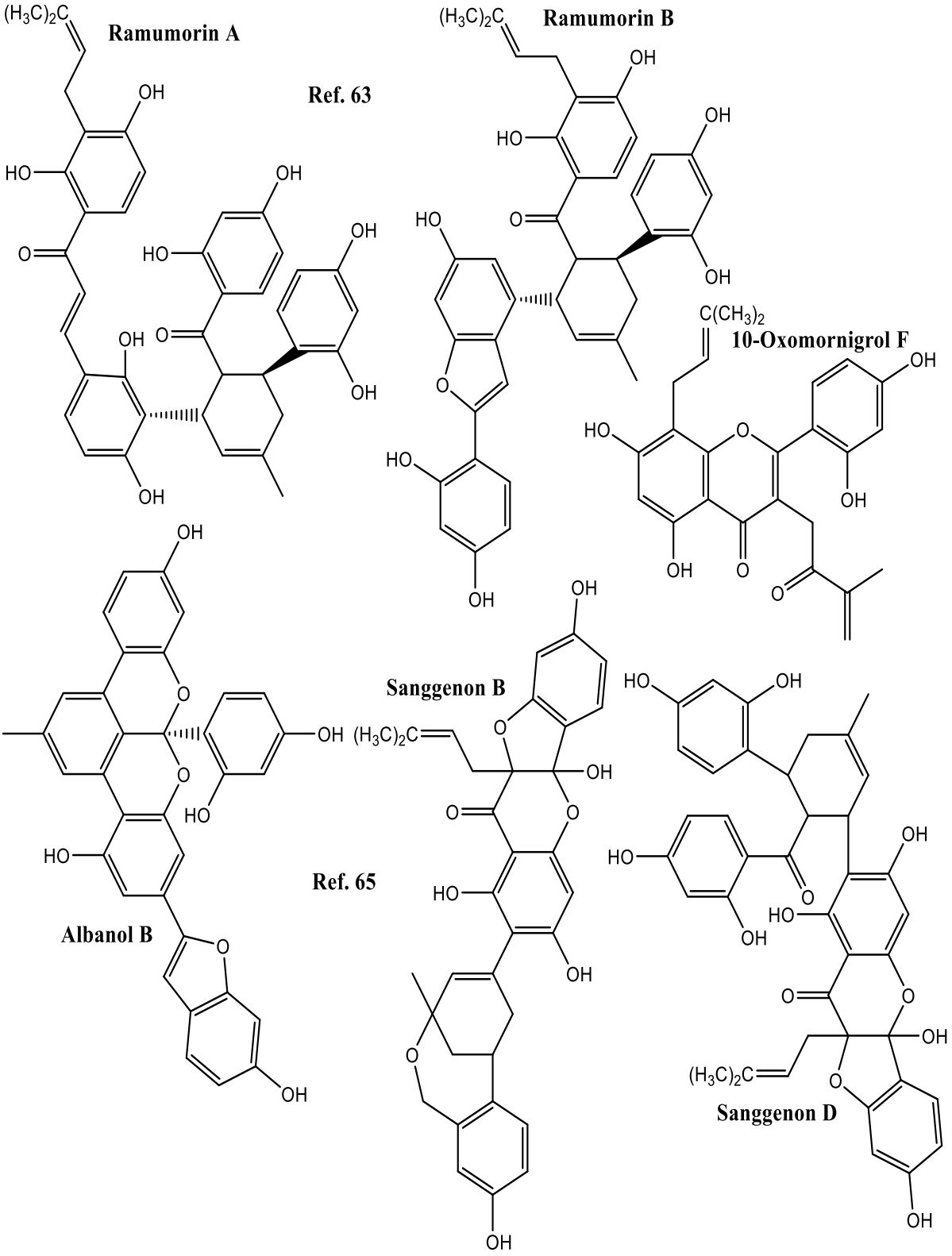

Figure 2E: Natural products isolated from *Morus alba.*

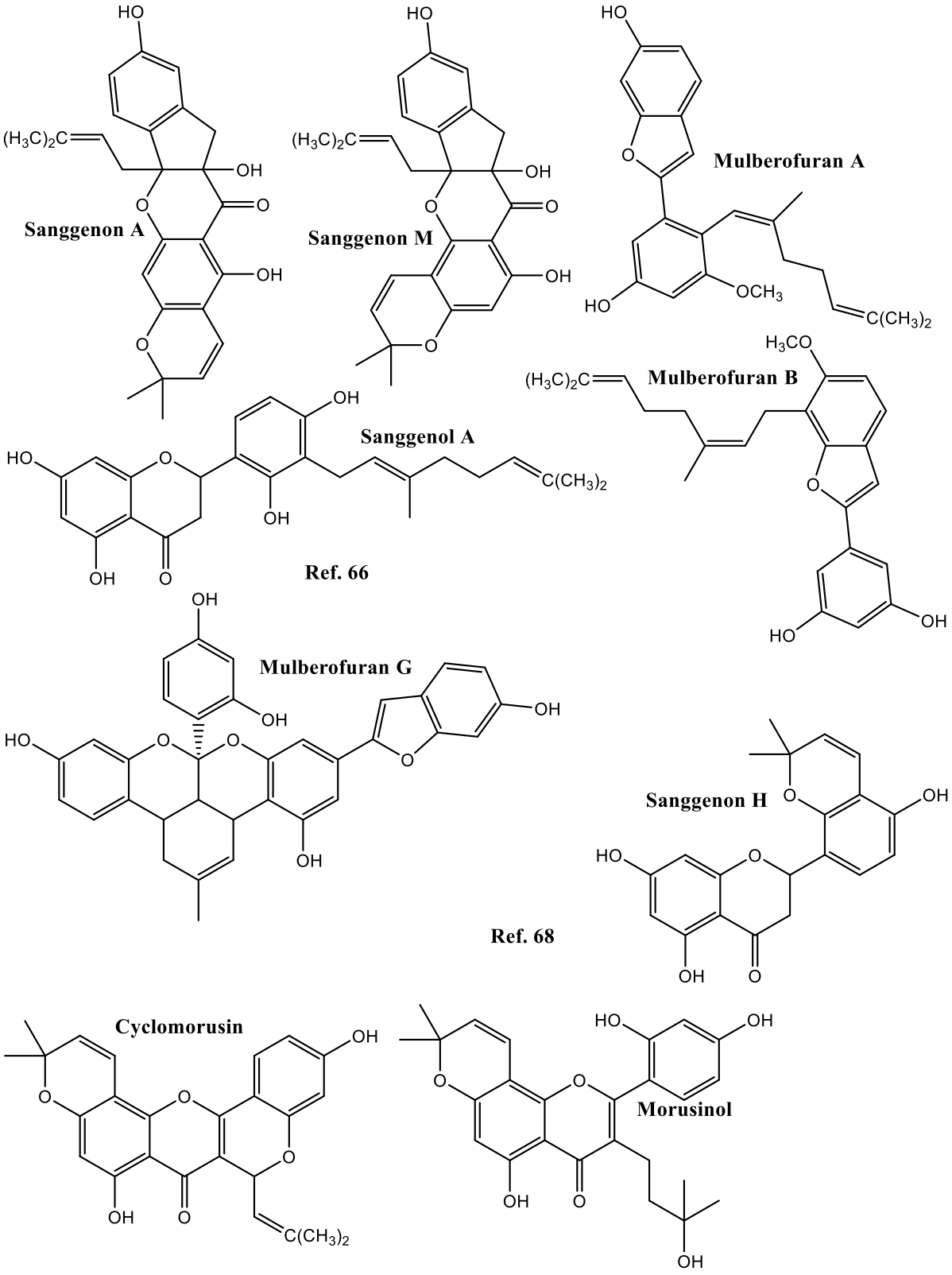

Figure 2F: Natural products isolated from *Morus alba.*

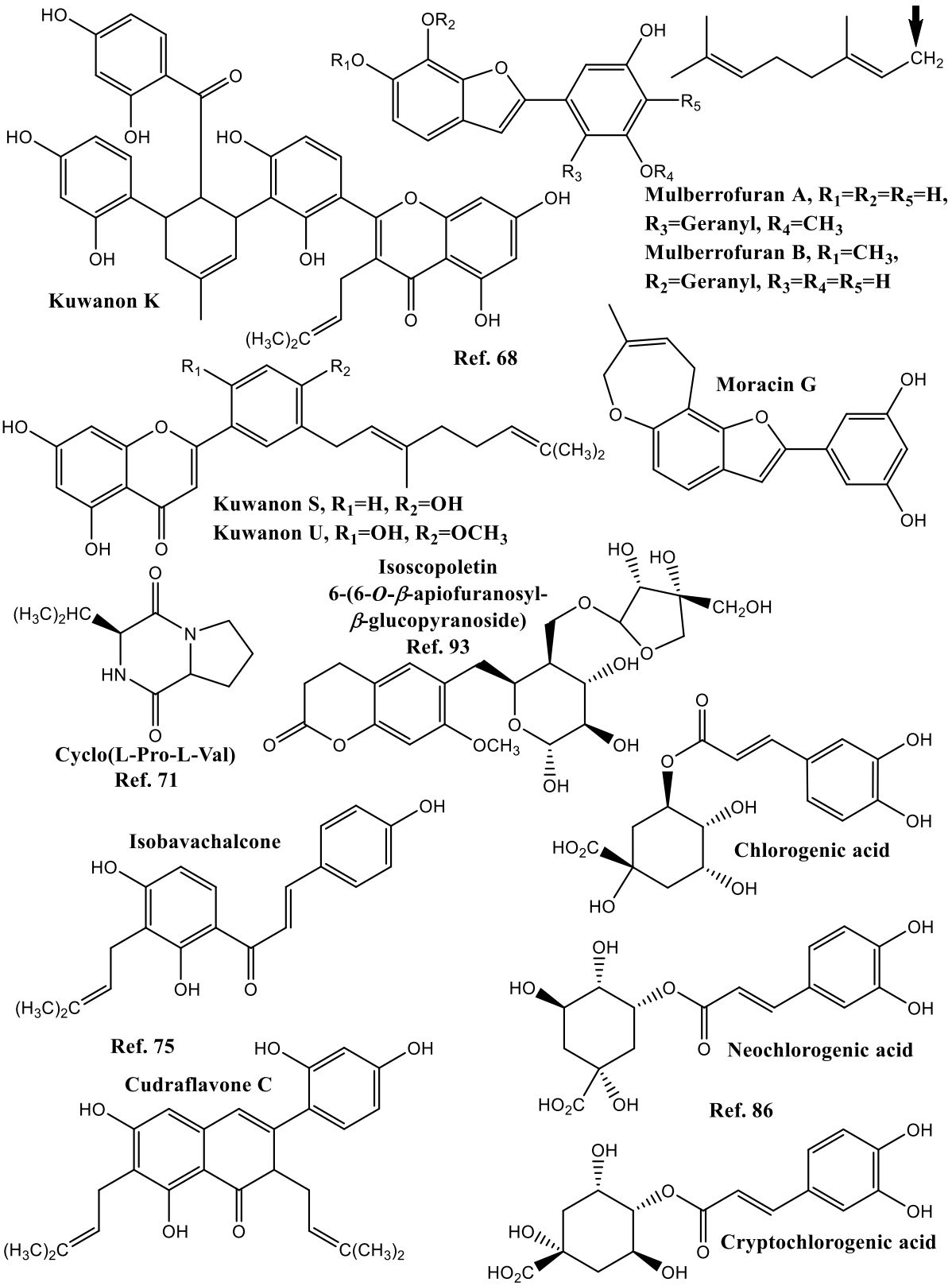

Figure 2G: Natural products isolated from *Morus alba.*

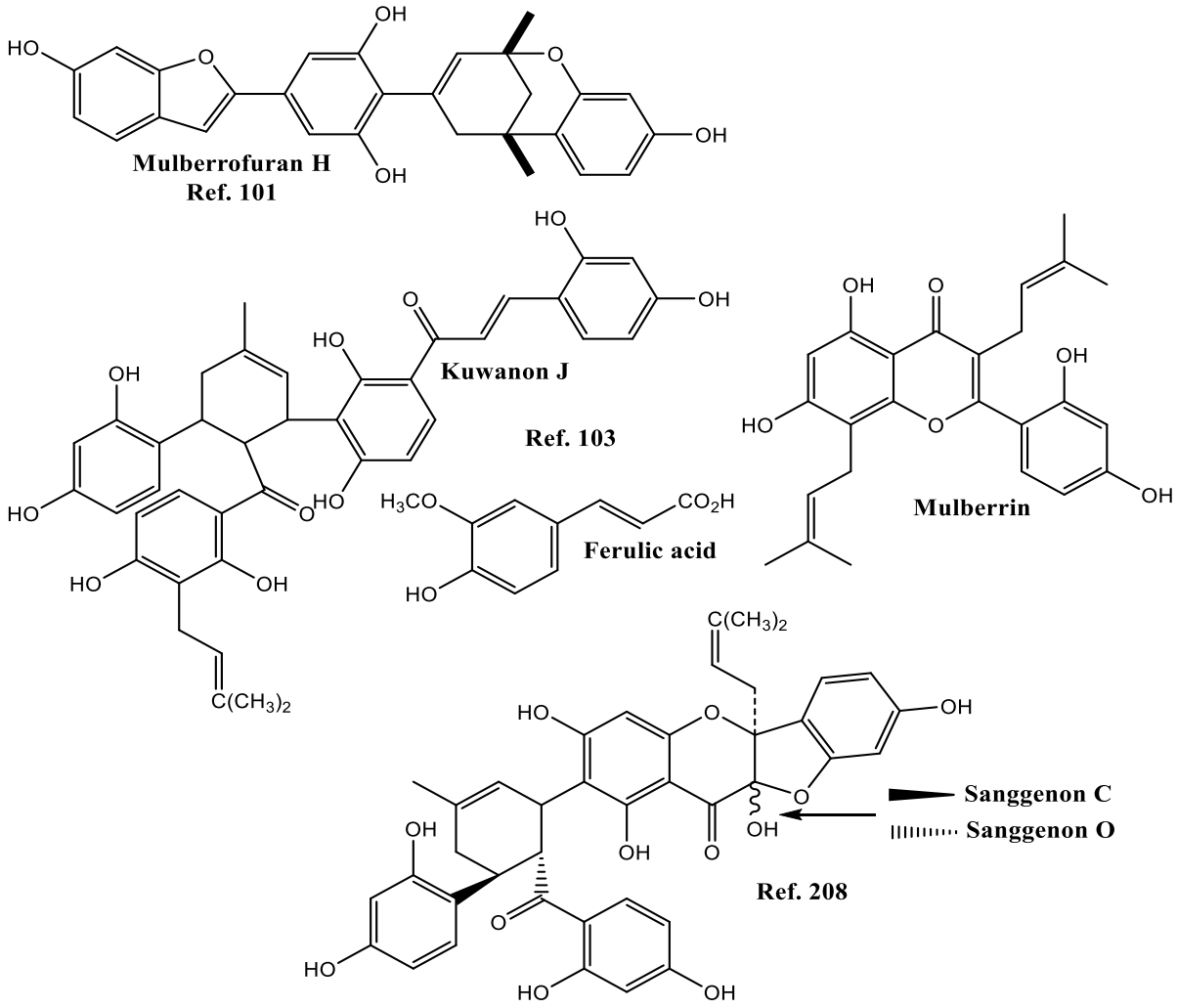

Figure 2H: Natural products isolated from *Morus alba.*

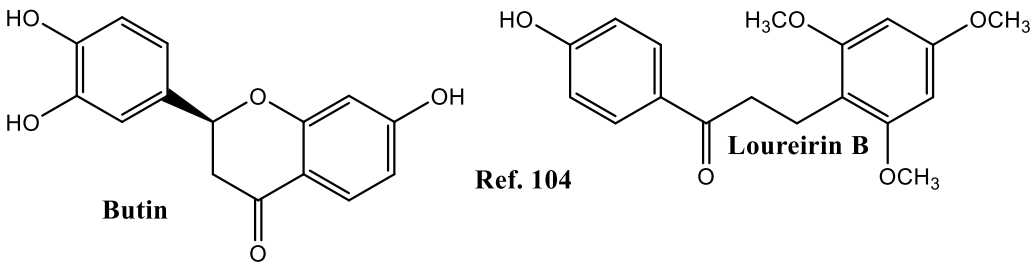

Figure 3: Natural products isolated from *Morus atropurpurea.*

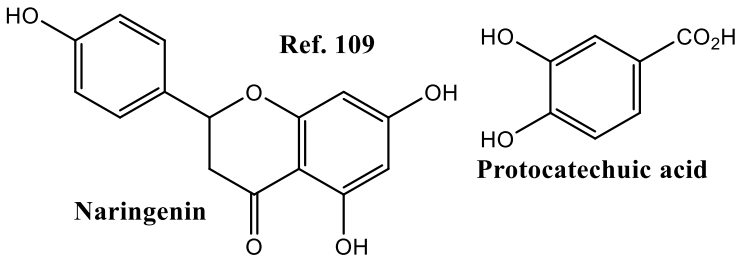

Figure 4: Natural products isolated from *Morus australis.*

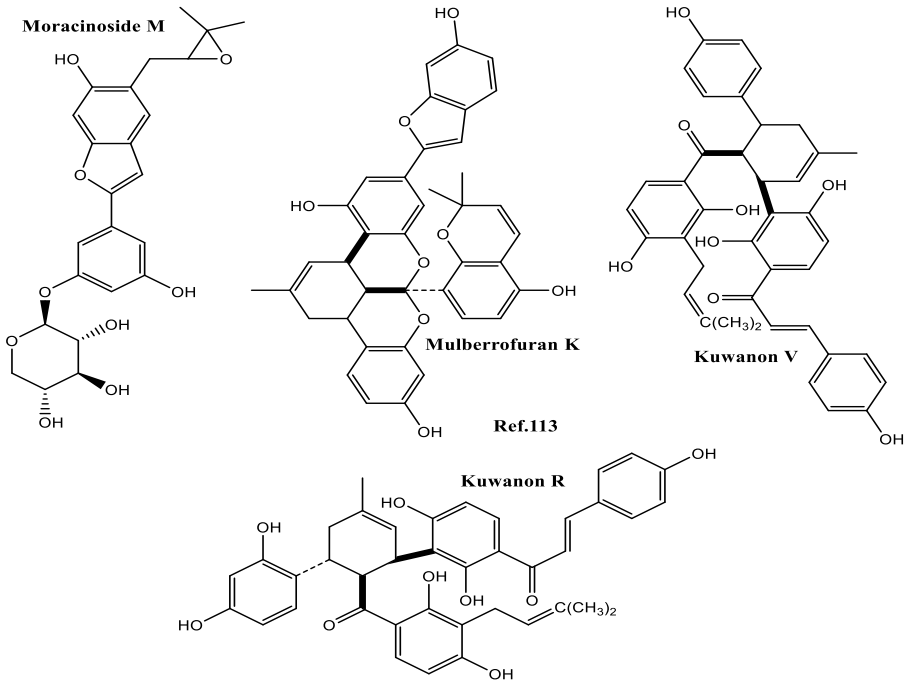

Figure 5: Natural products isolated from *Morus bombycis.*

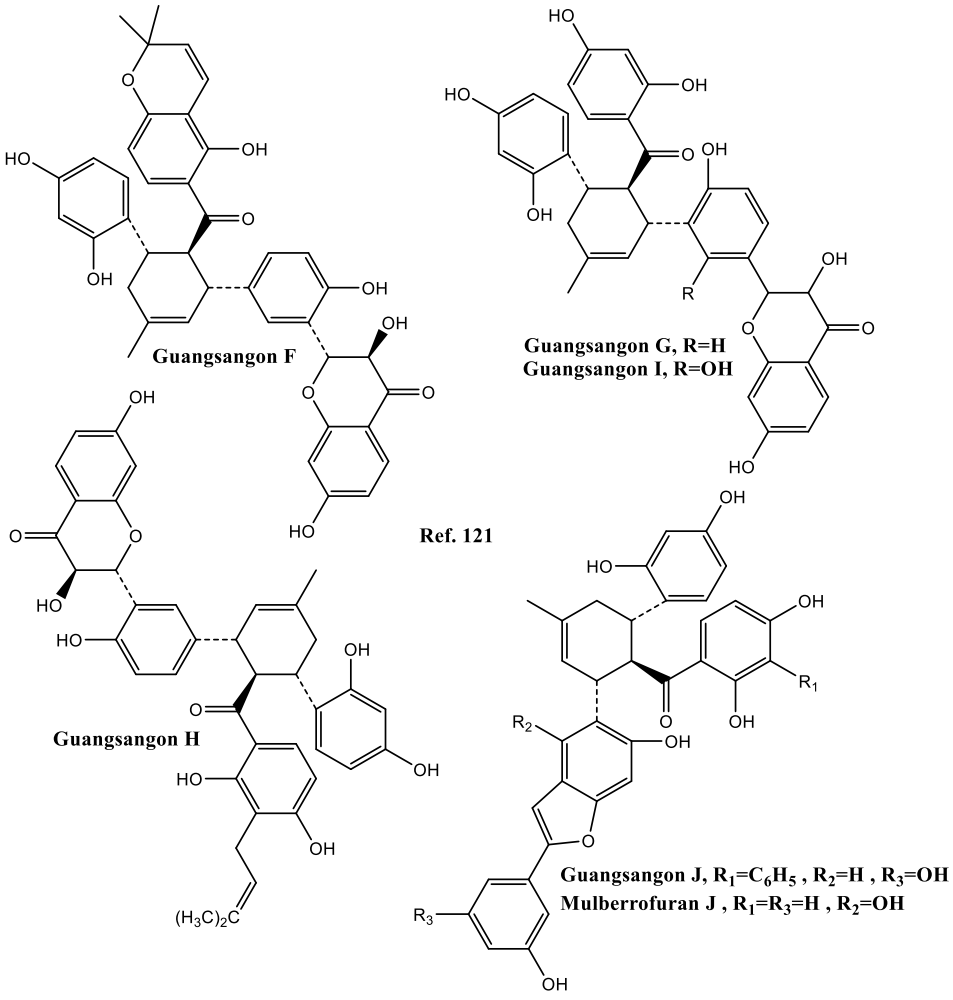

Figure 6A: Natural products isolated from *Morus macroura.*

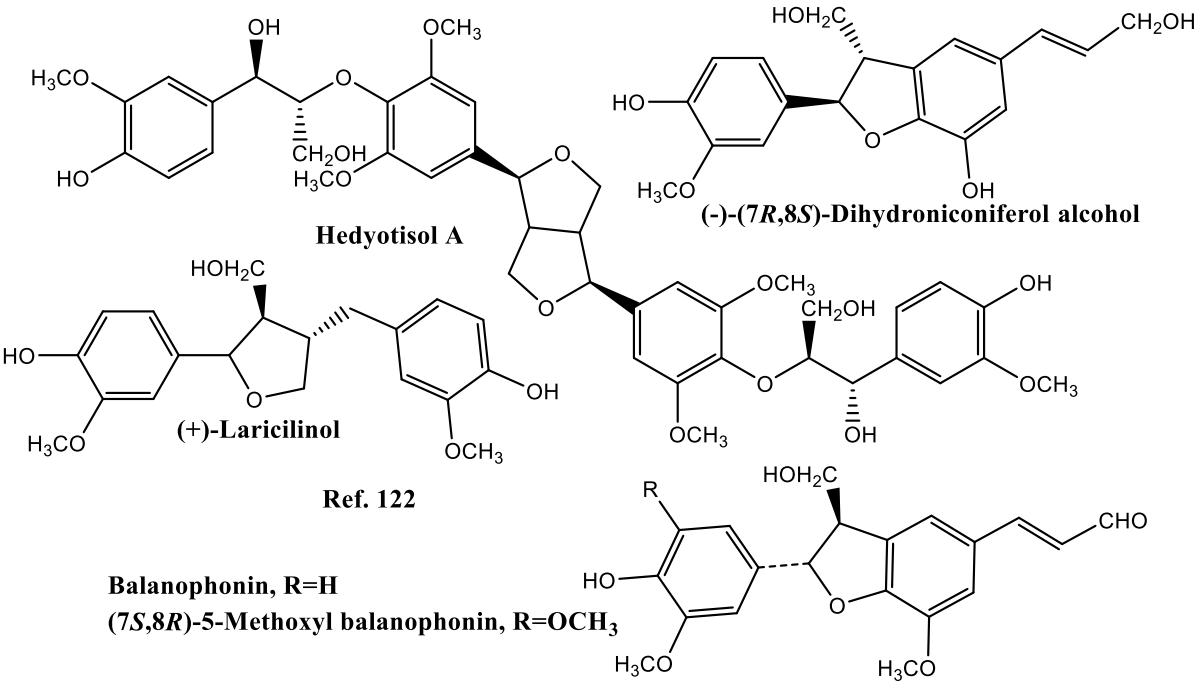

Figure 6B: Natural products isolated from *Morus macroura.*

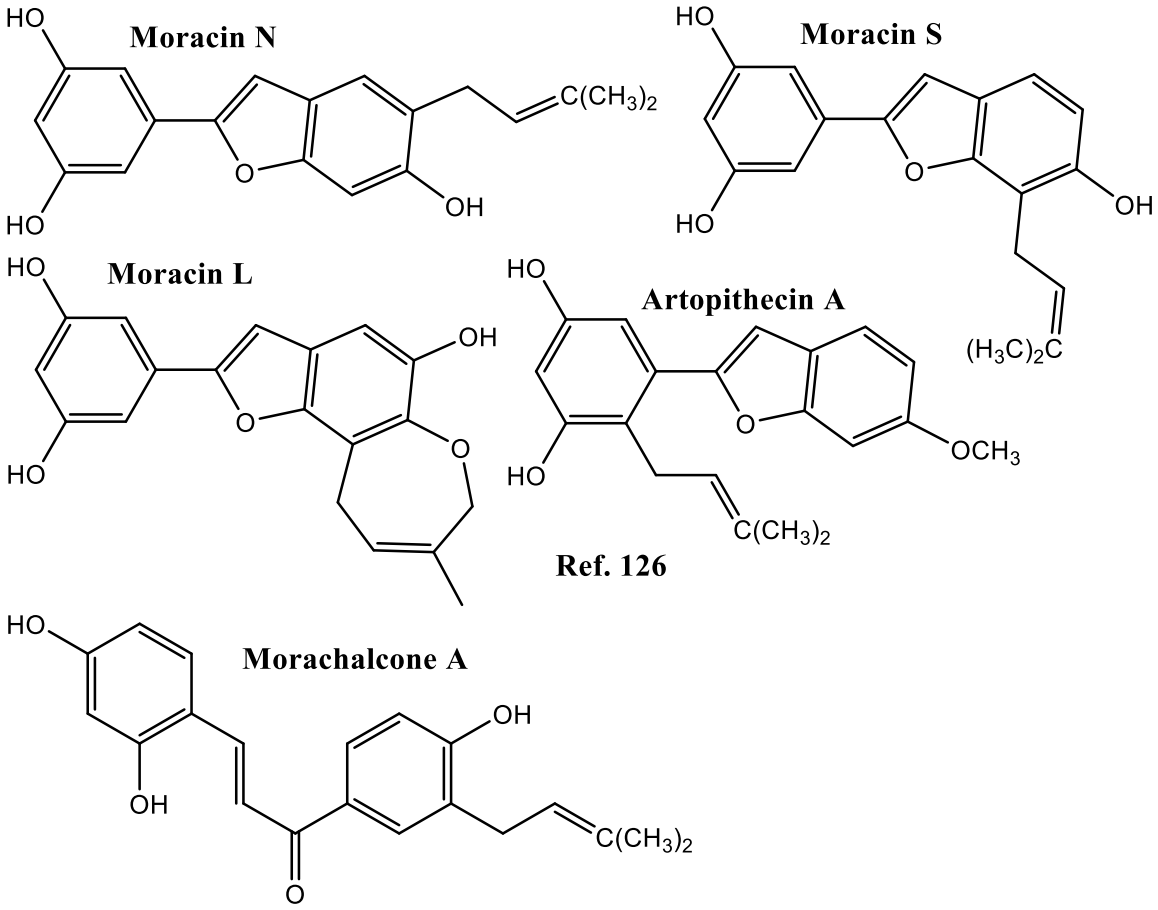

Figure 7: Natural products isolated from *Morus mesozygia.*

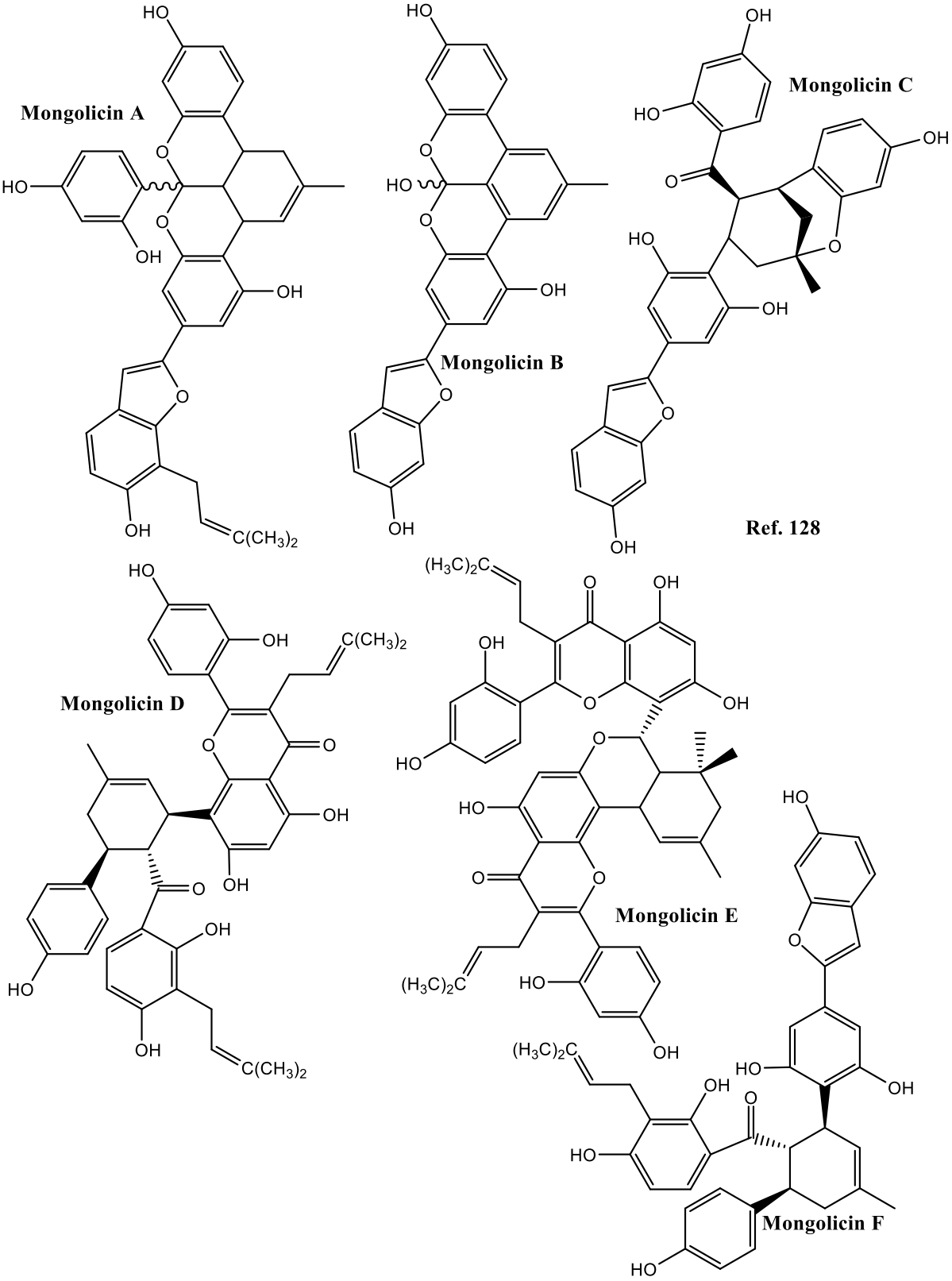

Figure 8A: Natural products isolated from *Morus mongolica.*

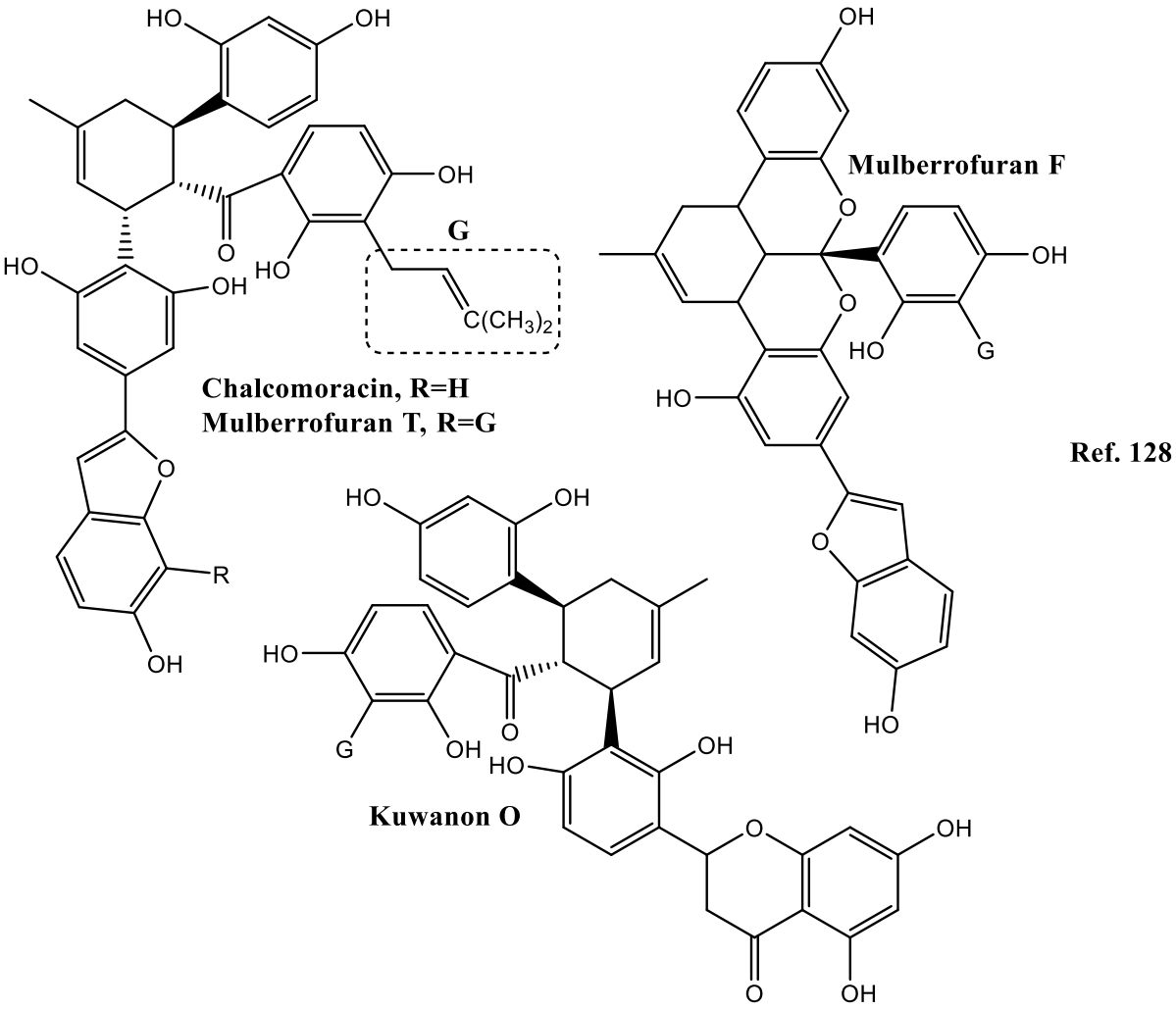

Figure 8B: Natural products isolated from *Morus mongolica.*

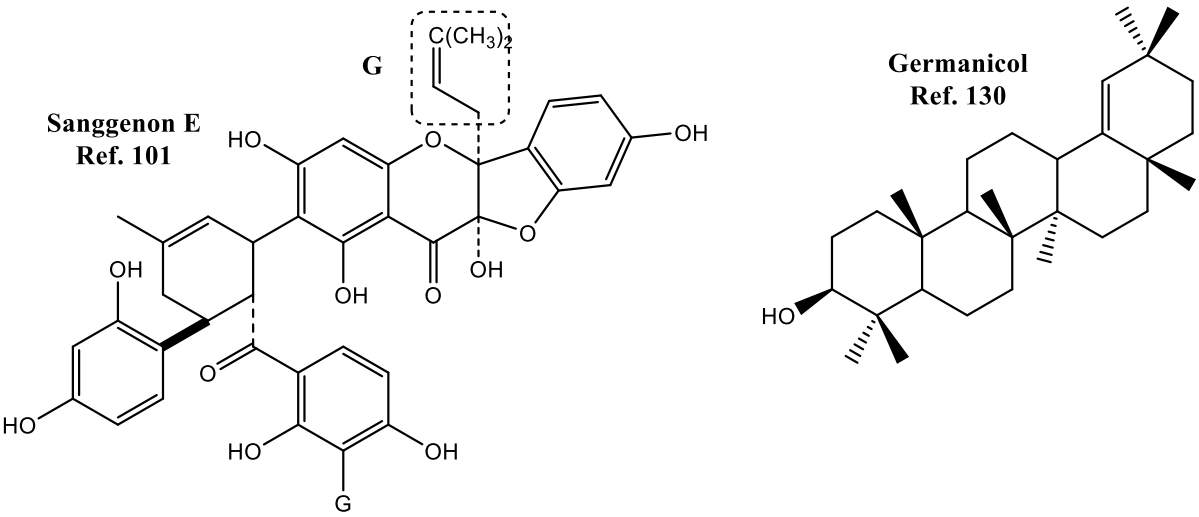

Figure 9: Natural products isolated from *Morus nigra.*

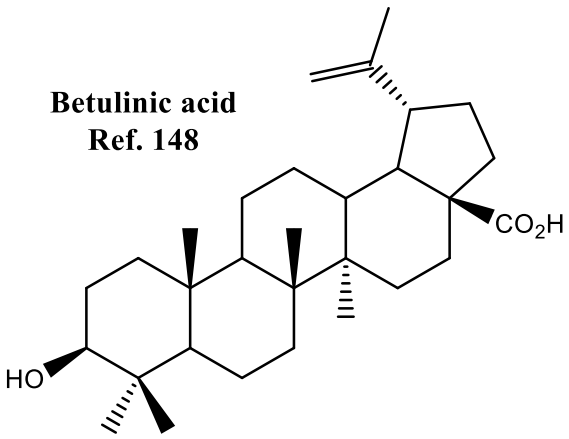

Figure 10: Natural products isolated from *rotundiloba* (hybrid with *M. alba*).

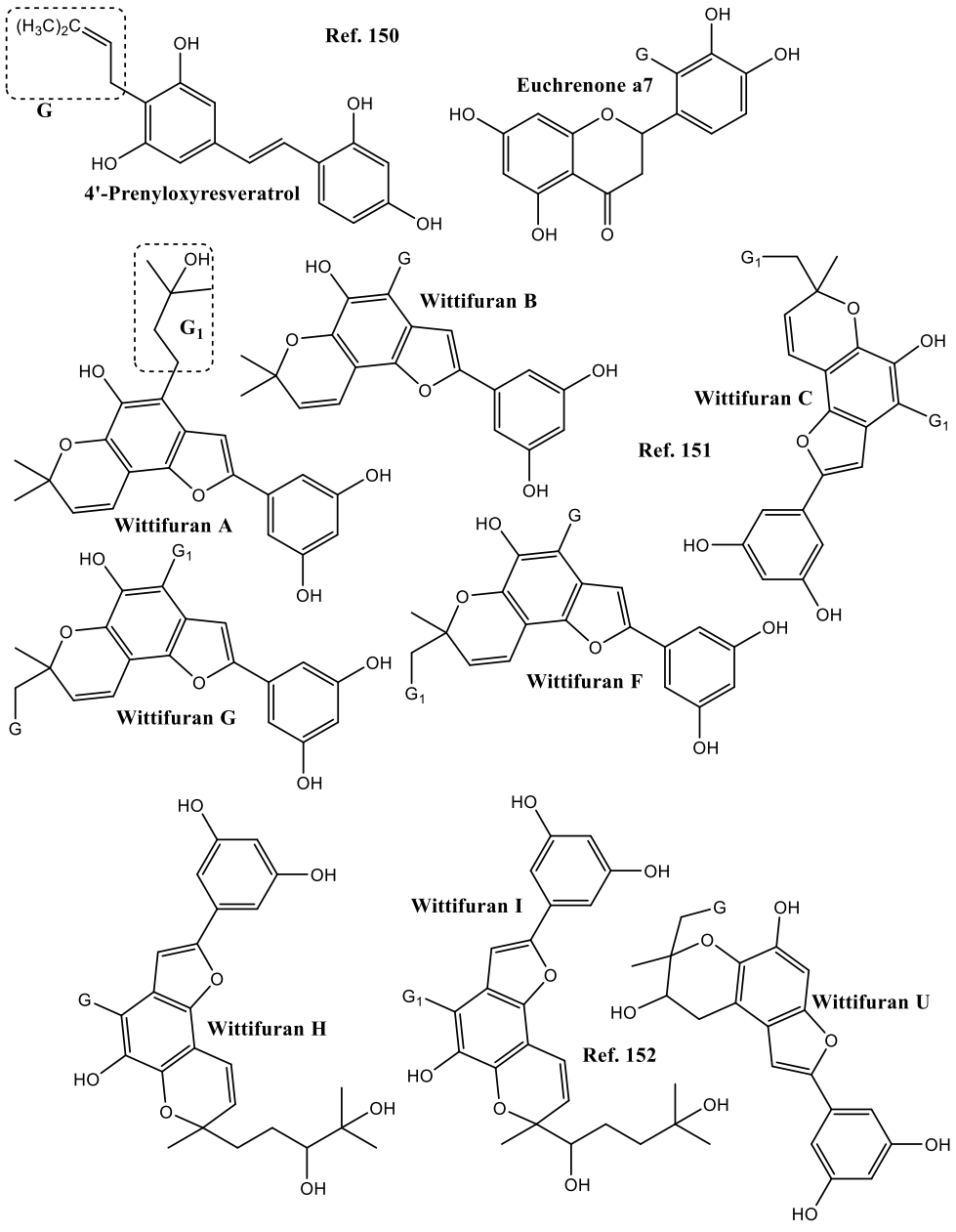

Figure 11: Natural products isolated from *Morus wittiorum*.

3. DISCUSSION

A great number of review articles about the genus *Morus* was published so far, and they are being published continuously. Some of them are highly informative and comprehensive, and the review articles of S. Dhiman ahc.[155] and M.K. Veenita ahc.[156] are highly selected examples. Expectedly (see **Table 1**) most of these review articles focus on *Morus alba*, and the article of P. Porasar ahc is a representative example.[157] To the best of our literature search, no review articles were published about the anti-inflammatory activity on the whole genus of *Morus*. The only review article that we found was published by I. Indawati and I. Kintoko.[158] This article has a severe lack of comprehensiveness: it is a mini-medium size, it focuses on two species, it practically focuses on *M. alba*, it cites a very small number of studies, it presents a very small number of natural products and it does not present any of their structures.

In **Table 1**, it was written "no reported anti-inflammatory activity of this species" since we found no articles that link these species with this activity. However, some published research articles about these species are of special interest to the topic of this review article. For example, Sanggenon A, which possess proven anti-inflammatory activity,[70] was isolated also from *Morus cathayana* by T. Fukal ahc.[159]

Another and more notable case is *Morus papyrifera*, which also was indicated in **Table 1** as "no reported anti-inflammatory activity of this species". S. Micheal ahc isolated Immunoglobulin E from the pollen of this species, and they link its presence to the allergenic properties of this plant.[160] This natural product induces inflammation.[161] In a later publication, P-C. Wu ahc reported the allergic activity of the pollen of this plant.[162] without linking it to natural products, keeping in mind the taxonomical debate, whether *Broussonetia papyrifera* is or is not *Morus papyrifera*.[163] Despite all this, aerial parts alkaloid extract of this plant had significant analgesic activity tested with three methods, including "acetic acid-induced writhing is a well-recommended model to assess the analgesic proprieties of drugs having analgesic and anti-inflammatory activity".[164]

Many of the cited articles in **Table 1** linked between the anti-inflammatory activity and single compounds isolated from *Morus* species. In this context, S. Yadav ahc[13] pointed the anti-inflammatory activity of natural products in *Morus*. When discussing these compounds, it is important to mention that the focus of our review article is on natural products isolated mainly from *Morus* plants. But these species contain also many other anti-inflammatory

active compounds, some are very powerful, found in many other plants, such as Epicatechin, Gallic acid, Vanillic acid and Quercetin. A good example of the link between single natural product isolated from *Morus alba* and anti-inflammatory activity was published by Y. Kavitha and A. Geetha[33] Roots methanolic extract had protective effect against Ethanol and Cerulein-induced model of pancreatitis in rats. HPLC analysis of the extract resulted significant amount of Cudraflavone B (**Figure 2A**). These results are consistent with earlier studies like J. Hošek ahc that isolated this compound from the same source.[165]

Due to the importance of the anti-inflammatory activity of single natural product in drug development, we highlighted this activity in **Table 2**. More articles are cited about anti-inflammatory activity of single compounds that were mentioned in **Table 1**.

Table 2: Selected Additional Published Articles about the Anti-inflammatory Activity of Single Compounds Mentioned in Table 1

Natural Product	Author/s	Method/s, Reference
Chlorogenic acid (**Figure 2G**)	M.D. dos Santos ahc	Carrageenan-induced paw edema in rats[166]
	A. Bisht ahc	Increasing Curcumin activity in LPS-induced TPH-1 microphages.[167]
	Y. Lee ahc	Reduction of pro-inflammatory biomarkers in STZ-induced diabetic rats.[168]
	G. La Rosa ahc	Reversed the stimulation of M03-13 cells with TNFα.[169]
	Q-q. Li ahc	Encapsulated, against DSS-induced colitis in rats.[170]
	J. Huang ahc	Review article.[171]
Cryptochlorogenic acid (**Figure 2G**)	X-L. Zhao ahc X. Ma ahc	Ameliorates LPS-induced inflammation in RAW 264.7 cells.[172,173]
Kuwanon C (**Figure 2C**)	W. Ko ahc	Ameliorates LPS-induced inflammation in RAW 264.7 cells.[174]
Kuwanon G (**Figure 2A**)	S.E. Jin ahc	Isolated from *Morus alba*, attenuates 5-LOX-activated MC/9 mast cells.[175]
Moracin M (**Figure 2D**)	F. Guo ahc	Inhibits LPS-induced inflammation in nucleus pulposus cells.[176]
Morin (**Figure 2A**)	C. Dhanasekar ahc	Suppresses Monosodium urate-induced inflammation in RAW 264.7 cells.[177]
	Y. Zhou ahc	Ameliorated atherosclerosis in ApoE−/−mice. *In vitro* studies are also presented.[178]
	Y. Qu ahc	Against IL-1β-induced human osteoarthritis chondrocytes.[179]
	L. Wu ahc	Attenuates oleic acid-induced inflammation and lipid accumulation in HepG2 cells.[180]
	S. Khamchai ahc	Anti-inflammation of brain blood barrier (ischemia) in rats.[181]

	D.G. Hong ahc	Alleviated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD in mice.[182]
	T. Jayakumar ac	Suppressed LPS-induced inflammation in RAW 264.7 cells.[183]
	N. Alla ahc	Attenuated cerebral ischemia in rats.[184]
	V. Prashanth ahc	Alleviated high fat diet-induced inflammation in mice.[185]
	S. Sales ahc	Suppressed heat killed bacteria-induced inflammation in H400 cells.[186]
	P. Arjsri ahc	Suppressed LPS-induced inflammation in A549 and H1299 cells.[187]
	S.A. Rajput ahc	Review articles.[188,189]
Morusin (**Figure 2A**)	S.E. Jin ahc	Isolated from *Morus alba*, attenuates 5-LOX-activated MC/9 mast cells.[175]
	C. Chen ahc	Mechanistic study of the inhibition of *Mycoplasma pneumonia* in mice.[190]
	Y. Jia ahc	Ameliorates IL-1β-induced chondrocyte inflammation and osteoarthritis.[191]
	C. Yang ahc	Protected ruminal epithelial cells against LPS-induced inflammation.[192]
	A. Panek-Krzysko, M. Stompor-Goracy H.N. Azzam ahc	Review articles.[193,194]
Mulberrin (**Figure 2H**)	P. Xia ahc	Reduces spinal cord injury-induced inflammation. Mechanism presented.[195]
	P. Ye ahc	Attenuated the expression of inflammatory cytokines in Doxorubicin-Induced cardiotoxicity in mice.[196]
	C. Ge ahc	Ameliorated inflammation caused by CCl_4-induced liver injury in mice.[197]
	S. Li ahc	Against inflammation caused by Triclocarban-induced liver injury in grass carp[198]
Mulberroside A (**Figure 2D**)	R. Lu ahc	Alleviated inflammation caused by osteoarthritis in mice and in cells isolated from them (more discussion after this table).[199]
	B. Shi ahc	Ameliorated inflammation caused by CCl_4-induced liver injury in mice.[200]
	T. Xu ahc	Mitigates inflammation in intervertebral disc degeneration in rats[201]
	M. Wang ahc	Review article[202]
Neochlorogenic acid (**Figure 2G**)	S.Y. Park ahc	Suppressed LPS-induced inflammation in RAW 264.7 cells.[203]
	S-C. Cheng ahc	Ameliorated inflammation of Ovalbumin-induced mouse model.[204]
	I-N. Tsai ahc	Inhibited inflammatory biomarkers in MES-13 diabetic mouse cells.[205]
Sanggenon C (**Figure 2H**)	Y. Gu ahc	Suppresses hypoxia-induced inflammation in cardiomyocytes.[206]
	Y. Zhao, J. Xu	Alleviated inflammation inreversible middle

		cerebral artery occlusion in rats.[207]
Umbelliferone (**Figure 2A**)	M-O. Sim ahc	Mitigated inflammation in chronic alcohol-fed rats.[209]
	V. Kumar ahc	(β-D-galactopyranoside) was active against complete Freund adjuvant-induced inflammation in rats.[210]
	R. Muthu ahc	Alleviated 1,2-dimethylhydrazine-induced rat colon tumorigenesis inflammation.[211]
	J-Y. Lim ahc	Suppresses inflammation caused by 2,4-dinitrochlorobenzene and house dust mite extract in mice.[212]
	S-B. Kim ahc	(6-Formyl) had anti-inflammatory activity in LPS-activated RAW 264.7 cells[213]
	L. Ouyang ahc	Was active against complete Freund adjuvant-induced inflammation in rats.[214]
	D.K. Lal ahc	Nanocomposite with MoS_2 was active against carrageenan-induced paw edema in rats.[215]
	P.N. Silva ahc	Was active against carrageenan-induced paw edema in mice.[216]
	A.I. Algefare, M.A. Alfwuaires	Ameliorates acrylamide-induced brain inflammatory damage.[217]
	A. Kornicka ahc Z. Lin ahc	Review articles[218,219]

S. Nattapong and L. Omboon reported “new source of whitening agent from a Thai Mulberry plant”, and they link the anti-inflammatory activity to Betulinic acid (**Figure 10**).[148] Scanning relevant literature reveals the fact that anti-inflammatory activity is key property of this compound, that was published in large number of articles. The works of K-S. Kim ahc,[220] Z. Ou ahc,[221] P. Hu and C. Zhu[222] and L. Zhu ahc[223] are just representative examples. The number of publications about the anti-inflammatory activity of Betulinic acid is large enough to be summarized and discussed as review articles: A. Chaudhary ahc,[224] and J.F. Oliveira-Costa[225]

Some of the natural products in **Table 2** (and others in this review article) such as Mulberroside A, have very high importance in nutrition, food supplements and drug development. For this reason, they were extensively studied and published. M. Mei ahc published the pharmacokinetics of bacterial conversion of Mulberroside A to Oxyresveratrol (**Figure 12**), another natural product with very high importance.[226]

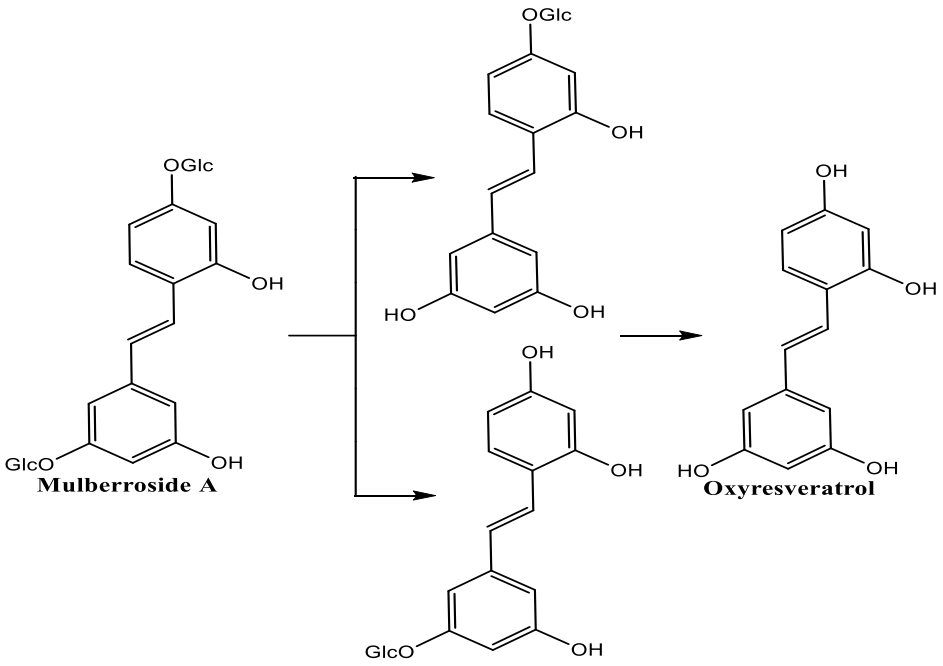

Figure 12: Bacterial Conversion of Mulberroside A to Oxyresveratrol.[226]

For the mentioned above reasons, several investigations were conducted to enhance the biological production of Mulberroside A: J. Komaikul ahc from cell suspension and root culture of *Morus alba*.[227] and C. Inyai ahc from *Morus alba* root culture by precursor feeding and co-elicitation.[228]

Finally, while finalizing our current review article, A. Bhati ahc published a review article titled "Anti-inflammatory and antioxidant mechanisms of *Morus* species: Part-specific insights from traditional Chinese medicine"[229] This a medium size review article with very helpful schemes. But it has clear weaknesses: it presents a small number of active natural products; it cites a small number of anti-inflammatory activity studies and it presents many other activities that makes the anti-inflammatory activity part relatively small. For these reasons, our review article is the most comprehensive so far.

4. CONCLUSIONS

1) *Morus* trees products possess wide range of medicinal properties-activities, including anti-inflammatory.

2) While some species were extensively studied and published, others were very limitedly published or not at all.

3) Based on the second conclusion, it is very important to conduct comprehensive research of the unstudied species.

4) *Morus* trees contain medicinally active components that can be excellent starting materials for drug development.

5) Some of these natural products are partially studied so far for medicinal activities. This also needs further research.

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