

**Isolation of phenolic compounds from the root bark of  
*Morus nigra***

Summary of Ph.D. Thesis

**Zoofishan Zoofishan**

Department of Pharmacognosy  
University of Szeged

Szeged  
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University of Szeged  
Graduate School of Pharmaceutical Sciences  
Program of Pharmacognosy  
Head: Prof. Judit Hohmann DSc.

**Department of Pharmacognosy**

**Supervisor:**

**Attila Hunyadi, Ph.D.**

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**Final Exam Committee:**

**Head:** Prof. Imre Máthé DSc.

**Members:** Ágnes Kéry PhD., István Zupkó PhD.

**Reviewer Committee:**

**Head:** Prof. György Dombi C.Sc.

**Reviewers:** Prof. Gabor Janicsak C.Sc., Prof. Gábor Vasas DSc.

**Members:** Rita Ambrus Ph.D, Zolt Szakonyi Ph.D.,

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## INTRODUCTION

Black mulberry is valued not only for its nutritional qualities and flavor but also for its use in traditional medicine. The roots of various *Morus* plants have a remarkable variety of phenolics including flavonoids, stilbenes, 2-arylbenzofurans, and a variety of Diels–Alder adducts. According to many comparative studies, *M. nigra* (black mulberry) is an at least similarly rich source of phenolic compounds as *M. alba* (white) but is much less studied even though it had also been naturalized in *Europe* centuries ago.

Prenylated phenolics are an outstanding subclass of naturally occurring phenolic compounds with relatively narrow distribution according to phytochemical literature. The Prenyl, isoprenyl, or 3-methyl-2-buten-1-yl is a terpenoid side chain present frequently on one or more specific positions of the phenolic skeleton via carbon or oxygen atom or both. Consequently, the combination of prenyl group with a phenolic backbone has provided a series of new interesting biological activities as it is evident from many isolated bioactive phenolics.

The root bark of *Morus nigra* contains a remarkable variety of prenylflavonoids isolated in the last several years with a chemical diversity due to their variability in hydroxylation/ methoxylation pattern and many of these substituents open possibilities to further cyclization. It has been acknowledged as a rich source of bioactive benzofuran derivatives and stilbenes, among which the 2-arylbenzofurans are commonly substituted by prenyl and geranyl groups.

*Morus nigra* has been used as a traditional medicine for numerous conditions (e.g. lung heat, cough, toothache, edema, and oliguria). Drugs of *M. nigra* are well-known ingredients for many preparations in Ayurveda and traditional Chinese medicines. In several cases, the folk medicinal use of the plants was confirmed by pharmacological investigations. Phenolic compounds isolated from the roots of

*Morus nigra* exert many different activities, including antitumor, anti-inflammatory, antioxidant, anti-nociceptive, hepatoprotective, and neuroprotective effects.

## **AIMS OF THE STUDY**

*Morus nigra* is a particularly rich source of phenolic compounds whose structural diversity and versatile pharmacology make them of high value when searching for new bioactive compounds. Further, semi-synthetic modifications of such compounds provide ample opportunities to obtain new compounds with improved physicochemical and biological properties.

In order to achieve the aims, the main tasks of the presented study were:

**Isolation of phenolic compounds from *Morus nigra* root bark.** It was our aim to use a strategic combination of different separation techniques to isolate and purify biologically active compounds from the root bark of *M. nigra*. This includes the identification of phenolic compounds already known from other *Morus* species, thereby extending the available knowledge on the plant part.

**Preparation of semi-synthetic derivatives.** To increase the chemical diversity of the compounds obtained, we aimed to perform a set of structural modifications on the selected compound. It was our aim to perform oxidation by using different oxidizing agents, and hydrogenation.

**Biological evaluation of the isolated and synthesized compounds.** The biological studies on the isolated compounds were planned in scientific cooperation. It was our objective to study the prepared compounds for antispasmodic activity, effect on the sarco/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase (SERCA), and/or for their antitumor potential.

**Evaluation of structure-activity relationship.** In connection with the bioactivity testing, it was our aim to evaluate the possible role of different structural elements in the bioactivity of the compounds.

## **MATERIALS AND METHODS**

The plant material used in this work is the roots of *Morus nigra* (Black Mulberry) growing in Hungary and collected in December 2013, from the farm nearby Ásotthalom, Hungary.

### **Isolation of pure compounds**

The compounds were isolated by multistep chromatographic methods, including open-column chromatography (OCC), Flash chromatography (FC), and high-performance liquid chromatography (HPLC). Normal (NP) or reversed-phase polyamide, silica, and cell lite were applied as stationary phases.

The isolated compounds were characterized and their structures were elucidated by NMR spectroscopy.

### **Preparation of semi-synthetic analogs**

Morusin was the major compound isolated from the *M. nigra* roots, therefore it was further subjected to semi-synthetic modifications.

#### **Oxidation of Morusin**

##### **Hypervalent iodine oxidation.**

To a stirred solution of morusin (20mg) and PIDA (Diacetoxyiodo)benzene (20.4mg) in anhydrous acetonitrile (10ml). The reaction mixture was stirred at 60% temperature for over seven hours and then extracted over silica using (2 x 15 ml) ethyl acetate. The residue was reduced under a rota evaporator to give (35mg) of the fraction. The purification was done with the help of RP-HPLC (ii) using a C18 column with an isocratic elution of Acetonitrile: water (7:3 v/v). The purified resultant was named as compound **12**

#### **Synthesis of hydrogenated morusin**

50.0 mg of Morusin (**1**) was dissolved in anhydrous ethyl acetate 10ml, 10 mg of Pd/C was added, and the solution was stirred under a hydrogen atmosphere for

4 hours. later, the catalyst was removed through washing with (5 X 20ml) ethyl acetate. The residue was dried under rota evaporator and purification was done through a C18 column.

### **Pharmacological Investigations**

For the antispasmodic screening, the Sprague-Dawley rats were applied for isolated organ bath studies. The distal ileum and tracheal rings were isolated and regular contractions were recorded. The concentrations eliciting the half of the maximum effect ( $EC_{50}$ ) and the maximum effects ( $E_{max}$ ) were calculated.

The SERCA activity was determined by the NADH-coupled enzyme assay in the fast-twitch skeletal muscle of a New Zealand female rabbit. A docking study was performed using the modeling program (Molecular Operating Environment). Spartan software was used to built and optimize the structure of compounds.

The antiproliferative properties of the prepared compounds were determined on the human breast cancer cell lines including estrogen receptor-positive (MCF-7) and triple-negative breast cancer (MDA-MB-231).

Functional efflux pump inhibition by morusin, its oxidized metabolite-mixtures, and the isolated neocyclomorusin was evaluated using rhodamine 123, a fluorescent dye, whose retention inside the cells was evaluated by flow cytometry.

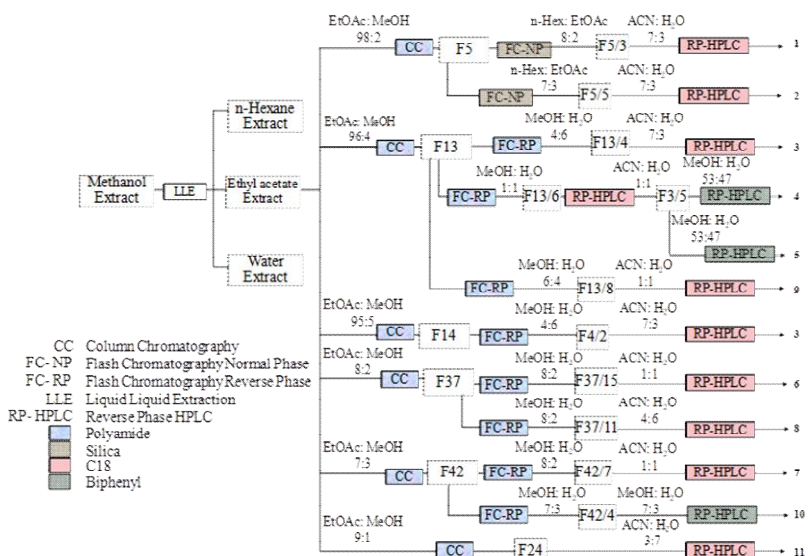
## **RESULTS AND DISCUSSION**

### **Isolation of pure compounds from the *morus nigra* roots**

The methanol extract of *Morus nigra* root bark was found to contain a wide variety of constituents. Solvent- solvent partition between n-hexane, ethyl acetate, and water (1:1 v/v), respectively, allowed the purification of phenolic compounds from both the highly lipophilic (n-hexane layer) and the highly polar (aqueous layer) contaminants. Further, the extract was fractionated by using large-scale classical column chromatography on polyamide. With a stepwise gradient elution (ethyl acetate –methanol; 98:2, 96:4, 95:5, 9:1,



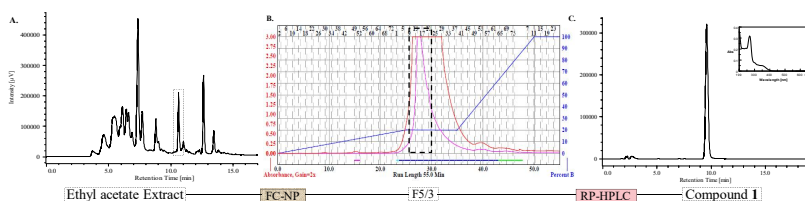
85:15, 8:5, 8:2, 7:5, 1:1 v/v), the phenolic compounds could be successfully eluted from the SP. The column matrix was eluted with pure methanol to wash the column thoroughly. Based on TLC, fifty-six fractions mostly containing phenolic compounds could be separated. After preliminary purification, an extensive chromatographic purification was performed using a strategic combination of methods of various selectivity; the outline of the separation procedure is shown in Fig. 1.



**Figure 1.** The chromatographic procedure followed for the isolation of phenolic compounds.

The purification process led to the isolation of 11 compounds (**Figure 1**). 1 Morusin, 2 Kuwanon U, 3 Kuwanon E, 4 Moracin P, 5 Moracin O, 6 Albanol A, 7 Albanol B, 8 oxyresviratol, 9 Kuwanon C, 10 Mulberofuran C, 11 Moracin M. For the purification of major compounds (compound 1), the NP flash chromatographic method was used on silica. At this point of separation, a high amount of Morusin (1) could be isolated using n-hexane – ethyl acetate (8:2, v/v) at a fair, ca. 94% purity. A further RP-HPLC purification step was

performed using acetonitrile – water (7:3, v/v) to reach 97% purity. Fig. 2 shows the RP-HPLC fingerprint of the pre-purified extract (before its separation on column 1), the flash chromatogram of column fraction F5, and the HPLC chromatogram of the isolated pure compound.



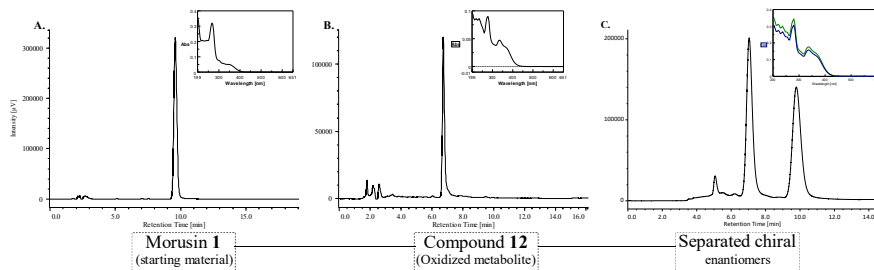
**Figure 2.** RP-HPLC chromatogram of the extract, **b.** flash chromatogram of first major fraction and **c.** the isolated Morusin

### Preparation of oxidative metabolite of Morusin

The reactions were performed by using different oxidizing agents (Cu, potassium permanganate, [bis(trifluoroacetoxy)iodo]benzene (PIFA) and (diacetoxyiodo)benzene (PIDA). For hypervalent iodine reagents, PIFA was found to be more aggressive therefore PIDA was favored, as it produces less complex mixtures. Subsequent small-scale experiments were performed using different reagents, and the amount of morusin was monitored by TLC throughout the oxidation process. Even though the major product could be observed by TLC, some of the mixtures were highly complex with a number of side products. Moreover, a significant amount of unchanged morusin also remained. An increased temperature was found preferable. Finally, with PIFA as an oxidizing agent and purification via RP-HPLC one major compound: Neocyclomorusin (**12**) was obtained in a 25% yield.

Since the ring closure of morusin to neocyclomorusin involves the formation of a new chiral center, compound **12** was also evaluated by chiral HPLC that confirmed it as a racemic mixture (Fig. 3C). After optimizing the chromatographic conditions for the chiral separation (Amylose-1 column, 80% Cyclohexane in 20% isopropanol over 30 min, 1 mL/min), semi-preparative separation of the enantiomers **12a** and **12b** was also

performed and 2 mg of each enantiomer was obtained. However, since the enantiopure compounds showed similar bioactivity, we did not proceed with further studies to assign their absolute configuration.



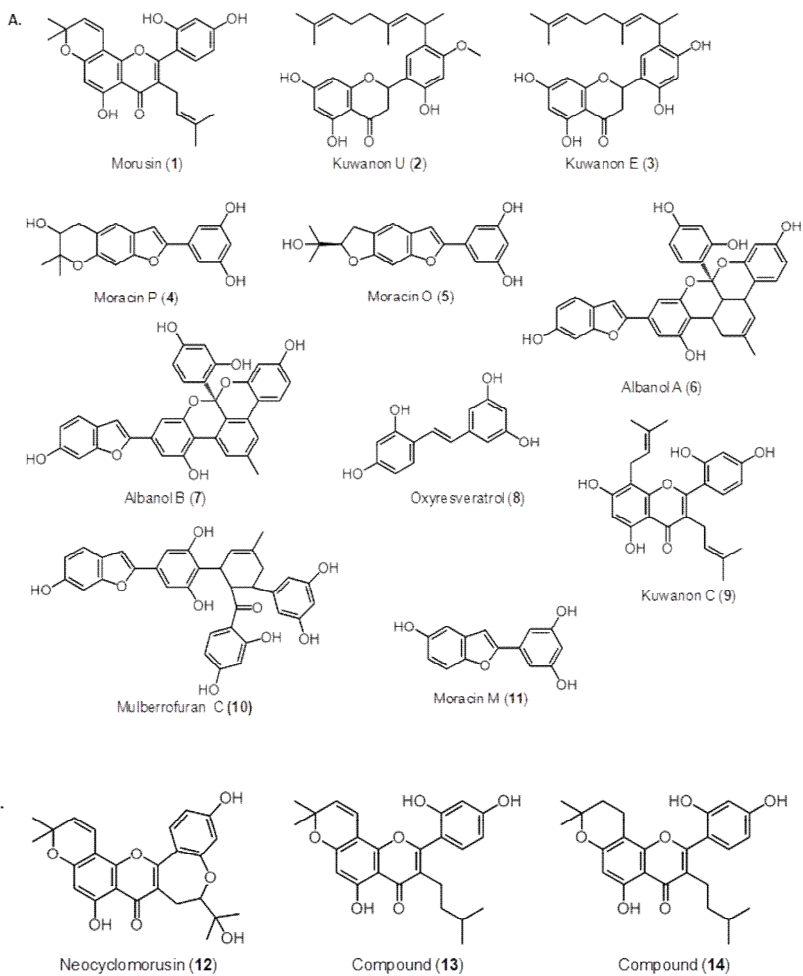
**Figure 3.** HPLC chromatogram of a major oxidative metabolite of morusin.

### Preparation of hydrogenated Morusin

Catalytic hydrogenation of morusin was straightforward by using Pd/C and hydrogen gas atmosphere (H<sub>2</sub> balloon), was applied. The geometry of a molecule plays an important part since contact with the catalyst is so important. The first site for hydrogenation appeared in the prenyl ring of the morusin, whereas later on both the D ring and the prenyl moiety were hydrogenated. The reaction resulted in isolated yields of 20% and 40% for the mono and dihydrogenated products respectively.

### STRUCTURE DETERMINATION OF THE ISOLATED COMPOUNDS

Eleven phenolic compounds were isolated and three compounds were synthesized in this study. The structure elucidation of compounds **1-3** and **6-12** was straightforward through comparing their <sup>1</sup>H and <sup>13</sup>C NMR data with published literature values, and they were identified as morusin (yellow solid; **1**), kuwanon U (yellow solid; **2**), kuwanon E (yellow solid; **3**), albanol A (yellow solid; **6**), albanol B (dark brown solid; **7**), oxyresviratrol (dark brown solid; **8**), Kuwanon C (yellow solid; **9**), mulberrofuran C (white solid; **10**), moracin M (red solid; **11**), and neocyclomorusin (yellow solid; **12**).



**Figure 4.** Structures of the compounds prepared in this study.

**A.** Compounds 1-11 were isolated from the root bark of *Morus nigra*. **B.** Compounds 12-14 were semi-synthesized from morusin (1).

## BIOACTIVITY OF THE ISOLATED COMPOUNDS

### ANTISPASMODIC ACTIVITY

In preliminary screening, morusin (**1**), kuwanon E (**3**), moracin P (**4**), and albanol A (**6**) had shown only non-significant relaxing activity (or no action) on the rat ileal contractions. Additionally, except for albanol A, these compounds elicited a very moderate tracheal tone reducing effects that were much lower than that of papaverine. However, a remarkable activity was found for kuwanon U (**2**), moracin O (**5**), and albanol B (**7**) on both experimental models, therefore these compounds were further studied for their efficacy. Furthermore, each of these compounds (**2**, **5**, and **7**) showed a tendency for higher  $E_{max}$  value on ileal contraction than that of papaverine, and in the case of moracin O (**5**), it was statistically significant. Regarding the compounds' activity on the tracheal tone, similar results were obtained.

**Table 1.** Smooth muscle relaxant activity of compounds **2**, **5**, and **7** on isolated rat ileum and trachea.  $EC_{50}$  and  $E_{max}$  values on the ileal contractions and tracheal tone are presented.

Compound	Ileal contractions		Tracheal tone	
	$EC_{50} \pm SEM$ ( $\mu M$ )	$E_{max} \pm SEM$ (%)	$EC_{50} \pm SEM$ ( $\mu M$ )	$E_{max}$ (mg $\pm SEM$ )
kuwanon U ( <b>2</b> )	0.13 $\pm$ 0.04	70.5 $\pm$ 6.1	0.033 $\pm$ 0.05	247.8 $\pm$ 9.9
moracin O ( <b>5</b> )	1.1 $\pm$ 0.43	85.3 $\pm$ 4.4*	0.062 $\pm$ 0.01	309.5 $\pm$ 17.7*
albanol B ( <b>7</b> )	1.3 $\pm$ 0.98	83.2 $\pm$ 3.9	0.100 $\pm$ 0.05	254.9 $\pm$ 19.3
papaverine	0.44 $\pm$ 0.15	63.6 $\pm$ 6.3	0.074 $\pm$ 0.03	233.7 $\pm$ 15.4

Papaverine was used as a positive control of both experimental models. \*:  $p < 0.05$  as compared to the effect of papaverine by means of one-way ANOVA followed by Tukey's posthoc test.

To the best of our knowledge, this is the first report of the smooth muscle relaxant activity of compounds **2**, **5**, and **7**. The bioactivity of these compounds is of high potential therapeutic interest: kuwanon U (**2**) and albanol B (**7**) are equipotent with the opium alkaloid antispasmodic drug papaverine, and moracin O (**5**) exerted an even stronger effect than that.

## SERCA ACTIVITY

Compounds **1-7** were also tested for their activity on skeletal muscle sarco/endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase 1 (SERCA1). Among the tested compounds, albanol A (**6**) and B (**7**) were identified as the most potent inhibitors of SERCA1 activity, whereas Moracin P (**4**) and O (**5**) were inactive. Binding of compounds **1-7** to SERCA1 (PDB ID: 3w5c), and the binding energies showed a good correlation to the compounds' activity as SERCA1 inhibitors. Further, based on similarities in SERCA isoforms, the compounds' effect was also tested on the viability of INS-1E rat insulinoma cells, a common model of pancreatic beta cells that express SERCA2b; the results are shown in Table 2.

**Table 2.** Interaction of phenolic compounds with SERCA1 and their effect on the viability of INS-1E beta-cells.

Compound	MOE-E Score	Log P	Serca ATPase Activity		Beta Cell Viability	
			IC <sub>50</sub> (μM)	R Square	IC <sub>50</sub> (μM)	R Square
Albanol A ( <b>6</b> )	-12.62	5.79	18.88	0.95	18.22	0.93
Albanol B ( <b>7</b> )	-10.85	5.77	24.56	0.96	18.17	0.85
Kuwanon E ( <b>3</b> )	-10.03	5.24	29.43	0.97	28.65	0.96
Kuwanon U ( <b>2</b> )	-9.43	5.64	35.62	0.91	64.82	0.95
Morusin ( <b>1</b> )	-8.84	5.23	43.57	0.97	28.65	0.91
Moracin P ( <b>4</b> )	-6.45	2.49	-	-	108.6	0.94
Moracin O ( <b>5</b> )	-5.21	2.83	-	-	111.4	0.96

SERCA1 binding site to the compounds was also analyzed experimentally using the fluorescence marker (FITC) to measure alterations in the cytosolic region, and using intrinsic tryptophan fluorescence to analyze alterations in the transmembrane region of the protein. Kuwanon E, U, Morusin, moracin P, and O showed binding in or near the ATP binding site as suggested by significantly decreased FITC fluorescence. Interaction in the transmembrane region was also observed for these compounds except for Moracin P and R, whereas no conformational change in either region of SERCA1 was seen with albanol A and B. These latter two compounds were also the strongest inhibitors with intensive binding energy to SERCA1, therefore their binding mode was studied by in silico docking more in

detail. Briefly, it was found that albanol A immerses in the luminal gate at the Ca<sup>2+</sup> release site in the ER lumen. Kuwanon U, as a compound representing the ability to induce conformational changes in both the cytosolic and transmembrane regions of SERCA1, was also analyzed in greater detail by molecular docking. This study confirmed the binding of kuwanon U in both regions, and suggested the assumption that its SERCA1 inhibition is due to the occupation of residues Phe487 and Gln202 in the cytosolic region which may prevent ATP binding.

### Anti-tumor activity

The *in vitro* anticancer activity of morusin (**1**) and its semi-synthetic derivatives (**12-14**) was evaluated against two human breast cancer cell lines: MCF-7 (estrogen receptor-positive; ER+) and MDA-MB-231 (triple-negative; TNBC) by MTT assay after a 72 h treatment, results are shown in Table 3

**Table 3.** Antiproliferative activities of morusin (**1**) and its oxidized (**12**) and reduced (**13-14**) derivatives against human breast cancer cell lines. C.I.: 95% confidence interval, n=6 from two biological replicates (n=3 each).

	IC <sub>50</sub> [95% confidence interval] (μM)	
	MCF-7	MDA-MB-231
<b>1</b>	29.0 [27.4 - 30.7]	~ 48.6
<b>12</b>	> 100	> 100
<b>13</b>	20.8 [19.4 - 22.4]	30.6 [28.0 - 33.4]
<b>14</b>	15.5 [14.0 - 17.1]	24.7 [23.2 - 26.2]

According to our results, the oxidative ring closure between the B-ring of morusin and the 3-prenyl group results in a complete loss of the antiproliferative activity against the two tested breast cancer cell lines. In contrast with this, saturation of the olefins in one or both prenyl functions leads to an increased activity, and particularly in the case of tetrahydromorusin (**14**), this increase is nearly two-fold on both cell lines. It is also noteworthy, that cell line specificity of morusin (i.e. ca. 1.5-times stronger effect on MCF-7 than on MDA-MB-231) did not change upon hydrogenation.

### Antitumor and efflux pump inhibitory activity on an MDR cancer cell model

Based on the ABCB1 inhibitory activity of the oxidized morusin mixtures, neocyclomorusin (**12**), isolated from such a mixture, was tested on a mouse lymphoma cancer cell line pair, i.e. L5178 cells and their MDR counterpart L5178B1 expressing the human ABCB1 transporter as mentioned in table 4.

**Table 4.** Antiproliferative, cytotoxic, and ABCB1-inhibitory activities of morusin (**1**) and the two enantiomers of neocyclomorusin (**12a** and **12b**) on L5178 cells and multi-drug resistant L5178<sub>B1</sub> cells. C.I.: 95% confidence interval, n=4. For ABCB1 inhibition, 20nM tariquidar was used as positive control (inh. 87.5%). Cross-resistance:  $CR = IC_{50}^{MDR} / IC_{50}^{PAR}$

	Antiproliferative			Cytotoxicity			ABCB1 inhibition (%)	
	IC <sub>50</sub> [95% C.I.] (μM)		CR	IC <sub>50</sub> [95% C.I.] (μM)		CR	2 μM	20 μM
	L5178	L5178B1		L5178	L5178B1			
1.	14.5 [12.6-16.6]	25.8 [22.7-29.2]	1.8	46.7 [40.4-53.9]	48.4 [44.4-52.6]	1.0	0	8.6
12 a.	6.5 [5.5 - 7.8]	27.9 [4.1 - 32.2]	4.3	27.2 [24.6 - 30.2]	47.2 [38.8 - 57.5]	1.0	0	55.3
12 b.	8.5 [7.3 - 9.9]	21.8 [19.9 - 23.8]	2.6	20.2 [17.5 - 23.3]	35.8 [31.3 - 41.0]	1.8	0	48.8

The two neocyclomorusin enantiomers (12a and 12b) exerted similar activities, indicating that the configuration of the newly formed stereocenter has little if any impact on their bioactivity. Further, they were more potent than their parent compound morusin against the L5178 lymphoma cells, both in terms of antiproliferative and cytotoxic activity. This was not the case on the MDR cells, in other words, the ABCB1 expressing MDR cells showed an increased cross-resistance to 12a and 12b as compared with that to morusin. This was particularly true in the antiproliferative assay's experimental setup. Further, as expected from the oxidized mixtures' activity, neocyclomorusin exerted a stronger effect as an inhibitor of ABCB1-mediated efflux, with a ca. 50% inhibition at 20μM.



## Summary

Results of our study, aiming to prepare and evaluate bioactive phenolic compounds from *Morus nigra* root bark, can briefly be summarized according to the following.

**Natural product isolation.** The crude methanol extract was fractionated by a multistep separation procedure, including OCC, TLC, NP-FC, RP-FC, and RP-HPLC. The structures of the isolated compounds were elucidated using the spectroscopic method (NMR). Eleven phenolic compounds were isolated, and two of them, moracin P (**4**) and albanol B (**7**) were isolated for the first time from the roots of the plant. The isolated compounds belong to different groups namely *geranyl and prenyl flavonoids, Diels-Alder type adducts, stilbene, and aryl benzofurans*. Contradictory literature data on the moracin derivatives' NMR signal assignments, allowing misidentification, were clarified through the unambiguous assignment of compound **4** as moracin P and compound **5** as moracin O.

**Semi-synthesis. Morusin (1)** was subjected to semi-synthetic transformations. A simple and effective method for the preparation of racemic neocyclomorusin (**12**) from morusin through a hypervalent iodine-catalyzed oxidation was developed, and the enantiomers **12a** and **12b** were also isolated by chiral HPLC to allow their bioactivity testing in enantiopure form. Further, two hydrogenated analogs of morusin were produced through catalytic hydrogenation.

**Bioactivity testing – antispasmodic activity.** Pharmacological analysis of the isolated compounds revealed that several compounds possess significant antispasmodic activity *ex vivo*. Kuwanon U (**2**), moracin O (**5**), and albanol B (**7**) exerted remarkably strong activity on rat ileal and tracheal smooth muscles. Kuwanon U and albanol B were found to be equipotent with the approved drug papaverine, whereas moracin O was proved to be superior to papaverine in both models.

**Bioactivity testing – activity on SERCA.** Several compounds were found efficient inhibitors of SERCA1, and their activity correlated with their *in silico* docking scores and their effect on SERCA2b expression, and with their ability to modulate viability and apoptosis in a pancreatic beta-cell model.

**Bioactivity testing – antitumor activity.** Both neocyclomorusin enantiomers showed stronger activity as ABCB1 inhibitors as compared with morusin, while, at the same time, over-expressed ABCB1 conferred stronger cross-resistance to them. Saturation of one or both non-aromatic olefins present in morusin led to a significantly increased cytotoxic activity on two breast cancer cell lines, and tetrahydromorusin was ca. twice as active in this regard than morusin.

Our results demonstrate that *Morus nigra* roots constitute a rich source of biologically active phenolic metabolites with great structural diversity. The investigated compounds, as well as the semi-synthetic analogs, can be regarded as promising starting materials in the search for new pharmaceutical discoveries in the future. In consequence, the elucidation of their mechanism of action can be a good basis for developing new effective agents against several pharmacological conditions.



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#### THE THESIS IS BASED ON THE FOLLOWING PUBLICATIONS:

1. **Zoofishan Z**; Kúsz N; Csorba A; Tóth G; Hajagos-Tóth J; Kothencz A; Hunyadi A. Antispasmodic Activity of Prenylated Phenolic Compounds from the Root Bark of *Morus nigra*. *Molecules* 2019; 24(13), 2497. If: 3.267\*
2. Heger V., Benesova B., Viskupicova J., Majekova M., **Zoofishan Z.**, Hunyadi A., Horakova L.. Phenolic compounds from *Morus nigra* regulate viability and apoptosis of pancreatic  $\beta$ -cells possibly via SERCA activity. *ACS Medicinal Chemistry Letters* 2020; 11(5), 1006-1013  
If: 3.750\*

#### OTHER PUBLICATIONS:

3. **Zoofishan, Z.**, Hohmann, J., & Hunyadi, A. (2018). Phenolic antioxidants of *Morus nigra* roots, and antitumor potential of morusin. *Phytochemistry Reviews* 2018; 17(5), 1031-1045.  
If: 4.400\*

#### PRESENTATIONS HELD IN THE SAME THEME OF THE THESIS:

1. **Zoofishan Z**; Kusz N; Toth G; Hajagos-toth J; Kothenez A; Gaspar R; Hunyadi A Antispasmodic phenolic compounds isolated from *morus nigra* root bark In: 67<sup>th</sup> International congress and annual meeting of the society for medicinal plant and natural product research (GA) 2019 Innsbruck, Austria
2. Heger V ; Rahnasto-Rilla M ; Viskupicova J ; **Zoofishan Z**; Hunyadi A; Horakova L ; Mastihubova M ; Lahtela-Kakkonen M Modulation of SIRT6 deactylation activity by flavonoid derivatives. In: Challenging organic syntheses inspired by nature- from natural products chemistry to drug discovery: Cost Action CM1407, 5<sup>th</sup> MC/WG Meeting 2018

3. Heger V; Viskupicova J; **Zoofishan Z**; Hunyadi A; Horakova L.  
Sarco/endoplasmic Ca<sup>2+</sup> -ATPase (SERCA) and pancreatic beta cells modified by prenylated phenolic compounds from *Morus nigra*  
In: COST ACTION CM1407 4th Meeting: CHALLENGING ORGANIC SYNTHESSES INSPIRED BY NATURE – FROM NATURAL PRODUCTS CHEMISTRY TO DRUG DISCOVERY.  
Lisszabon, Portugal, 2017.
4. **Zoofishan Z**; Kúsz N; Zomborszki Zoltán P; Csorba A; Hunyadi A.  
In vitro angiotensin-converting enzyme inhibition by phenolic compounds isolated from the root bark of *Morus nigra*  
PLANTA MEDICA INTERNATIONAL OPEN 4:(S 01) p. Mo-PO-94. (2017) GA 2017.  
Basel, Svájc: 2017.
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