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UHPLC-Q-Orbitrap HRMS-Based Metabolite Profiling of Mulberry (*Morus alba* L.) Leaves Collected from Wajo Regency, South Sulawesi

Lukman[1,*], Tuti H Zainal[2], Besse Hardianti[3]
[1]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Health Science, Almarisah Madani University, Makassar, South Sulawesi, Indonesia
[2]Department of Pharmaceutical and Technological Pharmacy, Faculty of Health Science, Almarisah Madani University, Makassar, South Sulawesi, Indonesia
[3]Department of Pharmacology and Clinical Pharmacy, Almarisah Madani University, Makassar, South Sulawesi, Indonesia

*Email: lukman_m01@yahoo.co.id; lukman@univeral.ac.id

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ABSTRACT

*Mulberry (*Morus alba *L.) leaves contain diverse secondary metabolites whose composition may vary according to geographical and environmental conditions. This study aimed to characterize the metabolite profile of* M. alba *leaves collected from Wajo Regency, South Sulawesi, Indonesia, using ultra-high-performance liquid chromatography coupled with Q-Orbitrap high-resolution mass spectrometry (UHPLC-Q-Orbitrap HRMS). The leaves were extracted by maceration with 96% ethanol, followed by qualitative phytochemical screening and UHPLC-Q-Orbitrap HRMS analysis. Phytochemical screening indicated the presence of alkaloids, phenolics, flavonoids, saponins, and terpenoids. The ethanol extract yielded 34 tentatively annotated metabolites, demonstrating a chemically diverse profile. Five constituents showed prominent relative peak areas, including 1-[(3-carboxypropyl) amino]-1-deoxy-β-D-fructofuranose, (2S)-4-methyl-2-({[(3S,4S,5R)-2,3,4-trihydroxy-5-(hydroxymethyl) tetrahydro-2-furanyl] methyl} amino) pentanoic acid, chlorogenic acid, isoquercetin, and quercitrin. Among the detected metabolites, quercitrin and isoquercetin exhibited the largest relative peak areas, accounting for 27.65% and 11.67% of the detected chromatographic signal, respectively. Flavonoids constituted a prominent group among the tentatively annotated metabolites, consistent with the qualitative phytochemical screening results. These findings provide a comprehensive preliminary chemical profile of* M. alba *leaves cultivated in Wajo Regency and establish baseline information for further phytochemical characterization, quantitative analysis, and investigation of their potential biological activities.*

Keywords: Morus alba *L., Leaves, Location, Metabolite profiling, UHPLC-Q-Orbitrap HRMS*

INTRODUCTION

Through photosynthesis and subsequent biochemical pathways, plants synthesize a diverse array of primary and secondary metabolites. While primary metabolites are produced abundantly for fundamental growth and development, secondary metabolites are synthesized in smaller quantities (Baslam *et al.*, 2020). These secondary compounds play crucial roles in plant defense mechanisms against herbivores and pathogens, as well as in their adaptation to environmental stress. Major classes of plant secondary metabolites include polyphenols, flavonoids, alkaloids, saponins, terpenes, and steroids, which possess significant pharmacological properties beneficial to human health (Twaij & Hasan, 2022; Yeshi *et al.*, 2022).

Polyphenols and flavonoids are widely recognized for their antioxidant activities, particularly their ability to scavenge and stabilize free radicals. These compounds have also been reported to exhibit cytotoxic effects against cancer cells, as well as antihypertensive and antidiabetic activities (Dias *et al.*, 2021; Lukman *et al.*, 2021; Zeb, 2020). Alkaloids are also associated with various pharmacological effects, including regulating heart rhythm, enhancing cardiac function, and stabilizing blood pressure (Reddy *et al.*, 2020). In addition, terpenes and steroids have been documented to have a wide range of biological activities, including anti-plasmodial, antiviral, anti-inflammatory, antioxidant, anticancer, antiseptic, and diuretic properties (Dembitsky, 2023; Ge *et al.*, 2022; Masyita *et al.*, 2022). Saponins are known for their surfactant properties, particularly their ability to reduce water surface tension, which underlies their widespread use in detergent-related formulations (Rai *et al.*, 2021).

In addition, mulberry leaves (*Morus alba* L.), which are rich in flavonoids, have attracted considerable attention in cosmetic applications due to their skin-whitening potential through tyrosinase inhibition (Jeon & Choi, 2019). Traditionally, mulberry leaves have also been used as ingredients in cosmetic preparations for skin brightening and photoprotection. These leaves contain diverse bioactive constituents, including flavonoids, alkaloids, saponins, and terpenes, which contribute to their broad pharmacological potential. Previous studies have demonstrated that the ethanol extract of mulberry leaves collected from Kupang exhibited strong antioxidant activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals, with an IC_{50} value of 8.35 µg/mL (Megawati *et al.*, 2019). Similarly, mulberry leaves from Jember Regency showed antioxidant activity with an IC_{50} of

43.95 µg/mL (Jurian *et al.*, 2016), while an ethanol extract of mulberry leaves from Bogor City demonstrated an IC_{50} value of 50.34 µg/mL and, at a concentration of 500 µg/mL, achieved a sun protection factor (SPF) value of 66.65 (Faizatun & Asto, 2018).

Previous studies have reported variations in the biological activities of mulberry leaves, which may be linked to differences in the samples' geographical origin. Environmental conditions influence both the qualitative and quantitative composition of plant secondary metabolites. Among these, temperature and water availability are key factors affecting secondary metabolite accumulation. Plants growing closer to water sources may exhibit higher levels of secondary metabolite production, although this relationship can vary by species and environmental context (Yang *et al.*, 2018). In addition, Sasmita & Purba (2019) showed that cultivation site influenced the growth performance of mulberry plants. Mulberries cultivated in Cianjur Alam Sutra, West Java, showed a higher growth rate (95%) than those grown at the Forestry Plant Breeding Center in Bali (85%) and in plant nursery gardens in East Kalimantan (80%). Similarly, the stem diameter of mulberries grown in Cianjur Alam Sutra, West Java (80 cm), was greater than that of plants cultivated in Bali (67 cm) and East Kalimantan (58 cm). However, detailed characterization of the metabolite composition of mulberry leaves from this geographical area remains limited.

High-resolution mass spectrometry coupled with ultra-high-performance liquid chromatography provides a powerful analytical approach for comprehensive metabolite profiling of complex plant extracts. UHPLC enables efficient chromatographic separation, while Q-Orbitrap high-resolution mass spectrometry provides accurate mass measurements that facilitate molecular formula prediction and metabolite annotation. Despite the availability and potential value of mulberry cultivated in Wajo Regency, detailed UHPLC-Q-Orbitrap HRMS-based characterization of its leaf metabolite profile has not been reported. Therefore, the present study aimed to characterize the metabolite profile of the 96% ethanol extract of *M. alba* leaves collected from Wajo Regency, South Sulawesi, using UHPLC-Q-Orbitrap HRMS. The findings are expected to provide baseline chemical information for subsequent phytochemical characterization and investigations into the biological potential of locally cultivated mulberry.

MATERIALS AND METHODS

Plant material and sample preparation

Mulberry leaves were collected from plants cultivated in Walennae, Sabbangparu District, Wajo Regency, South Sulawesi, Indonesia, in June 2022. The leaves were sorted and washed under running water to remove adhering impurities, such as soil and sand. The cleaned samples were oven-dried at 40 °C for 2 days. After drying, the simplicia were re-sorted, pulverized, and passed through an 18-mesh sieve before extraction.

Extraction of mulberry leaves

The ethanol extract of mulberry leaves was prepared using a previously reported method (Lukman *et al.*, 2023). Briefly, 400 g of dried simplicia powder was macerated in 96% ethanol for 3 × 24 h. The powdered sample was first placed in a maceration vessel, wetted with solvent, and allowed to stand for 30 min. Additional solvent was then added until the material was fully immersed. The mixture was kept at room temperature, protected from direct sunlight, and stirred occasionally during maceration. After maceration, the filtrate was separated from the residue by filtration through filter paper. The residue was re-macerated twice under the same conditions. All filtrates were combined and concentrated using a rotary evaporator (Büchi) under reduced pressure to obtain a viscous extract, which was then further dried in a desiccator.

Phytochemical screening

Qualitative phytochemical screening of the 96% ethanol extract was conducted to determine the presence of major secondary metabolite classes. Alkaloids were tested with Mayer's and Dragendorff's reagents; phenolic compounds with the ferric chloride ($FeCl_3$) test; flavonoids with the magnesium–hydrochloric acid reaction; saponins with the foam test; and terpenoids with the Liebermann–Burchard reaction. The presence or absence of each metabolite class was determined based on the characteristic reaction observed for each test.

Preparation of sample for UHPLC-Q-Orbitrap HRMS analysis

Approximately 50 mg of the 96% ethanol extract was accurately weighed and dissolved in 50 mL of methanol. The solution was sonicated for 30 min to extract soluble constituents, then centrifuged to remove insoluble material. The supernatant was filtered through a 0.2-µm polytetrafluoroethylene (PTFE) membrane filter before UHPLC-Q-Orbitrap HRMS analysis.

UHPLC conditions

Chromatographic separation was performed on an Accucore™ C18 column (100 × 2.1 mm, 1.5 µm). The mobile phase

consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B). Gradient elution was programmed as follows: 0–1 min, 5% B; 1–25 min, linear increase from 5% to 95% B; 25–28 min, 95% B; 28–30 min, return to 5% B; and 30–35 min, re-equilibration at 5% B. The flow rate was 0.2 mL/min, and the column temperature was 30°C.

UHPLC-HRMS analysis

The injection volume was 5 µL, and the mass detection range was set to m/z 100–1500. We analyzed five independently prepared analytical solutions of the same ethanol extract to assess the consistency of the detected metabolite profile. We injected each sample into the UHPLC-HRMS system for analysis.

Data analysis

Chromatographic and mass spectral data from each sample were processed using Xcalibur software version 4.2. The software was used to evaluate retention times, select spectral peaks, predict molecular compositions, and compile a list of detected compounds based on their mass data.

RESULTS AND DISCUSSION

This study aimed to characterize the metabolite profile of mulberry leaves collected from Solo Jampu Village, Sabbangparu District, Wajo Regency, South Sulawesi. A total of 400.0 g of dried simplicia was macerated, yielding 16.096 g of dry ethanol extract (4.02% yield). The phytochemical screening results presented in Table 1 showed that the ethanol extract of mulberry leaves from Wajo Regency contained several major classes of secondary metabolites, including alkaloids, phenolics, flavonoids, saponins, and terpenoids. The detection of these compound groups indicates that the extract possesses substantial chemical diversity, which may contribute to its potential biological and pharmacological activities. These findings also provide preliminary evidence that mulberry leaves are a rich source of bioactive constituents.

Table 1 Phytochemical screening results of the ethanol extract of mulberry leaves collected from Wajo Regency

Phytochemical group Test or reagent	Observations	Expected result	Conclusion
Alkaloids			
Mayer Reagent	White precipitate		+
Dragendorf Reagents	Brown precipitate		+
Phenolic			
$FeCl_3$	Brown precipitate	Brown precipitate	+
Flavonoids			
HCl + Mg	Red coloration	Red coloration	+
Saponins			
Foam test	Persistent foam	Persistent foam	+

Terpenoids Lieberman-Burchard Reagent	Red coloration	Red coloration	+

The presence of phenolic and flavonoid compounds is particularly noteworthy, as these metabolites are widely recognized for their antioxidant properties and are often reported as major bioactive constituents in mulberry leaves. These compounds contribute to free radical scavenging activity and may also be associated with other biological effects, such as anti-inflammatory, antidiabetic, and cytoprotective activities. Therefore, the positive detection of phenolics and flavonoids in the present study is consistent with previous reports.

In addition, the presence of alkaloids, saponins, and terpenoids further supports the extract's bioactive potential. Alkaloids exhibit a wide range of pharmacological properties depending on their chemical structure, while saponins are associated with both surfactant characteristics and various biological activities. Terpenoids have also been widely reported to possess antioxidant, anti-inflammatory, and antimicrobial properties. Overall, the phytochemical screening results support the subsequent UHPLC-Q-Orbitrap HRMS analysis, which was conducted to provide a more detailed characterization of the metabolite profile of the mulberry leaf extract.

The mulberry leaf extract obtained by maceration was subsequently analyzed using UHPLC-Q-Orbitrap HRMS. This analytical technique was selected for its high sensitivity and selectivity in metabolite profiling (Nahar *et al.*, 2020). In addition, UHPLC-Q-Orbitrap HRMS separates ion mixtures based on mass-to-charge ratio (m/z), provides structural information through ion fragmentation patterns, requires only a small sample volume, and supports both qualitative and quantitative analysis (Rathod *et al.*, 2019).

In this study, the mass spectrometry system was ionized using electrospray ionization (ESI). In ESI, analyte molecules are dispersed from the capillary into charged droplets under a high electric field, facilitating ion formation before mass analysis. The generated ions were then detected and analyzed using the Orbitrap-based mass (Rathod *et al.*, 2019).

Figure 1 presents the chromatographic profile of the ethanol extract of mulberry leaves collected from Wajo Regency, while Table 2 summarizes the tentatively identified compounds. The chromatogram shows multiple well-resolved peaks across the retention time range, indicating a chemically diverse mixture of metabolites in the extract. The

variation in peak intensity further suggests differences in the relative abundance of the detected constituents. In particular, several prominent peaks in the chromatogram correspond to major compounds identified in the extract, indicating that certain metabolites were present at higher levels than others.

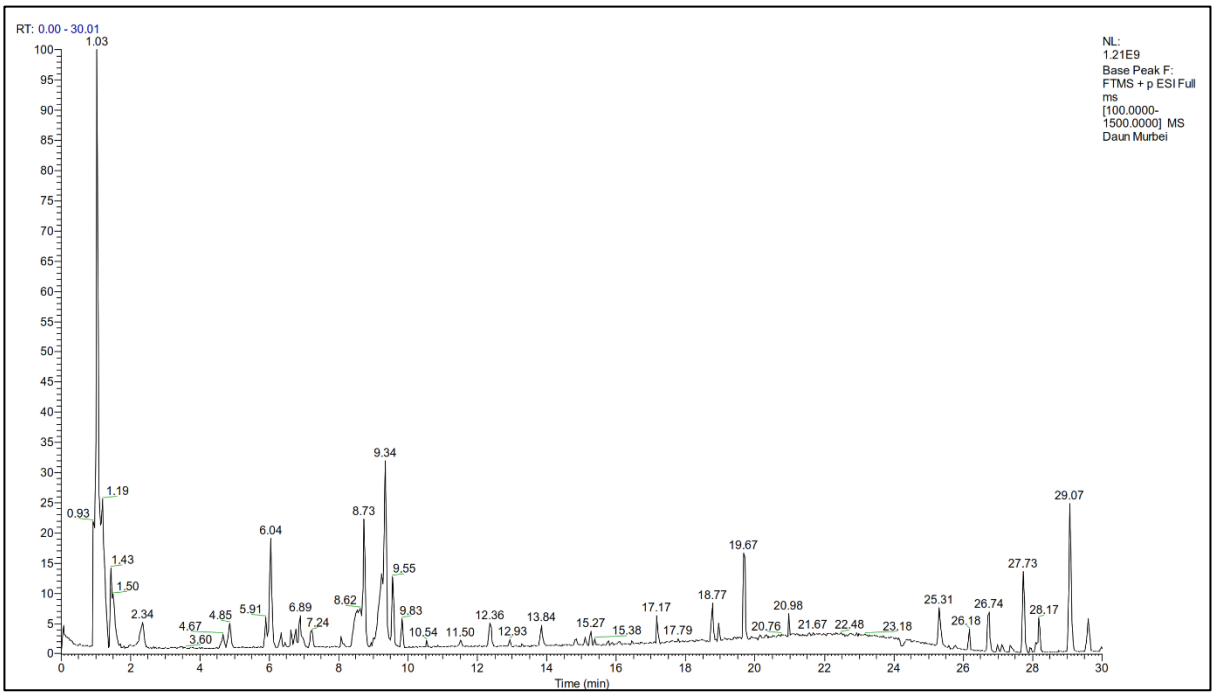


Figure 1 UHPLC-Q-Orbitrap HRMS chromatogram of the ethanol extract of mulberry leaves collected from Wajo Regency, South Sulawesi

Table 2 Tentatively identified metabolites in the ethanol extract of mulberry leaves from Wajo Regency using UHPLC-Q-Orbitrap HRMS

Retention time (min)	Compound name	Molecular formula	Molecular weight	Peak area (%)
1.07	1-[(3-Carboxypropyl)amino]-1-deoxy-beta-D-fructofuranosa	$C_{10}H_{19}NO_7$	265.11559	6.40
1.07	Linamarin	$C_{10}H_{17}NO_6$	247.10539	0.64
1.08	5'-O-beta-D-Glucosylpyridoxine	$C_{14}H_{21}NO_8$	331.12621	0.67
1.08	1-{[(3S,4S,5R)-2,3,4-trihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]methyl}-2-pyrrolidine carboxylic acid	$C_{11}H_{19}NO_7$	277.11586	0.47
1.09	Lotaustralin	$C_{11}H_{19}NO_6$	261.12099	0.64
1.09	(2S)-3-methyl-2-({[(3S,4S,5R)-2,3,4-trihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]methyl}amino)butanoic acid	$C_{11}H_{21}NO_7$	279.13118	3.79
1.15	N-Glicosyl-L-asparagine	$C_{10}H_{18}N_2O_8$	294.10594	1.27
1.50	(2S)-4-methyl-2-({[(3S,4S,5R)-2,3,4-trihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]methyl}amino)pentanoic acid	$C_{12}H_{23}NO_7$	293.14653	7.13
5.92	Rehmaionoside C	$C_{19}H_{32}O_8$	388.20912	0.48

Retention time (min)	Compound name	Molecular formula	Molecular weight	Peak area (%)
5.92	(−)-trans-methyl dihydrojasmonate	$C_{13}H_{22}O_3$	226.15665	0.51
6.06	4-[2-Amino-3-(beta-D-glucopiranosiloxy)phenyl]-4-oxobutanoic acid	$C_{16}H_{21}NO_9$	371.12074	0.58
6.06	Chlorogenic acid	$C_{16}H_{18}O_9$	354.09404	10.54
6.93	(4S)-4-hydroxy-3,5,5-trimethyl-4-[(1E)-3-{[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-il]oxy}but-1-en-1-il]cyclohek-2-en-1-on	$C_{19}H_{30}O_8$	386.19277	0.86
8.13	Rutin	$C_{27}H_{30}O_{16}$	610.15087	2.32
8.74	Quercetin	$C_{15}H_{10}O_7$	302.04173	1.70
8.74	Isoquercetin	$C_{21}H_{20}O_{12}$	464.09419	11.67
9.21	Yatein	$C_{22}H_{24}O_7$	400.15151	0.34
9.33	Kaempferol	$C_{15}H_{10}O_6$	286.04680	4.47
9.35	Quercitrin	$C_{21}H_{20}O_{11}$	448.09899	27.65
9.69	Luteolin 7-O-malonylglucoside	$C_{24}H_{22}O_{14}$	534.09911	1.78
11.51	Flazine	$C_{17}H_{12}N_2O_4$	308.07863	1.09
14.84	5-O-Methyl embelin	$C_{18}H_{28}O_4$	308.19786	0.98
15.12	Octinoxate	$C_{18}H_{26}O_3$	290.18743	1.15
15.94	Di-n-amyl phthalate	$C_{18}H_{26}O_4$	306.18230	0.36
17.19	(−)-8-Prenylnaringenin	$C_{20}H_{20}O_5$	340.13027	2.28
18.31	Butylphthalide	$C_{12}H_{14}O_2$	190.09924	0.67
18.94	Glabridin	$C_{20}H_{20}O_4$	324.13527	0.26
18.97	Stearidonic acid	$C_{18}H_{28}O_2$	276.20830	1.87
19.38	Lactone dehydrocostus	$C_{15}H_{18}O_2$	230.13027	0.36
19.71	Nandrolone	$C_{18}H_{26}O_2$	274.19274	1.63
20.40	Mammea A/BA	$C_{25}H_{26}O_5$	406.17656	0.62
22.20	Androstanolone	$C_{19}H_{30}O_2$	290.22389	0.54
26.74	Pheophorbide A	$C_{35}H_{36}N_4O_5$	592.26744	3.96

A total of 34 compounds were detected in the extract. Among these, five compounds showed relatively prominent peak areas, namely 1-[(3-carboxypropyl) amino]-1-deoxy-β-D-fructofuranose, (2S)-4-methyl-2-({[(3S,4S,5R)-2,3,4-trihydroxy-5-(hydroxymethyl) tetrahydro-2-furanyl] methyl} amino) pentanoic acid, chlorogenic acid, isoquercetin, and quercitrin, with retention times of 1.07, 1.50, 6.06, 8.74, and 9.35 min, respectively. Among all detected constituents, quercitrin (27.65%) and isoquercetin (11.67%) were the most abundant compounds. The relatively large peak areas of these compounds indicate that they are major contributors to the overall chemical profile of the mulberry leaf extract.

Overall, the detected constituents included flavonoids, alkaloids, phenolics, polyphenols, and steroids. Based on the relative peak areas, flavonoids appeared to

be the dominant compound class in the mulberry leaf extract from Wajo Regency. This finding suggests that flavonoids are a major component of mulberry leaves collected from this area and may contribute substantially to their biological potential. The predominance of flavonoids is also consistent with previous studies reporting that mulberry leaves are rich in phenolic and flavonoid compounds with important biological activities. Similarly, Jan *et al.* (2022) reported that mulberry leaves cultivated in Kashmir, India, contained several major metabolites, including chlorogenic acid, moracin, morin, 1-deoxynojirimycin, and syringic acid. The detection of chlorogenic acid and flavonoid derivatives in the present study therefore supports previous evidence that mulberry leaves are an important source of bioactive metabolites.

CONCLUSION

The 96% ethanol extract of mulberry leaves collected from Wajo Regency, South Sulawesi, exhibited a chemically diverse metabolite profile. Qualitative phytochemical screening confirmed the presence of alkaloids, phenolics, flavonoids, saponins, and terpenoids. UHPLC-Q-Orbitrap HRMS analysis tentatively annotated 34 metabolites, with quercitrin and isoquercetin showing the largest relative peak areas among the detected constituents. Chlorogenic acid was also identified as a prominent metabolite in the extract. These findings provide baseline chemical information on mulberry leaves cultivated in Wajo Regency and support further studies involving confirmatory compound identification, quantitative analysis using authentic standards, and evaluation of the biological relevance of the major metabolites.

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