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LC–MS/MS Profiling and *In Silico* ADMET and PASS Evaluation of Bioactive Metabolites from *Drynaria quercifolia* (L.) J.Sm. and *Curcuma aeruginosa* Roxb.

Abstract

Drynaria quercifolia and *Curcuma aeruginosa* rhizomes are well recognized for their medicinal properties in the traditional system of medicine. The rizhomes are used as a remedy for arthritis related inflammatory diseases. The present study investigated the phytochemical composition and computational pharmacological potential of ethanolic extracts of both the rhizomes for its to anti-gout potential. LC–MS/MS analysis using MRM and SIM approaches enabled selective validation of bioactive phytochemicals such as chlorogenic acid, catechin, quercetin-O-glucoside, naringenin, kaempferol derivatives, hesperidin, hyperoside, demethoxycurcumin and ar-turmerone. Integrated *in silico* ADMET analysis demonstrated that most identified phytoconstituents exhibited favorable gastrointestinal absorption, acceptable drug-likeness, and moderate toxicity profiles. PASS prediction analysis suggested potential xanthine oxidase inhibitory, kidney stimulant, uric acid excretion stimulant and xanthine dehydrogenase inhibitory activities for several metabolites. Naringenin and kaempferol showed comparatively higher predicted xanthine oxidase inhibitory potential, approaching that of febuxostat, whereas ar-turmerone exhibited predicted renal protective and uricosuric activities, indicating a possible complementary role in uric acid elimination. The study findings well supported the traditional claims as it could identify the bioactives that have potential antigout properties.

Keywords

Drynaria quercifolia; *Curcuma aeruginosa*; Gout; LC–MS/MS; ADMET; PASS

Introduction

In recent years there has been a constant increase in the inflammatory disorders among the population worldwide. The change in food habits, pollution, and lifestyle leads to a high rate of inflammatory disorders. Gout is one such chronic inflammatory arthritis caused by the deposition of monosodium urate crystals in joints due to persistent hyperuricemia, commonly affecting the big toe, ankles, knees and wrists (Dalbeth *et al.,* 2019; Richette *et al.,* 2020). It affects approximately 1–4% of the global population, with increasing disease burden associated with ageing, obesity, dietary factors, metabolic syndrome, hypertension, and chronic kidney disease (Kuo *et al.,* 2015; Singh & Gaffo, 2020). In India, COPCORD studies have reported a prevalence of 0.06–0.13% (Misra *et al.,* 2024).

Gout develops primarily as a consequence of disturbances in purine metabolism that result in excessive accumulation of uric acid. Purines originating from endogenous nucleic acid turnover and dietary sources undergo sequential degradation to hypoxanthine and xanthine, which are subsequently converted to uric acid by xanthine oxidoreductase (XOR), a molybdenum-containing enzyme that exists in two interconvertible forms, xanthine dehydrogenase and xanthine oxidase (XO) Thus, XO is a central enzyme in uric acid production and an important therapeutic target in gout.

Drynaria quercifolia (L.) J. Sm and *Curcuma aeruginosa* Roxb. rhizomes are traditionally important medicinal rhizomes widely employed in the management of inflammatory joint pains and rheumatic disorders. The rhizomes possess significant antioxidant, xanthine oxidase inhibitory, membrane-stabilizing, and cellular anti-inflammatory activities, including modulation of TNF-α, IL-6, COX-2 and iNOS-associated inflammatory pathways relevant to gout pathogenesis (Narthanaa *et al.,* 2025a; Narthanaa *et al.,* 2025b; Narthanaa *et al.,* 2025c). Although *Drynaria quercifolia* is traditionally consumed as a soup and *Curcuma aeruginosa* is incorporated into Ayurvedic formulations for managing inflammatory conditions, their phytochemical profiles and associated pharmacological potential have not been comprehensively investigated. In particular, the integration of LC–MS-based metabolite characterization with computational pharmacological assessment remains inadequately explored.

Advanced analytical techniques Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS) are widely employed to characterize the phytochemical constituents in medicinal plants. LC–MS/MS coupled with Selected Ion Monitoring (SIM) and Multiple Reaction Monitoring (MRM) provides highly sensitive and selective profiling of targeted phytoconstituents in complex herbal extracts (Wolfender *et al.,* 2015). The integration of these analytical platforms provides comprehensive insight into the phytochemical composition and pharmacological relevance of medicinal plants.

In recent years, computational pharmacology has emerged as a powerful strategy for accelerating natural product-based drug discovery. In silico approaches such as Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) prediction and Prediction of Activity Spectra for Substances (PASS) analysis enable rapid screening of bioactive compounds for pharmacokinetic behavior, biological activity, drug-likeness and toxicity profiles prior to experimental validation (Lipinski *et al.,* 2001; Lagunin *et al.,* 2000). These approaches significantly reduce time, cost and experimental limitations associated with conventional drug development while improving the identification of promising lead molecules (Daina *et al.,* 2017; Pires *et al.,* 2015).

Therefore, the present study aimed to identify the major bioactive constituents of both species through LC–MS analysis coupled with SIM and MRM and evaluate their pharmacokinetic, toxicological and potential pharmacological properties using computational approaches.

Materials and Methods

Plant Material Collection and Authentication

Rhizomes of *Drynaria quercifolia* were collected from Kolli Hills, Tamil Nadu and *Curcuma aeruginosa* were purchased from Beltola Bazaar, Guwahati, Assam. Both the rhizomes were germinated and the plants were authenticated by the Botanical Survey of India, Southern Regional Centre, Coimbatore, Tamil Nadu and voucher specimens were preserved for future reference.

Extraction

The shade-dried rhizomes were powdered and subjected to Soxhlet extraction using ethanol as solvent. The extracts were filtered and concentrated under reduced pressure using a rotary vacuum evaporator to obtain dried crude extract slurry, which was subsequently diluted and used for LC–MS/MS analysis.

LC–MS/MS Analysis

To obtain sensitive and stable responses the negative ionization mode was selected on account of the higher and more stable signal strengths. Subsequently, the MS/MS ion transitions were screened in MRM scanning mode to enhance the selectivity of detection using range of collision energy 10-35 ev and collision gas N2. Agilent chemvista library was used to match and identify the compounds detected in the study.

Ethanolic extract of *Drynaria quercifolia* was diluted with ethanol and then soluble extract was filtered using 0.45 micron Millipore filter. 5 µL filtrate of the sample was injected into the LC-ESI-QTOF system. LC-MS analysis was done by using UPLC-MS equipped with a binary pump. LC is connected to QTOF mass spectrometer coupled with ESI. The MS used was Agilent 6520 QTOF with negative ionization mode. ESI parameters used capillary temperature 110 °C, gas atomizer 40 L/h, and source voltage +2.7 kV. Full scan mode from m/z 100–1000 was done with source temperature 40 °C. UPLC column used was Acquity UPLC HSS C18 1.8 µm, 2.1x150 mm. Solvent A was 5 mM ammonium formic; solvent B was 0.1% formic acid in acetonitrile. Solvents were set at a total flow rate of 0.6 mL/min. linear gradient of solvent A was from 95% to 5% in 5 min.

In Silico ADMET and PASS Analysis

Phytocompounds identified through LC–MS/MS analysis were subjected to *in silico* pharmacokinetic and biological activity prediction studies. ADMET properties such as absorption, distribution, metabolism, excretion, toxicity and drug-likeness were evaluated using SwissADME, ADMETlab 3.0 and ProTox-3 platforms. PASS online analysis was performed to predict the probable biological activities of the identified compounds, particularly their xanthine oxidase inhibitory and anti-inflammatory potential.

Results and Discussion

LC–MS/MS-Based Targeted Phytochemical Profiling

LC–MS/MS (MRM) Profiling

Targeted LC–MS/MS analysis using Multiple Reaction Monitoring (MRM) and Selected Ion Monitoring (SIM) enabled sensitive profiling and validation of phytoconstituents in both extracts (Figs. 1A–B; Tables 1&2). A total of 12 compounds were detected in *D. quercifolia*, including chlorogenic acid, catechin, quercetin-O-glucoside, naringenin, kaempferol-3-O-glucoside, hesperidin and apigenin-7-O-glucuronide, whereas 13 phytoconstituents were identified in *C. aeruginosa*, predominantly comprising flavonoids, flavonoid glycosides, phenolic acids, catechins and curcuminoid-related metabolites such as hyperoside, myricetin-3-O-rhamnoside, ar-turmerone and demethoxycurcumin.

Fig. 1A. LC–MS/MS MRM chromatogram of ethanolic extract of *D. quercifolia*

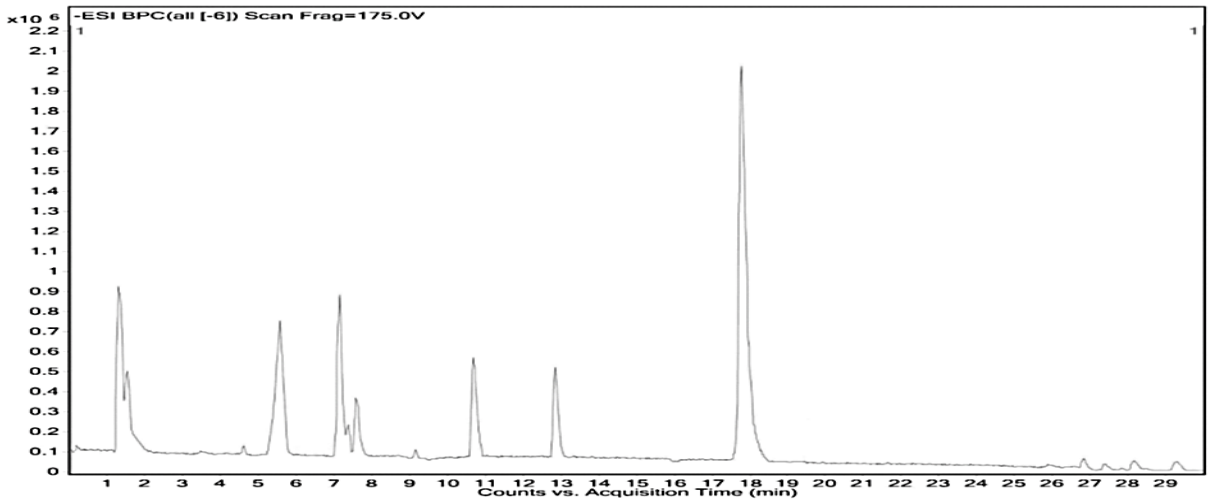


Table.1 Phytoconstituents detected in ethanolic extract of *Drynaria quercifolia* by LC–MS/MS (MRM) analysis

S. No.	Compound	RT (min)	Molecular Formula	Ion Mode	MW (Da)	Observed m/z ([M–H]⁻)
1	Chlorogenic acid	1.38	$C_{16}H_{18}O_9$	ESI⁻	354.31	353.0886
2	Chrysoeriol-7-O-glucoside	7.21	$C_{22}H_{22}O_{11}$	ESI⁻	462.15	461.0896
3	Catechin	7.59	$C_{15}H_{14}O_6$	ESI⁻	290.08	289.0689
4	Quercetin-O-glucoside	10.69	$C_{21}H_{18}O_{13}$	ESI⁻	464.37	463.1047
5	(+)-Gallocatechin	12.84	$C_{15}H_{14}O_7$	ESI⁻	306.07	305.0639
6	Naringenin	17.71	$C_{15}H_{12}O_5$	ESI⁻	272.26	271.0246
7	Ar-turmerone	25.81	$C_{15}H_{20}O$	ESI⁻	216.32	215.3241
8	Demethoxycurcumin	26.79	$C_{20}H_{18}O_5$	ESI⁻	338.36	337.3624
9	Kaempferol-3-O-glucoside	27.42	$C_{21}H_{20}O_{11}$	ESI⁻	448.38	447.1231
10	Gallic acid	27.87	$C_7H_6O_5$	ESI⁻	170.03	169.0648
11	Hesperidin	28.22	$C_{28}H_{34}O_{15}$	ESI⁻	610.15	609.2148

12	Apigenin-7-O-glucuronide	29.45	$C_{21}H_{18}O_{11}$	ESI^-	446.02	445.0049

Fig. 1B. LC–MS/MS MRM chromatogram of ethanolic extract of *C. aeruginosa*

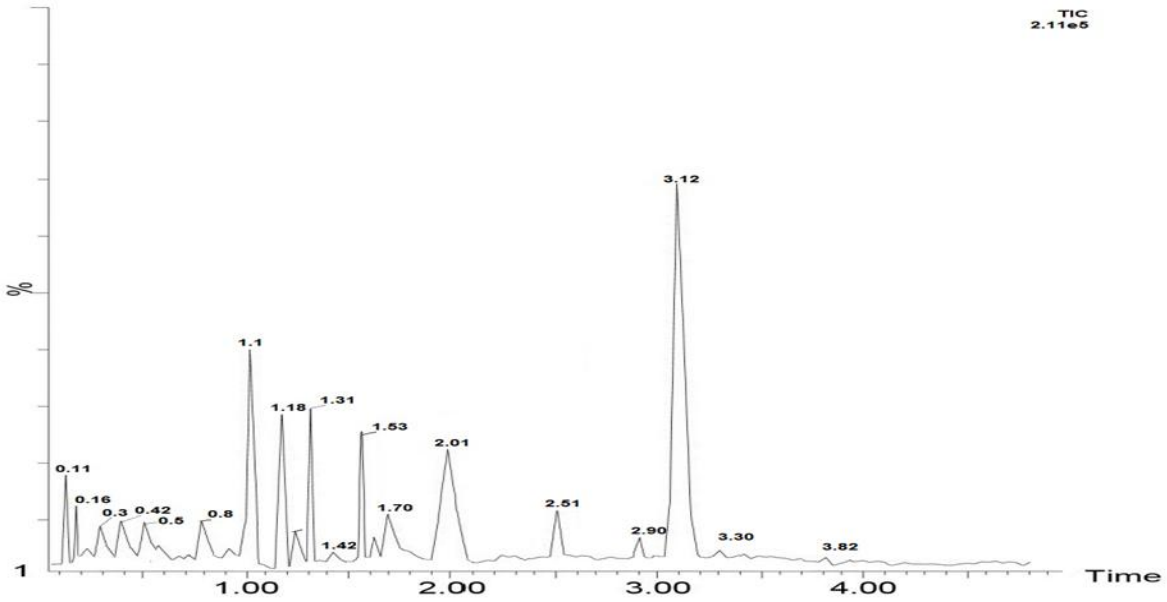


Table.2 . Phytocompounds detected in the ethanolic extract of *C. aeruginosa* by LC–MS/MS

S. No.	Compound	RT (min)	Molecular Formula	Ion Mode	MW (Da)	Parent Ion m/z ($[M–H]^-$)	Product Ions (m/z)
1	Procyanidin dimer (B1/B2)	0.1012	$C_{30}H_{26}O_{12}$	ESI^-	578.52	577.4159	425, 393, 367
2	3′-Hydroxydaidzein	0.1125	$C_{15}H_{10}O_5$	ESI^-	270.05	269.0451	242, 217
3	Quercetin-O-glucoside	0.3015	$C_{21}H_{18}O_{13}$	ESI^-	464.37	463.1047	301, 179, 151
4	(+)-Gallocatechin	0.8014	$C_{15}H_{14}O_7$	ESI^-	306.07	305.0639	219, 233
5	Epicatechin derivative	1.1011	$C_{17}H_{18}O_{11}$	ESI^-	398.23	397.1258	365, 381
6	3,4-O-Dimethylgallic acid	1.1805	$C_9H_{10}O_5$	ESI^-	198.05	197.0595	139, 153
7	Kaempferol-3-O-glucoside	1.3145	$C_{21}H_{20}O_{11}$	ESI^-	448.38	447.1231	285, 269, 247
8	Myricetin-3-O-rhamnoside	1.4219	$C_{21}H_{20}O_{12}$	ESI^-	464.05	463.0887	317
9	Hyperoside	1.6015	$C_{21}H_{20}O_{12}$	ESI^-	464.03	463.0877	503
10	Apigenin-7-O-apiofuranosyl-6,8-di-C-glucoside	1.6571	$C_{26}H_{28}O_{14}$	ESI^-	724.32	723.3217	635, 679

11	5,6,7,3′,4′-Pentahydroxyisoflavone	1.7011	$C_{15}H_{10}O_7$	ESI^-	302.04	301.0346	274, 200
12	Ar-turmerone	2.9014	$C_{15}H_{20}O$	ESI^-	216.32	215.3241	81
13	Demethoxycurcumin	3.1201	$C_{20}H_{18}O_5$	ESI^-	338.36	337.3624	175

SIM-Based Validation of Selected Marker Compounds

SIM-based validation further confirmed selected marker compounds including naringenin and ar-turmerone in *D. quercifolia*, as well as ar-turmerone, demethoxycurcumin and kaempferol-3-O-glucoside in *C. aeruginosa*, based on characteristic parent-to-product ion transitions (Fig. 2A–E; Table 3). The identified phytoconstituents collectively indicate the presence of bioactive polyphenolic and terpenoid compounds potentially associated with antioxidant, anti-inflammatory and anti-gout activities.

Fig. 2A. SIM chromatogram of naringenin in ethanolic extract of *D. quercifolia*

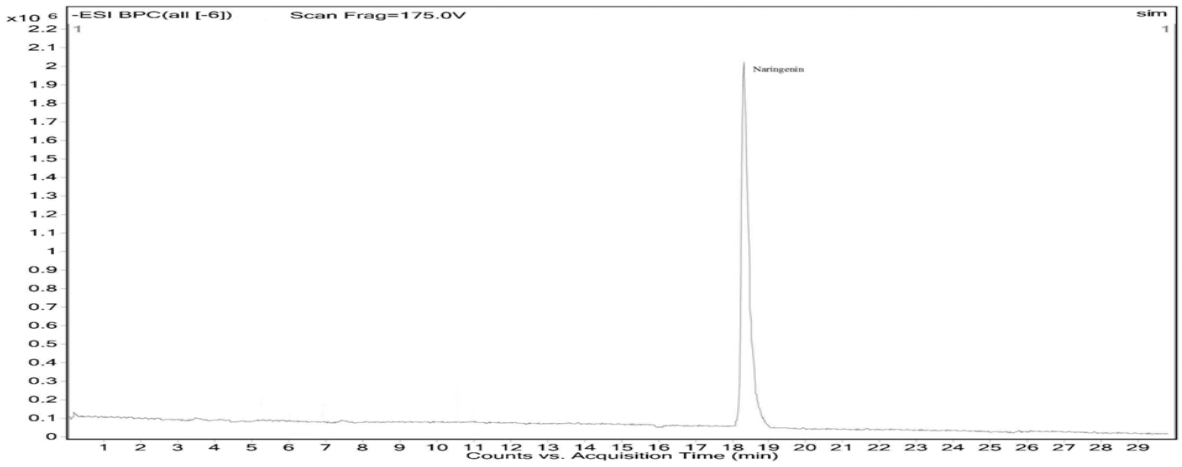


Fig. 2B. SIM chromatogram of ar-turmerone in ethanolic extract of *D. quercifolia*

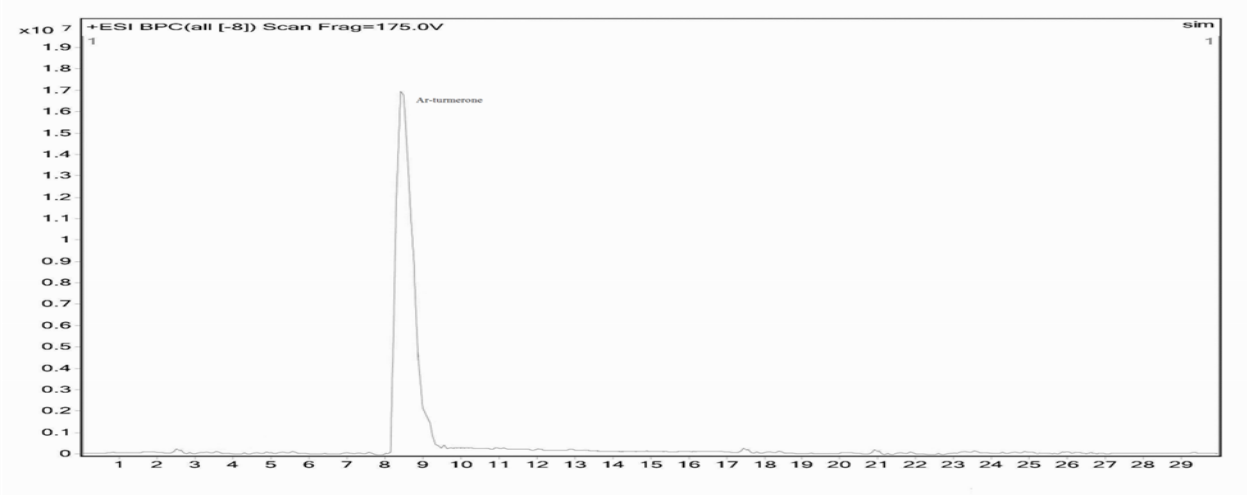


Fig. 2C. SIM chromatogram of ar-turmerone in ethanolic extract of *C. aeruginosa*

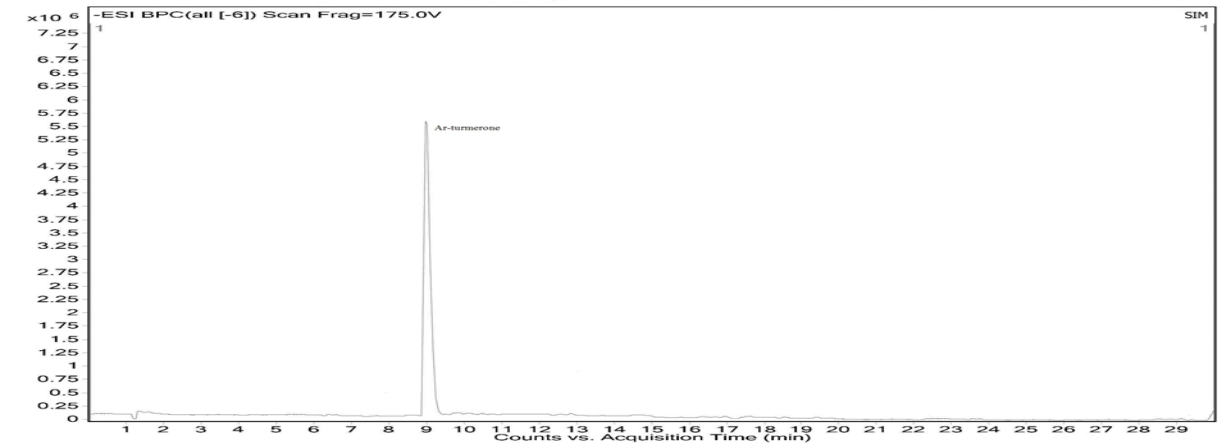


Fig. 2D. SIM chromatogram of demethoxycurcumin in ethanolic extract of *C. aeruginosa*

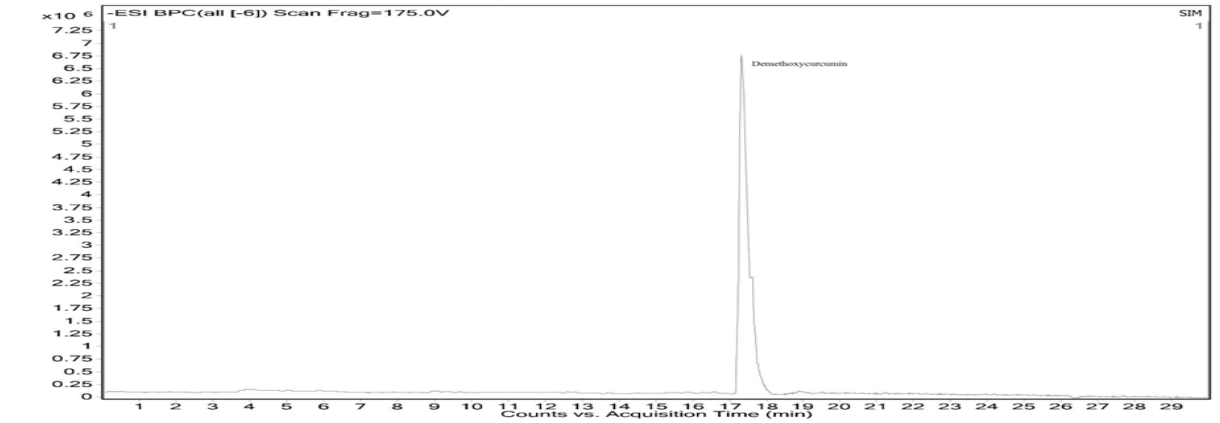


Fig. 2E. SIM chromatogram of kaempferol-3-O-glucoside in ethanolic extract of *C. aeruginosa*

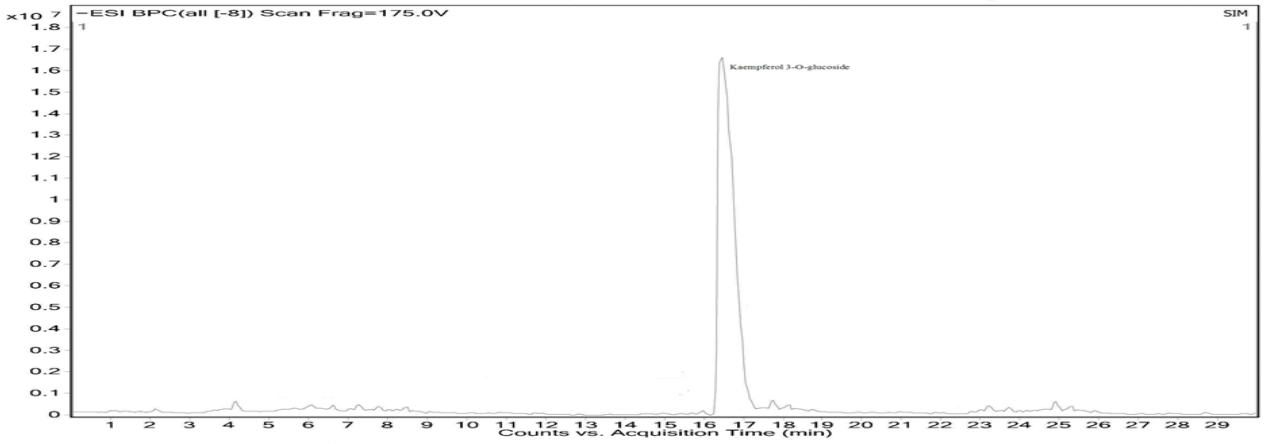


Table 3. SIM-based validation of selected marker compounds identified in ethanolic extracts of *Drynaria quercifolia* and *Curcuma aeruginosa*

S. No.	Plant Extract	Compound	RT (min)	Molecular Formula	Ion Mode	MW (Da)	Parent Ion m/z ([M–H]⁻)	Product Ion(s) m/z
1	*D. quercifolia*	Naringenin	18.32	$C_{15}H_{12}O_5$	ESI^-	272.26	271.2039	151.0596
2		Ar-turmerone	8.49	$C_{15}H_{20}O$	ESI^-	216.32	215.1682	81.2514
3	*C. aeruginosa*	Ar-turmerone	2.9014	$C_{15}H_{20}O$	ESI^-	216.32	215.3241	81, 242
4		Demethoxycurcumin	3.1201	$C_{20}H_{18}O_5$	ESI^-	338.40	337.3624	175, 337
5		Kaempferol-3-O-glucoside	1.3145	$C_{21}H_{20}O_{11}$	ESI^-	448.31	447.1231	285, 269, 247

In Silico ADMET and PASS Evaluation of LC-MS Identified Phytoconstituents

The comparative ADMET and PASS evaluation of SIM-validated LC–MS/MS identified phytoconstituents and the reference drug febuxostat is presented in Table 4. All selected compounds demonstrated high predicted gastrointestinal absorption together with favorable Lipinski and Veber drug-likeness profiles, indicating suitable oral bioavailability characteristics.

Flavonoid-derived compounds such as naringenin and kaempferol exhibited relatively higher polar surface area values while maintaining acceptable pharmacokinetic behavior. In contrast, ar-turmerone showed comparatively higher lipophilicity and predicted blood–brain barrier permeability. Metabolic and toxicity profiling indicated high plasma protein binding and moderate clearance values for all evaluated compounds. Selective cytochrome P450 inhibitory interactions were predicted for naringenin, demethoxycurcumin, kaempferol and febuxostat, whereas ar-turmerone demonstrated comparatively lower CYP-mediated interaction potential. PASS prediction analysis revealed notable xanthine oxidase inhibitory activity for kaempferol (Pa = 0.749) and naringenin (Pa = 0.677), showing activity trends comparable to febuxostat (Pa = 0.892). Additionally, ar-turmerone exhibited predicted kidney function stimulatory and uric acid excretion stimulatory activities, indicating complementary anti-gout-related pharmacological properties. Overall, the LC–MS/MS validated phytoconstituents demonstrated favorable pharmacokinetic and bioactivity profiles supporting their relevance for further molecular docking and experimental validation studies.

Table 4. Summary of ADMET and PASS profiles of SIM-validated LC–MS/MS identified compounds and standard febuxostat

Compound	GI Absorption	Lipinski Compliance	BBB Permeability	Toxicity Class	Key PASS Predicted Activity (Pa)
Naringenin	High	Yes	No	IV	XO inhibitor (0.677)
Ar-turmerone	High	Yes	Yes	IV	Kidney stimulant (0.497); Uric acid excretion stimulant (0.234)
Demethoxycurcumin	High	Yes	No	IV	XO inhibitor (0.217)
Kaempferol	High	Yes	No	V	XO inhibitor (0.749); Xanthine dehydrogenase inhibitor (0.675)
Standard – Febuxostat	High	Yes	No	VI	XO inhibitor (0.892); Gout treatment (0.848)

The present study employed an integrated phytochemical and computational approach to characterize the bioactive constituents present in the ethanolic rhizome extracts of *Drynaria quercifolia* and *Curcuma aeruginosa*. LC–MS/MS provided more selective phytochemical characterization through SIM validation of flavonoids, flavonoid glycosides, catechins, phenolic acids and curcuminoid-related compounds including chlorogenic acid, catechin, quercetin-O-glucoside, naringenin, kaempferol derivatives, hesperidin, hyperoside, demethoxycurcumin and ar-turmerone. These phytochemicals have previously been associated with antioxidant, anti-inflammatory, urate-lowering and xanthine oxidase inhibitory activities (Cos *et al.,* 1998; Chen *et al.,* 2011). Flavonoids such as kaempferol, catechin, quercetin derivatives and naringenin are known to suppress reactive oxygen species generation and xanthine oxidase-mediated uric acid production, thereby reducing monosodium urate crystal-associated inflammation (Lin *et al.,* 2014). Similarly, demethoxycurcumin and ar-turmerone have been reported to regulate inflammatory cytokine signaling and oxidative stress pathways (Hewlings & Kalman, 2017; Menon & Sudheer, 2007). LC–MS/MS therefore provided greater biological relevance by identifying polar polyphenolic metabolites directly associated with anti-gout pharmacology.

Integrated ADMET and PASS analyses indicated that most identified phytoconstituents possessed acceptable gastrointestinal absorption, favorable drug-likeness profiles and moderate toxicity predictions consistent with Lipinski and Veber criteria (Lipinski *et al.,* 2001; Veber *et al.,* 2002). Polyphenolic compounds such as naringenin and kaempferol demonstrated comparatively balanced pharmacokinetic profiles, whereas highly lipophilic hydrocarbons exhibited reduced absorption characteristics and multiple drug-likeness violations. PASS analysis predicted potential xanthine oxidase inhibitory, uricosuric, kidney function stimulatory and xanthine dehydrogenase inhibitory activities among several compounds. Notably, kaempferol and naringenin exhibited comparatively higher predicted xanthine oxidase inhibitory probabilities approaching the pharmacological profile of febuxostat, while ar-turmerone demonstrated predicted renal-supportive and uricosuric-associated properties (Lagunin *et al.,* 2000). Although computational predictions alone cannot confirm pharmacological efficacy, they provide support evidence for the anti-gout potential of the identified metabolites.

Conclusion

In summary, the present investigation provided a detailed chemical and computational characterization of the ethanolic rhizome extracts of *Drynaria quercifolia* and *Curcuma aeruginosa* using LC–MS/MS approaches integrated with ADMET and PASS-based predictive analysis. Bioactive components such as naringenin, kaempferol derivatives, demethoxycurcumin and ar-turmerone, are identified to possess promising pharmacological properties associated with gout management. These findings correlated well with previously reported biochemical, antioxidant and THP-1 monocytic cell line studies thereby strengthening their therapeutic significance. Collectively, the results highlight the medicinal potential of these rhizomes as promising natural sources for further study to develop an anti-gout drug and provide scientific evidence for the claims made in traditional system of medications.

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UNDER PEER REVIEW

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Declaration of AI Use

This manuscript was prepared through the intellectual contributions of the author(s) to the study design, data analysis, interpretation of results, and scholarly content. ChatGPT, Claude and Perplexity were used solely to assist with grammatical refinement and reference formatting during manuscript revision. The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.