Records of Natural Products

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SHORT REPORT

Anti-inflammatory xanthones from the fruits of *Hypericum patulum* Thunb.

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Abstract: Twenty-four known xanthones were isolated from the 80% ethanol extract of the fresh ripe fruits of *Hypericum patulum* Thunb. Their structures were elucidated by extensive NMR and ESI-MS spectroscopic analysis and comparison with literature data. Compounds **4**, **7**, **14**, and **18–19** were first reported in this genus. Compounds **1**, **3**, **9–11**, **13**, **15–17**, and **20–21** were first reported from this species. Anti-inflammatory studies have shown that compounds **1–2, 8, 12–13** and **15** have a significant inhibition rate of NO release compared to dexamethasone (DEX). The anti-inflammatory activity data formed the basis for the structure-activity relationship analysis of the isolated compounds.

Keywords: *Hypericum patulum* Thunb, Xanthones, anti-inflammatory activity, structure-activity relationship, chemotaxonomy

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1 Plant Source

Hypericum patulum Thunb. ex Murray was gathered from Huaxi, Guiyang City China from July to August 2018. The plant material was identified by Professor Qing-wen Sun of Guizhou University of Traditional Chinese Medicine as the fresh ripe fruits of *H. patulum*, and the specimen (No. 20180801) is deposited in the Herbarium of Guizhou Medical University (GMB).

2 Previous Studies

H. patulum belongs to the Hypericaceae family, a plant taxon comprising over 400 species worldwide. It is primarily distributed in the Chinese provinces of Yunnan, Guizhou, and Hubei (Li et al., 2020) The secondary metabolites of *H. patulum* encompass diverse structural types, mainly dianthrones, phloroglucinol derivatives (PPAPs), benzophenones, xanthones, terpenoids, fatty acids, and volatile oils (Yin et al., 2004; Xiao & Mu, 2007). These compounds exhibit a range of bioactivities such as anti-inflammatory, anti-tumor, and anti-depressant effects (Xie et al., 2010; Zhang et al., 2020) Although xanthones possess potential therapeutic value, the relationship between the chemical structure and anti-inflammatory activities is unclear. In this study, we conducted a systematic assessment of the anti-inflammatory effects of these compounds. The research aimed to elucidate how structural modifications influence their anti-inflammatory activity and further explored the chemotaxonomic implications of these compounds.

3 Present Study

Triple extraction (1.5 h each) of fresh *H. patulum* fruits (40 kg) was performed using 30% ethanol. The solvent volumes used were 8-fold for the first extraction and 6-fold for the second and third extractions. After the extract solutions were combined, the solvent was evaporated under reduced pressure to afford the crude extract (3 kg). The crude extract was then subjected to separation on a D-101 macroporous adsorption resin column, eluting with water and 80% ethanol in sequence. This yielded the water-eluted fraction (797 g) and the 80% ethanol-eluted fraction (1395 g). The 80% ethanol-eluted fraction was further purified by normal-phase silica gel column chromatography and eluted with a gradient of CH_2Cl_2-MeOH (10:0–6:4). Based on thin-layer chromatography (TLC) analysis, **11** fractions were obtained.

Twenty-four known xanthones were isolated by various modern chromatographic techniques, which were

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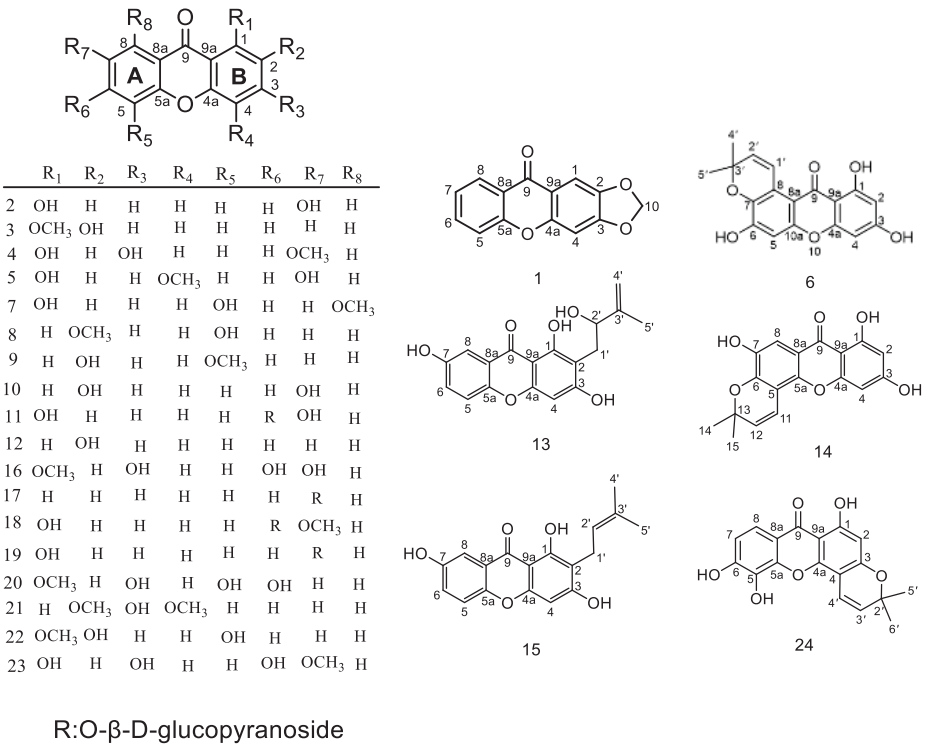

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
2	OH	H	H	H	H	H	OH	H
3	OCH_3	OH	H	H	H	H	H	H
4	OH	H	OH	H	H	H	OCH_3	H
5	OH	H	H	OCH_3	H	H	OH	H
7	OH	H	H	H	OH	H	H	OCH_3
8	H	OCH_3	H	H	OH	H	H	H
9	H	OH	H	H	OCH_3	H	H	H
10	H	OH	H	H	H	H	OH	H
11	OH	H	H	H	H	R	OH	H
12	H	OH	H	H	H	H	H	H
16	OCH_3	H	OH	H	H	OH	OH	H
17	H	H	H	H	H	H	R	H
18	OH	H	H	H	H	R	OCH_3	H
19	OH	H	H	H	H	H	R	H
20	OCH_3	H	OH	H	OH	OH	H	H
21	H	OCH_3	OH	OCH_3	H	H	H	H
22	OCH_3	OH	H	H	OH	H	H	H
23	OH	H	OH	H	H	OH	OCH_3	H

Figure 1. Structure of **1–24** xanthones isolated from *H. patulum*

2,3-Methylenedioxyxanthone (**1**) (Cruz et al., 2001), 1,7-Dihydroxyxanthone (euxanthone) (**2**) (Cai et al., 2012), 2-Hydroxy-1-methoxyxanthone (**3**) (Wei et al., 2011), Isogentisin (**4**) (Ando et al., 2007), 1,7-Dihydroxy-4-methoxyxanthone (**5**) (Kijjoa et al., 1998), Toxyloxanthone B (**6**) (Dong et al., 2015), 1,5-Dihydroxy-8-methoxyxanthone (**7**) (Thu et al., 2017), 5-Hydroxy-2-methoxyxanthone (**8**) (Rath et al., 1996), 2-Hydroxy-5-methoxyxanthone (**9**) (Nielsen & Arends, 1979), 2,7-Dihydroxyxanthone (**10**) (Kong et al., 2011), 1,7-Dihydroxyxanthone-6-*O*-*β*-*D*-glucopyranoside (**11**) (Yan et al., 2019), 2-Hydroxyxanthone (**12**) (Cai et al., 2012), (±)1,3,7-Trihydroxy-2-(2-hydroxy-3-methyl-3-butenyl)-xanthone (**13**) (Tanaka & Takaishi, 2006), Oblongixanthone A (**14**) (Huang et al., 2009), 1,3,7-Trihydroxy-2-(3-methylbut-2-enyl)-xanthone (**15**) (Cortez et al., 1998), 3,6,7-Trihydroxy-1-methoxyxanthone (**16**) (Fu et al., 2006), Hyperelatone H (**17**) (Yan et al., 2019), 1-Hydroxy-7-methoxyxanthone-6-*O*-*β*-*D*-glucopyranoside (**18**) (Tosa et al., 1997), Wubangziside B (**19**) (Li et al., 1998), 3,5,6-Trihydroxy-1-methoxyxanthone (**20**) (Tanaka et al., 2009; Gonda et al., 2000), 3-Hydroxy-2,4-dimethoxyxanthone (**21**) (Castelão et al., 1977), 2,5-Dihydroxy-1-methoxyxanthone (**22**) (Cheng et al., 2008), 1,3,6-Trihydroxy-7-methoxyxanthone (**23**) (Zhou et al., 2013), Isojacereubin (**24**) (Wu et al., 1998) (Figure 1).

The anti-inflammatory activity of the **14** isolated xanthones derivatives were initially evaluated using total NO assay kit and DEX was employed to be the positive control, with detailed experimental procedures available in the published literature (Wu et al., 2025) (Table 1).

According to the result (Table 1), compounds **1–2**, **8**, **12–13** and **15** had significant inhibitory effects on the production of NO in inflammatory cells, and the inhibition rates were 66.45 ± 0.49%, 61.82 ± 1.04%, 72.77 ± 1.54%, 51.45 ± 1.83%, 67.84 ± 1.99%, 73.18 ± 2.96%. The potent anti-inflammatory effects exhibited by certain xanthone derivatives could be explained by their specific structural features. (1) Methoxy substitution: Structural-activity analysis reveals that methoxy substitution at ortho- and para-positions relative to the hydroxyl group on the B-ring of xanthones derivatives leads to significant attenuation of anti-inflammatory activity. (2) Glycosyl substitution: The compound showed no significant anti-inflammatory activity in the presence of a glycosyl group on the A-ring. For example, compound **11** has no significant effect on the NO secretion of cells after replacing a glycosyl group at the 6-position of the A ring, and has no obvious anti-inflammatory activity. Compound **2** without glucosyl substitution on the A ring showed good anti-inflammatory activity.

4 Chemotaxonomic Discussion

A comprehensive literature review of the 24 compounds revealed that their distribution patterns across the Calophyllaceae, Hypericaceae, and Clusiaceae provide notable chemotaxonomic insights. Compounds **1–3** occur in multiple genera within these families, suggesting conserved biosynthetic pathways and possible shared evolutionary origins. Specifically, compounds **1** and **3** are found in both *Hypericum* (Hypericaceae) and genera of Calophyllaceae, while compound **2** is present in several calophyllaceous genera

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Table 1. Inhibitory effects of the 14 isolated xanthone derivatives on NO production

Compound	Inhibitory rate (%)	Compound	Inhibitory rate (%)
1	66.45 ± 3.60	10	49.90 ± 1.66
2	61.82 ± 2.49	11	20.19 ± 1.70
3	42.52 ± 1.95	12	51.45 ± 1.83
4	40.78 ± 2.06	13	67.84 ± 1.99
5	34.07 ± 2.28	15	73.18 ± 2.96
6	43.45 ± 2.29	17	41.34 ± 3.26
8	72.77 ± 1.54	21	11.00 ± 1.84
DEX	84.93 ± 0.43		

Note: Safe concentration 100 μM (compounds **1**, **2**, **11**); 50 μM (compounds **8**, **21**); 25 μM (compounds **3–4**, **6**, **10**, **12**, **15**, **17**); 12.5 μM (compound **13**); 10 μM (compound **5**).

as well as in *Cratoxylum* and *Harungana* (Hypericaceae) and in *Garcinia* (Clusiaceae). This overlap supports a close phytochemical relationship among these families within the Malpighiales.

Additionally, compounds **5–6**, **8–9**, **13–16**, **20–21**, and **24** are predominantly distributed across numerous species of *Hypericum*, reinforcing the chemical coherence of this genus. However, compounds **15** and **21** are also detected in Calophyllaceae (*Calophyllum* and *Kielmeyera*), further underscoring a specific chemotaxonomic link between *Hypericum* and these genera. Notably, compounds **1–3**, **5–6**, **15–16**, and **24** have all been isolated from *Garcinia* (Clusiaceae), highlighting the phytochemical continuity among these three families. Collectively, these findings indicate that certain secondary metabolites are shared across Calophyllaceae, Hypericaceae, and Clusiaceae, reflecting both ancestral metabolic traits and convergent evolution. The recurring co-occurrence of compounds in *Hypericum*, *Kielmeyera*, *Calophyllum*, and *Garcinia* offers valuable chemical markers for elucidating phylogenetic relationships and evolutionary diversification within the Malpighiales.

The distribution patterns of compounds **4**, **10**, **12**, and **19** across multiple plant families offer significant chemotaxonomic insights. The presence of compound **4** in phylogenetically distant lineages—Polygalaceae (*Polygala alpestris*), Gentianaceae (*Gentiana lutea*), and Calophyllaceae (*Calophyllum pisiferum*)—implies the conservation of its biosynthetic pathway over evolutionary time. Similarly, the isolation of compound **10** from both Typhaceae (*Sparganium stoloniferum*) and Hypericaceae (*Hypericum chinense*) further supports its role as a shared secondary metabolite transcending taxonomic boundaries. Notably, compound **12** exhibits an exceptionally broad phylogenetic distribution, occurring in five distinct families: Hypericaceae (*Hypericum*), Calophyllaceae (*Calophyllum*), Sapotaceae (*Manilkara*), Fabaceae (*Caesalpinia*), and Clusiaceae (*Garcinia*). This widespread occurrence may reflect either the retention of ancestral metabolic traits across divergent lineages or the repeated emergence of a functional biosynthetic capacity driven by similar ecological or physiological constraints. Collectively, these compounds (**4**, **10**, **12** and **19**) serve as valuable chemical markers for tracing conserved metabolic features and convergent evolutionary adaptations, thereby contributing to a deeper understanding of phytochemical diversity and phylogenetic relationships across distantly related plant groups.

Compounds **11** and **17** have been reported from *Hypericum elatoides* (Hypericaceae). Compound **7** was isolated from *Vismia parviflora* (Hypericaceae). Compound **13** was obtained from *Hypericum chinense* (Hypericaceae). Compound **14** has been found in *Garcinia oblongifolia* and *Garcinia gracilis* (Clusiaceae), as well as in *Bauhinia championii* (Fabaceae). These findings collectively highlight distinct yet overlapping phytochemical profiles within and beyond the Hypericaceae. The occurrence of multiple compounds (e.g., **7**, **11**, **13**, **17**) within different genera of Hypericaceae (*Hypericum*, *Vismia*) reinforces the chemical coherence of this family.

In summary, although the compounds isolated in this study have been reported in a limited number of other plant families, their distribution is predominantly concentrated within the Calophyllaceae, Hypericaceae, and Clusiaceae. These compounds can thus be regarded as characteristic phytochemical constituents shared among these three families, providing valuable chemotaxonomic markers that reflect their close phylogenetic relationships and possible common biosynthetic origins within the order Malpighiales.

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Author Contributions

Shun Wang, Jing-Yi Xue and Jian-Ping Yang: Original draft preparation, performing the experiments. Li Jiang and Shi-Hai Zhang: data analysis. Ye-Lin Shi, Xue Ma and Yong-Jun Li: review and editing, funding acquisition, supervision. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request. Source data are provided with this paper.

Ethics Approval

We have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products.

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