



HAL
open science

Chemical constituents from the latex of *Garcinia parvifolia* and their anti-Unfolded Protein Response activity

Dimitri Bréard, Thomas Charpentier, Anne-Marie Le Ray, Nadège Blon, Nelly Bataillé-Simoneau, Marc Litaudon, Khalijah Awang, Thomas Guillemette, Pascal Richomme, Guillaume Viault

► **To cite this version:**

Dimitri Bréard, Thomas Charpentier, Anne-Marie Le Ray, Nadège Blon, Nelly Bataillé-Simoneau, et al.. Chemical constituents from the latex of *Garcinia parvifolia* and their anti-Unfolded Protein Response activity. *Phytochemistry*, 2025, pp.114522. <10.1016/j.phytochem.2025.114522>. <hal-05051921>

HAL Id: hal-05051921

<https://hal.science/hal-05051921v1>

Submitted on 19 May 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Journal Pre-proof

Chemical constituents from the latex of *Garcinia parvifolia* and their anti-Unfolded Protein Response activity

Dimitri Bréard, Thomas Charpentier, Anne-Marie Le Ray, Nadège Blon, Nelly Bataillé-Simoneau, Marc Litaudon, Khalijah Awang, Thomas Guillemette, Pascal Richomme, Guillaume Viault

PII: S0031-9422(25)00145-1

DOI: <https://doi.org/10.1016/j.phytochem.2025.114522>

Reference: PHYTO 114522

To appear in: *Phytochemistry*

Received Date: 3 December 2024

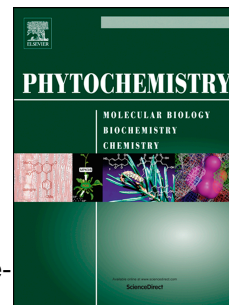
Revised Date: 25 April 2025

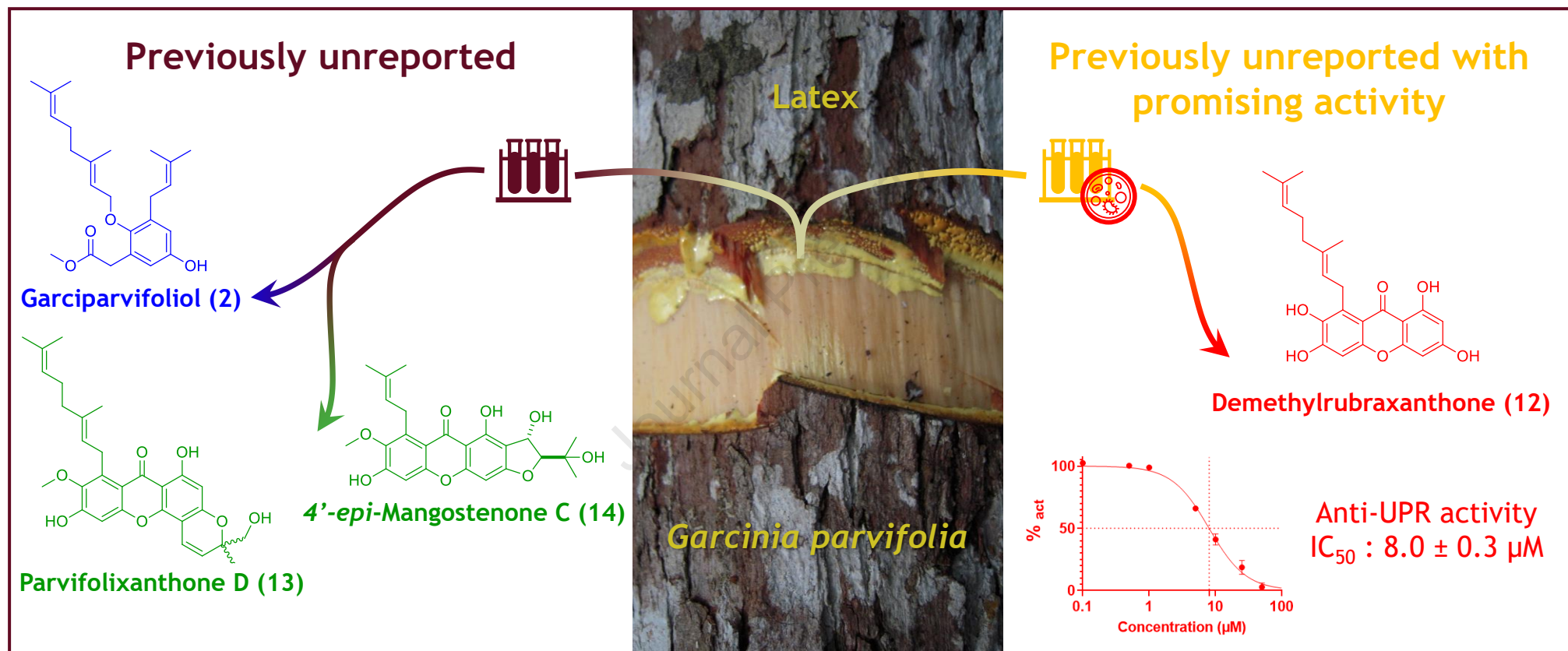
Accepted Date: 26 April 2025

Please cite this article as: Bréard, D., Charpentier, T., Le Ray, A.-M., Blon, N., Bataillé-Simoneau, N., Litaudon, M., Awang, K., Guillemette, T., Richomme, P., Viault, G., Chemical constituents from the latex of *Garcinia parvifolia* and their anti-Unfolded Protein Response activity, *Phytochemistry*, <https://doi.org/10.1016/j.phytochem.2025.114522>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Ltd.





Three undescribed xanthenes (12-14) and one unreported terpenophenol (2) were isolated from the latex of *Garcinia parvifolia*. Compound 12 exhibited remarkable anti-UPR activity.

16 **ABSTRACT**

17 Inhibition of the Unfolded Protein Response (UPR) pathway of phytopathogenic fungi represents a
18 promising strategy for the discovery of natural products capable of attenuating fungal resistance to
19 plant defense metabolites. Polyprenylated xanthenes isolated from Clusiaceae and Calophylaceae
20 have recently been identified as inhibitors of this fungal resistance pathway whereas *Garcinia*
21 *parvifolia* (Miq.) Miq. is known for its high xanthone content. Consequently, systematic phytochemical
22 investigation of the latex and bioguided fractionation based on anti-UPR cell-based assay were
23 conducted. A total of sixteen compounds were isolated, including one previously unreported
24 terpenophenol with an original structure (**2**) and three previously undescribed xanthenes (**12-14**), the
25 latter obtained through bioguided fractionation. Among the isolated compounds,
26 demethylrubraxanthone (**12**) exhibited notable anti-UPR activity, with an IC_{50} value of $8.0 \pm 0.3 \mu\text{M}$. To
27 address the limited availability of (**12**) in the latex, a semisynthesis from rubraxanthone (**1**) was
28 eventually conducted.

29

30 **KEYWORDS**

31 *Garcinia parvifolia*; Clusiaceae; Phytochemical analysis; Bioguided fractionation; Xanthenes;
32 Demethylrubraxanthone; UPR inhibitors; Plant pathogenic fungi; Crop protection

33

34

35 1. Introduction

36 The rising prevalence of pesticide usage has a direct and detrimental impact on the environment,
37 resulting in soil and water contamination, reduction in biodiversity together with a multitude of
38 adverse effects on human health, including the development of cancers, disruption of the endocrine
39 system as well as neurological dysfunction (Rani *et al.*, 2021). The prolonged usage of these pesticides
40 leads to the emergence of resistance in targeted pathogens, thereby reducing the effectiveness of
41 plant protection products and resulting in an increase in their use (Fisher *et al.*, 2018). Two significant
42 challenges will confront the agricultural sector in the coming years : ensuring food safety and modifying
43 production methods in a manner that is environmentally conscious, on the one hand, and considering
44 the impact of climate change on the dynamics and geographical distribution of pathogens on the other
45 hand (Chaloner *et al.*, 2021). There is therefore an urgent need to find alternative crop protection
46 solutions that respect the "One Health" concept, with the aim of protecting environmental, animal,
47 and human health (Destoumieux-Garzón *et al.*, 2018).

48 It is estimated that there are several thousand species of fungi that are phytopathogens and are
49 worldwide responsible for significant economic losses in agriculture (Fisher *et al.*, 2012). During the
50 process of penetration and colonization of the host plant, the phytopathogenic fungus encounters the
51 plant's defense mechanisms. Among these defense systems, "chemical" defenses are represented by
52 specialized metabolites with antimicrobial activity produced by the plant. These include phytoalexins,
53 which are biosynthesized in response to infection. The accumulation of phytoalexins in the infection
54 zone gives rise to the emergence of protection mechanisms in the plant pathogenic fungus. These
55 mechanisms involve signaling pathways enabling genes expression. Three principal signaling pathways
56 have been identified: the Cell Wall Integrity (CWI), the High Osmolarity Glycerol (HOG) and the
57 Unfolded Protein Response (UPR). These pathways are essential for the defense mechanisms of
58 phytopathogenic fungus. The inhibition of one or more of these pathways by a molecule applied at a
59 sub-toxic dose has both the effects of weakening the attacker and restoring the antifungal activity of
60 the phytoalexins (Joubert *et al.*, 2011a, 2011b; N'Guyen *et al.*, 2021). In a previous study, an original

61 cell-based screening assay that enabled the detection of different natural products originating from an
62 in-house library or from bioguided fractionation as anti-UPR inhibitors was developed. Xanthoness
63 isolated from *Calophyllum* or *Garcinia* species appeared as promising inhibitors of the UPR pathway,
64 and the reduction of necrosis linked to *A. brassicicola* or *Botrytis cinerea* fungi was finally validated *in*
65 *planta* (Charpentier *et al.*, 2023).

66 *Garcinia parvifolia* is an edible tropical plant that has been shown to contain a wealth of
67 polyhydroxylated and polyprenylated xanthoness exhibiting a wide range of biological activities (Lim,
68 2012; Meunier *et al.*, 2024; Wijayanti *et al.*, 2021; Xu *et al.*, 2001). The objective of this study is to
69 present a phytochemical analysis of *Garcinia parvifolia* latex with the aim of identifying new UPR
70 inhibitors. To this end, systematic phytochemical investigation of latex and bioguided fractionation
71 based on the anti-UPR cell-based assay were conducted.

73 2. Results and Discussion

74 2.1. Systematic phytochemical investigation

75 2.1.1. Phytochemical study

76 To date, no phytochemical studies have been conducted on the minor constituents of *Garcinia*
77 *parvifolia* latex. In fact, in 1988, Pattalung *et al.* isolated rubraxanthone (**1**) as the major compound
78 from the latex and described its antibacterial activity (Pattalung *et al.*, 1988). The latex was first
79 dissolved in MeOH and subsequently filtered to remove any residual bark fragments. The anti-UPR
80 activity of the resulting filtrate (GpLM) was assessed using a cell-based assay methodology previously
81 described (Charpentier *et al.*, 2023) and showed a 85% activity percentage at 100 mg.L⁻¹ (Fig. 1). This
82 result suggests the possibility of identifying active molecules, following the example of the study
83 carried out on *Calophyllum caledonicum* (Chambaud *et al.*, 2024). The HPLC-PDA-ELSD-MSⁿ analysis of
84 the filtrate revealed the presence of five main compounds, one of which being predominant and
85 another almost exclusively detected in ESLD (Supplementary data, Fig. S1). Several minor compounds
86 with similar UV profiles were also detected throughout the chromatogram. The majority of these

87 compounds exhibited characteristics associated with xanthones, including UV absorptions
88 (Abdalrahim, 2012) and molecular weights between 396 and 480 Da (Feng *et al.*, 2020). The main
89 compound, already described as such (Pattalung *et al.*, 1988), was identified as rubraxanthone (**1**) on
90 the basis of the ^1H and ^{13}C NMR data of the filtrate (Supplementary data, Fig. S2-S3) supported by the
91 MW of 410 Da deduced from the negative and positive LC-ESI-MSⁿ at m/z 409 and 411, respectively
92 (Lee and Chan, 1977). The methanolic filtrate was extracted with cyclohexane and both fractions were
93 subjected to successive flash, preparative and semipreparative chromatography to afford a previously
94 undescribed compound (SciFinder® database), garciparvifoliol (**2**), together with nine known
95 xanthones; rubraxanthone (**1**), isocowanol (**3**), α -mangostin (**4**), parvifolixanthone C (**5**), 9-
96 hydroxycalabaxanthone (**6**), isocowanin (**7**), parvixanthone C (**8**), parvixanthone G (**9**), cratoxylone (**10**)
97 and a cyclohexenone derivative named TPTQ (**11**) (Ampofo and Waterman, 1986; Bennett *et al.*, 1993;
98 Lee and Chan, 1977; Rukachaisirikul *et al.*, 2006; Sen *et al.*, 1980; Wahyuni *et al.*, 2004; Xu *et al.*, 2001;
99 Yates and Stout, 1958) (Fig. 2 and Supplementary data, Fig. S4).

100 The molecular formula $\text{C}_{24}\text{H}_{34}\text{O}_4$ of (**2**), was deduced from HRESIMS data (m/z 409.2358 $[\text{M} + \text{Na}]^+$;
101 calculated 409.2349) and 1D NMR data. The UV spectrum was similar to that of nahocol, having an
102 aryl prenyl ether structure (Tsuchiya *et al.*, 1998). The positive MS and MS² spectra exhibited a $[\text{M} +$
103 $\text{Na}]^+$ ion at m/z 409 with prominent fragment ions at m/z 340 $[\text{M} - \text{C}_5\text{H}_9 + \text{Na}]^+$ and 272 $[\text{M} - \text{C}_{10}\text{H}_{17} +$
104 $\text{Na}]^+$, suggesting the presence of a prenyl (69 Da) and a geranyl (137 Da) moieties in the molecule
105 (Piccinelli *et al.*, 2011). In negative mode, the $[\text{M} - \text{H}]^-$ ion at m/z 385 exhibited a similar loss of 137 Da
106 (m/z 248) confirming the presence of a geranyl group as well as a fragment at m/z 353 $[\text{M} - \text{CH}_3\text{OH} -$
107 $\text{H}]^-$ suggesting the presence of a methanol moiety (32 Da) (Gates, 2021). In addition, a product ion at
108 m/z 216 $[\text{M} - \text{C}_{10}\text{H}_{17} - \text{CH}_3\text{OH} - \text{H}]^-$ was formed by the successive losses of geranyl and methanol groups
109 (169 Da).

110 An aromatic singlet integrating for two protons (δ_{H} 6.58) showed correlations to two different carbons
111 (δ_{C} 115.8 and 114.9) in the HMQC spectrum, suggesting the presence of a 1,2,3,5-tetrasubstituted
112 benzene ring. This fortuitous equivalence (in chloroform-*d*) was confirmed by an additional ^1H NMR

113 experiment in benzene- d_6 (Supplementary data, Fig. S9) showing two *meta*-coupled hydrogens at δ_H
114 6.54 (1H, s, $J = 3.0$ Hz) and 6.49 (1H, s, $J = 3.0$ Hz) instead of the singlet at δ_H 6.58. The joint presence
115 of a prenyl and geranyl group suggested by the MS² data was confirmed by the ¹H NMR data (Table 1),
116 which showed signals corresponding to five olefinic methyl groups (δ_H 1.62, 1.67, 1.69, 1.70 and 1.75),
117 three vinylic protons (δ_H 5.11, 5.27 and 5.54) and two geranyl-characteristic methylenes at δ_H 2.10 (4H,
118 m). The COSY correlations (Fig. 3) between the vinylic proton at δ_H 5.27 (1H, m) and the benzylic
119 methylene group at δ_H 3.34 (2H, d, $J = 7.2$ Hz) as well as the vinylic proton at δ_H 5.54 (1H, m) and the
120 oxymethylene group at δ_H 4.28 (2H, d, $J = 6.9$ Hz) confirmed the presence of a prenyl and an oxygeranyl
121 unit as substituents of the benzene ring. The presence of a methyl ethanoate side chain was confirmed
122 by the characteristic signals of an ester carbonyl (δ_C 172.5), a methoxy group at δ_H/δ_C 3.70 (3H, s)/52.2
123 and a methylene group at δ_H/δ_C 3.65 (2H, s)/35.6. In addition, the last singlet proton (δ_H 4.65) for which
124 there was no correlation in the HMQC spectrum, was consequently assigned to a hydroxy group. In the
125 HMBC spectrum (Fig. 3), this hydroxy signal was correlated with the carbons of the two aromatic *meta*-
126 coupled protons, locating this substituent at C-5. The position of the methyl ethanoate, geranyl and
127 prenyl side chains at C-1, C-2 and C-3, respectively, was unambiguously established from the two and
128 three bond CH correlations observed in the HMBC spectrum (Fig. 3). Hydroquinone substituted by a
129 methyl ethanoate group and an isoprenoid moiety through an ether linkage have been previously
130 identified in various *Sargassum* brown algae and have been named nahocol (Jung *et al.*, 2008;
131 Tsuchiya *et al.*, 1998). However, the isoprenoid structure of the nahocol displayed a hydroxy group
132 and was systematically linked to the benzenic ring at the C-3' position *via* the oxygen atom (Fernando
133 *et al.*, 2022). Consequently, in comparison with the literature data (Hooper and Davies-Coleman, 1995;
134 Jung *et al.*, 2008; Noshita *et al.*, 2009; Tsuchiya *et al.*, 1998), **(2)** was defined as methyl (*E*)-2-(2-((3,7-
135 dimethylocta-2,6-dien-1-yl)oxy)-5-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)acetate, and was named
136 garciparvifoliol due to its original structure.

137 Rubraxanthone **(1)**, isocowanol **(3)**, α -mangostin **(4)**, parvifolixanthone C **(5)**, 9-hydroxycalabaxanthone
138 **(6)**, isocowanin **(7)**, parvixanthone C **(8)**, parvixanthone G **(9)**, cratoxylone **(10)** and TPTQ **(11)**, all

139 previously isolated from different organs of *Garcinia parvifolia*, except for (6), were identified by
140 comparison with literature data (Ampofo and Waterman, 1986; Bennett *et al.*, 1993; Lee and Chan,
141 1977; Meunier *et al.*, 2025, 2024; Pattalung *et al.*, 1988; Rukachaisirikul *et al.*, 2006; Ryu *et al.*, 2010;
142 Sen *et al.*, 1980; Syamsudin *et al.*, 2013; Wahyuni *et al.*, 2004; Xu *et al.*, 2001).

143 The specific rotations of parvixanthone C (8) and parvixanthone G (9) were recorded at +8.5 and +7.8,
144 respectively, contrary to those previously described (-126 and -8, respectively) (Xu *et al.*, 2001). Chiral-
145 phase HPLC confirmed a scalemic mixture of both enantiomers of (8) and (9) with ratios of 40/60 and
146 44/56, respectively (Supplementary data, Fig. S14). The optical rotation of TPTQ (11) was recorded at
147 +11.1, as previously described (Wahyuni *et al.*, 2004).

148

149 2.1.2. Biological assays

150 The isolated compounds were evaluated at 10 and 100 μ M for their activity as inhibitors of fungal IRE1
151 using a previously established screening assay, one compound being considered active when its
152 percentage of activity is below 80% and a hit below 50% (Charpentier *et al.*, 2023). Out of eleven
153 compounds, nine were inactive while (4) and (10) exhibited a low activity of 81% and 63%, respectively
154 (Fig. 1). These results are not surprising due to the presence of a methoxy group at the C7 position for
155 the nine xanthenes. Indeed, Charpentier *et al.* (Charpentier *et al.*, 2023) have recently demonstrated
156 that this group could mask the activity, as in the case of γ -mangostin, the most active compound, which
157 differs only from (4) with a hydroxy instead of methoxy group at the C7 position.

158 This systematic phytochemical investigation allowed us to isolate eleven of the most abundant
159 compounds, including one previously undescribed. However, the very low anti-UPR activities of the
160 isolated compounds do not provide an adequate explanation for the activity observed in the crude
161 extract. Therefore, it can be assumed that the latter is associated with very dilute specialized
162 metabolites. In order to isolate and identify them, bioguided fractionation will be undertaken.

163

164 2.2. Bioguided fractionation

165 The latex was first dissolved in MeOH and subsequently filtered to remove any residual bark fragments.
166 The resulting filtrate was fractionated by flash chromatography to obtain thirteen fractions (F1 to F13).
167 A screening assay at 100 mg.L⁻¹ was used to rapidly decipher the biological potential of these fractions
168 (Chambaud *et al.*, 2024). Four fractions exhibited a better or similar activity than pure latex (85%), the
169 best one being F9 with 69%, the three others, F7, F11 and F12, being comprised between 83 and 88%
170 (Fig. 1). F7 was characterized, thanks to the previous results, as a mixture of rubraxanthone (**1**), α -
171 mangostin (**4**) and TPTQ (**11**), with an ELSD ratio of 85/5/10. Similarly, F11 was characterized as a
172 mixture of parvixanthone G (**9**) and cratoxylone (**10**), with an 80/20 ELSD ratio. The activity of F7 and
173 F11 was probably due to the partial activity of the aforementioned (**1**) and (**10**), so that these fractions
174 were not further investigated.

175 F9 and F12 were successively fractionated by preparative and semipreparative chromatography to give
176 three previously unreported xanthenes (SciFinder[®] database) named demethylrubraxanthone (**12**),
177 parvifolixanthone D (**13**) and 4'-*epi*-mangostenone C (**14**) as well as four known xanthenes, isocowanol
178 (**3**) parvixanthone C (**8**), garcinone D (**15**) and bannaxanthone C (**16**) (Bennett *et al.*, 1993; Han *et al.*,
179 2008; Sen *et al.*, 1986) (Fig. 2 and Supplementary data, Fig. S4).

180 The molecular formula C₂₃H₂₄O₆ of (**12**), was deduced from HRESIMS data (m/z 395.1498 [M - H]⁻;
181 calculated 395.1500) and 1D NMR data. The UV spectrum of (**12**) exhibited the same maximal
182 wavelengths as those of (**1**), indicating the same xanthone skeleton. Direct comparison of the ¹H and
183 ¹³C NMR spectra of compound (**12**), with those of (**1**), it exhibited the same characteristic signals of
184 phenolic hydroxy group (δ_H 13.67) located at C-1, aromatic protons (δ_H/δ_C 6.17/98.4, 6.28/93.5 and
185 6.83/101.2) located at C-2, C-4 and C-5, respectively, as well as signals for a geranyl moiety located at
186 C-8. The lack of a signal at δ_H 3.79 (3H, s) confirmed that (**12**) only differed from (**1**) by a demethylation
187 of the methoxy group at position C-7. Therefore (**12**) was identified as 1-[(2E)-3,7-dimethyl-2,6-
188 octadien-1-yl]-2,3,6,8-tetrahydroxy-9H-Xanthen-9-one (Table 1) which was already mentioned in a
189 patent (Bataillé-Simoneau *et al.*, 2023), but here isolated and described for the first time from natural
190 source. Consequently, (**12**) was named demethylrubraxanthone.

191 The molecular formula $C_{29}H_{32}O_7$ of (**13**), was deduced from HRESIMS data (m/z 491.2072 [M - H]⁻;
192 calculated 491.2075) and 1D NMR data. The UV spectrum of (**13**) indicated a typical xanthone
193 chromophore. The 1H NMR and ^{13}C NMR data of (**13**) were almost identical to those of rubraxanthone
194 (**1**) and isocowanin (**7**), except that the signal at C-4 (aromatic proton or prenyl moiety) was absent
195 (Table 1). The 1D NMR data combined with the HMQC experiment indicated signals for *cis*-olefinic
196 protons at δ_H/δ_C 6.90 (1H, d, $J = 10.1$ Hz)/117.2 and 5.69 (1H, d, $J = 10.1$ Hz)/125.0 together with a
197 methyl group at δ_H/δ_C 1.42 (3H, s)/23.5, hydroxymethyl signals at δ_H/δ_C 3.60 (1H, d, $J = 11.6$ Hz)/68.6
198 and 3.67 (1H, d, $J = 11.6$ Hz)/68.6 and an oxygenated sp^3 carbon at δ_C 82.0, indicating the presence of
199 a 2-hydroxymethyl-2-methyl ring. The HMBC correlations of H-4' with C-3 (δ_C 160.8) and H-3' with C-4
200 (δ_C 101.0) indicated that this unit is fused at its ether linkage C-3 and C-4 in the A-ring (Fig. 3). The
201 specific rotation of (**13**) was recorded at +7.9 and chiral-phase HPLC analysis confirmed a scalemic
202 mixture of both C-2' enantiomers with a ratio of 48/52 (Supplementary data, Fig. S30). These
203 observations and comparison with literature data, in particular with tetrandraxanthone B (Sukandar
204 *et al.*, 2019) and daedalin A (Morimura *et al.*, 2007), indicated that (**13**) was 2'-(hydroxymethyl)-2'-
205 methylpyrano[3,4]1,6-dihydroxy-8-(3,7-dimethyl-2,6-octadienyl)xanthone which was named
206 parvifolixanthone D.

207 The molecular formula $C_{24}H_{26}O_8$ of (**14**), was deduced from HRESIMS data (m/z 441.1555 [M - H]⁻;
208 calculated 441.1555) and 1D NMR data. The UV spectrum of (**14**) indicated a typical xanthone
209 chromophore. The 1H NMR spectrum (Table 1) exhibited the characteristic signals of a hydroxy group
210 (δ_H 13.91) located at C-1, aromatic protons (δ_H/δ_C 6.42/88.1 and 6.81/101.8) located at C-4 and C-5,
211 respectively, methoxy group (δ_H/δ_C 3.71/60.2) located at C-7, as well as signals of a prenyl moiety
212 located at C-8. The NMR data further showed the presence of two methyls adjacent to an oxygen
213 function (δ_H/δ_C 1.09/25.1 and 1.16/25.8) and two oxygenated methine protons (δ_H/δ_C 5.29/68.5 and
214 4.28/99.6), in addition with two broad singlet protons (δ_H 4.72 and 5.67) readily assigned to hydroxy
215 groups. In the COSY spectrum, one hydroxy signal at δ_H 5.67 was correlated with the methine at δ_H
216 5.29. Therefore, these data evidenced the presence of a 4-hydroxy-5-(1-hydroxy-1-

217 methylethyl)dihydrofuran moiety. The *trans* relationship of the two oxygenated methine protons was
218 established on the basis of the coupling constant value of 2.9 Hz in the ^1H NMR spectrum (Kwon *et al.*,
219 2016). In the HMBC spectrum, the proton at δ_{H} 5.29 showed correlation with an aromatic carbon at δ_{C}
220 167.0 through 3J , which implied that the furan ring oxygen was located at C-3. Finally, the structure
221 was characterized as the C-4' epimer of mangostenone C isolated from *Garcinia mangostana*
222 (Suksamrarn *et al.*, 2006) and confirmed by comparison of ^1H NMR data in chloroform-*d*
223 (Supplementary data, Fig. S34). The absolute stereochemistry of mangostenone C was not established
224 by the authors but the *cis* relationship of the two oxygenated methine protons was deduced on the
225 basis of the coupling constant value of 6.1 Hz (Suksamrarn *et al.*, 2006). The specific rotation of (**14**)
226 was recorded at +14.3, in contrast with mangostenone C (-28.3). Chiral-phase HPLC analysis confirmed
227 a scalemic mixture of both *trans* epimers of mangostenone C with a ratio of 40/60 (Supplementary
228 data, Fig. S39). Consequently, (**14**) was named 4'-*epi*-mangostenone C.

229 Garcinone D (**15**) and bannaxanthone C (**16**) previously isolated from the bark of *G. parvifolia* or
230 reported in the genus *Garcinia* were identified by comparison with literature data (Bennett *et al.*, 1993;
231 Han *et al.*, 2008; Meunier *et al.*, 2024).

232 The compounds newly isolated by the bioguided fractionation were evaluated at 10 and 100 μM for
233 their activity as inhibitors of fungal IRE1 (Fig. 1). Compound (**16**) showed a low activity of 63%,
234 comparable to (**10**) previously tested. Most importantly, demethylrubraxanthone (**12**) appeared as a
235 potential hit with a residual UPR activity of 0%. Therefore, a dose-response experiment was performed
236 and the IC_{50} was determined to be $8.0 \pm 0.3 \mu\text{M}$ (Supplementary data, Fig. S40), *i.e.* comparable to the
237 previously reported γ -mangostin (Charpentier *et al.*, 2023) or caledonixanthone N and P (Chambaud
238 *et al.*, 2024). Of the sixteen molecules isolated, fourteen were identified as polyhydroxylated
239 xanthenes, of which (**12**) and (**16**) were the most active compounds (Fig. 1B). These two compounds
240 share a catechol group at C6-C7 and C5-C6, respectively. The catechol group was also present in
241 previously identified active compounds such as γ -mangostin (Charpentier *et al.*, 2023), confirming the
242 importance of this group for IRE1 protein inhibition. In addition, the other isolated xanthenes,

243 including compound (1), contain a methoxy group at C-7 and did not show anti-UPR activity as
244 previously observed for α -mangostin (Charpentier *et al.*, 2023).

245

246 **2.3. Alternative sources of active compound (12)**

247 Considering the promising anti-UPR activity and the relatively low yield of (12) in the latex, alternative
248 strategies for the large-scale obtention of (12) were eventually investigated. Firstly, the structural
249 similarity between (1) and (12) prompts us to consider the semisynthetic route as being a promising
250 strategy for obtaining (12) from (1). Following the procedure described by Gokaraju (Gokaraju, 2009),
251 the demethylation of (1) with $AlCl_3$, resulted in the formation of (12), with a yield of 69% (Fig. 4).

252 Then, with the goal of identifying alternative and/or renewable sources of (1), a comprehensive review
253 of the literature was conducted. It revealed that the highest yield of (1) referenced was 0.64% from
254 the stem bark of *Garcinia eugenifolia* (Taher *et al.*, 2007), while the best referenced yield as a
255 renewable source, was 0.07% in the pericarp of *Garcinia mangostana* fruits (Ibrahim *et al.*, 2018).
256 These results were markedly lower than those obtained in the latex, which yielded 44% in one
257 purification step. This led us to study different organs of *Garcinia parvifolia* for the identification of
258 (12).

259 Finally, different extracts (cyclohexane, DCM, AcOEt and MeOH) of four organs of *G. parvifolia*
260 available in the laboratory, bark, leaves, mature and immature fruits, were made. The HPLC profiles of
261 these extracts indicated that (1) was found in MeOH, EtOAc and DCM extracts of bark and (12) in EtOAc
262 and DCM extracts of bark (Supplementary data, Fig. S41). No traces of (1) were found in renewable
263 organs such as leaves or fruits.

264 Therefore, the semisynthesis of (12) from (1) isolated from the latex of *Garcinia parvifolia* appeared as
265 the most efficient alternative way to produce (12) in sufficient quantity, opening the way for further
266 study of its biological properties.

267

268 3. Conclusions

269 A phytochemical analysis of the latex of *Garcinia parvifolia* permitted the isolation of sixteen
270 molecules. Of these, eleven were identified as known xanthenes, one was an original terpenophenol
271 structure named garciparvifoliol (**2**), and three were undescribed xanthenes (**12-14**). One of these
272 previously unreported compounds, demethylrubraxanthone (**12**), exhibited a notable activity, with an
273 IC₅₀ of 8.0 ± 0.3 μM using the anti-UPR cell-based assay. This result validates the effectiveness of
274 bioguided fractionation in comparison to a systematic phytochemical investigation, enabling the
275 identification of fractions containing minority but bioactive metabolites even when starting from a
276 weakly active extract. Subsequently, xanthone (**12**) was semisynthesized from the main compound,
277 rubraxanthone (**1**), which was readily isolated from latex with a 44% yield. The active compound (**12**)
278 was thus obtained in sufficient quantity for future investigation of its biological properties. This study
279 has thus identified a previously undescribed natural product (**12**) that inhibits the UPR pathway and is
280 accessible from a renewable resource, the latex of *Garcinia parvifolia*. Furthermore, chemical or
281 enzymatic demethylation of rubraxanthone (**1**) from latex without purification would provide a
282 bioactive material that could be a potential alternative solution for crop protection against fungal
283 diseases.

284

285 4. Experimental

286 4.1. General experimental procedure

287 Optical rotations were measured with a P3000 digital polarimeter. Ultraviolet-visible spectra were
288 recorded on a Genesys 180 UV-Visible spectrophotometer with compounds dissolved at 1 mg.mL⁻¹ in
289 MeOH then diluted 1/50. ¹H, ¹³C, and 2D NMR spectra were recorded in the appropriate deuterated
290 solvent (chloroform-*d*, acetone-*d*₆ or benzene-*d*₆) on a Jeol JNM-ECZ400S spectrometer operating at
291 400 MHz (¹H). HRESIMS data were obtained on a Waters Xevo G2-XS Q-TOF mass spectrometer. Flash
292 chromatography fractionations were performed on a CombiFlash Rf-200 system. Samples were
293 adsorbed on silica gel (60 Å, 40-63 μm) and purified on Interchim SI-HC columns (50 μm). Preparative

294 HPLC purifications were performed on a Shimadzu LC-20AP solvent delivery system coupled to an SPD-
295 40 UV detector and an FRC-10A fraction collector using LabSolutions software and an Agilent Pursuit
296 XRs C18 column (250 x 21.2 mm; 5 μm ; 100 \AA). Semipreparative HPLC purifications and chiral-phase
297 HPLC analyses were performed on an HP 1100 instrument coupled to a photodiode array detector and
298 a fraction collector, using Chemstation software and a Phenomenex Luna C18(2) column (250 x 10 mm;
299 5 μm ; 100 \AA) or Lux i-Amylose-1 column (250 x 4.6 mm; 5 μm ; 1000 \AA). HPLC analyses were performed
300 on a Shimadzu Prominence-i LC-2030 3D coupled to a PDA and a Sedere ELSD-LT 90, assisted by
301 LabSolutions software. LC-MSⁿ analyses were performed on a Bruker Esquire 3000 Plus spectrometer
302 equipped with an HPLC 2695 instrument and a 2487 UV detector assisted by DataAnalysis software. A
303 Phenomenex Gemini C18 column (150 x 4.6 mm; 3 μm ; 110 \AA) was used for HPLC and LC-MSⁿ analysis.

304

305 **4.2. Plant material**

306 Latex, bark, leaves, mature and immature fruits of *Garcinia parvifolia* (Miq.) Miq. (Clusiaceae) were
307 collected by one of us (M.L.) at Hyman Simpanan Meranto Gua Musang, Kelantan, Malaysia, in May
308 2009. Plant material was authenticated by the botanist Teo Leong Eng and a voucher specimen (KL-
309 5670) was kept on the Herbarium of the Department of Chemistry, University of Malaya, Kuala Lumpur,
310 Malaysia.

311

312 **4.3. Extraction, isolation and semisynthesis**

313 For the systematic phytochemical investigation, the dried latex of *Garcinia parvifolia* (10 g) was
314 dissolved in 500 mL of MeOH and filtrated (100-160 μm) to remove bark fragments (0.9 g). The filtrate
315 (GpLM) was then extracted three times with 500 mL of cyclohexane to yield two fractions after
316 concentration *in vacuo* at 40 °C. A part (350 mg) of the methanolic fraction (GpLM2; 8.1 g) was
317 subjected to a C18 preparative column using a gradient of (A) water and (B) MeCN at 21.24 mL.min⁻¹
318 (60% to 75% B in 20 min, 75% B for 5 min, 75% to 100% in 10 min, then 100% B for 5 min) and UV
319 detection. Fractions obtained (M2A to M2H) were monitored by HPLC-PDA-ELSD. Fraction M2A (tR =

320 22.5 min, 1.3 mg) was identified as **(3)**, M2B (tR = 24.0 min, 101 mg) as **(1)**, M2C (tR = 28.8 min, 12 mg)
321 as **(4)**, M2D (tR = 31.2 min, 3.6 mg) as **(2)**, M2E (tR = 32.3 min, 1.8 mg) as **(5)**, M2G (tR = 35.8 min, 2.6
322 mg) as **(6)**, and M2H (tR = 39.4 min, 12 mg) as **(11)**.

323 Cyclohexanic fraction (GpLC; 1.0 g) was fractionated by flash chromatography on a silica column (80 g)
324 using (A) petroleum ether (40-60 °C) and (B) CHCl₃/AcOEt (1:1) as eluents (0% B 0-5 min, 0-10% B 5-15
325 min, 10% B 15-25 min, 10-20% B 25-35 min, 20% B 35-45 min, 20-30% B 45-55 min, 30% B 55-65 min,
326 30-40% B 65-70 min, 40% B 70-83 min, 40-50% B 83-93 min, 50% B 93-103 min, 50-60% B 103-113 min,
327 60% B 113-123 min, 60-70% B 123-128 min, 70% B 128-133 min, 70-100% B 133-143 min, 100% B 143-
328 153 min, then 100% acetone until 173min), at a flow rate of 44 mL.min⁻¹ and UV detection. Fractions
329 obtained (C1 to C22) were monitored by HPLC-PDA-ELSD and LC-MSⁿ. Fraction C8 (tR = 45 min, 29 mg)
330 was identified as **(6)** and C14 (tR = 72 min, 267 mg) as **(1)**. Fractions C12 and C13 with similar
331 chromatographic profiles were mixed (tR = 60 min, 149 mg) and identified as **(11)**. Fraction C10 (31
332 mg) was fractionated by flash chromatography on a silica column (4 g) using (A) cyclohexane and (B)
333 toluene/AcOEt (1:1) as eluents (0% B 0-5 min, 0-10% B 5-10 min, 10% B 10-15 min, 10-20% B 15-20
334 min, 20% B 20-25 min, 20-25% B 25-30 min, 25% B 30-40 min, 25-30% B 40-45 min, 30% B 45-50 min,
335 30-35% B 50-55 min, 35% B 55-65 min, 35-40% B 65-70 min, 40% B 70-75 min, 40-100% B 75-80 min,
336 100% B 80-90 min), at a flow rate of 12 mL.min⁻¹ and UV detection. Fractions obtained (C10A to C10D)
337 were monitored by HPLC-PDA-ELSD. Fraction C10C (tR = 22 min, 10 mg) was identified as **(11)**. Fraction
338 C10B (13 mg) was subjected to a C18 semipreparative column using a water (A) and MeCN (B) gradient
339 (40% B for 5 min, 40% to 100% B in 30 min then 100% B for 5 min) at 4.7 mL.min⁻¹ and PDA detection.
340 Fractions obtained (C10B1 to C10B3) were monitored by HPLC-PDA-ELSD. Fraction C10B2 (tR = 24.0
341 min, 5.5 mg) was identified as **(2)** and C10B3 (tR = 26.2 min, 1.4 mg) as **(7)**. Fraction C18 (31 mg) was
342 subjected to a C18 preparative column using a mixture of water and MeCN (3.5:6.5) at 21.24 mL.min⁻¹
343 (isocratic mode for 40 min) and UV detection. Fractions obtained (C18A to C18H) were monitored by
344 HPLC-PDA-ELSD. Fraction C18A (tR = 7.6 min, 1.2 mg) was identified as **(8)**, C18B (tR = 10.0 min, 1.2
345 mg) as **(9)**, C18C (tR = 12.1 min, 0.6 mg) as **(10)** and C18G (tR = 30.5 min, 4.6 mg) as **(3)**.

346 For the bioguided fractionation, the dried latex of *Garcinia parvifolia* (10 g) was dissolved in 500 mL of
347 MeOH and filtrated (100-160 μm) to remove bark fragments (1 g). The filtrate (GpLM) was
348 concentrated *in vacuo* at 40 °C and fractionated by flash chromatography on a silica column (220 g)
349 using (A) petroleum ether (40-60 °C) and (B) $\text{CHCl}_3/\text{AcOEt}$ (1:1) as eluents (0% B 0-5 min, 0-100% B 5-
350 85 min, then 100% acetone until 100 min, and finally 100% MeOH until 110 min) at a flow rate of 100
351 mL^{-1} and UV detection. Fractions obtained (F1 to F15) were monitored by HPLC-PDA-ELSD and LC-MSⁿ.
352 Fraction F4 (t_R = 33 min, 127 mg) was identified as **(6)**, F7 (t_R = 46 min, 4.6 g) as mainly **(1)** and F10 (t_R
353 = 66 min, 335 mg) as **(3)**. Fraction F9 (191 mg) was subjected to a C18 preparative column using a
354 mixture of water and MeCN (3.5/6.5) at 21.24 $\text{mL}\cdot\text{min}^{-1}$ (isocratic mode for 30 min then 100% of MeCN
355 for 10 min) and UV detection. Fractions obtained (F9A to F9H) were monitored by HPLC-PDA-ELSD.
356 Fraction F9D (t_R = 18.9 min, 23 mg) was identified as **(12)**. Fraction F9E (12 mg) was subjected to a C18
357 semipreparative column using a 0.1% formic acid in water (A) and MeCN (B) gradient (55% to 80% B in
358 30 min) at 4.7 $\text{mL}\cdot\text{min}^{-1}$ and PDA detection. Fractions obtained (F9E1 to F9E3) were monitored by HPLC-
359 PDA-ELSD. Fraction F9E2 (t_R = 25.1 min, 3.4 mg) was identified as **(3)**. Fraction F9F (5.8 mg) was
360 subjected to a C18 semipreparative column using a 0.1% formic acid in water (A) and MeCN (B) gradient
361 (60% to 90% B in 30 min) at 4.7 $\text{mL}\cdot\text{min}^{-1}$ and PDA detection. Fractions obtained (F9F1 and F9F2) were
362 monitored by HPLC-PDA-ELSD. Fraction F9F1 (t_R = 26.0 min, 2 mg) was identified as **(13)**. Fraction F12
363 (156 mg) was subjected to a C18 preparative column using a water (A) and MeCN (B) gradient (40% B
364 0-5 min, 40-100% B 5-35 min, then 100% B up to 40 min) at 21.24 $\text{mL}\cdot\text{min}^{-1}$ and UV detection. Fractions
365 obtained (F12A to F12F) were monitored by HPLC-PDA-ELSD. Fraction F12B (t_R = 17.9 min, 21 mg) was
366 identified as **(14)**, F12C (t_R = 20.2 min, 28 mg) as **(8)**, F12D (t_R = 23.7 min, 12 mg) as **(15)**, and F12E (t_R
367 = 27.8 min, 3.5 mg) as **(16)**.

368 To investigate the other organs of *G. parvifolia*, ultrasound-assisted extractions were conducted in
369 accordance with the following procedure: 4 g of powder from each organ were extracted for 15 min
370 at 30 °C with 40 mL of consecutive solvent. The sequence was as follows: once cyclohexane, once DCM,

371 x3 AcOEt and x3 MeOH. Each extract was filtered on a fritted glass with a Celite 545 layer and
372 subsequently evaporated in vacuo at 40 °C. The extracts obtained were monitored by HPLC-PDA-ELSD.
373 Rubraxanthone (**1**) (60 mg, 0.15 mmol, 1 eq.) was dissolved in dry 1,2-dichloroéthane (0.9 mL), then
374 dry pyridine (0.44 mL) was added. The system was stirred at room temperature for 15 min, then AlCl₃
375 (5 eq.) was slowly added in the reaction mixture. A spatula tip of NaI was added, and the reaction
376 mixture was heated under reflux for 2 h. After it cooled at room temperature, system was quenched
377 with HCl (1 M) and brine was added. The mixture was extracted with THF (3 times) and combined
378 organic layer was evaporated to dryness. The crude was purified by silica gel column chromatography
379 eluted with pet-ether b.p. 40-60°/acetone (8:2) to afford (**12**) (40.3 mg, 69%).

380 Garciparvifoliol (**2**): methyl 5-hydroxy-2-(2-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-3-(3-methylbut-2-en-
381 1-yl)phenyl)acetate; brownish gum; UV (MeOH) λ_{\max} (log ϵ): 204 (4.45), 288 (3.31) nm; ¹H and ¹³C NMR
382 data see Table 1; HRESIMS: m/z 409.2358 [M + Na]⁺ (calcd for C₂₄H₃₄O₄Na, 409.2355) (Supplementary
383 data, Fig. S5-S13).

384 Demethylrubraxanthone (**12**): 1,3,6,7-tetrahydroxy-8-(3,7-dimethyl-2,6-octadienyl)xanthone; orange
385 powder; UV (MeOH) λ_{\max} (log ϵ): 204 (4.47), 241 (4.32), 256 (4.38), 312 (4.17), 362 (3.87) nm; ¹H and
386 ¹³C NMR data see Table 1; HRESIMS: m/z 395.1498 [M - H]⁻ (calcd for C₂₃H₂₃O₆, 395.1490)
387 (Supplementary data, Fig. S16-S22).

388 Parvifolixanthone D (**13**): 2'-(hydroxymethyl)-2'-methylpyrano[3,4]1,6-dihydroxy-8-(3,7-dimethyl-2,6-
389 octadienyl)xanthone; yellow powder; [α]_D¹⁸ +7.9 (c 0.18, acetone); UV (MeOH) λ_{\max} (log ϵ): 204 (4.48),
390 256 (4.39), 286 (4.30), 320 (4.04), 366 (3.70) nm; ¹H and ¹³C NMR data see Table 1; HRESIMS: m/z
391 491.2072 [M - H]⁻ (calcd for C₂₉H₃₁O₇, 491.2070) (Supplementary data, Fig. S23-S29).

392 4'-*epi*-Mangostenone C (**14**): 1,6-dihydroxy-7-methoxy-8-(3-methylbut-2-enyl)-4'-hydroxy-5'-(1-
393 hydroxy-1-methylethyl)-4',5'-dihydrofurano(2',3':3,2)xanthone; brown powder; [α]_D¹⁸ +14.7 (c 0.63,
394 MeOH); UV (MeOH) λ_{\max} (log ϵ): 224 (5.38), 245 (4.64), 314 (4.33) nm; ¹H and ¹³C NMR data see Table
395 1; HRESIMS: m/z 441.1555 [M - H]⁻ (calcd for C₂₄H₂₅O₈, 441.1549) (Supplementary data, Fig. S31-S38).

396

397 **4.4. Biological experimental procedures**

398 The extract and fractions were evaluated on the UPR cell-based assay at concentrations of 100 mg.L⁻¹
399 following the procedure previously described (Chambaud *et al.*, 2024). Additionally, the purified
400 molecules were evaluated at 100 and 10 µM, in accordance with the procedure previously described
401 (Charpentier *et al.*, 2023).

402

403 **Acknowledgments**

404 This work was carried out in the framework of the International French Malaysian Natural Product
405 Laboratory (IFM-NatProLab/IRP) established between CNRS-ICSN and the University Malaya. The
406 authors also acknowledge PTM PHYTO (SFR QUASAV) and PTM ASTRAL (SFR MATRIX) for the
407 instruments.

408

409 **Funding**

410 This research did not receive any specific grant from funding agencies in the public, commercial, or
411 not-for-profit sectors.

412

413 **Appendix A. Supplementary data**

414 Supplementary data to this article can be found online.

415

416 **CRedit author statement**

417 Dimitri Bréard: Formal analysis; Investigation; Validation; Visualization; Writing - original draft; Writing
418 - review & editing. Thomas Charpentier: Formal analysis; Validation; Writing - review & editing. Anne-
419 Marie Le Ray: Conceptualization; Supervision; Writing - review & editing. Nadège Blon: Investigation.
420 Nelly Bataillé-Simoneau: Resources; Writing - review & editing. Marc Litaudon: Resources; Writing -
421 review & editing. Khalijah Awang: Resources; Writing - review & editing. Thomas Guillemette:
422 Resources; Writing - review & editing. Pascal Richomme: Conceptualization; Supervision; Writing -

423 review & editing. Guillaume Viault: Conceptualization; Supervision; Writing - original draft; Writing -

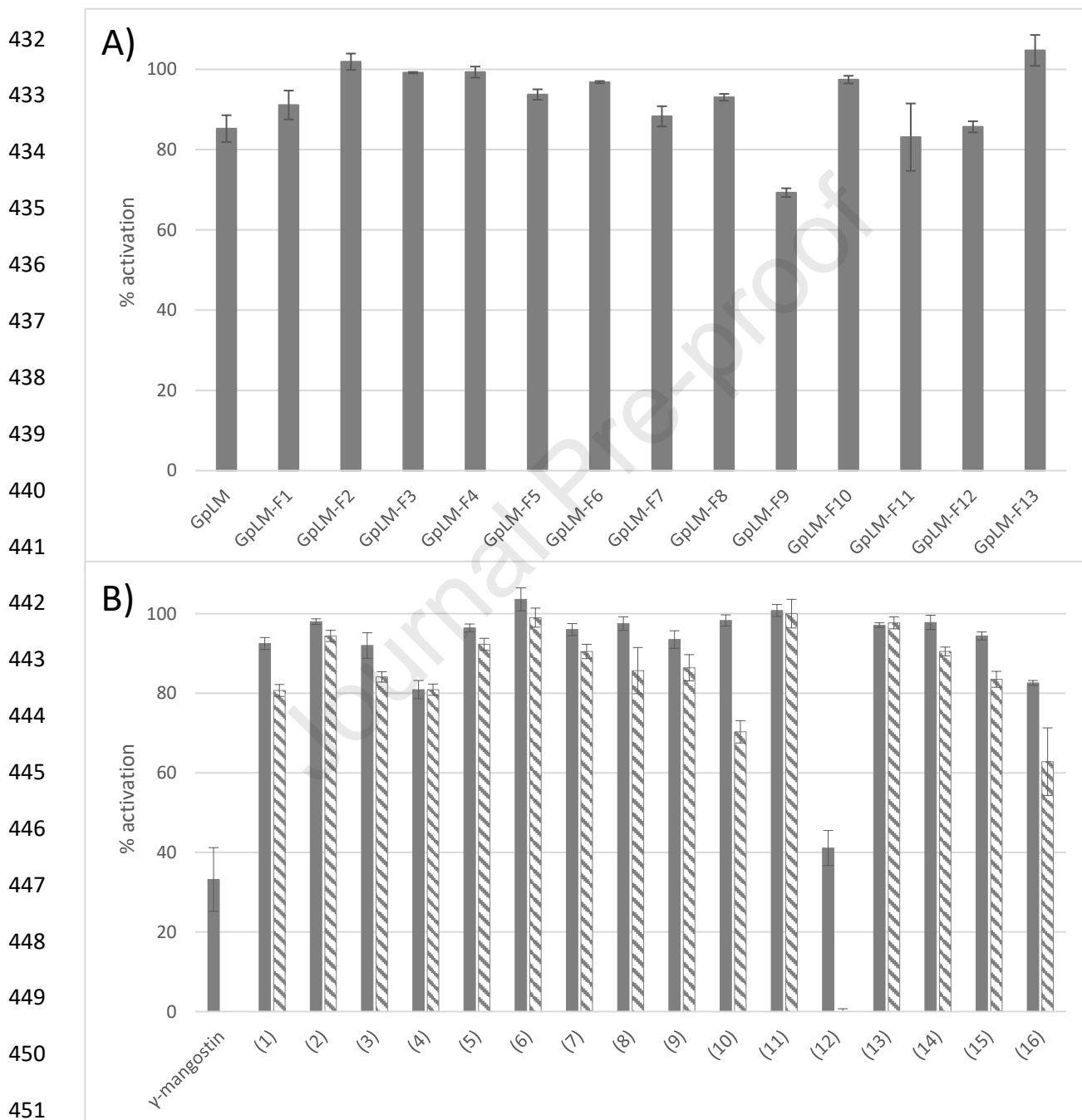
424 review & editing.

425

Journal Pre-proof

426 **Figures and Tables**

427 Figure 1. Results of the UPR cell-based assay (n=3). A) Screening assay at 100 mg.mL⁻¹ for the
 428 methanolic filtrate of *Garcinia parvifolia* latex (GpLM) and fractions F1 to F13 (GpLMF1 to GpLMF13).
 429 B) Assay at 10 (full bar plots) and 100 μ M (hatched bar plots) for compounds isolated from systematic
 430 phytochemical investigation (**1-11**) and from bioguided fractionation (**12-16**) compared to the
 431 previously reported γ -mangostin (Charpentier *et al.*, 2023).



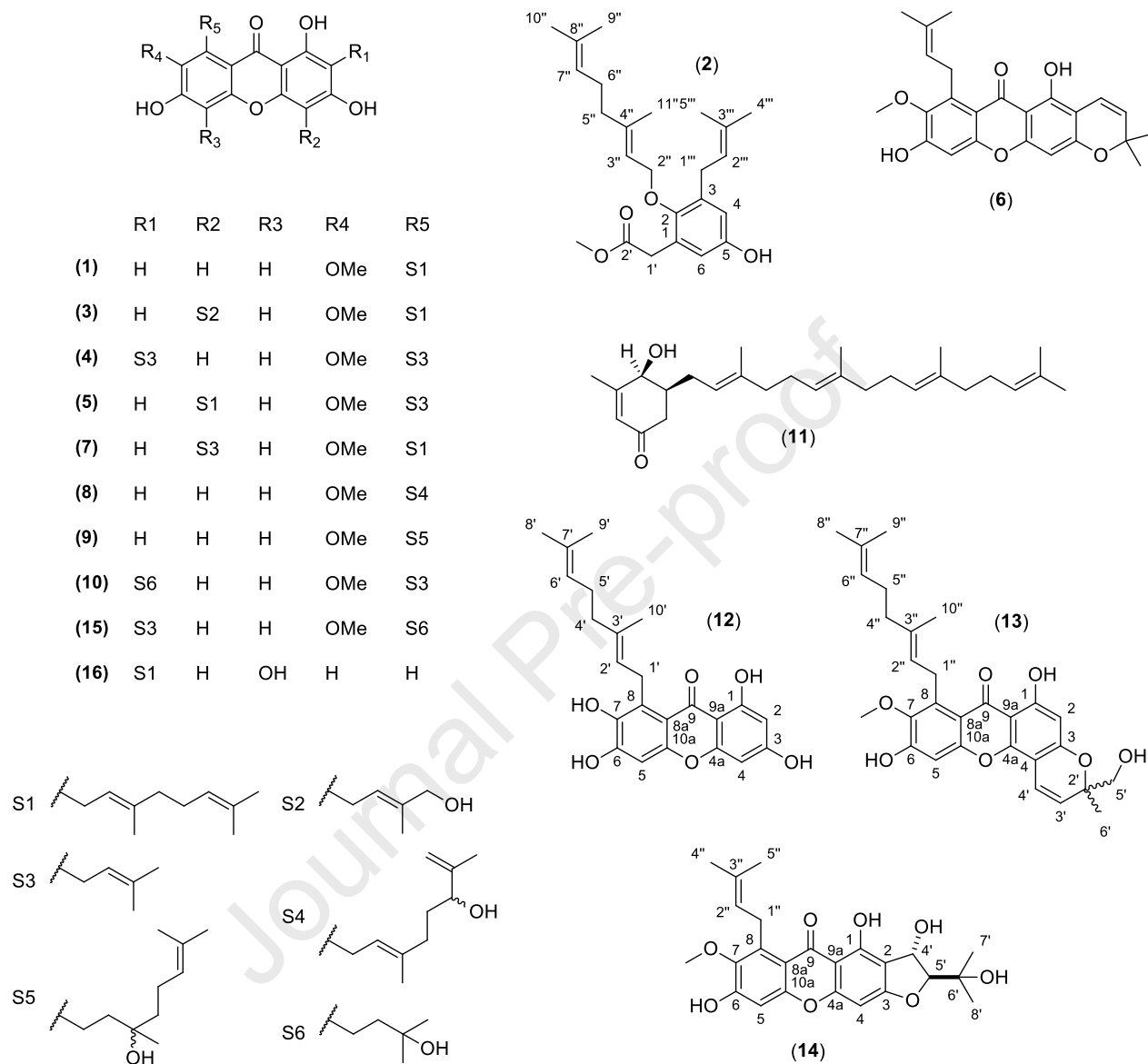
452

453

454

455 Figure 2. Structures of isolated compounds (1-16) from the latex of *G. parvifolia*.

456



457

458

459

460

461

462

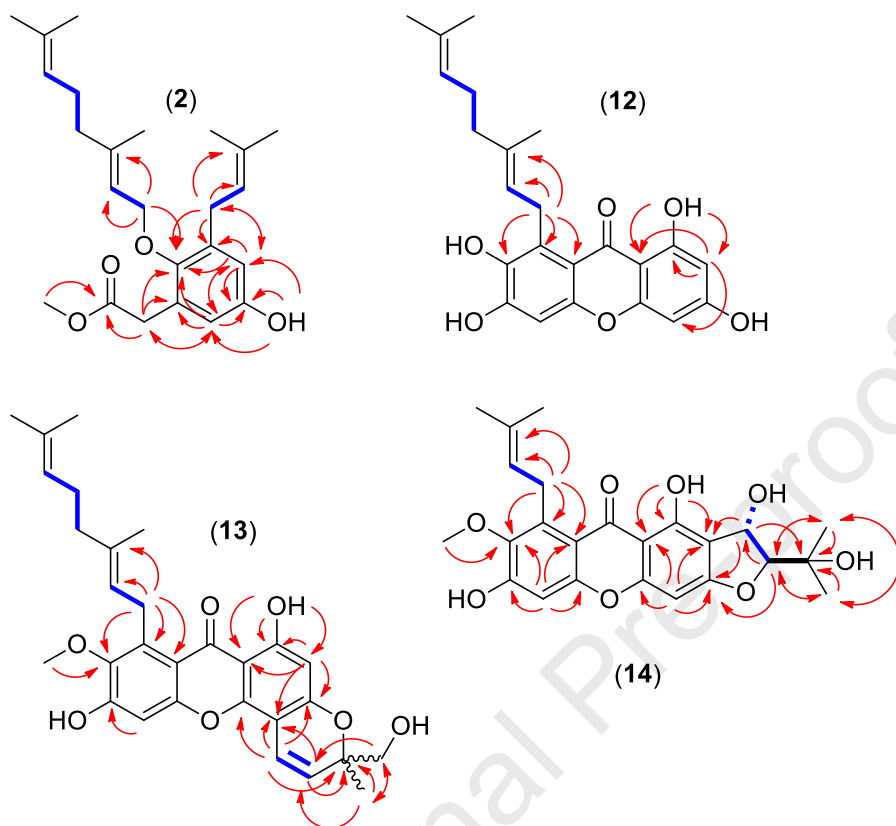
463

464

465

466 Figure 3. Key ^1H - ^1H COSY (blue line) and ^1H - ^{13}C HMBC (red arrow) correlations of compounds (2),
467 (12), (13) and (14).

468



469

470

471

472

473

474

475

476

477

478

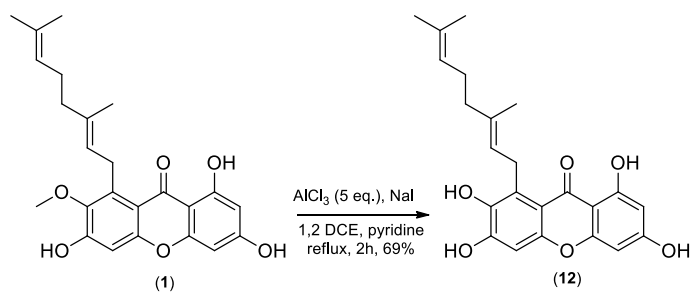
479

480

481

482 Figure 4. Semisynthesis of (12) from (1).

483



506 Table 1

507 ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data of (2) and (12-14) (δ in ppm, J in Hz).

No	2 ^a		12 ^b		13 ^b		14 ^c	
	δ_{H} , mult. (J)	δ_{C}	δ_{H} , mult. (J)	δ_{C}	δ_{H} , mult. (J)	δ_{C}	δ_{H} , mult. (J)	δ_{C}
1	-	128.6	-	164.9	-	164.3	-	159.1
2	-	149.3	6.17, s	98.4	6.09, s	99.2	-	111.2
3	-	136.5	-	165.1	-	160.8	-	167.0
4	6.58, s	115.8	6.28, s	93.5	-	101.0	6.42, s	88.1
4a	-	-	-	153.6	-	151.8	-	157.5
5	-	151.6	6.83, br. s	101.2	6.97, s	103.0	6.81, s	101.8
6	6.58, s	114.9	-	152.7	-	156.4	-	154.8
7	-	-	-	141.8	-	145.1	-	143.7
8	-	-	-	129.0	-	138.0	-	136.4
8a	-	-	-	111.9	-	111.3	-	109.6
9	-	-	-	183.1	-	182.9	-	181.8
9a	-	-	-	103.8	-	104.1	-	102.9
10a	-	-	-	158.0	-	158.8	-	157.4
1'	3.65, s	35.6	4.18, d (6.6)	26.2	-	-	-	-
2'	-	172.5	5.33, t (6.6)	124.4	-	82.0	-	-
3'	-	-	-	135.0	5.69, d (10.1)	125.0	-	-
4'	-	-	1.95, m	40.6	6.90, d (10.1)	117.2	5.29, d (2.9)	68.5
5'	-	-	2.02, m	27.4	3.60, d (11.6)	68.6	4.28, d (2.9)	99.6
6'	-	-	5.04, m	125.2	3.67, d (11.6)	23.5	-	69.7
7'	-	-	-	131.5	1.42, s	-	1.16, s	25.8
8'	-	-	1.56, s	25.7	-	-	1.09, s	25.1
9'	-	-	1.52, s	17.7	-	-	-	-
10'	-	-	1.84, s	16.6	-	-	-	-
1''	-	-	-	-	4.12, d (6.4)	26.8	4.01, d (6.5)	25.8
2''	4.28, d (6.9)	71.0	-	-	5.28, m	124.8	5.16, m	123.6
3''	5.54, m	120.1	-	-	-	135.1	-	130.5
4''	-	141.0	-	-	1.98, m	40.5	1.77, s	18.0
5''	2.10, m	39.8	-	-	2.07, m	27.3	1.62, s	25.6
6''	2.10, m	26.5	-	-	5.04, m	125.2	-	-
7''	5.11, m	124.0	-	-	-	131.6	-	-
8''	-	132.0	-	-	1.52, s	17.7	-	-
9''	1.69, d (0.8)	25.8	-	-	1.56, s	25.8	-	-
10''	1.62, s	17.8	-	-	1.83, d (1.1)	16.6	-	-
11''	1.67, d (0.5)	16.6	-	-	-	-	-	-
1'''	3.34, d (7.2)	28.4	-	-	-	-	-	-
2'''	5.27, m	122.6	-	-	-	-	-	-
3'''	-	133.3	-	-	-	-	-	-
4'''	1.70, s	18.0	-	-	-	-	-	-
5'''	1.75, d (0.9)	25.9	-	-	-	-	-	-
1-OH	-	-	13.67, s	-	13.60, s	-	13.91, s	-
5-OH	4.65 (s)	-	-	-	-	-	-	-
7-OMe	-	-	-	-	3.81, s	61.3	3.71, s	60.2
2'-OMe	3.70, s	52.2	-	-	-	-	-	-
4'OH	-	-	-	-	-	-	5.67, br. s	-
6'OH	-	-	-	-	-	-	4.72, br. s	-

508 ^a In chloroform-*d*, ^b In acetone-*d*₆, ^c In dms-*d*₆

509

23

510 **References**

- 511 Abdalrahim, F.A.A., Khalid, M.A.S., Mohammad, J.S., Zhari, I., Amin, M.S.A.M., 2012. Quantification of
 512 α -, β - and γ -mangostin in *Garcinia mangostana* fruit rind extracts by a reverse phase high
 513 performance liquid chromatography. *J. Med. Plants Res.* 6, 4526–4534.
 514 <https://doi.org/10.5897/JMPR11.1253>
- 515 Ampofo, S.A., Waterman, P.G., 1986. Xanthenes from three *Garcinia* species. *Phytochemistry* 25,
 516 2351–2355. [https://doi.org/10.1016/S0031-9422\(00\)81694-5](https://doi.org/10.1016/S0031-9422(00)81694-5)
- 517 Bataillé-Simoneau, N., Charpentier, T., Guillemette, T., Le Ray, A.-M., Richomme, P., Simoneau, P.,
 518 Viault, G., 2023. Compositions and methods for controlling phytopathogenic infections. *WO*
 519 2023/099609 A1.
- 520 Bennett, G.J., Harrison, L.J., Sia, G.-L., Sim, K.-Y., 1993. Triterpenoids, tocotrienols and xanthenes
 521 from the bark of *Cratoxylum cochinchinense*. *Phytochemistry* 32, 1245–1251.
 522 [https://doi.org/10.1016/S0031-9422\(00\)95100-8](https://doi.org/10.1016/S0031-9422(00)95100-8)
- 523 Chaloner, T.M., Gurr, S.J., Bebbler, D.P., 2021. Plant pathogen infection risk tracks global crop yields
 524 under climate change. *Nat. Clim. Chang.* 11, 710–715. [https://doi.org/10.1038/s41558-021-](https://doi.org/10.1038/s41558-021-01104-8)
 525 01104-8
- 526 Chambaud, M., Le Ray, A.-M., Hamzi, R., Charpentier, T., Blon, N., Bréard, D., Le Pogam, P., Litaudon,
 527 M., Dumontet, V., Bataillé-Simoneau, N., Guillemette, T., Simoneau, P., Schinkovitz, A.,
 528 Guilet, D., Viault, G., Richomme, P., 2024. Xanthone inhibitors of unfolded protein response
 529 isolated from *Calophyllum caledonicum*. *J. Nat. Prod.* 87, 1628–1634.
 530 <https://doi.org/10.1021/acs.jnatprod.4c00328>
- 531 Charpentier, T., Viault, G., Le Ray, A.-M., Bataillé-Simoneau, N., Helesbeux, J.-J., Blon, N., Bastide, F.,
 532 Marchi, M., Aligon, S., Bruguière, A., Dinh, C.P., Benbelkacem, Z., Dallery, J.-F., Simoneau, P.,
 533 Richomme, P., Guillemette, T., 2023. Natural products targeting the fungal unfolded protein
 534 response as an alternative crop protection strategy. *J. Agric. Food Chem.* 71, 13706–13716.
 535 <https://doi.org/10.1021/acs.jafc.3c03602>
- 536 Destoumieux-Garzón, D., Mavingui, P., Boetsch, G., Boissier, J., Darriet, F., Duboz, P., Fritsch, C.,
 537 Giraudoux, P., Le Roux, F., Morand, S., Paillard, C., Pontier, D., Sueur, C., Voituren, Y., 2018.
 538 The one health concept: 10 years old and a long road ahead. *Front. Vet. Sci.* 5, 14.
 539 <https://doi.org/10.3389/fvets.2018.00014>
- 540 Feng, Z., Lu, X., Gan, L., Zhang, Q., Lin, L., 2020. Xanthenes, a promising anti-inflammatory scaffold:
 541 structure, activity, and drug likeness analysis. *Molecules* 25, 598.
 542 <https://doi.org/10.3390/molecules25030598>
- 543 Fernando, I.P.S., Fernando, P.W.P., Kim, T., Ahn, G., 2022. Structural diversity, biosynthesis, and
 544 health-promoting properties of brown algal meroditerpenoids. *Crit. Rev. Biotechnol.* 42,
 545 1238–1259. <https://doi.org/10.1080/07388551.2021.2001639>
- 546 Fisher, M.C., Hawkins, N.J., Sanglard, D., Gurr, S.J., 2018. Worldwide emergence of resistance to
 547 antifungal drugs challenges human health and food security. *Science* 360, 739–742.
 548 <https://doi.org/10.1126/science.aap7999>
- 549 Fisher, M.C., Henk, D.A., Briggs, C.J., Brownstein, J.S., Madoff, L.C., McCraw, S.L., Gurr, S.J., 2012.
 550 Emerging fungal threats to animal, plant and ecosystem health. *Nature* 484, 186–194.
 551 <https://doi.org/10.1038/nature10947>
- 552 Gates, P.J., 2021. Atmospheric pressure chemical ionisation mass spectrometry for the routine
 553 analysis of low molecular weight analytes. *Eur. J. Mass Spectrom.* 27, 13–28.
 554 <https://doi.org/10.1177/14690667211005055>
- 555 Gokaraju, G.R., 2009. A process for producing γ -mangostin. *WO* 2009/093259 A2.
- 556 Han, Q.-B., Yang, N.-Y., Tian, H.-L., Qiao, C.-F., Song, J.-Z., Chang, D.C., Chen, S.-L., Luo, K.Q., Xu, H.-X.,
 557 2008. Xanthenes with growth inhibition against HeLa cells from *Garcinia*
 558 *xipshuanbannaensis*. *Phytochemistry* 69, 2187–2192.
 559 <https://doi.org/10.1016/j.phytochem.2008.05.019>

- 560 Hooper, G.J., Davies-Coleman, M.T., 1995. Sesquiterpene hydroquinones from the South African soft
561 coral *Alcyonium fauri*. Tetrahedron Lett. 36, 3265–3268. [https://doi.org/10.1016/0040-](https://doi.org/10.1016/0040-4039(95)00461-K)
562 4039(95)00461-K
- 563 Ibrahim, S.R.M., Abdallah, H.M., El-Halawany, A.M., Radwan, M.F., Shehata, I.A., Al-Harshany, E.M.,
564 Zayed, M.F., Mohamed, G.A., 2018. Garcixanthones B and C, new xanthones from the
565 pericarps of *Garcinia mangostana* and their cytotoxic activity. Phytochem. Lett. 25, 12–16.
566 <https://doi.org/10.1016/j.phytol.2018.03.009>
- 567 Joubert, A., Bataille-Simoneau, N., Champion, C., Guillemette, T., Hudhomme, P., Iacomi-Vasilescu, B.,
568 Leroy, T., Pochon, S., Poupard, P., Simoneau, P., 2011a. Cell wall integrity and high osmolarity
569 glycerol pathways are required for adaptation of *Alternaria brassicicola* to cell wall stress
570 caused by brassicaceous indolic phytoalexins: camalexin activation of HOG and CWI
571 pathways. Cell. Microbiol. 13, 62–80. <https://doi.org/10.1111/j.1462-5822.2010.01520.x>
- 572 Joubert, A., Simoneau, P., Champion, C., Bataillé-Simoneau, N., Iacomi-Vasilescu, B., Poupard, P.,
573 François, J.M., Georgeault, S., Sellier, E., Guillemette, T., 2011b. Impact of the unfolded
574 protein response on the pathogenicity of the necrotrophic fungus *Alternaria brassicicola*.
575 Mol. Microbiol. 79, 1305–1324. <https://doi.org/10.1111/j.1365-2958.2010.07522.x>
- 576 Jung, M., Jang, K.H., Kim, B., Lee, B.H., Choi, B.W., Oh, K.-B., Shin, J., 2008. Meroditerpenoids from
577 the brown alga *Sargassum siliquastrum*. J. Nat. Prod. 71, 1714–1719.
578 <https://doi.org/10.1021/np800321y>
- 579 Kwon, J., Hiep, N.T., Kim, D.-W., Hong, S., Guo, Y., Hwang, B.Y., Lee, H.J., Mar, W., Lee, D., 2016.
580 Chemical constituents isolated from the root bark of *Cudrania tricuspidata* and their
581 potential neuroprotective effects. J. Nat. Prod. 79, 1938–1951.
582 <https://doi.org/10.1021/acs.jnatprod.6b00204>
- 583 Lee, H.H., Chan, H.K., 1977. 1,3,6-trihydroxy-7-methoxy-8-(3,7-dimethyl-2,6-octadienyl)xanthone
584 from *Garcinia cowa*. Phytochemistry 16, 2038–2040. [https://doi.org/10.1016/0031-](https://doi.org/10.1016/0031-9422(77)80129-5)
585 9422(77)80129-5
- 586 Lim, T.K., 2012. *Garcinia parvifolia*, in: Edible Medicinal and Non-Medicinal Plants. Springer,
587 Dordrecht, pp. 115–119.
- 588 Meunier, M., Bréard, D., Boisard, S., Blanchard, P., Litaudon, M., Awang, K., Schinkovitz, A., Derbré,
589 S., 2024. Looking for actives in the haystack: merging HRMS²-based molecular networking,
590 chemometrics, and ¹³C NMR-based dereplication approaches. J. Nat. Prod. 87, 2398–2407.
591 <https://doi.org/10.1021/acs.jnatprod.4c00647>
- 592 Meunier, M., Haack, M., Awad, D., Brück, T., Awang, K., Litaudon, M., Saubion, F., Legeay, M., Bréard,
593 D., Guilet, D., Derbré, S., Schinkovitz, A., 2025. Matrix free laser desorption ionization
594 coupled to trapped ion mobility mass spectrometry: an innovative approach for isomer
595 differentiation and molecular network visualization. Talanta 287, 127626.
596 <https://doi.org/10.1016/j.talanta.2025.127626>
- 597 Morimura, K., Yamazaki, C., Hattori, Y., Makabe, H., Kamo, T., Hirota, M., 2007. A tyrosinase inhibitor,
598 daedalin A, from mycelial culture of *Daedalea dickinsii*. Biosci. Biotechnol. Biochem. 71,
599 2837–2840. <https://doi.org/10.1271/bbb.70266>
- 600 N’Guyen, G.Q., Raulo, R., Porquier, A., Iacomi, B., Pelletier, S., Renou, J.-P., Bataillé-Simoneau, N.,
601 Champion, C., Hamon, B., Kwasiborski, A., Colou, J., Benamar, A., Hudhomme, P., Macherel, D.,
602 Simoneau, P., Guillemette, T., 2021. Responses of the necrotrophic fungus *Alternaria*
603 *brassicicola* to the indolic phytoalexin brassinin. Front. Plant Sci. 11, 611643.
604 <https://doi.org/10.3389/fpls.2020.611643>
- 605 Noshita, T., Kiyota, H., Kidachi, Y., Ryoyama, K., Funayama, S., Hanada, K., Murayama, T., 2009. New
606 cytotoxic phenolic derivatives from matured fruits of *Magnolia denudata*. Biosci. Biotechnol.
607 Biochem. 73, 726–728. <https://doi.org/10.1271/bbb.80597>
- 608 Pattalung, P.N., Wiriyaichitra, P., Ongsakul, M., 1988. The antimicrobial activities of rubraxanthone
609 isolated from *Garcinia parvifolia* (miq.) miq. J. Sci. Soc. Thailand 14, 67–71.
610 <https://doi.org/10.2306/scienceasia1513-1874.1988.14.067>

- 611 Piccinelli, A.L., Lotti, C., Campone, L., Cuesta-Rubio, O., Campo Fernandez, M., Rastrelli, L., 2011.
612 Cuban and brazilian red propolis: botanical origin and comparative analysis by high-
613 performance liquid chromatography–photodiode array detection/electrospray ionization
614 tandem mass spectrometry. *J. Agric. Food Chem.* 59, 6484–6491.
615 <https://doi.org/10.1021/jf201280z>
- 616 Rani, L., Thapa, K., Kanojia, N., Sharma, N., Singh, S., Grewal, A.S., Srivastav, A.L., Kaushal, J., 2021. An
617 extensive review on the consequences of chemical pesticides on human health and
618 environment. *J. Clean. Prod.* 283, 124657. <https://doi.org/10.1016/j.jclepro.2020.124657>
- 619 Rukachaisirikul, V., Naklue, W., Phongpaichit, S., Towatana, N.H., Maneenoon, K., 2006.
620 Phloroglucinols, depsidones and xanthenes from the twigs of *Garcinia parvifolia* .
621 *Tetrahedron* 62, 8578–8585. <https://doi.org/10.1016/j.tet.2006.06.059>
- 622 Ryu, H.W., Curtis-Long, M.J., Jung, S., Jin, Y.M., Cho, J.K., Ryu, Y.B., Lee, W.S., Park, K.H., 2010.
623 Xanthenes with neuraminidase inhibitory activity from the seedcases of *Garcinia*
624 *mangostana*. *Bioorg. Med. Chem.* 18, 6258–6264.
625 <https://doi.org/10.1016/j.bmc.2010.07.033>
- 626 Sen, A.K., Sarkar, K.K., Majumder, P.C., Banerji, N., 1986. Garcinone-D, a new xanthone from *Garcinia*
627 *mangostana* Linn. *Indian J. Chem. B.* 25, 1157–1158.
- 628 Sen, A.K., Sarkar, K.K., Mazumder, P., Banerji, N., Uusvl' Ori, R., HAsset, T.A., 1980. A xanthone from
629 *Garcinia mangostana*. *Phytochemistry* 19, 2223–2225. [https://doi.org/10.1016/S0031-](https://doi.org/10.1016/S0031-9422(00)82235-9)
630 [9422\(00\)82235-9](https://doi.org/10.1016/S0031-9422(00)82235-9)
- 631 Sukandar, E.R., Kaennakam, S., Rassamee, K., Ersam, T., Siripong, P., Tip-pyang, S., 2019.
632 Tetrandraxanthenes a–l, prenylated and geranylated xanthenes from the stem bark of
633 *Garcinia tetrandra*. *J. Nat. Prod.* 82, 1312–1318.
634 <https://doi.org/10.1021/acs.jnatprod.9b00046>
- 635 Suksamrarn, S., Komutiban, O., Ratananukul, P., Chimnoi, N., Lartpornmatulee, N., Suksamrarn, A.,
636 2006. Cytotoxic prenylated xanthenes from the young fruit of *Garcinia mangostana*. *Chem.*
637 *Pharm. Bull.* 54, 301–305. <https://doi.org/10.1248/cpb.54.301>
- 638 Syamsudin, Supargiyono, Subagus Wahyuno, Partomuan Simanjuntak, Mustofa, 2013. Heme
639 polymerization inhibitory activities of xanthone from *G. parvifolia* (miq) miq stem bark as an
640 antimalarial agent. *Asian J. Chem.* 25, 1311–1314.
641 <https://doi.org/10.14233/ajchem.2013.12962>
- 642 Taher, U., Idris, M.S., Arbain, D., 2007. Antimicrobial, antioxidant and cytotoxic activities of *Garcinia*
643 *eugenifolia* and *Calophyllum nervosum*. *IJPT* 6, 93–98.
- 644 Tsuchiya, N., Sato, A., Haruyama, H., Watanabe, T., Iijima, Y., 1998. Nahocols and isonahocols,
645 endothelin antagonists from the brown alga, *Sargassum autumnale*. *Phytochemistry* 48,
646 1003–1011. [https://doi.org/10.1016/S0031-9422\(97\)00476-7](https://doi.org/10.1016/S0031-9422(97)00476-7)
- 647 Wahyuni, F.S., Byrne, L.T., Dachriyanus, Dianita, R., Jubahar, J., Lajis, N.H., Sargent, M.V., 2004. A new
648 ring-reduced tetraprenyltoluquinone and a prenylated xanthone from *Garcinia cowa*. *Aust. J.*
649 *Chem.* 57, 223–226. <https://doi.org/10.1071/CH03175>
- 650 Wijayanti, M., Ilmi, H., Kemalhayati, E., Tumewu, L., Wardana, F.Y., Suciati, Hafid, A.F.,
651 Widyawaruyanti, A., 2021. *In vitro* antimalarial activity of *Garcinia parvifolia* miq. Stem
652 extracts and fractions on *Plasmodium falciparum* lactate dehydrogenase (LDH) assay. *J. Basic*
653 *Clin. Physiol. Pharmacol.* 32, 839–844. <https://doi.org/10.1515/jbcpp-2020-0414>
- 654 Xu, Y.-J., Lai, Y.-H., Imiyabir, Z., Goh, S.-H., 2001. Xanthenes from *Garcinia parvifolia*. *J. Nat. Prod.* 64,
655 1191–1195. <https://doi.org/10.1021/np0101393>
- 656 Yates, P., Stout, G.H., 1958. The Structure of Mangostin. *J. Am. Chem. Soc.* 80, 1691–1700.
657 <https://doi.org/10.1021/ja01540a046>
658

Highlights

- Sixteen compounds were isolated from the latex of *Garcinia parvifolia*
- Compound (**2**) was an original structure of terpenophenol
- Compounds (**12-14**) were previously undescribed xanthenes
- Compound (**12**) exhibited a notable anti-Unfolded Response Activity
- Semisynthesis of (**12**) from the main compound (**1**) of the latex was achieved

Journal Pre-proof

Declaration of interests

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

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Journal Pre-proof