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1 **Convergent evolution leading to the appearance of furanocoumarins in citrus plants.**

2

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12

13 **Summary:**

14 Furanocoumarins are defense molecules mainly described in four plant families that are
15 phylogenetically distant. Molecular characterization of the biosynthetic pathway has been
16 started for many years in Apiaceae and Rutaceae. The results obtained thus far in Apiaceae
17 indicated a major role of cytochromes P450 (P450s) in the CYP71 family. In the present
18 work, we describe the importance of another subfamily of P450s, CYP82D, identified by
19 using a deep analysis of the citrus (Rutaceae) genome and microarray database. CYP82D64 is
20 able to hydroxylate xanthotoxin to generate 5-OH-xanthotoxin. Minor and limited amino acid
21 changes in the CYP82D64 coding sequence between *Citrus paradisi* and *Citrus hystrix*
22 provide the enzyme in the latter with the ability to hydroxylate herniarin, but with low

23 efficiency. The kinetic constants of the enzyme are consistent with those of other enzymes of
24 this type in plants and indicate that it may be the physiological substrate. The activity of the
25 enzyme is identical to that of CYP71AZ6 identified in parsnip, showing possible evolutionary
26 convergence between these two families of plants. It is highly possible that these molecules
27 are derived from the synthesis of ubiquitous coumarins throughout the plant kingdom.

28 **Keywords:** Cytochrome P450, CYP82, Furanocoumarins, *Citrus*, Convergent evolution

29

30 **Author contributions:**

31 MLM and ADJ did the cloning and functional characterization of the enzymes. ADJ and VC
32 did the qPCR experiments and metabolic analysis. AO did the enzymatic characterization. CV
33 produced the phylogenetic tree. YF, FB and AH supervised the project. AH wrote the article.

34

35 **Introduction**

36 Furanocoumarins (FCs) are specialized metabolites that have been widely reported as being
37 involved in the defense of plants against aggressors [1]. These molecules, although described
38 in higher plants, are mainly distributed in 4 families: Apiaceae, Moraceae, Fabaceae and
39 Rutaceae [2,3]. Two main kinds of FCs exist depending on the position of the furan ring on
40 the coumarin core molecule. The tracks leading to either linear or angular molecules are
41 catalyzed by enzymes belonging to the UbiA Prenyltransferases. A prenylation occurring on
42 C6 leads to the synthesis of the linear demethylsuberosin whereas a prenylation on C8 gives
43 osthenol (Figure 1) [4–6] The presence of both isomers are, thus far, only reported in
44 Apiaceae and are reported to reflect a coevolutionary process between plants and caterpillars
45 [7]. These four plant families are quite distant from a phylogenetic point of view, and the

46 independent appearance of these molecules remains unexplained at the molecular level. The
47 first enzymes involved in the synthesis of these molecules to be characterized were a psoralen
48 synthase (CYP71AJ1-3) and an angelicin synthase (CYP71AJ4) [8,9]. Both enzymes belong
49 to the cytochrome 450 enzyme superfamily. *CYP71AJ4*, identified in *Pastinaca sativa*, may
50 result from the duplication of *CYP71AJ3* followed by neofunctionalization [8]. This
51 assumption is consistent with the high amino acid sequence identity shared by the two
52 proteins (69.8 %) and is reinforced by the results published by Roselli et al., who showed their
53 clustering in the parsnip genome (the genes are 7.6 kb apart) [10]. Relatively minor changes
54 in the peptidic sequence of psoralen synthase therefore allowed the appearance of the angular
55 FC angelicin and subsequent angular molecules, thus participating in the arms race between
56 plants and insects. An extensive study of this specific CYP71AJ subfamily has led to the
57 identification of numerous orthologous genes, but their function could not be demonstrated
58 [11].

59 Krieger et al have highlighted another cytochrome P450 subfamily, CYP71AZ, involved in
60 the synthesis of FC [12]. CYP71AZ4 is able to hydroxylate psoralen, leading to the synthesis
61 of xanthotoxol, whereas CYP71AZ1 and CYP71AZ6 catalyze the hydroxylation of
62 xanthotoxin, generating 5-OH-xanthotoxin (Figure 1). Interestingly, CYP71AZ6 seems quite
63 specific to a single molecule (xanthotoxin), while CYP71AZ4 can transform different types of
64 molecules, including a FC (psoralen) and coumarins (6-methoxycoumarin, scopoletin, 7-
65 methoxy-3-methylcoumarin, and 7-methoxycoumarin) [12]. Finally, Krieger et al also showed
66 that CYP71AZ3 seems to be specific and dedicated to the hydroxylation of esculetin, another
67 coumarin [12]. All higher plants are able to produce coumarins and the fact that some
68 members of the CYP71AJ and CYP71AZ families are involved in the synthesis of coumarins
69 and/or FCs [11,12] provides new insights for understanding the evolutionary processes
70 leading to the appearance of FCs that might have diverged from coumarins. To date, the

71 different enzymes described to be involved in the synthesis of FCs belong to the same large
72 CYP71 cytochrome P450 family. This family is responsible for the synthesis of highly
73 diversified and specialized metabolites. For example, members of the family are involved in
74 the synthesis of artemisin [13], menthofuran [14], camalexin [15,16], cyanogenic glucosides
75 [17] or DIMBOA [18]. The diversity of chemical structures, biosynthetic pathways and plant
76 species make this enzyme family a major actor in the adaptation of plants to their
77 environments.

78 The CYP71 family is not the only cytochrome P450 that seems to be involved in the synthesis
79 of such molecules (Figure S5). The functional characterization of CYP82C2 and CYP82C4
80 isolated from *Arabidopsis thaliana* reinforces the assumption that FCs are derived from
81 coumarins. Kruse et al showed that these enzymes convert *in vivo* xanthotoxin to 5-OH-
82 xanthotoxin when overexpressing *Arabidopsis* mutants are incubated in a culture media
83 containing the substrate (Figure 1) [19], while this plant is not otherwise able to synthesize
84 this kind of molecule. In 2018, Rajniak et al. showed that CYP82C4 is also involved in the
85 oxidation of fraxetin (a coumarin), leading to the synthesis of sideretin [20], which is
86 described as being important in iron homeostasis [21]. Taken together, these results indicate
87 that the functionalization of coumarins into FCs may be realized in different ways (CYP71 or
88 CYP82) throughout higher plants, thus supporting the convergent evolution hypothesis.

89 Rutaceae are reported to produce coumarins and linear FCs [22–24], but less is known about
90 the enzymes involved in this synthesis. However, a cytochrome P450 associated with an
91 evolutionary process related to the synthesis of FC was described. Gravot et al. showed that
92 the cinnamate 4-hydroxylase (C4H) of *Ruta graveolens* was adapted to the presence of FCs.
93 Although inhibited by psoralen and xanthotoxin through mechanism-based inactivation, the
94 C4H isolated from *R. graveolens* displayed a lower sensitivity to these molecules than the
95 C4H of *Helianthus tuberosus* [25]. Citruses belong to the Rutaceae family. The consumption

96 of these fruits has a wide range of beneficial effects for human health, since they are rich in
97 vitamin C, folates, alimentary fibers and minerals [26]. In addition to these positive effects, it
98 has also been demonstrated that the presence of FCs generates deleterious effects such as
99 phototoxicity and photosensitivity [27–30] and a drug interaction effect known as "the
100 grapefruit juice effect" that can cause overdose in humans by inhibiting liver cytochromes
101 P450 involved in the detoxification of xenobiotics [31–33]

102 In this work, we investigated the biosynthesis of FCs in citrus species, focusing on the
103 CYP82 family. The expression pattern of four genes and their functional characterization
104 showed that two of them perform the hydroxylation of xanthotoxin to produce 5-OH-
105 xanthotoxin. The physiological relevance of this result is supported by a quantitative PCR
106 approach that shows a clear correlation between gene expression and the amount of these
107 molecules.

108

109 **Material and methods**

110 **Citrus data**

111 Citrus genomic and transcriptomic data were collected from the Phytozome project database
112 (<https://phytozome.jgi.doe.gov/>) and the RNAseq database published by Voo et al [34].

113 **Phylogenetic analysis**

114 The tree was built with the maximum likelihood (PhyML) method. The alignment was
115 performed with MUSCLE using the default settings [35]. The variable regions creating gaps,
116 the C-terminal region and the N-terminal membrane anchor were removed. One hundred
117 iterations were performed, and the bootstrap values were calculated. The tree was rooted with
118 CYP71AJ3, CYP71AJ4, CYP71AZ3, CYP71AZ5 and CYP71AZ6 from *P. sativa*,

119 CYP71AU3, CYP71AU4 and CYP71AH4 from *Vitis vinifera*, and CYP83B1 and CYP83A1
120 from *A. thaliana*.

121 **RT-PCR and cloning strategy**

122 RNA was extracted from flavedo of *C. paradisi* Star Ruby and *C. hystrix* fruits using the
123 E.Z.N.A.® Plant RNA kit following the manufacturer's recommendations (Omega Bio-Tek).
124 Residual genomic DNA was removed using amplification-grade DNase I (Sigma-Aldrich).
125 Reverse transcription was performed with a High-Capacity RNA-to-cDNA Kit (Applied
126 Biosystems). The coding sequences were amplified with high-fidelity PrimeSTAR® Max
127 DNA polymerase (Takara) and ligated into the pCR8 plasmid using the pCR8 TA/GW/Topo
128 kit (Invitrogen). The designed primers were as follows: *CYP82D64* Fw 5' ATG GAG TTC
129 CTA TTC ACA GCT GTA ATA ATC ACT GCC C 3', *CYP82D64* Rev 5' TCA ATG ATG
130 ATG ATG ATG ATG AAA GCC ATA GGG GTT GGC A 3'; *CYP82D83* Fw 5' ATG GAC
131 ATT CTT GGT TCG TCT CAA AC 3', *CYP82D83* Rev 5' TCA ATG ATG ATG ATG ATG
132 ATG GCC GTA CAA AGA AGC AGA AAG AC 3'; *CYP82D92* Fw 5' ATG GAC TTC CTT
133 GTT TTA ACA TCT CAA C 3', *CYP82D92* Rev 5' TCA ATG ATG ATG ATG ATG ATG
134 GCC ATA CAG AGA AGC AGA GAG 3'; and *CYP82D179* Fw 5' ATG GAC TTT CTT
135 GTT TCA CGT CAA AC 3', *CYP82D179* Rev 5' TCA ATG ATG ATG ATG ATG ATG
136 GCC GTA CAA AGA AGC AGA AAG 3'. For each ORF, we added a 6xHIS tag before the
137 stop codon. Finally, the ORF was transferred into the pYeDP60 GW [12] plasmid using
138 Gateway LR Clonase II Enzyme mix (Invitrogen).

139

140 **Expression of proteins and enzymatic characterization**

141 The recombinant proteins were produced in a yeast expression system [36]. The culture
142 conditions, the preparation of microsomes and the biochemical screening were as described
143 by Krieger et al. (2018).

144 qPCR

145 Reverse transcription was performed with a High-Capacity RNA-to-cDNA Kit (Applied
146 Biosystems). The primers used were *EF1 α* Fw 5'-TGG TGA TGC TGG GTT TGT TA-3',
147 *EF1 α* Rev 5'-CAC GCT CTT GAT GAC TCC AA-3' for the reference gene; *CYP82D64* Fw
148 (1) 5'-GGC GCC ATG CTT TCC A-3', *CYP82D64* Rev (1) 5'-ACG ACC GGG AAA TTC
149 TTG TG-3'; and *CYP82D64* Fw (2) 5'-CAC CAC GTG AAG CAA TGG AA-3', *CYP82D64*
150 Rev (2) 5'-TGC CAG CCG GGA CAT G-3'. qPCR was performed with SYBR *Premix Ex*
151 *Taq* (Takara) based on the manufacturer's recommendations. The amplification program was
152 95°C for 30 sec, followed by 40 cycles of 95°C for 5 sec and 60°C for 34 sec. The PCR was
153 followed by a single run at 95°C for 15 sec, 60°C for 60 sec, and 95°C for 15 sec in order to
154 assess the melting curve and therefore the specificity of the PCRs.

155

156 Enzymatic characterization

157 All the enzymatic reactions were conducted in 0.1 M KPi buffer. pH and temperature range
158 were set between 6.0 to 8.0 and 15 °C to 40 °C. For the kinetic determination of optimal
159 temperature and pH, saturating concentrations of substrates were used (100 μ M) in phosphate
160 buffer. For k_m kinetic parameter determination, xanthotoxin concentration was set between
161 0.5 and 300 μ M and the reaction was conducted at optimal pH and temperature. 20 μ l of the
162 yeast microsomal preparation was added to each enzymatic incubation and enzymatic
163 reactions were running during 5 min and stopped by the addition of 10 μ l HCl 1N. Substrates
164 and the resulting products were analyzed by HPLC at a wavelength of 320 nm as described by
165 Vialart *et al.* Kinetic parameters were calculated using the SigmaPlot 12.0 software.
166 Identification of the chemical structure of the products was done by comparison with their
167 elution time in comparison to 5-OH-xanthotoxin standard molecule and by LTQ orbitrap as
168 described by Krieger *et al.* (2018)

169 **Phytochemical analysis**

170 Methanol extraction and phytochemical analyses were performed as previously described by
171 Dugrand et al. [22].

172

173 **Results**

174 **Identification of cytochrome P450 coding sequences belonging to the CYP82 subfamily** 175 **in Citrus genomic and microarray databases.**

176 The Phytozome database (<https://phytozome.jgi.doe.gov/>) contains the genomes of *Citrus*
177 *sinensis* and *Citrus clementina*. These genomes were annotated [37,38], but regarding
178 cytochromes P450, the annotation was limited to the superfamily level. According to Nelson,
179 two P450s belong to the same family if they share more than 40% amino acid identity and are
180 in the same subfamily if they share more than 55%
181 (<http://drnelson.utmem.edu/CytochromeP450.html>). To seek candidate genes, we performed a
182 sequence homology search using the BlastN and tBlastX algorithms and CYP82C2 and
183 CYP82C4 from *A. thaliana* as bait sequences. This first investigation led us to identify 79
184 P450 candidate sequences that were further restricted to 42 CYP82 partial sequences in the
185 two *Citrus* species (16 for *C. sinensis* and 26 for *C. clementina*). Most were redundant, which
186 led us to finally consider only 8 different coding sequences (Table 1). All the sequences were
187 affiliated with the CYP82C (CYP82C46) and CYP82D (CYP82D64, 81, 82, 83, 84, 92, and
188 179) subfamilies according to the cytochrome P450 annotation committee
189 (<http://drnelson.utmem.edu/CytochromeP450.html>).

190 To complete this first analysis, we compared our results with the database provided by Voo et
191 al [34]. This analysis showed that 2 sequences of the 8 selected previously, i.e., CYP82D64
192 (i.e., contigs Cit.29478 and Cit.2373 in the database) and CYP82D79 (i.e., *Cit.5945* in the

193 database), had differential expression (Table 1) between flavedo oil cavities (tissue with a
194 high concentration of FCs, [22,23]) and albedo tissue (lack of FCs). These first analyses
195 supported these two sequences as strong candidates involved in FC biosynthesis in *Citrus spp.*
196

197 To obtain a more detailed overview of the distribution of this P450 subfamily, we performed a
198 phylogenetic analysis including 91 members of the CYP82 subfamily available in databases
199 in the literature and various other databases (Supplemental figure 1). The tree was rooted with
200 11 sequences belonging to the CYP71 or CYP83 subfamily. This analysis showed that the
201 already-characterized CYP82C2 and CYP82C4 were located on different branches than the
202 CYP82D identified in citrus plants (Figure 2). Within the more specific citrus clade, we could
203 not distinguish different groups that could provide clues for functional characterization since
204 the genes were distributed between *C. sinensis* (unable to produce FCs) and *C. clementina*
205 (producing FCs) [23].

206

207 **Functional characterization of the CYP82D candidates.**

208 In our analysis, CYP82D64, CYP82D83, and CYP82D179 were detected in both plants,
209 whereas CYP82D82 and CYP82D81 were specific to *C. sinensis* and CYP82D92 was found
210 only in *C. clementina*. Since the aim of our study was to identify genes involved in the
211 synthesis of FCs, we focused our attention on CYP82D92, CYP82D64, CYP82D83, and
212 CYP82D179, detected either in *C. clementina* alone or in both plants. The study performed by
213 Krieger et al showed that minor modification of the sequence of CYP71AZ can lead to
214 significant changes in substrate specificity and/or enzyme activity. To limit the risk of cloning
215 gene variants displaying low FC biosynthetic activities, we amplified and cloned the cDNA
216 coding sequences from *C. paradisi*, a citrus species producing diverse and large amounts of
217 FCs [22,23]. The amplified sequences of *C. paradisi* showed minor changes (98 to 100%

218 identity) in comparison to the genomic sequences of *C. sinensis* or *C. clementina*. These
219 differences were, however, not located in the enzyme active sites [39].

220 To identify their function, the 4 His-tagged P450s were expressed in a yeast heterologous
221 expression system, and their expression was assessed by Western blot (Supplemental figure
222 2). CYP82D64, CYP82D92 and CYP82D179 were efficiently produced and further incubated
223 in the presence of NADPH and the different intermediates of the biosynthetic pathway
224 (demethylsuberosin, marmesin, xanthotoxol, xanthotoxin, bergaptol, bergapten, 5-OH-
225 xanthotoxin, 8-OH bergapten and isopimpinellin) (Figure 1). Only metabolization of
226 xanthotoxin could be observed in the presence of CYP82D64 (Figure 4A). The elution time
227 and the fragmentation spectrum (maximum fragmentation intensities for m/z of 172, 217 and
228 205, for a total m/z of 233) were identical to those of 5-OH-xanthotoxin (Figure 4 B-E). No
229 enzymatic activity could be detected for any other protein tested.

230

231 **Plasticity of substrate specificity between two CYP82D64 variants isolated from *C.*** 232 ***paradisi* and *C. hystrix*.**

233 Several studies have provided evidence that only a few modifications to an amino acid
234 sequence can alter the specificity of an enzyme. Concerning the synthesis of coumarins and
235 FCs, this has been shown for CYP71AZ3, 4 and 6, which are able to transform esculetin,
236 psoralen and xanthotoxin, respectively [12]. We cloned the CYP82D64 orthologous gene
237 from combava (*C. hystrix*) fruits, a citrus species known to be a very high producer of FCs
238 [23]. The CDS that we obtained from this plant was named CYP82D64v2 and showed several
239 differences compared with the *C. paradisi* coding sequence (CYP82D64v1), especially in the
240 substrate recognition sites SRS3, 4 and 6, which were reported to be important for the
241 enzymatic activity of cytochromes P450 [39] (Figure 4). Microsomes prepared from yeast

242 overexpressing CYP82D64v2 were able to convert xanthotoxin into 5-OH xanthoxine at the
243 same rate as CYP82D64v1. Surprisingly, CYP82D64v2 was also able to transform herniarin
244 (7-methoxycoumarin) at a rather low rate into a product that was identified as 5-hydroxy-7-
245 methoxycoumarin (Figure 5).

246

247 **Enzymatic characterization of CYP82D64v1 and v2**

248 The optimal pH of both CYP82D64s was assessed in phosphate buffer with a pH ranging
249 from 6.0 to 8.0. Under these conditions, we showed that the hydroxylation activity of
250 xanthotoxin was effective over the entire pH range and was optimal at a pH of 7.3
251 (Supplemental figure 3). The activity in the presence of herniarin could not be detected below
252 a pH of 6.4, but the optimal activity was obtained at a pH of 7.2. The optimal temperature of
253 the hydroxylation of both molecules was close to 28°C (27.8°C for xanthotoxin and 28.1°C
254 for herniarin) (Supplemental figure 4). Finally, the kinetic constants (k_m) of CYP82D64v1
255 and v2 were determined to be 4.6 \pm 1.7 μ M and 7.4 \pm 4.0 μ M for xanthotoxin, respectively.
256 These k_m values were rather low and consistent with those reported in studies performed on
257 other cytochromes P450. This specificity may reflect a physiological activity. Because of the
258 too-low enzymatic activity, the k_m could not be determined for herniarin.

259

260 ***In vivo* expression of CYP82D64**

261 Although the k_m of the reaction was consistent with a physiological function, we
262 wanted to assess if there was a relationship between the expression level of the mRNA coding
263 for CYP82D64 and the amounts of xanthotoxin and 5-OH-xanthotoxin produced in *C.*
264 *paradisi* fruit at different stages of maturity: young, intermediate and mature (Figure 6A). We
265 observed that the expression level of *CYP82D64* mRNA significantly decreased during fruit

266 development (Figure 6B). It was reduced 2.3-fold between the young and intermediate fruits
267 and 18-fold between the intermediate-stage and ripe fruits. Regarding the expression of
268 *CYP82D64* mRNA, the concentrations of xanthotoxin and 5-OH-xanthotoxin also decreased
269 significantly. The average content of the 2 molecules decreased 2.5-fold between the
270 maturation of young fruits to the intermediate stage and 7.4-fold during the transformation
271 from intermediate-stage to ripe fruits.

272

273 **Discussion**

274 The Rutaceae and Apiaceae families are quite distant in terms of angiosperm
275 evolution. Interestingly, however, they are both able to produce FCs [23,24], although the
276 diversity of molecules differs between them. Apiaceae, including parsnip, are able to
277 synthesize both linear (i.e., psoralen derivatives) and angular isomers (i.e., angelicin
278 derivatives) [8]. Rutaceae and, in particular, the Citrus genus produce only a linear isomer
279 [23]. The first step involved in the production of these molecules concerns the C2'-
280 hydroxylation of coumaroyl-CoA, leading to the synthesis of umbelliferone [10,40,41].
281 Umbelliferone is commonly described in many higher plants. This step is catalyzed by 2-
282 oxoglutarate-dependent dioxygenase in *R. graveolens* [40] and *P. sativa* [10], which belong to
283 the same DIOX30 clade [41], and therefore seems to be well conserved across angiosperms.
284 The prenylation of umbelliferon has not yet been described in citrus but was reported for
285 Apiaceae plants and is catalyzed by a UbiA prenyltransferase [4]. A recent study by Munakata
286 and colleagues showed that in *Ficus carica*, a Moraceae able to produce FCs,
287 prenyltransferase had a different evolutionary origin than the enzyme involved in the
288 synthesis of demethylsuberosin in Apiaceae. It might therefore be possible that convergent
289 evolution occurred at this stage [42].

290 Studies based on biochemical approaches performed in the 1980s pointed out that in
291 Apiaceae, many enzymatic steps happening after the synthesis of demethylsuberosin (Figure
292 1) were catalyzed by enzymes belonging to the cytochrome P450 superfamily [43,44]. These
293 results were confirmed by the identification of the CYP71AJ [8,9] and CYP71AZ subfamilies
294 [12], which are involved in the synthesis of psoralen, angelicin, xanthotoxol and 5-OH-
295 xanthotoxin. To identify the genes involved in the same reaction in other plant species, we
296 searched for *CYP71AJ* or *CYP71AZ* orthologous genes in citrus databases. Since this
297 investigation was unsuccessful, we extended our investigation to other cytochrome P450
298 families. Based on the work performed by Kruse and colleagues [19], who described the
299 hydroxylation of 8-methoxypsoralen (i.e., xanthotoxin) by a P450 isolated from *Arabidopsis*,
300 we focused on the CYP82 family. Among several candidate genes, we characterized
301 CYP82D64 as a xanthotoxin hydroxylase. This enzyme displayed the same enzymatic
302 function as CYP71AZ6 isolated from parsnip [12]. The low K_m and the close relationship
303 between the expression level of the gene and the accumulation of 5-OH-xanthotoxin suggest
304 that this reaction also occurs *in planta* as a physiological reaction.

305 In this study, we provided evidence that CYP82D64 was able to hydroxylate herniarin.
306 This result is in line with that from a study recently published by Rajniak supporting the role
307 of CYP82C4 in the production of sideretin, another coumarin [20]. This report, in addition to
308 our results, highlights that the CYP82 family participates in the synthesis of both FCs and
309 coumarins, as does the CYP71AZ subfamily in Apiaceae. These elements provide new
310 insights in favor of the evolution of the FC biosynthetic pathway from the coumarin
311 biosynthetic pathway. These results are also consistent with the extreme diversity of the
312 CYP71 and CYP82 subfamilies (53 CYP71s and 25 CYP82s reported to date), demonstrating
313 the plasticity of these enzymes that seem to be deeply involved in the adaptation of plants to
314 their environments. Indeed, similar to the CYP71 subfamily, CYP82 members are associated

315 with highly functionally diverse families of molecules with very different chemical structures
316 such as alkaloids, terpenes or phenolic compounds. For example, CYP82N3 and CYP82N4
317 enzymes of *Papaver somniferum* hydroxylate alkaline benzyloquinolines [45]. CYP82E4
318 from *Nicotiana tabacum* corresponds to a nicotine N-demethylase [46]. CYP82G1 of *A.*
319 *thaliana* is involved in the synthesis of volatile homoterpenes [47]. CYP82D63 from *Mentha*
320 *piperita* and CYP82D33 from *Ocimum basilicum* hydroxylate flavones [48]. CYP82D64 from
321 *C. paradisi* and CYP82C2 from *A. thaliana* hydroxylate xanthotoxin, and CYP82C4
322 hydroxylates fraxetin. This functional diversity was distributed over the entire generated
323 phylogenetic tree (Figure 2).

324 In this work, we provide some new lines of evidence in favor of a convergent
325 evolution theory for explaining the presence of FCs in Rutaceae and Apiaceae. It is highly
326 possible that the same process occurred in Moraceae and Fabaceae, two other plant families
327 producing large amounts of these specialized molecules. It is therefore not excluded that other
328 P450 families or subfamilies play an important role in the synthesis of FCs and the
329 subsequent adaptation of these plants to their environments. Such convergent evolution is not
330 unique in the plant kingdom. Genes encoding enzymes belonging to different families may
331 have identical functions, such as the anthocyanin-5-O-glucosyltransferases of *Dianthus*
332 *caryophyllus* and *A. thaliana*. In this case, the enzymes have different structures but share the
333 same glycosylation of anthocyanin function [49]. Similarly, ferulate-5-hydroxylase
334 (CYP788A1) from *Selaginella moellendorffii* shares only 37% identity with angiosperm
335 P450s but plays the same role as these P450s in the synthesis of S units of lignin [50].

336

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342

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527

528 **Figures:**

529 Figure 1: schematic representation of the furanocoumarin biosynthetic pathway and the
530 enzymatic steps catalyzed by cytochrome P450s.

531 Red arrows: known steps; gray arrows: P450 putative steps; black arrows: catalyzed by other
532 enzyme families.

533

534 Figure 2: phylogenetic tree of the CYP82 family.

535 The alignment of peptidic sequences was performed with MUSCLE using the default settings.

536 The tree was built with the maximum likelihood (PhyML) method. The highly variant regions

537 creating gaps, the C-terminal region and the N-terminal membrane were removed. One

538 hundred iterations were performed, and the bootstrap values are shown at the nodes of

539 branches. Sequences marked with orange are the citrus candidate genes, and sequences in blue

540 are cytochromes P450 already described to metabolize furanocoumarins. The tree was rooted

541 with CYP71AJ3, CYP71AJ4, CYP71AZ3, CYP71AZ5, and CYP71AZ6 from *Pastinaca*

542 *sativa*; CYP71AU3, CYP71AU4 and CYP71AH4 from *Vitis vinifera*; and CYP83B1 and

543 CYP83A1 from *A. thaliana*. Legend: AA, *Ammi majus*; AL, *Arabidopsis lyrata*; AT,

544 *Arabidopsis thaliana*; BN, *Brassica napus*; BR, *Brassica rapa*; BO, *Brassica oleracea*; CA,

545 *Citrus aurantium*; CC, *Citrus clementina*; CH, *Citrus hystrix*; CS, *Citrus sinensis*; CP, *Citrus*

546 *paradise*; DC, *Daucus carota*; EC, *Eschscholzia californica*; GM, *Glycine max*; GS, *Glycine*

547 *soja*; MS, *Medicago sativa*; MP, *Mentha piperita*; NT, *Nicotiana tabacum*; OB, *Ocimum*

548 *basilicum*; PS, *Pisum sativum*; PSo, *Papaver somniferum*; SH, *Sinopodophyllum hexandrum*;

549 SR, *Stevia rebaudiana*; TC, *Tanacetum cinerariifolium*; TH, *Tarenaya hassleriana*; VV, *Vitis*

550 *vinifera*; .

551

552 Figure 3: enzymatic conversion of xanthotoxin by CYP82D64.

553 A) DAAD chromatogram, B) UV spectrum of the product, C) MS analysis of the product, D)

554 MS analysis of commercial 5-OH-xanthotoxin, E) UV spectrum of commercial 5-OH-

555 xanthotoxin.

556

557 Figure 4: sequence comparison of CYP82D64 variants isolated from *C. clementina*, *C.*
558 *paradisi* and *C. hystrix*.

559 Red stars highlight the differences, and green stars show the substrate recognition sites [39].

560 The *C. clementina* sequence was predicted from the CDS available in Phytozome.

561

562 Figure 5: enzymatic conversion of herniarin by CYP82D64v2.

563 A) DAAD chromatogram, B) UV spectrum of the product, C) MS analysis of the product, D)

564 MS analysis of commercial 5-hydroxy-7-methoxycoumarin, E) UV spectrum of commercial

565 5-hydroxy-7-methoxycoumarin.

566

567 Figure 6: comparison of the expression level of *CYP82D64* mRNA to the xanthotoxin and 5-

568 OH-xanthotoxin contents in *C. paradisi* fruits. A) Three stages of maturity were tested:

569 immature, intermediate and mature fruits. B) Expression level of CYP82D64 and

570 concentrations of xanthotoxin and 5-OH-xanthotoxin.

571

572 **Supplemental Data**

573 Supplemental figure 1: list of the P450 sequences used to create the phylogenetic tree in

574 Figure 2

575

576 Supplemental figure 2: Western blot analysis of microsomes prepared from yeast expressing

577 CYP82D64, CYP82D83, CYP82D92 and CYP82D179. Void: yeast transformed with empty

578 pYeDP60 plasmid; Positive: yeast expressing CYP71AZ4 (Krieger et al, 2018).

579

580 Supplemental figure 3: optimal pH determination for CYP82D64v1 and v2

581 A) Optimal pH for CYP82D64v1 with xanthotoxin, B) optimal pH for CYP82D64v2 with
582 xanthotoxin, C) optimal pH for CYP82D64v2 with herniarin.

583

584 Supplemental figure 4: optimal temperature determination for CYP82D64v1 and v2

585 A) Optimal temperature for CYP82D64v1 with xanthotoxin, B) optimal temperature for
586 CYP82D64v2 with xanthotoxin, C) optimal temperature for CYP82D64v2 with herniarin.

587

588 Supplemental figure 5: Phylogenetic tree constructed with the predicted cytochrome P450s
589 belonging to the Clan71 of *Citrus sinensis* and *Citrus clementina*. The tree has been rooted
590 with CYP51G1. Sequence alignment was performed using MAFFT relying on Multiple
591 sequence alignment default settings (<https://mafft.cbrc.jp/alignment/software>). The tree was
592 buildt with IQ-TREE multicore version 1.6.11 for Linux 64-bit built Jun 6 2019 and FigTree.

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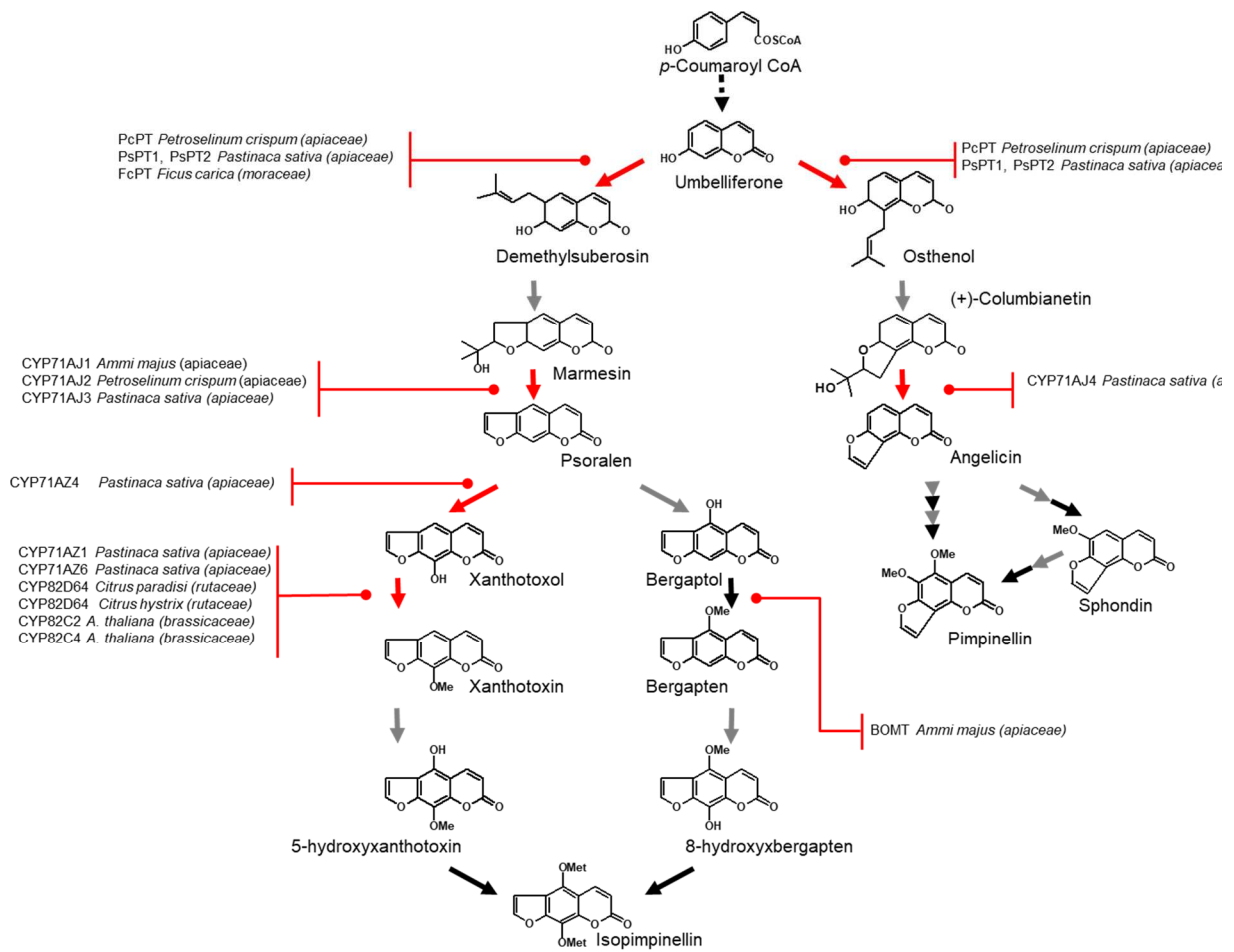
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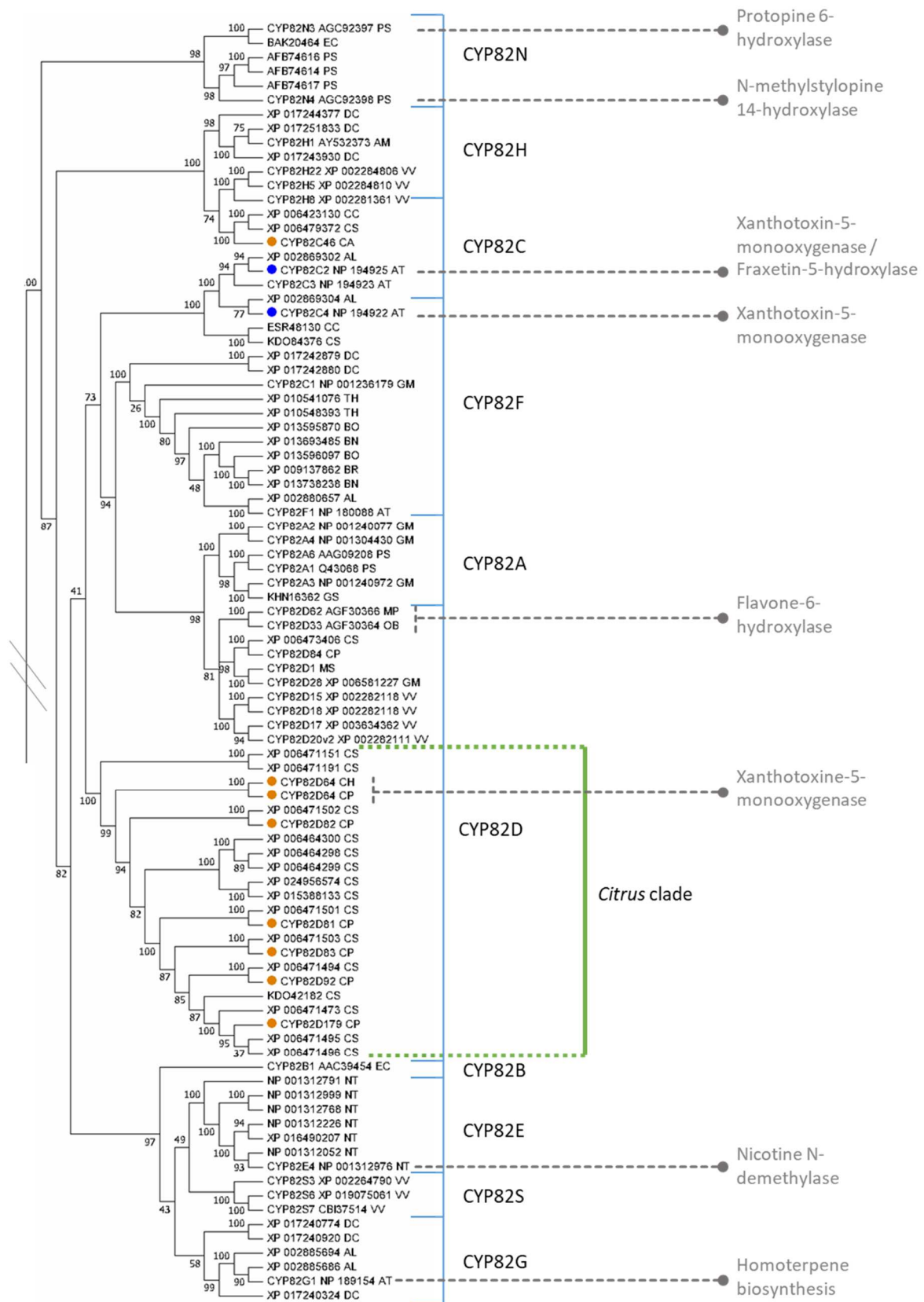
603 **Main figures**

604 Figure 1:



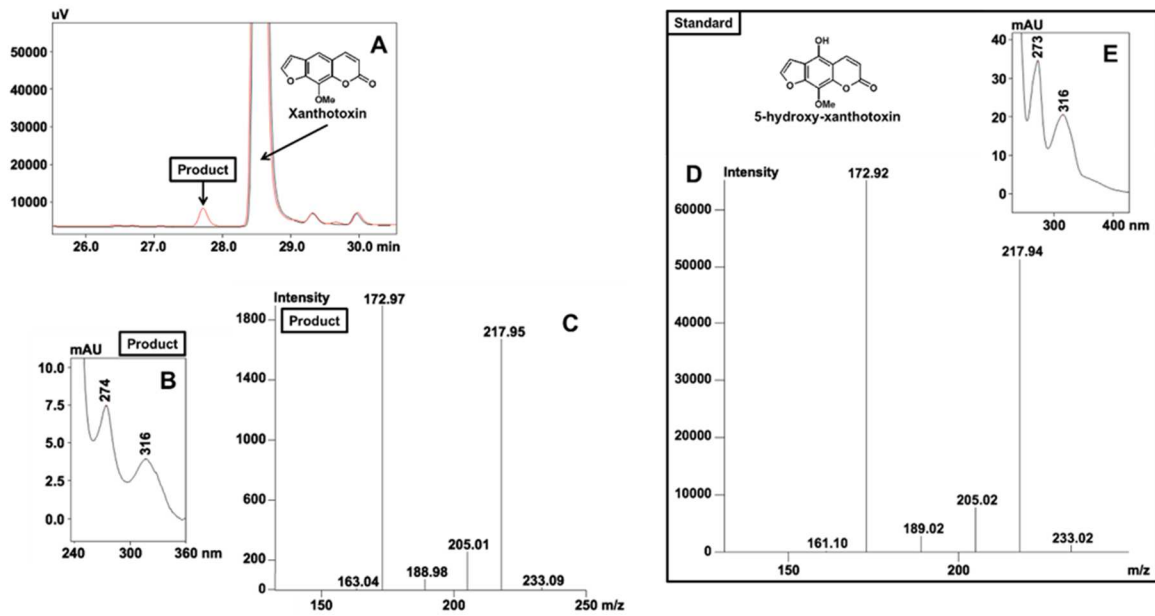
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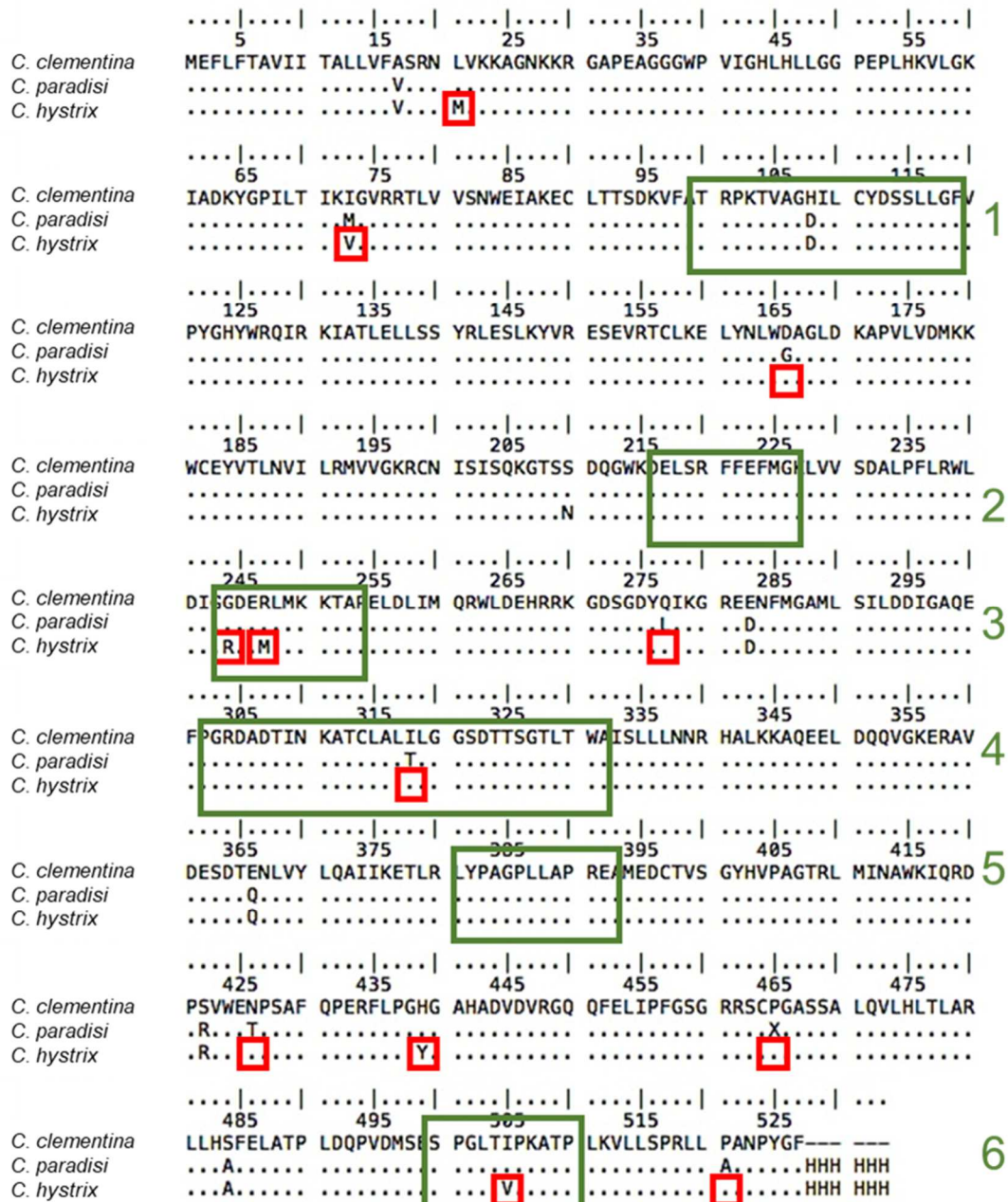
610 Figure 3



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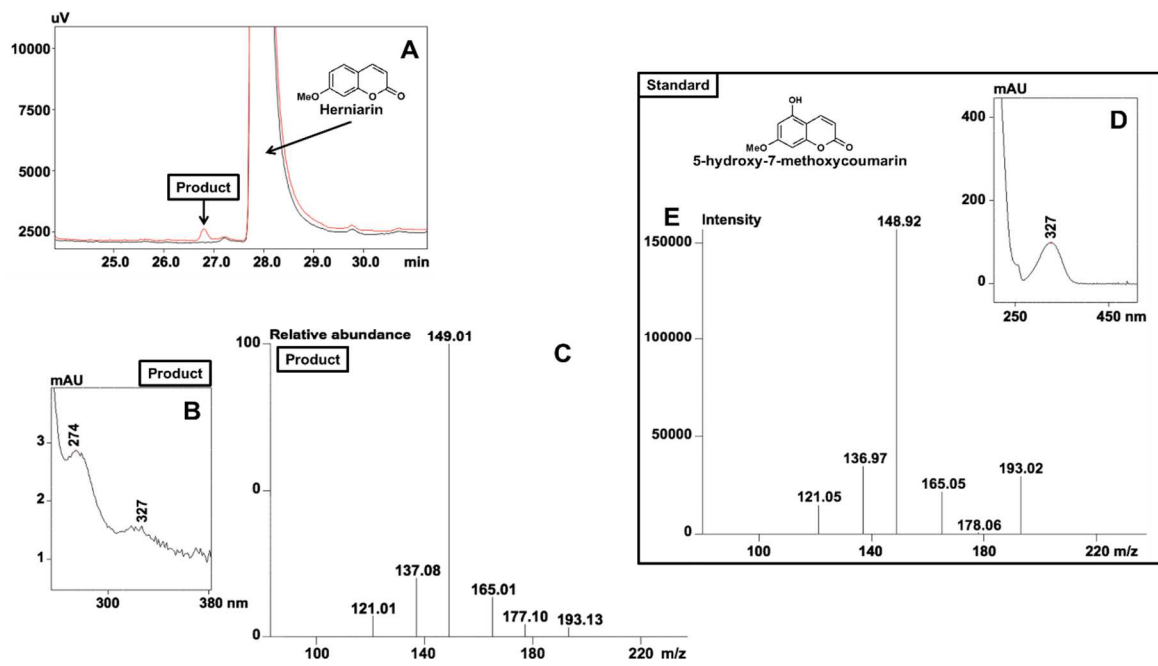
613 Figure 4



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615

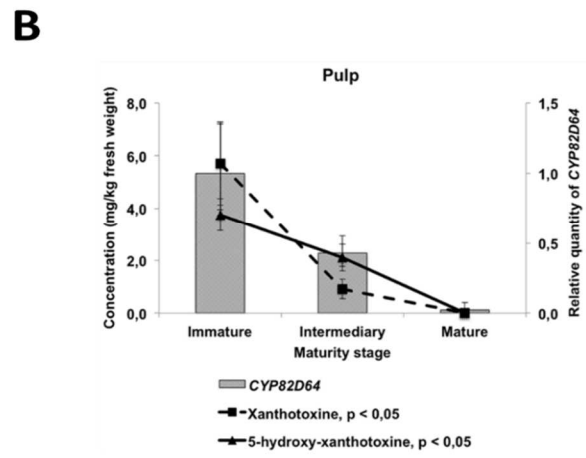
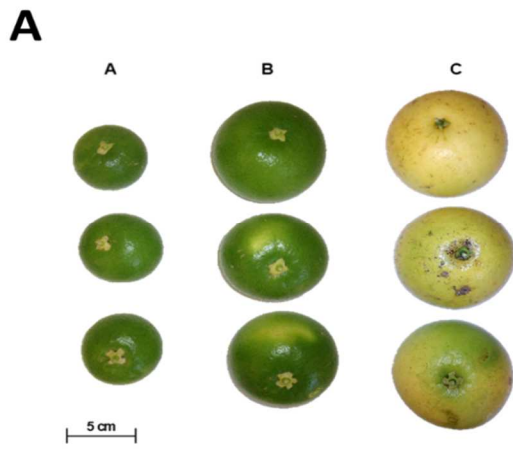
616 Figure 5



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619 Figure 6



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622 Table 1

	Phytozome ID	
	<i>C. clementina</i>	<i>C. sinensis</i>
CYP82C46	Ciclev10028201m	orange1.1g010622m
CYP82D64	Ciclev10025349m	orange1.1g009723m
CYP82D81	-	orange1.1g009844m
CYP82D82	-	orange1.1g009347m
CYP82D83	Ciclev10000845m	orange1.1g009786m
CYP82D84	Ciclev10000852m	orange1.1g009899m
CYP82D92	Ciclev10000846m	-
CYP82D179	Ciclev10000844m	orange1.1g026655m

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632 Supplemental Figures

633

634 Supplemental Figure 1

635 >NP_001312791_(NT)

636 APEIPGAWPIIGHLRQLSGTDKFPRI LGALADKYGPVFTLRIGMYPYLIVNNWEAAKDCLTTHDKDFAARPTSMAGESIGYKYARFT
637 YANFGPYYNQVRK LALQHVPSSTKLEKMKHIRVSELETSIKELYSLTLGQKVNISKWFEQLTLNIIVKTCIGKRYSDDEEAQRFRKAF
638 KGIMFVVVGQIVLYDAIPLFKYFDFQGH IQLMKNKIYKDLSILQGWLDHMMNKDVQDAIDAMLKVTQLFSQATVIKSTVLSLILDG
639 NDTTAVHLI WVMSLLLNNPHVMKQGQEEIDMKV GKERWIEDTDIKNLVYLQAI VKETLRLYPPVPFLLPHEAVQDCKVTGYHIPK
640 GTRLYINAWKVHRDPEIWSEPEK FMPNRFLT SKANIDARGQNF EFIPFGSGRRSCPGIGFATLVTHLTFGRLLQGFDFSKPSNTPIDM
641 TEGVGVTL PKVNQVEVLITPRL

642 >NP_001312999_(NT)

643 PPKIPGGWPVIGHLFYFNNNGDFSQKLGDLADKYGPVFTFRLGFRRFLAVSSYEAMKECFSTNDIHFADRPALLYGEYLCYNNAML
644 AVAKYGPYWKKNRKLVNQELLSVSRLEKFKHVRFSIVQKNIKQLYN-
645 CDSVKINLS DWIDKLTFDIILKMVVGKTYNNGHGEILKAAFQKFMVQAMEIELYDVFPFFKWLDLTGNIKAMKQTFKDIDNIIQGW
646 LDEHIKKRETQDFIDVLLSKRSNYSHDTTIKATVFTLVLDATDTLALHIK WVMALMINNKVMKKAQEEMDTIVGRDRWVEENDI
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649 >NP_001312768_(NT)

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652 CDSVKINLS DWIDKLTFDIILKMVVGKNYNNGHGEILKVAFQKFMVQAMEMELYDVFPFFKWLDLTGNIKAMKQTFKDIDNIIQG
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654 DIKNLVYLQAI VKEVLR LHPPAPLSVQHLSVEDCVVNGYHIPKGTALLTNIMKLQRDPQTWPNPDKFDPERFLTTHATIDYRGQHY
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656 >NP_001312226_(NT)

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663 >XP_016490207_(NT)

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668 PKGTRLFANVMKLQRDPK LWSNPKDFDPERFFA--
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734 >BAK20464_(EC)
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741 >AFB74616_(PSo)
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746 ERYTTEECEVGRFNPAGTRLLVNIWKIHRDPSVWENPSDFQPERFLCDKVGVLDLYGQNYELIPFGAGRRVCPAIVSSLQTMHYAL
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845 GTEASITTLIWATSLILNNSVLEKKAELDIQVGKERYICESDLSKLTYLQAVVKETLRLYPPAPLSRPFEEEDCTIGGYTVKKGTR
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897 >XP_017242880_(DC)

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904 >CYP82C46_(CA)

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909 GTRLIVNLWKMHRDPSIWANPSEFIPERFLNENANLEVKGQDFEFLPFGSGRRKCPGISFALQVLHLTLARLLHAFELGTVSDTLVD

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911 >XP_006479372_(CS)

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918 >XP_006423130_(CC)

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925 >XP_017244377_(DC)

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932 >XP_017243930_(DC)

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1039 APVAGGAWPVIGHLHLLGGQEPHRL LGDMADKYGIPTMKMGLNRALVVS NWEIAKECFTINDKPFANRPRSMAMDLLGYNFL
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1041 EHATDFFDLGKGFVSDALPFLRWLDIGGYEKL M KKTAKEFDLVFQGWLDEHKS KRGSDFMYVMLS LFD DDDTDTVIKAI CSLI
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1045 >XP_024956574_(CS)
1046 APRAGGAWPLVGHHLHLLGGPEPAHRVLGDMADKYGIPTMKLG V KQALMVSNWEIAKECFTTNDKAFASRPKTMAMELLEYNF
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1049 VAAADTTVVTLTWAIAIALLNNRDVLKKAQDELDIQVGTQRQVNGSDMRNLVYLQAMIKETMRLYPALPLLLPHESIEECTVNGYH
1050 VPAGTQLFVNAWKIQRDPCVWEEPCQFQPERFLTTHKDIDVRGQNFELIPFGSGRRMCPAVSYGLQVMQLMLASLVHGFDFTPSPG
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1052 >XP_015388133_(CS)
1053 APEAGGAWPLIGHLHILRGSEPAHRVLGNMADKYGPIFTMKLGVKQALVVS NWEIAKECFTTNDKAFAGRPKTMATELLGYNFLV
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1059 >XP_006471502_(CS)
1060 PPEAGGAWPVIGHLHLL-
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1063 LPFLRWFDIGGDERAMKKNARELDVLAQGWLDEHKRKRSEDFMDVMLSILRDDDADTINKATCLALILAASDTSKITLTWILSL
1064 LNHRDVLKKAQNELDVHIGKRRQVNELDIKNLVYLQAIKEAMRLYPAGPLAAPHASTEDCTVNDYFVPAGTVLYVNVWKIHRDP
1065 RVWPEPYKFKPERFLTTHKHIDVRGQNFELLPFSSGRRMCPGPSFAIPVTHLTLATLLHGDFDFETPLDEPDMSEGMSLTLVKITPV
1066 KVLITPRL
1067 >CYP82D82_(CP)
1068 PPEAGGAWPVIGHLHLL-
1069 GRFPLHRVLGDMADKYGPIFTIRMGVHRALVVS NWEMAKECLTTHDRVFASRPKALVAEILGFNFMSMFGFSPYGPHWRQIRKIATL
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1075 >XP_006471501_(CS)
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1079 LALILGAADTTVTTLTWVMSLLLNRDILNKAQNELDIQVGTQRQVNESDIKNLVYLQAILKEAMRLYPAGPLLVPHESIEECTVN
1080 GYHVPASTQLFINAWKIQRDPSVWEEPSKFQPERFLTRHKDIDVKGQNFELLPFSSGRRMCPGVSFALQVMQFTLASLLQGFNFATP
1081 SNEPDMGEGLGLTMEKSQPFEVLVTPRL
1082 >CYP82D81_(CP)
1083 APEAGGAWPVIGHLHLLRGPKPPYRVFDKMADKYGPIFIIRMGKNPALIVSNWEIAKECLTTHDKVFANRPKTLAMEILGYNFSMF
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1085 WKELLTRFFEMSGKFV ASDALPFMRWLDIGGDERSMKKIAKELDVIAQGWLEEHKRRDSEDFMYVMLSILGDRDVTINKAICL

1086 ALILGAADTTVTLTLVMSLLLNRDILNKAQNELDIQVGAKRQVNESDIKNLVYLQAILKEAMRLYPAGPLLVPHESIEECTVNGY
1087 HVPAGTQLFINAWKIQRDPVSWEEPCKFQPERFLTRHKDIDVKGQNFELLPFSSGRRMC PGVSFALQVMQFTLASLLQGFNFATPSN
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1089 >KDO42182_(CS)
1090 APEAGGAWPVIGHLHLGGPEPLHRVLGSMADKYGPIFTIKIGINRALVSSWEMAKECLTTNDKIFASRPKTLAMEILGYNFSMFG
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1093 IAGLDTTTLVTLTWVISLLLNRDILDKVQNELDIQVGTKRQVNESDLKNLVYLQATLKEAMRLYPVPLLPHEAIEECTVNGYHVP
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1096 >XP_006471494_(CS)
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1099 WMELLTRSFEMSGKFVVS DALPFLRWLDIGGDERSMKNIAEELDNLLQGWLEKHKRKRNSLDFMSVMLLILGDRD VDTVNKATC
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1103 >CYP82D92_(CP)
1104 APEAGGAWPVTGHLHLLGGPEPPHRVLGAMADKYGPIFTIKMGNRALVSSNWEMAKECLTTHDKVFASRPKTLAMEIFGYNFS
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1107 LGLILAATDTTAVTLTWVISLLLNRDILNKAQNELDIQVGTKRQVNESDIKNLVYLQAILKETMRLYPVPLLVPHESMEECIVNG
1108 YHVPAGTQIFINAWKLQRDPVSWEEPCKFHPKTF LTRQKDIDVKGQNFELLPFSSGRRMC PGVSFALQVMQFTLASLLHGDFATP
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1113 KELLTRFFEMSGKFVVS DALPFLRWLDIGGDERSMK KIAKELDVVQGWLEEHKMKRDS EDFMYVMLSILGDRD VDTINKAICLG
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1117 >CYP82D83_(CP)
1118 APEAGGAWPVIGHLHLLGGPEPPHRVLGCMADKYGPIFTIKMGINRALVSSNWEMAKECLTTHDKVFASRPKTLAMEILGYNFSM
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1122 VPSGTQLFINVWKLQRDPHVWEECKFQPERFLTRHKD TDVRGQNFELLPFSSGRRMC PGVSFAPQVMQFTLASLLHGFDIATPSN
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1124 >CYP82D179_(CP)

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1133 GFSPYGSYWRETRKIATLELLSNHRLGKLRHVREYELKTSKLDLYELWDKLLVEMKRWFTDTIRNVVLRMIVGKGCSDVG-

1134 EEWIELLTRFSEMSGKFVSDALPFLRWLDIGGDERSMKKIAKELDIVVQGWLEEHKRKRDSLDFMSVMLSILSDRDVDTINKATC

1135 LGLVLAATDTTITL TWVISLLLNHRDILNKAQNELDILVGAQRQVNESDIKNLVYLQAILKEAMRLYPAAPLLIPHESIEECTISGYN

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1142 LGLVLAATDNTKMTL TWVISLLLNHRDILNKAQNELDILVGTQRQVNESDIKNLVYLQAILKEAMRLYPGSPLLIPHKSIEECTISGY

1143 NVPTSTQLIINWKLQRDPHVWEEPCKFQPERFLTRHKDIDVRGQNFELLPFGSGRRITCPGVSFALQVMEFTLASLLHGFD FATPSN

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1149 LGLVLAATDNTKMTL TWVISLLLNHRDILNKAQNELDILVGTQRQVNESDIKNLVYLQAILKEAMRLYPGSPLLIPHKSIEECTISGY

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1152 >CYP82D62_AGF30366_(MP)

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1159 >CYP82D33_AGF30364_(OB)

1160 PPEASGAWPVIGHLRIMSGAGIPHVNLGMLADKHGPIFSIRLVHRVVVVSSEVIKELFTTNDVAVSSRPSVKAGKHLAYDNAML

1161 GFASYGAYWRQLRKIVSLELLSNRRLELQSHVSMSETGQFVKELYKLWEKVVVDMKRWL GELNMNVVMRMVAGKRFNAEETK

1162 RCRRVMGDFFFYLAGFFVPADALPYLGWLDLGGHEKRMKKA AKELDEVVGEWLAEHREREKAQDFMDVMISVVKEFDVDTIIKA
1163 TCGTLIAGGTDTTAVVFWALSLLLNSHVLKKAQQELDKHV GKDRRVKESDLNLIYLQAI VKETLRLYPGPLAGTRRFTEDCV
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1166 >XP_006473406_(CS)
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1170 TDTTNTVNLWALSLLLNNRRELEKVKKELDSVVGKERLLCESDIEKLVYLQAVIKETLRLYPAGPLAGARQFTEDCTVAEYHVPKG
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1172 MTGTAGLTNIRATPLEILLKPR L
1173 >CYP82D84_(CP)
1174 PPEAAGKWP MIGHLHLLAGPQLPHLALGALADKYGPLFSIRIGVHPALVSSWEMAKELFTKHDV DISSRPKLTVGKLLGHNYANF
1175 GFSPYNAYWREMRKITALELLSNRRLELLKHIRATEVEGEIKELYKIWTKILLEMKKWFGDLN LNVILMMIAGKRYFETEVRRYRA
1176 AIRNFFRLGGVFLVRDALPFLGWLDIGGYEKAMKKTAKELDSVIEEWIEEHRKK E-
1177 LDFIDVLLSVLEGFDVDTVIKATMTIIVGATDTTNTVNLWALSLLLNGREXDKVKKEWESVVGKERVLR ES D IEKLG YVQAVIK
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1180 >CYP82D1_(MS)
1181 PPLASGGWPLIGHLHLLGSSNQPYITLGNLADKYGPIFTLRVGVHNAV VVSTWELAKEIFTTHDVISSRPKFTA AKILGHDIYANFGF
1182 SPYGDYWQMMRKVTASELLSTRRFETLRDIRDSEVKKSLMELCNSGFDLKVEMKRFLGDMNLNVIMRMIAGKRY-
1183 EREVRKVRWVFREFFRLTGLFVVGDAIPFLGWLDLGGHV KEMKKAAREMDSVVCGWLEDHRH-
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1185 VVKETLRLYPAGPLSGARQFTKDCTVGGYNIRAGTRILNLWKMHRDPRVWSEPLEFQPERFLNTHKDVDVKGQHYELLPFGGGR
1186 RSCPGITFGLQMTNLALASFLQAFEVTTPSNAQVDMSATFGLTNIKTTPLEVI AKPR L
1187 >CYP82D28_XP_006581227_(GM)
1188 PPAASGGWPLIGHLHLLGGSGQLYETLGLTADMYGPIFSIRIGVHPAVVSSWELAKECFTTLDVTVSSRPKFTA AKILTYNYASFAF
1189 APYGDFWRDMHKITVSELLSTRQAEMLRGIRDSEVSSSRELQRAWAELLVEMKQWFGEMNLNVILRMVAGKRYCQEQRARRVR
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1193 ENVDMSATFGLTLIKTTPLEVLAKPR L
1194 >CYP71AJ3_(PSa)
1195 PPSPPR-LPIIGNLHQIG--
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1198 YKSLLLQIMDMLGYRSIEDFFPSLGVVDITGLKGKVEKAANGVDAFLEGVLKNHTNPSTSKDFVSILLEIQES-
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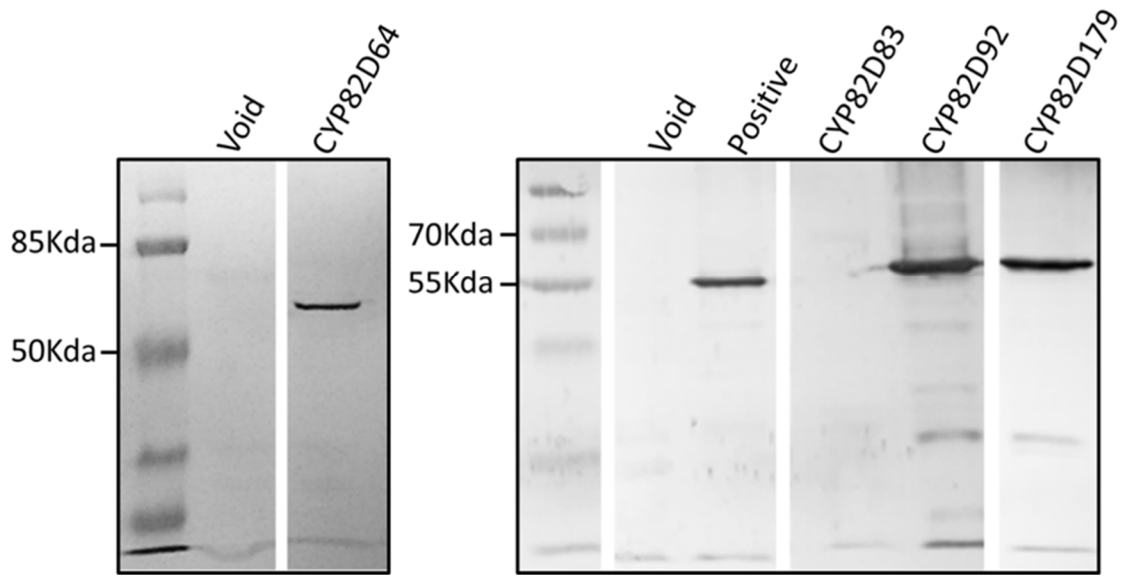
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1203 PPSPPR-LPIIGNLHQIG--
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1208 IGGKSKIEEVDLVKMNYLKAVMKESMRLYITA-FLLPREAKQDVKLMGYDISSGTQVLINTWETARDPSLWDNPEEFRPERFLN--
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1210 >CYP71AZ4_(Psa)
1211 PPGPRG-
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1213 HWRNVKRMCTLELFTQKRAQFFRPVREDEVSRMVGRLSEAAAAEDVNA YECFTNFATSIIISRVAFGKRYDNLGKEKFQRMVADIE
1214 AMFAAFFVSDFFPMFGWIDL SGVKA VLDRNFNEMDTFYQELIDEHXKPD RPGLDIDVMLKNKGSFLTMDSIKAILLN VFSGGIGTT
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1216 VNTWGIGRDPKYWKNPLEFMPERFFE-
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1218 >CYP71AZ5_(Psa)
1219 PPGPRG-
1220 LPFIGNFYQLYKAPSSHEYLWNLSKRYGSLVTLHMGSVPVLVVSSPKMAQQVMKTQDLIYCSRAQMTGTTKLSYNGLDMAFAPY
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1226 >CYP71AZ3_(Psa)
1227 PPGPPG-
1228 LPFIGNFHQLYKASSTHEYLWLSKQYGLVTLRMGSVPILVVSSPKMAKEVLQTQDLIYCSRPMAMTGMQKLSYNGLDVAFSPYTD
1229 QWRHTRKFCTLELFTQKRAQLFRPVREQEVS RMIARLSETAAAKDVNA YEWFSNLATCIISRVAFGKRYDGIGKERFQRMSEIDA
1230 MFIGFFVSDFFPMFGWIDL SGMRDRLDRTFKDLDMFYQELIDEHLKPNRLEDLIDVMLKNEGSSLTKDSMKAILLN VFNGGTGTTA
1231 TVLAWAMTALLRNQGVMMKKAQEEIRSVIGKKGKVD EDDFPSPYLRAVVKETMRLYPPAPVLPRETMESSIIEYMKPKTVVY
1232 ISMWAIGRDPKTWKNPMEFVPERFLE-
1233 RPDINYKQQFEYVPGAGRRICAGINLGVTTVELALANLLYTFDWEPPAFEDIDDETTNGLALQKKNALYIRPKKYM
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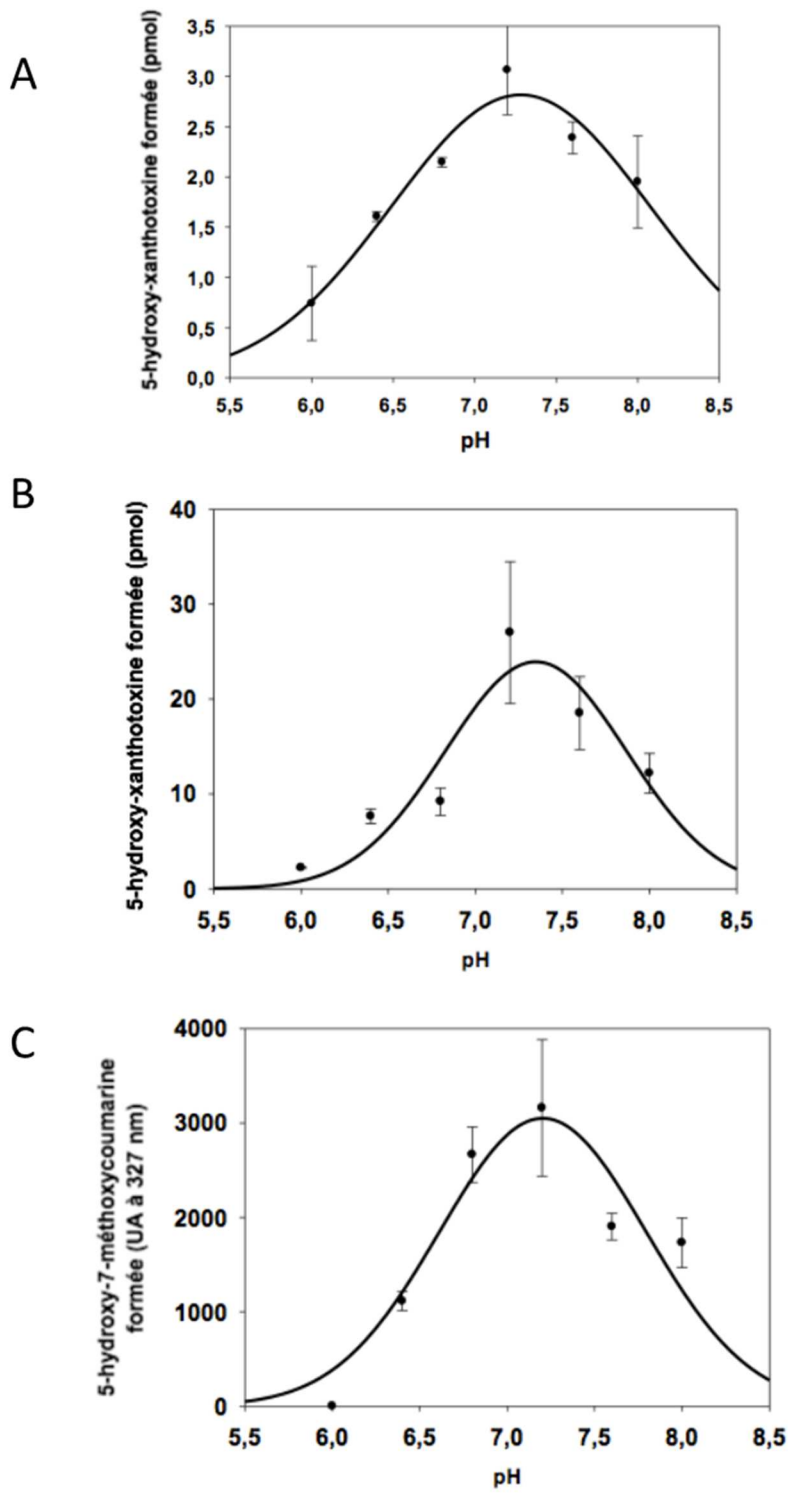
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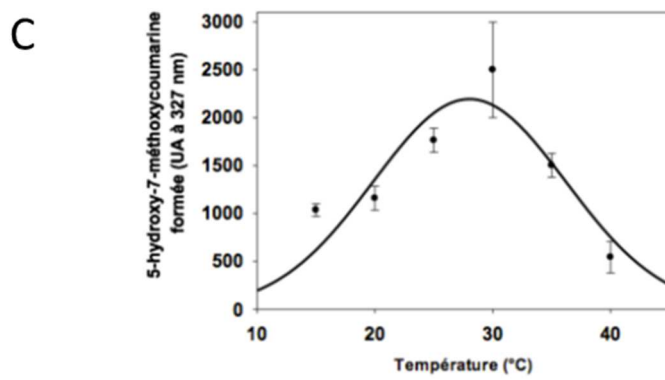
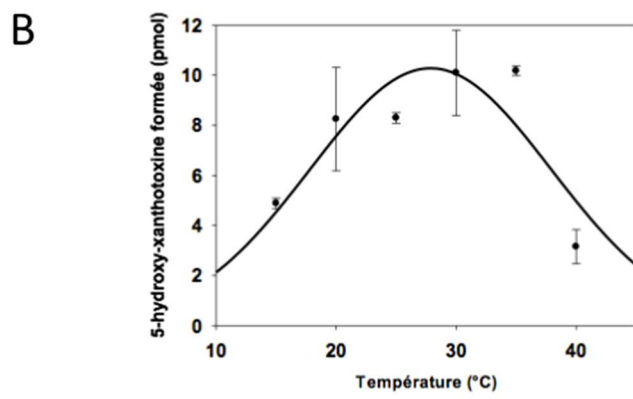
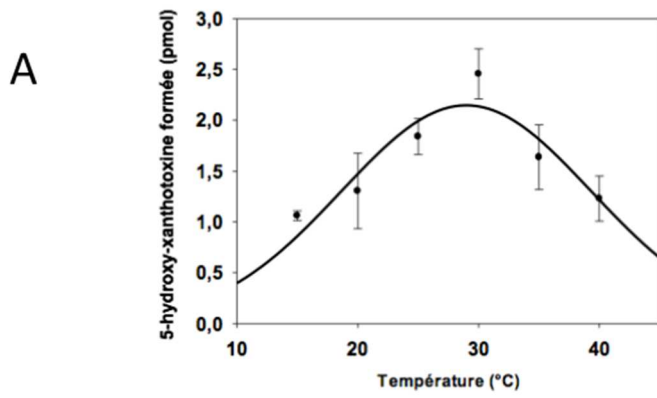
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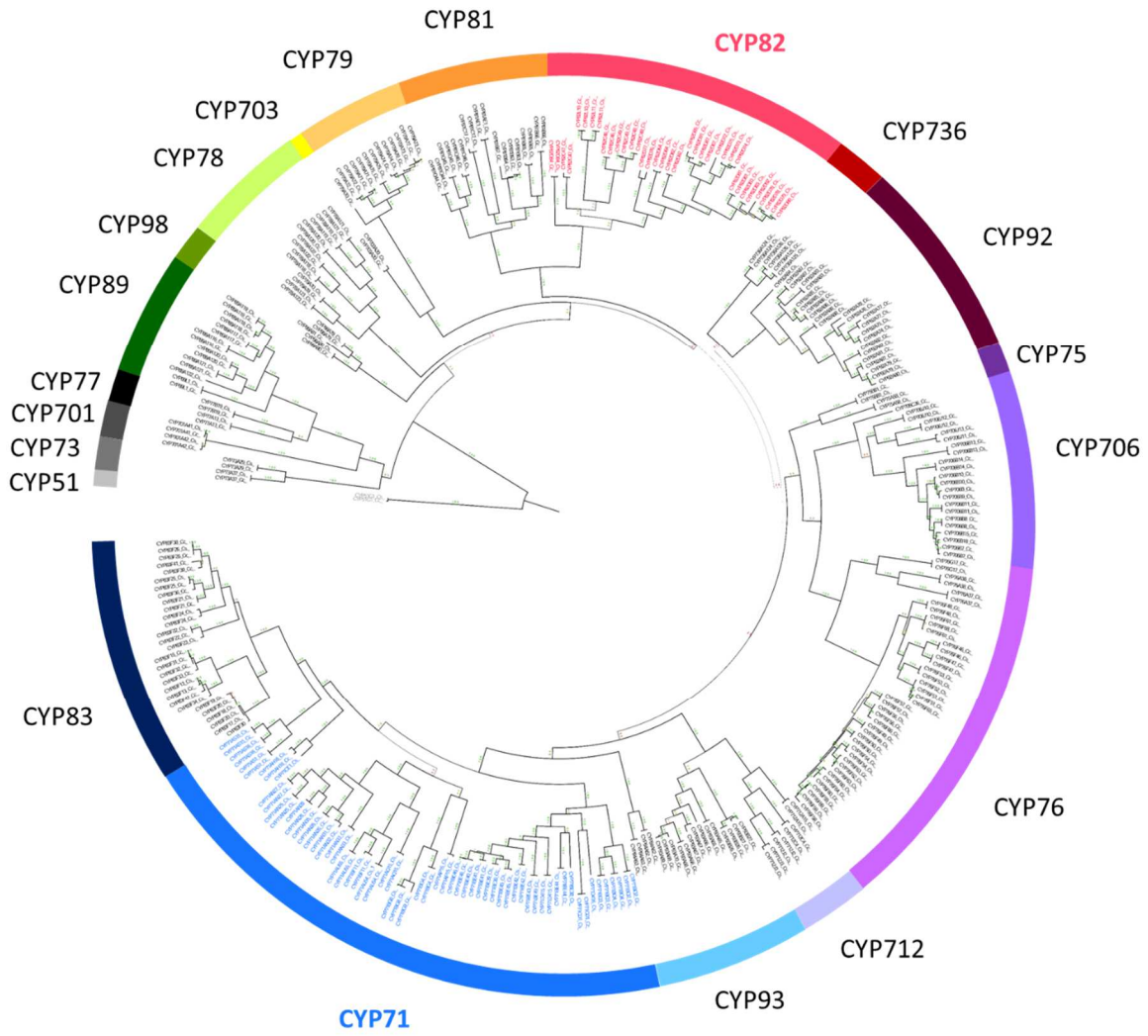


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1369 Supplemental figure 5

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