

Supplementary File 1

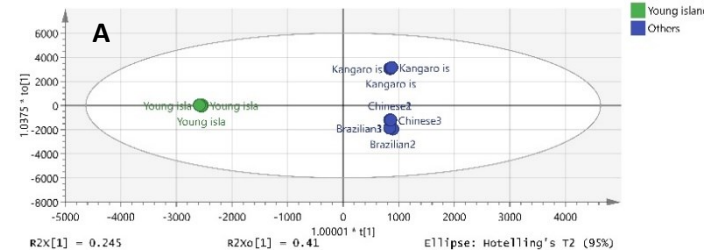
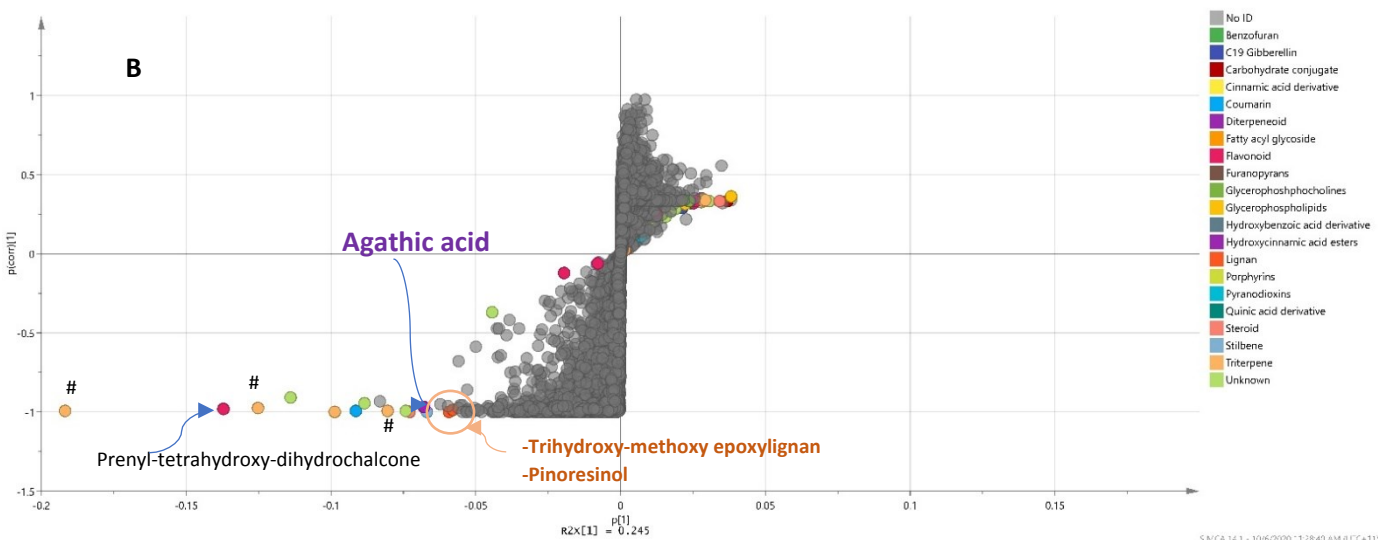
## Broad-spectrum pharmacological activity of Australian propolis and metabolomic-driven identification of marker metabolites of propolis samples from three continents

### Table of Contents

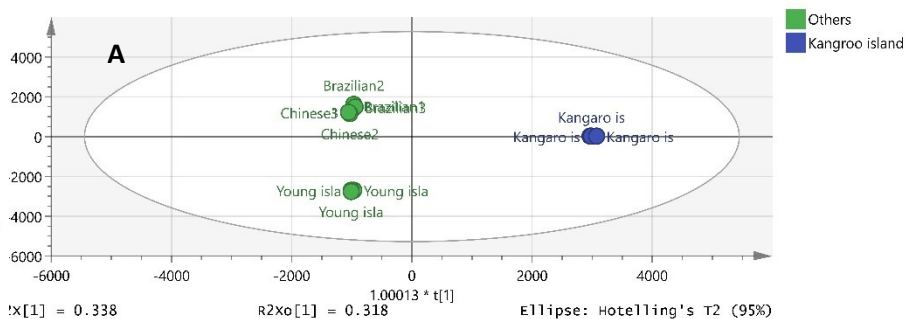
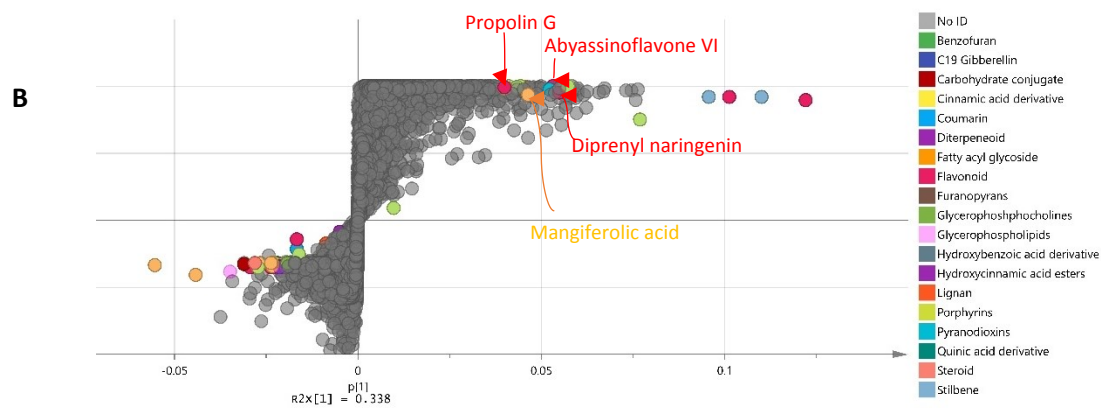
Figure S1: UPLCMS OPLS-DA analysis of AP-1 against the AP-2; Kangaroo island, Brazilian and Chinese samples, A) score scatter plot B) loading scatter S-plot (# Hydroxymangiferolic acid isomers).....	4
Figure S2: UPLCMS OPLS-DA analysis of Kangaroo island propolis samples against the AP-1, Brazilian and Chinese samples, A) score scatter plot B) loading scatter S-plot.....	4
Figure S3 3.00_515.1200m/z (Di-O-caffeoylquinic acid).....	5
Figure S4 3.27_327.1215m/z (3,4-dihydroxy-2-(4-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)benzoic acid).....	5
Figure S5 3.33_357.1320m/z (Butyl 3-O-beta-D-glucopyranosyl-butanoate).....	6
Figure S6 3.36_678.1593n (Tri-O-caffeoylquinic acid).....	6
Figure S7 3.47_375.1429m/z ((7S,8S,7'R,8'R)-3,3',4'-trihydroxy-4-methoxy-7,7'-epoxylignan).....	7
Figure S7 3.59_360.1532n (Casegravol isovaleric acid).....	7
Figure S8 4.09_440.1799n (Abyssinoflavanone VI).....	7
Figure S9 4.19_301.0699m/z (Dihydrokaempferide).....	8
Figure S10 4.22_311.1258m/z (3',4',5-trihydroxy-3-prenyloxy-(E)-stilbene).....	8
Figure S11 4.47_358.1387n pinoresinol (lignan).....	9
Figure S12 4.48_315.0846m/z (Cyclocalopin F).....	9
Figure S13 4.66_380.1964n ( (E)-2,4-bis(3-methyl-2-buten-1-yl)-3,3',4',5-tetrahydroxystilbene).....	10
Figure S14 4.68_270.1595n (3β-hydroxy-estra-5,7,9-trien-17-one).....	11
Figure S15 4.76_669.2691m/z (Coagulin R –hexoside).....	12
Figure S16 4.87_478.1247n (5-hydroxy-3-(4-hydroxy-3,5-dimethoxy-benzoyl)-2-(3-hydroxy-4-methoxy-phenyl)-6-methoxy-inden-1-one).....	13
Figure S17 5.06_314.1502n (Gibberellin A120).....	14

Figure S18 5.06_357.1308m/z (3,5,3',4'-Tetrahydroxy-2-prenyl-(E)-stilbene) .....	14
Figure S19 5.09_394.1390n ((E)-3-{2,3-dihydro-2[2-[(E)-p-coumaroyloxy]-1-methylethyl]-5-benzofuranyl}-2-propenoic acid) .....	15
Figure S20 5.13_270.0494n Trihydroxy flavone (Apigenin/Galangin).....	16
Figure S21 5.52_315.1573m/z ((E)-3-(2,3-dihydro-2-(1-hydroxy-1-methylethenyl)-7-prenyl-5-benzofuranyl]-2-propenoic acid).....	16
Figure S22 5.95_380.1945n ((E)-2,6-bis(3-methyl-2-buten-1-yl)-3,3',5,5'-tetrahydroxystilbene) .....	17
Figure S23 5.96_342.1442n (Prenyl-tetrahydroxy-dihydrochalcone) .....	18
Figure S24 6.15_490.3635n (Barringtonol C-like) .....	18
Figure S25 6.34_299.1630m/z (ArtepillinC).....	18
Figure S26 6.46_489.3562m/z (6beta-acetoxy-24-methylcholestan-3beta,5alpha,22R,24-tetrol) .....	19
Figure S27 6.59_344.2306n (Methyl 4,6-O-(10-undecenylidene)hexopyranoside) .....	20
Figure S28 6.94_424.1860n (Propolin C/D/F) .....	20
Figure S29 6.94_720.3287n isomer of 6.62_720.3285n.....	21
Figure S30 6.98_408.1906n (3',8-diprenylnaringenin) .....	22
Figure S31 7.12_334.2115n (Agathic acid).....	23
Figure S32 7.37_337.1057m/z (pinobanksin-3-pentanoate).....	23
Figure S33 6.92_355.1185m/z pinobanksin 3-pentanoate.....	23
Figure S34 7.43_369.1107m/z (6-cinnamylchrysin) .....	24
Figure S35 7.45_385.1056m/z (Dimethoxy-6",6"-dimethylpyranoflavone).....	24
Figure S36 7.57_385.1061m/z (Gibberellin A29/A1/A34/A36/A58/A60) .....	24
Figure S37 7.76_407.1835m/z (8-geranyl naringenin(bonannione A,sophoraflavanone A)).....	25
Figure S38 8.96_471.3450m/z (hydroxymangiferolic acid/hydroxyisomangiferolic acid (3,23-Dihydroxycycloart-24-en-26-oic acid)).....	25
Figure S39 8.96_471.3458m/z (hydroxymangiferolic acid/hydroxyisomangiferolic acid (3,23-Dihydroxycycloart-24-en-26-oic acid)).....	26
Figure S40 9.21_471.3448m/z (hydroxymangiferolic acid/hydroxyisomangiferolic acid (3,23-Dihydroxycycloart-24-en-26-oic acid)).....	26
Figure S41 9.04_491.2414m/z (Propolin G/Solophenol A/Nymphaeol C (Geranyl-tetrahydroxy-prenylflavanone)) .....	27

Figure S42 9.21_492.2487n (Propolin G/Solophenol A/Nymphaeol C (Geranyl-tetrahydroxy-prenylflavanone)) .....	27
Figure S43 9.50_613.3172m/z (Spirostenyl-hexoside) .....	28
Figure S44 9.51_496.3161n (PG(P-18:0/0:0)) .....	28
Figure S45 9.68_512.3120n (PG(18:0/0:0)).....	28
Figure S46 9.69_455.3493m/z (Mangiferolic acid/isomangiferolic acid/12-Hydroxy-3,4-secocycloarta-4(28),24-dien-3-oic acid) .....	29
Figure S47 10.10_525.3209m/z (GPC(20:4)) .....	30
Figure S48 10.38_514.3308n (Spirost-5-en-3,11-diyl diacetate) .....	31
Figure S49 10.65_528.3449n ((24E)-3alpha-Acetoxy-15alpha,22S-dihydroxylanosta-7,9(11),24-trien-26-oic acid).....	32
Table S1 UPLC-DAD quantified phenolics in propolis samples (Mean ±SD).....	33
Figure S50. The abundance of Artepillin C among propolis samples (UPLC-qTOF-MS).....	35
References.....	35



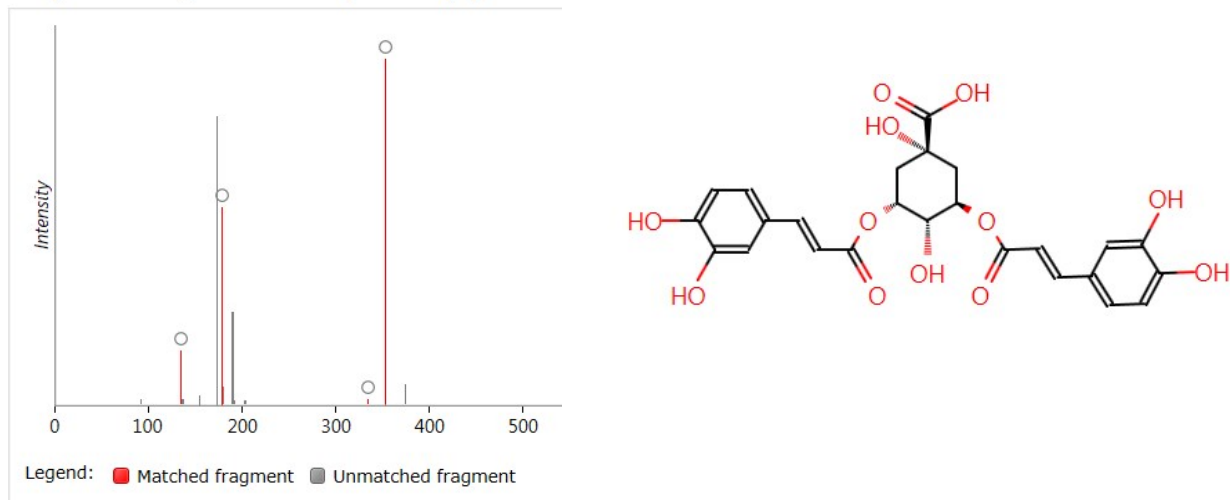
**Figure S1: UPLCMS OPLS-DA analysis of AP-1 against the AP-2; Kangaroo island, Brazilian and Chinese samples, A) score scatter plot B) loading scatter S-plot (# Hydroxymangiferolic acid isomers).**



**Figure S2: UPLCMS OPLS-DA analysis of Kangaroo island propolis samples against the AP-1, Brazilian and Chinese samples, A) score scatter plot B) loading scatter S-plot**

**Figure S3 3.00\_515.1200m/z (Di-O-caffeoylquinic acid)**

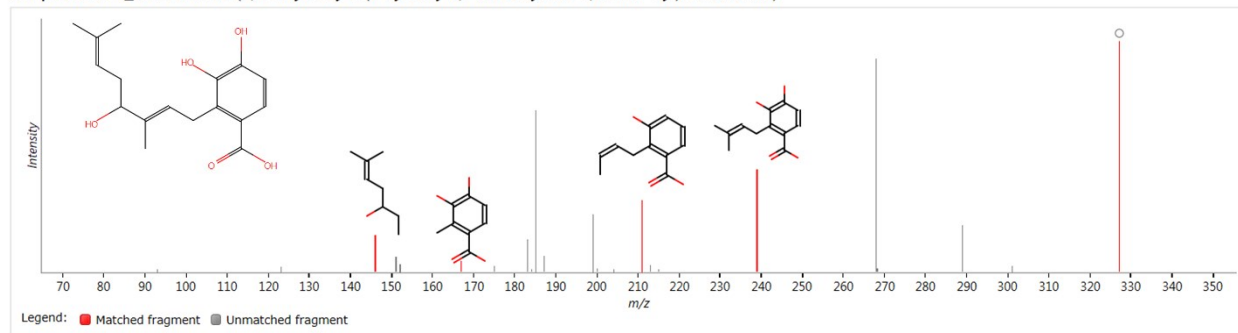
**Compound 3.00\_515.1200m/z (Dicafeoylquinic ac**



(TATEFUJI, IZUMI et al. 1996)

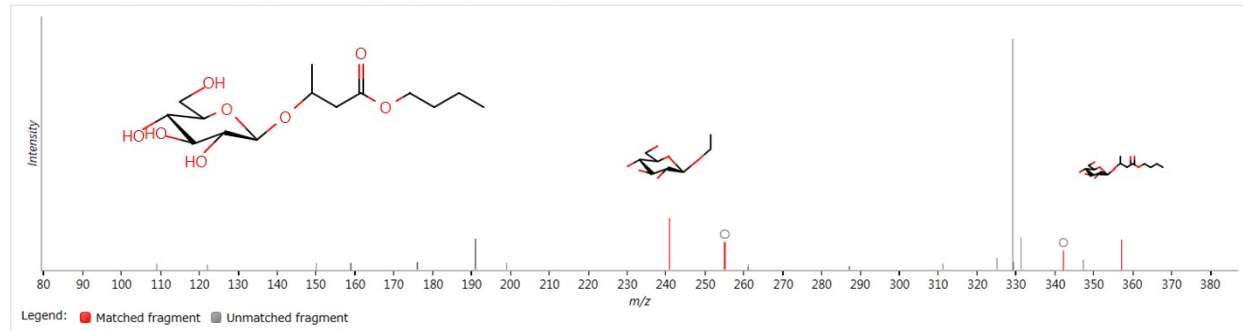
**Figure S4 3.27\_327.1215m/z (3,4-dihydroxy-2-(4-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)benzoic acid)**

**Compound 3.27\_327.1215m/z (3,4-dihydroxy-2-(4-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)benzoic acid)**



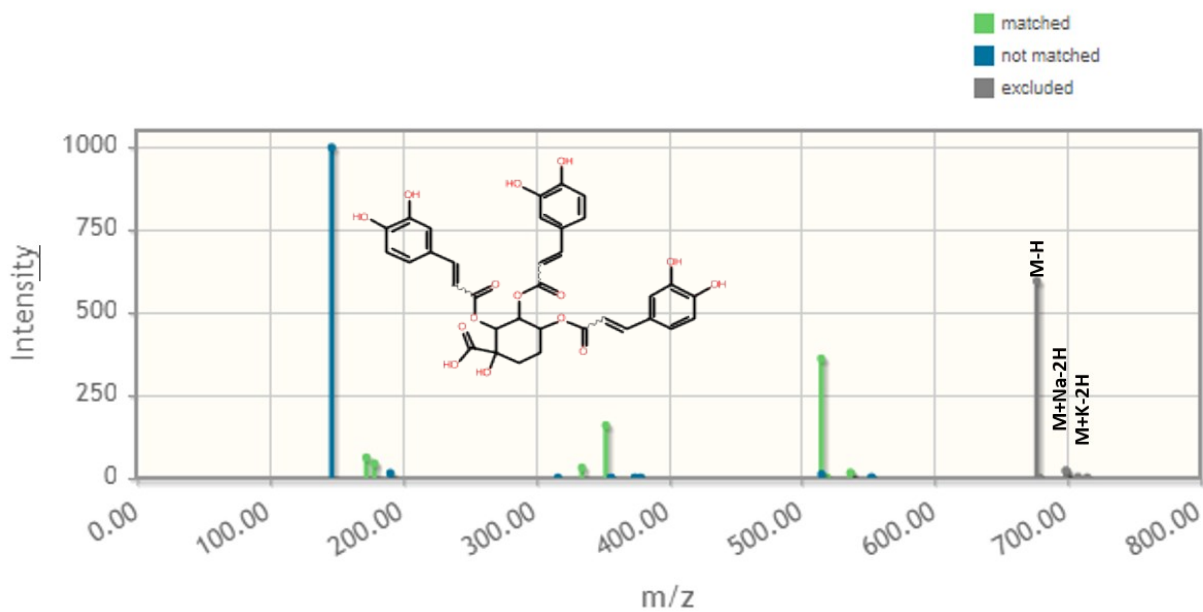
**Figure S5 3.33\_357.1320m/z (Butyl 3-O-beta-D-glucopyranosyl-butanoate)**

Compound 3.33\_357.1320m/z (Butyl 3-O-beta-D-glucopyranosyl-butanoate)



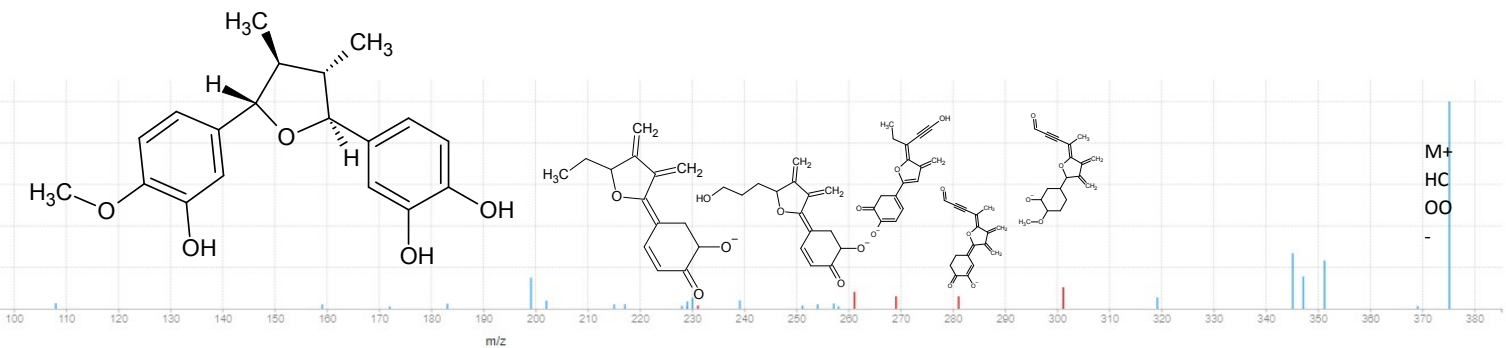
**Figure S6 3.36\_678.1593n (Tri-O-caffeoylquinic acid)**

3,4,5-Tri-*O*-caffeoylquinic acid (Matsui, Ebuchi et al. 2004, Mishima, Inoh et al. 2005, Nakajima, Shimazawa et al. 2007)



**Figure S7 3.47\_375.1429m/z ((7S,8S,7'R,8'R)-3,3',4'-trihydroxy-4-methoxy-7,7'-epoxylignan)**

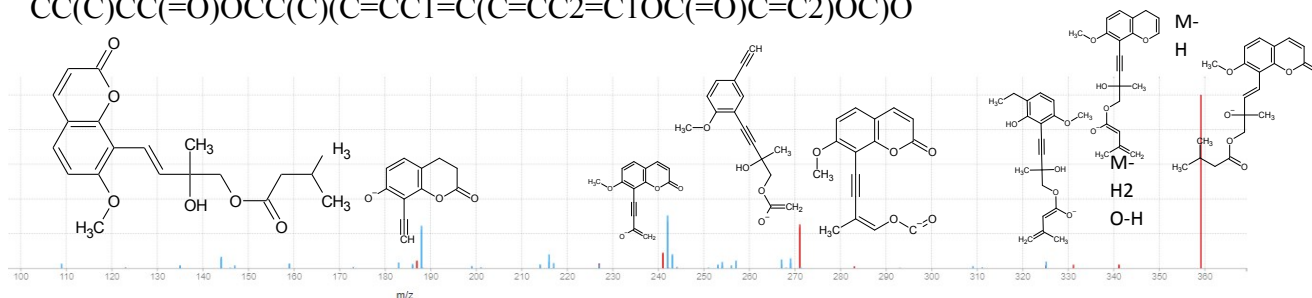
(Aguero, Svetaz et al. 2011)



\*Matched fragments colored red

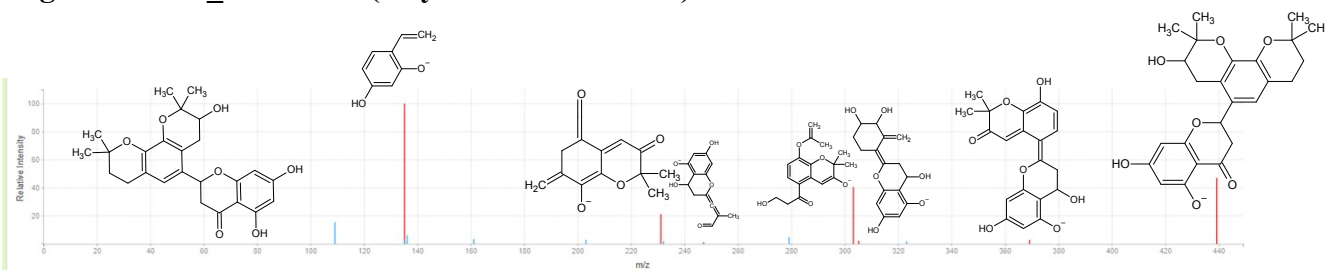
**Figure S7 3.59\_360.1532n (Casegravol isovaleric acid)**

CC(C)CC(=O)OCC(C)(C=CC1=C(C=CC2=C1OC(=O)C=C2)OC)O



\*Matched fragments colored red

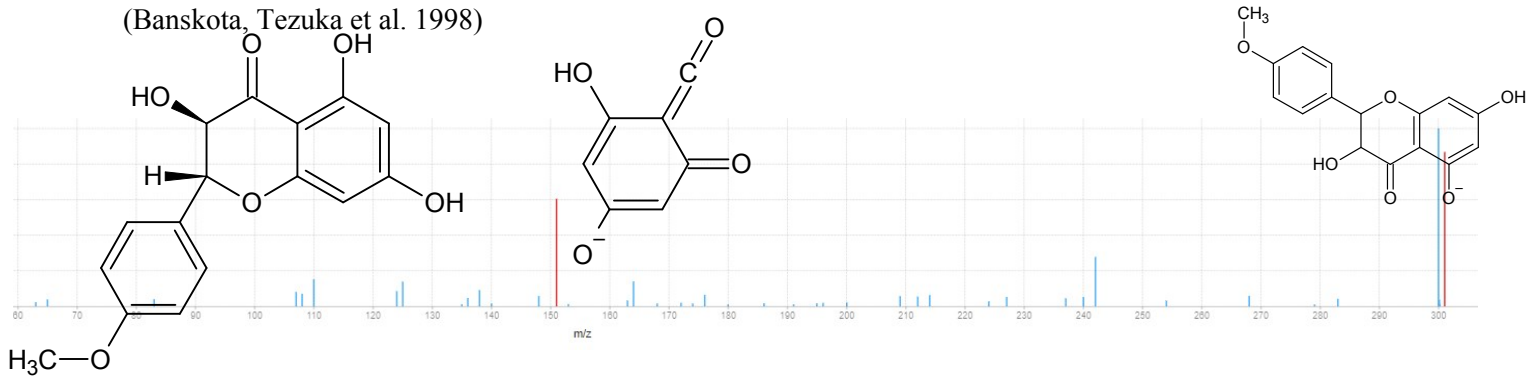
**Figure S8 4.09\_440.1799n (Abyssinoflavanone VI)**



\*Matched fragments colored red

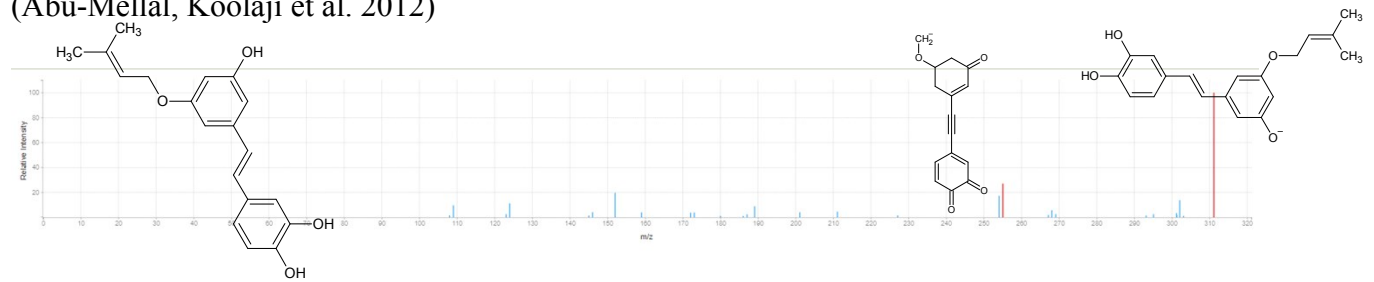
**Figure S9 4.19\_301.0699m/z (Dihydrokaempferide)**

(Banskota, Tezuka et al. 1998)



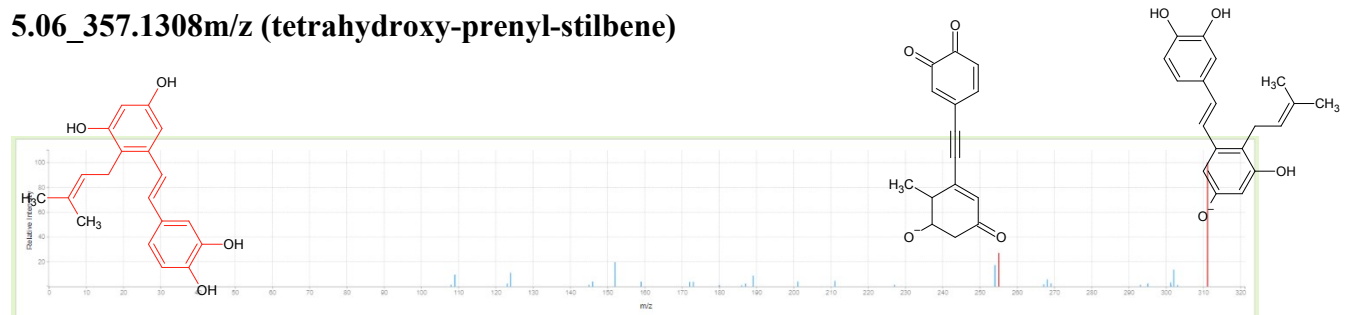
**Figure S10 4.22\_311.1258m/z (3',4',5-trihydroxy-3-prenyloxy-(E)-stilbene)**

(Abu-Mellal, Koolaji et al. 2012)



**LogP4.4 (eluted first)**

**5.06\_357.1308m/z (tetrahydroxy-prenyl-stilbene)**



**Compound 60:**

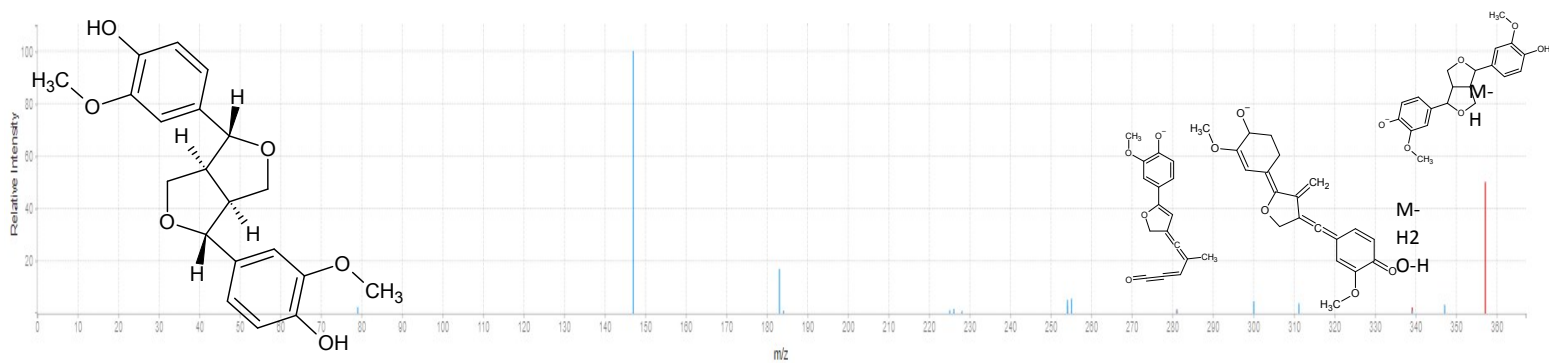
LogP4.5 (more lipophilic → 5.06\_357.1308m/z)

\*Matched fragments colored red



### Figure S11 4.47\_358.1387n pinoresinol (lignan)

(Li, Awale et al. 2008)



\*Matched fragments colored red

### Figure S12 4.48\_315.0846m/z (Cyclocalopin F)

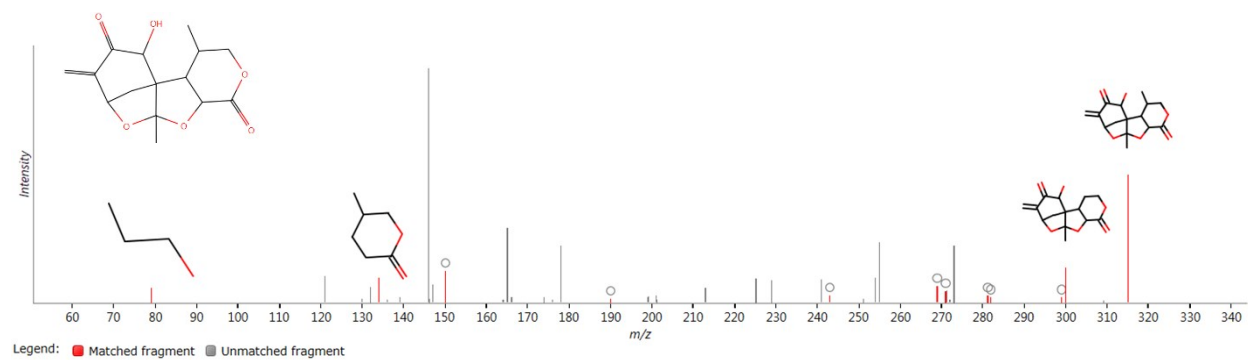
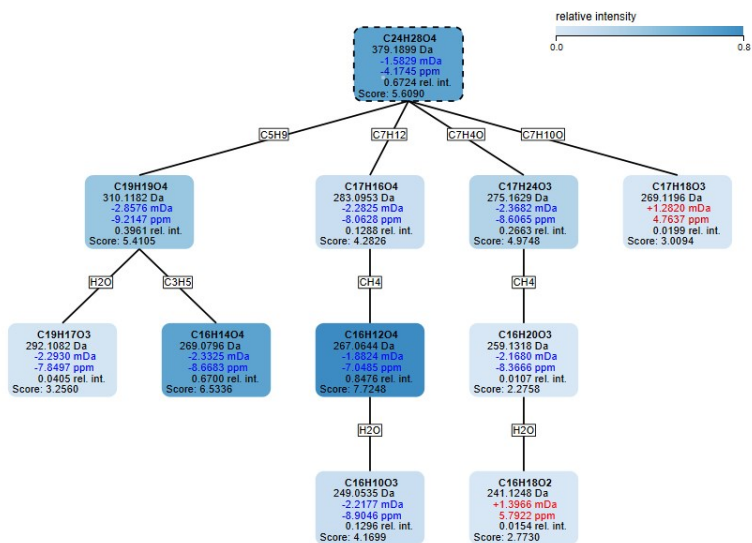
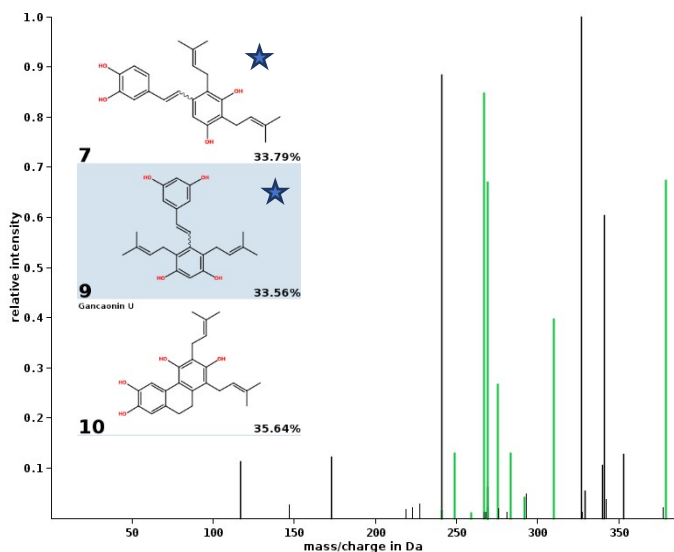
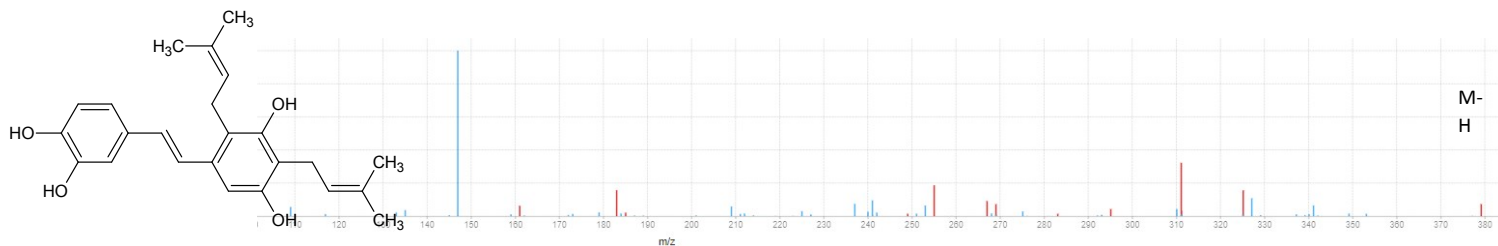


Figure S13 4.66\_380.1964n ( (E)-2,4-bis(3-methyl-2-buten-1-yl)-3,3',4',5-tetrahydroxystilbene)

(Duke, Tran et al. 2017)



\*Matched fragments coloured green



\*Matched fragments colored red

Fragment m/z	Structure
161.023	<chem>O=C=C=C=C=C=CC([O-])CO</chem>
183.0103	<chem>O=C=C=C=C=C=C1C=CC(=O)C([O-])=C1</chem>
185.0591	<chem>CC=CC#CC=C1C=CC(=O)C([O-])=C1</chem>
241.1248	<chem>[CH-]=C(C#CC1=CC(=O)C(=O)C=C1)CCCC(C)C</chem>
249.0535	<chem>CC[CH-]C#CC(C#CC1=CC(=O)C(=O)C=C1)=C=C=O</chem>
255.0645	<chem>CC1C(=O)C=C([O-])C=C1C#CC1=CC(=O)C(=O)CC1</chem>
259.1318	<chem>CC(C)CCC1C(=O)C=C([O-])C=C1#CC=CCO</chem>
267.0644	<chem>CCC1C(=O)C=C([O-])C=C1C#CC1=CC(=O)C(=O)C=C1</chem>
269.0796	<chem>CCC1C(=O)C=C([O-])C=C1C#CC1=CC(=O)C(=O)CC1</chem>
269.1196	<chem>CC(C)CC[CH-]C(C#CC1=CC(=O)C(=O)CC1)=C=C=O</chem>
283.0953	<chem>CC(C)CCC1C(=O)C=C([O-])C=C1C#CC#CC(=O)C=O</chem>
295.1312	<chem>C=C(C)C#CC1=CCC(C#CC2CCC(O)C([O-])C2)=CC1=O</chem>
311.1279	<chem>CC(C)CCC1C(=O)C=C([O-])C=C1C#CC1=CC(=O)C(=O)CC1</chem>
311.167	<chem>CC#CC(=O)C=C(C#CC1=CC(=O)C([O-])CC1)CCCC(C)C</chem>
325.1817	<chem>CC(C)=C=C=C1C(=O)C=C(C#CCCC([O-])C(CCC(C)C)C1=O</chem>
379.1899	<chem>CC(C)=CCc1c(O)cc(C=Cc2ccc(O)c(O)c2)c(CC=C(C)C)c1[O-]</chem>

Figure S14 4.68\_270.1595n (3 $\beta$ -hydroxy-estra-5,7,9-trien-17-one)

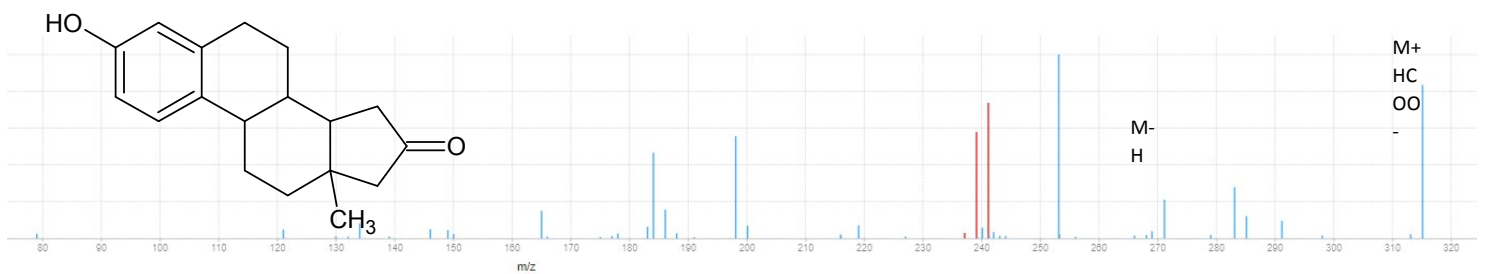
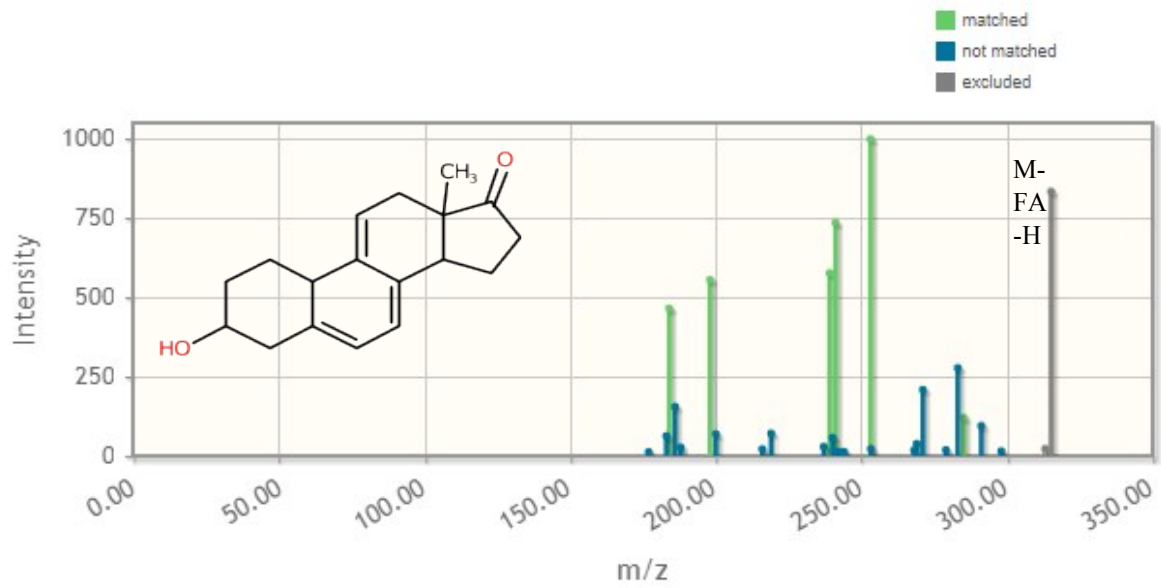
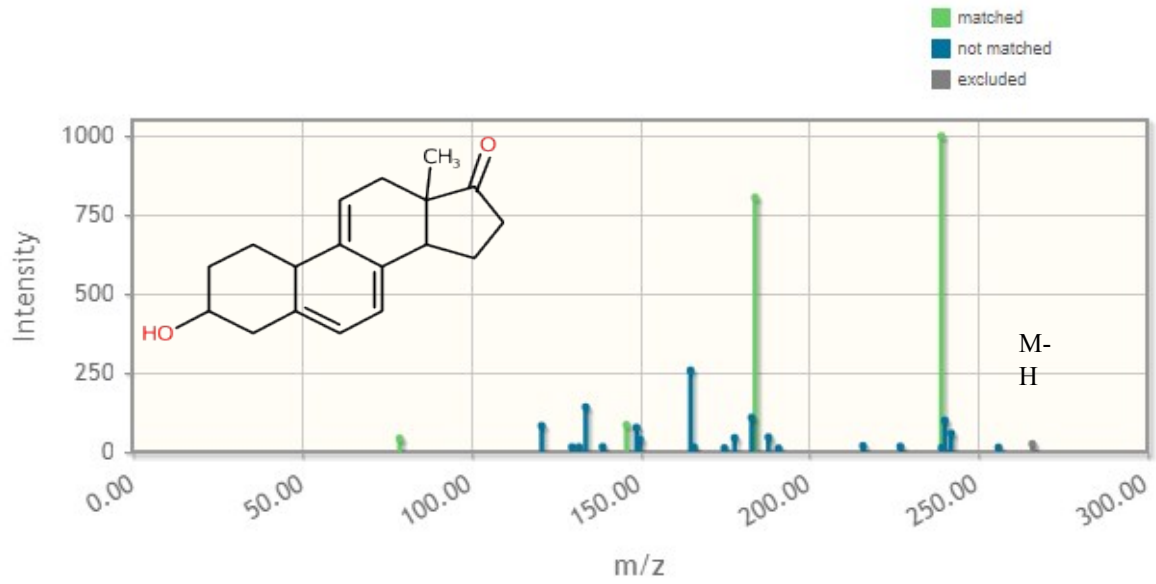
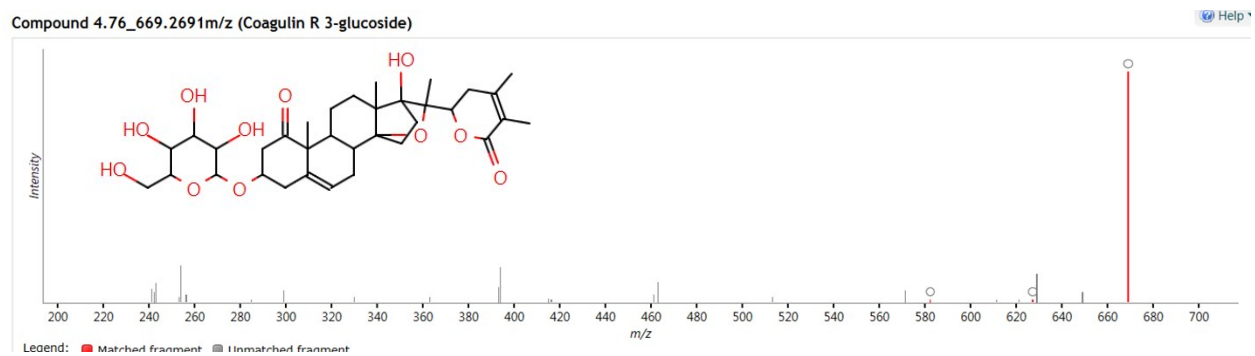
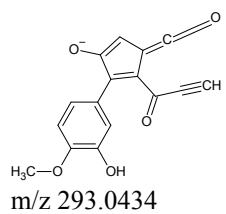
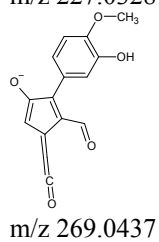
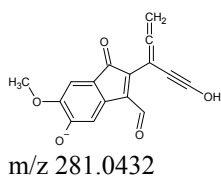
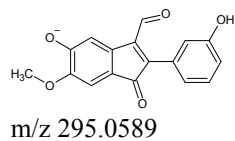
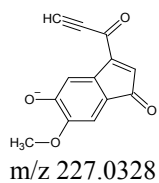
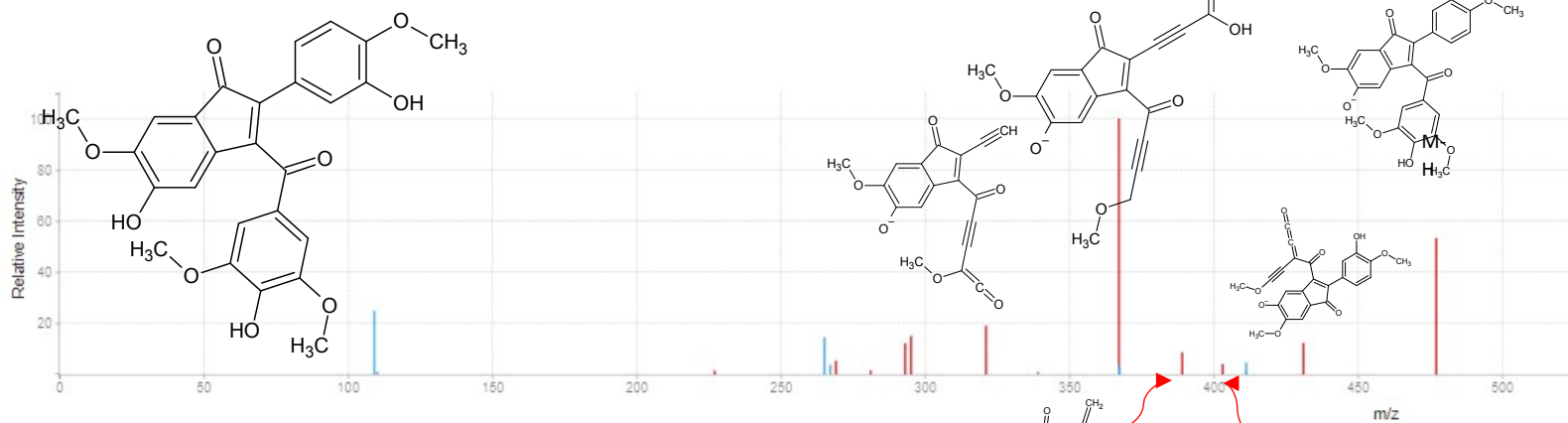


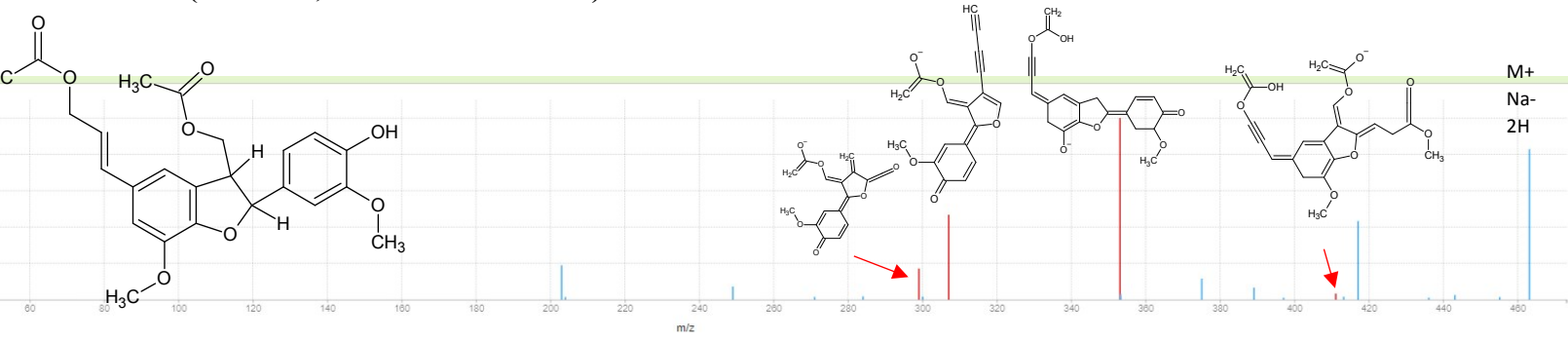
Figure S15 4.76\_669.2691m/z (Coagulin R –hexoside)



**Figure S16 4.87\_478.1247n (5-hydroxy-3-(4-hydroxy-3,5-dimethoxy-benzoyl)-2-(3-hydroxy-4-methoxy-phenyl)-6-methoxy-inden-1-one)**



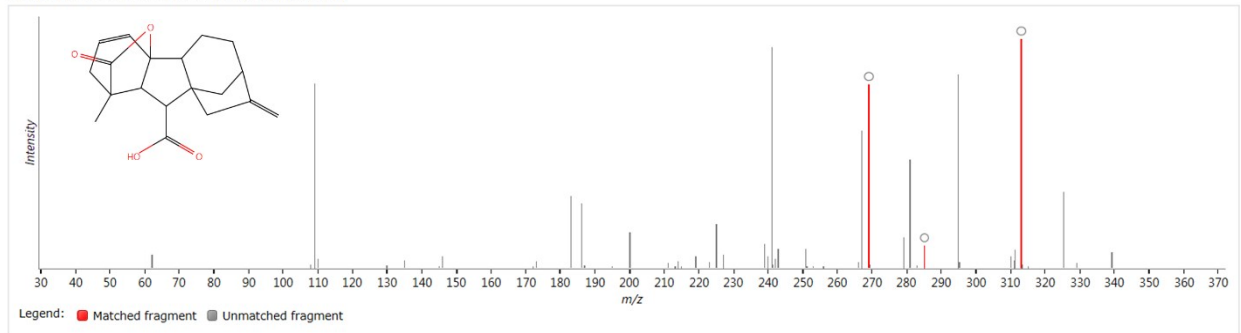
**4.97\_463.1334m/z (Dimeric coniferyl acetate)**  
**(Bankova, Nikolova et al. 1996)**



**Figure S17 5.06\_314.1502n (Gibberellin A120)**

(Kim, Kim et al. 2019, Nani, Sardi et al. 2020)

Compound 5.06\_314.1502n (Gibberellin A120)



**Figure S18 5.06\_357.1308m/z (3,5,3',4'-Tetrahydroxy-2-prenyl-(E)-stilbene)**

(Abu-Mellal, Koolaji et al. 2012)

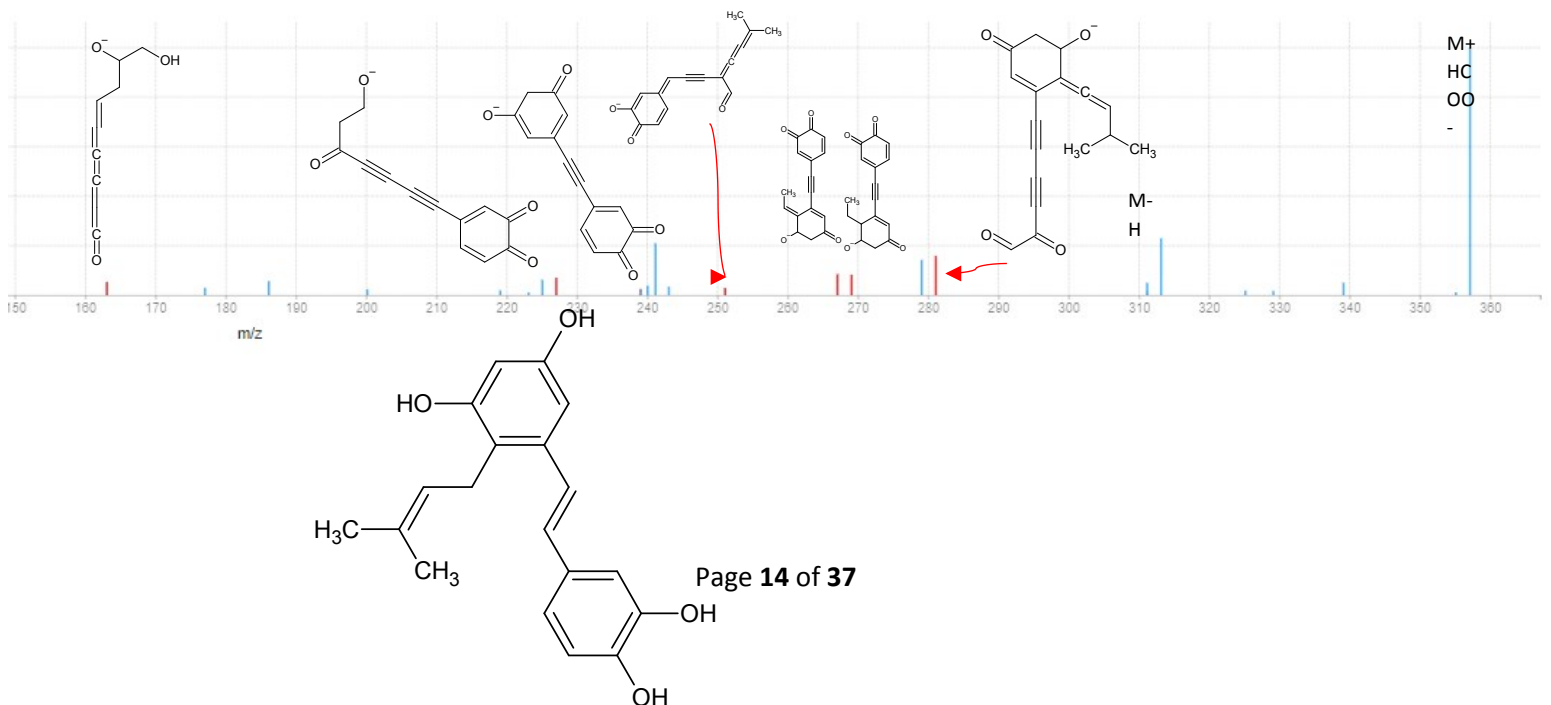
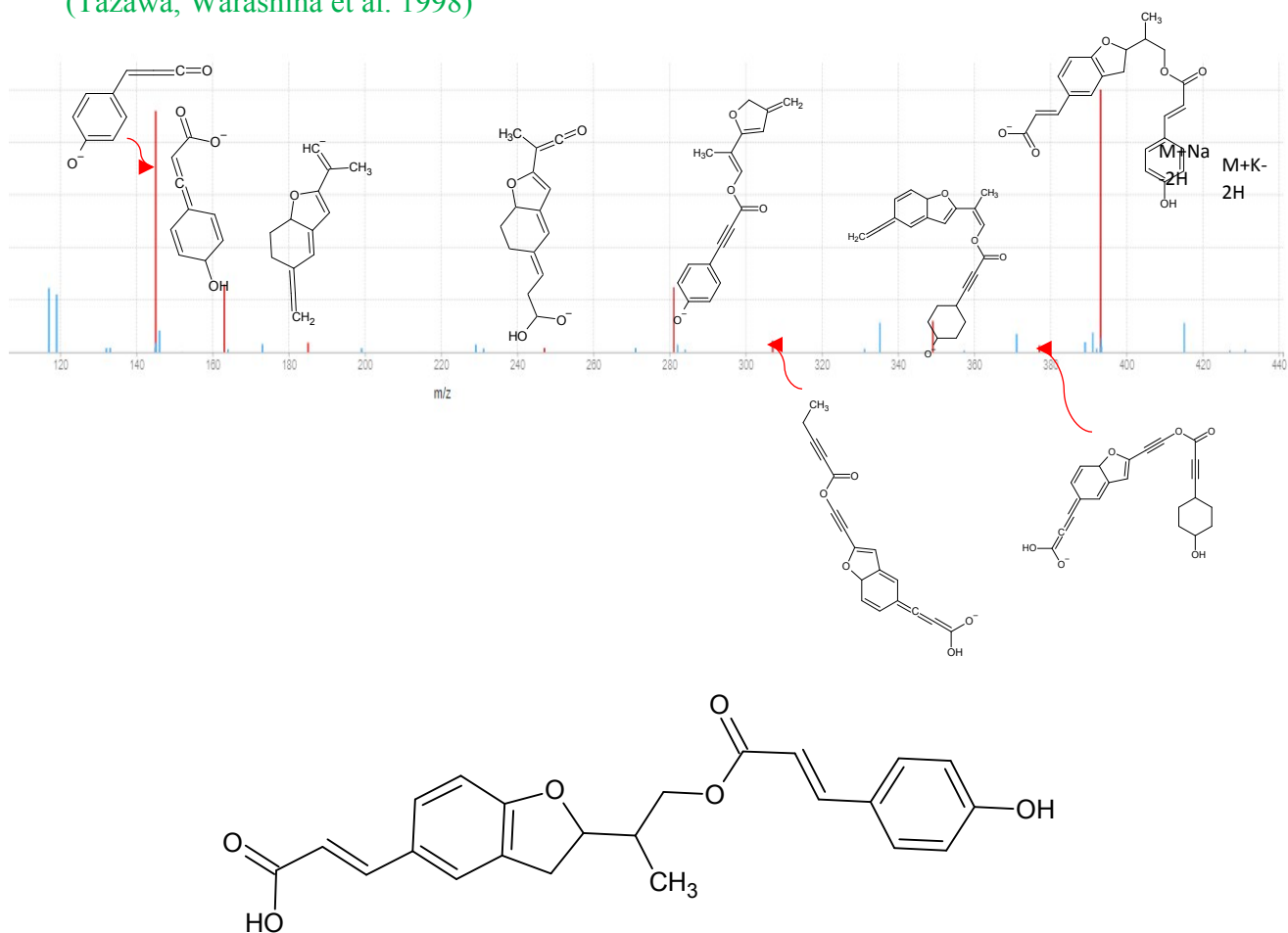


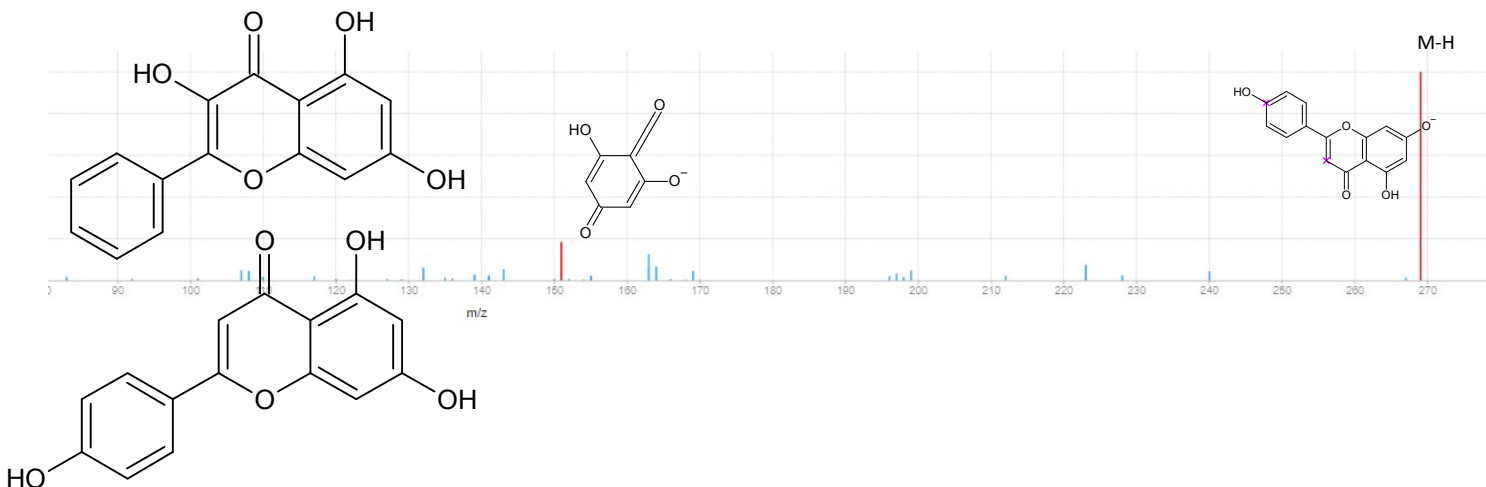
Figure S19 5.09\_394.1390n ((E)-3-{2,3-dihydro-2[2-[(E)-p-coumaroyloxy]-1-methylethyl]-5-benzofuranyl}-2-propenoic acid)  
M-H

(Tazawa, Warashina et al. 1998)



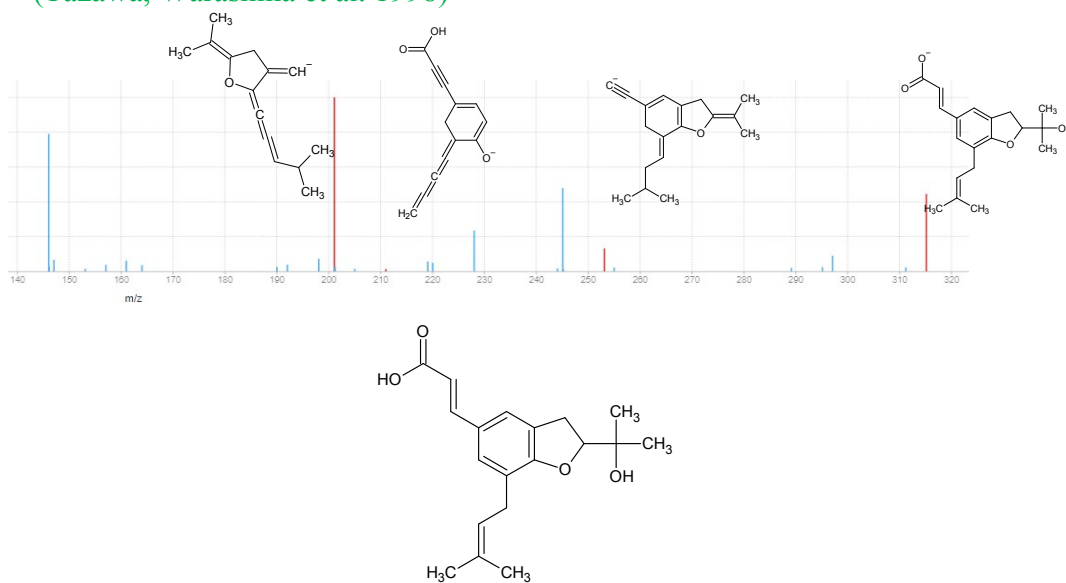
**Figure S20 5.13\_270.0494n Trihydroxy flavone (Apigenin/Galangin)**

(Bankova, Popov et al. 1983, Tazawa, Warashina et al. 1998, Usia, Banskota et al. 2002, Agüero, Gonzalez et al. 2010, Li, Awale et al. 2010, Shaheen, Zarga et al. 2011)



**Figure S21 5.52\_315.1573m/z ((E)-3-(2,3-dihydro-2-(1-hydroxy-1-methylethenyl)-7-prenyl-5-benzofuranyl)-2-propenoic acid)**

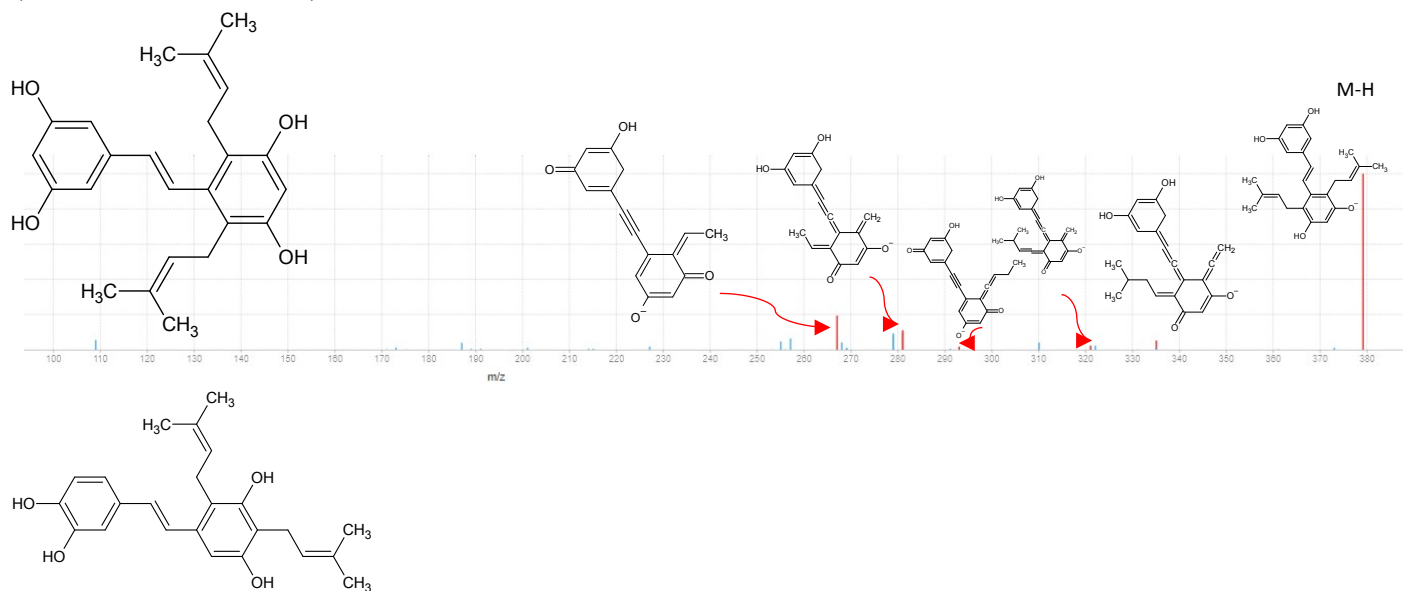
(Tazawa, Warashina et al. 1998)



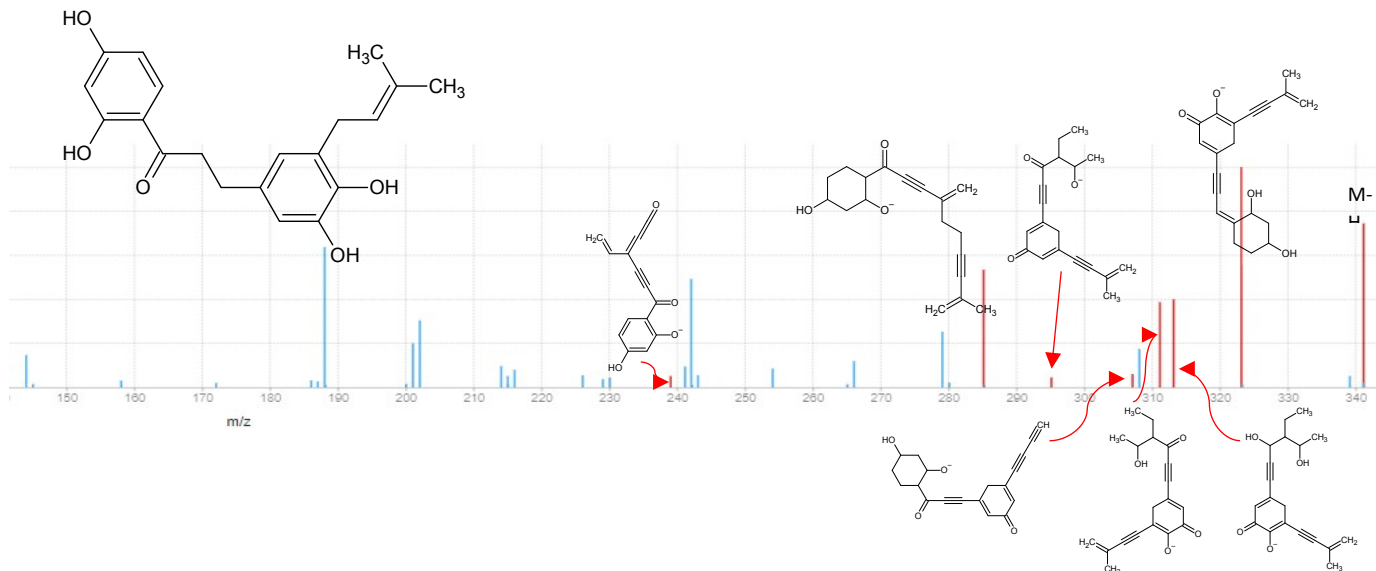


**Figure S22 5.95\_380.1945n ((E)-2,6-bis(3-methyl-2-buten-1-yl)-3,3',5,5'-tetrahydroxystilbene)**

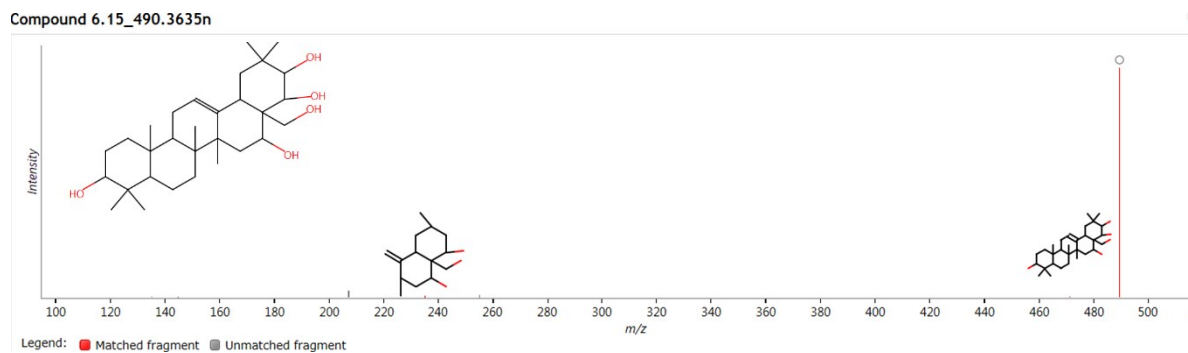
(Duke, Tran et al. 2017)



**Figure S23 5.96\_342.1442n (Prenyl-tetrahydroxy-dihydrochalcone)**

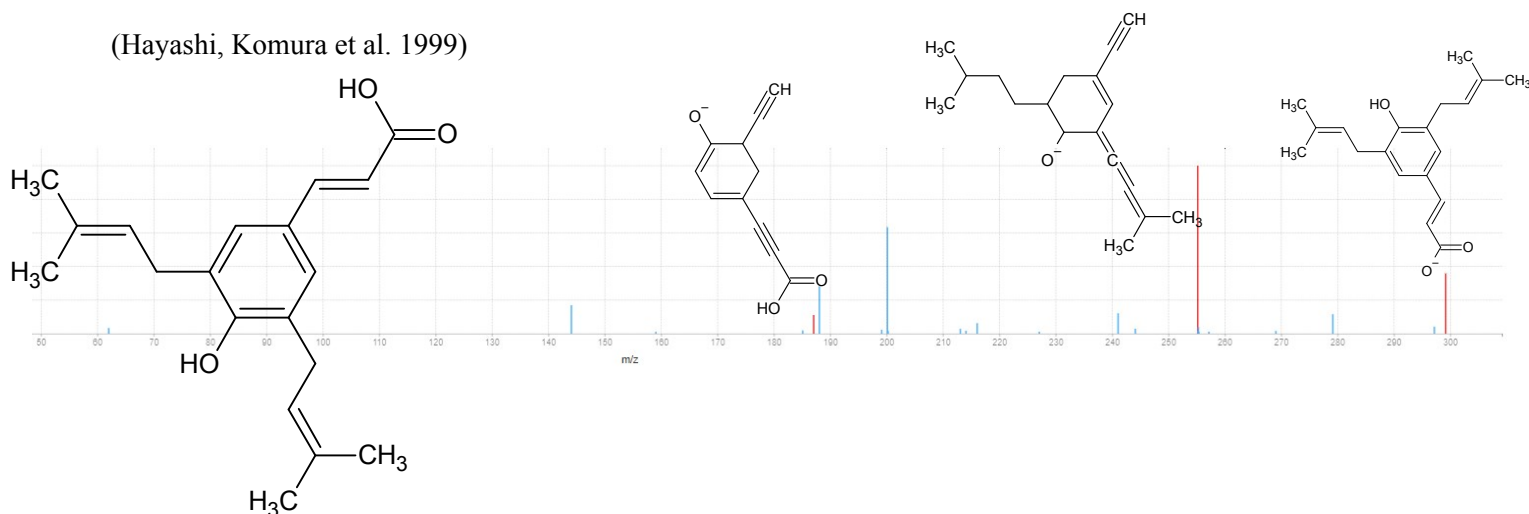


**Figure S24 6.15\_490.3635n (Barringtogenol C-like)**



**Figure S25 6.34\_299.1630m/z (ArtepillinC)**

(Hayashi, Komura et al. 1999)



**Figure S26 6.46\_489.3562m/z (6beta-acetoxy-24-methylcholestan-3beta,5alpha,22R,24-tetrol)**

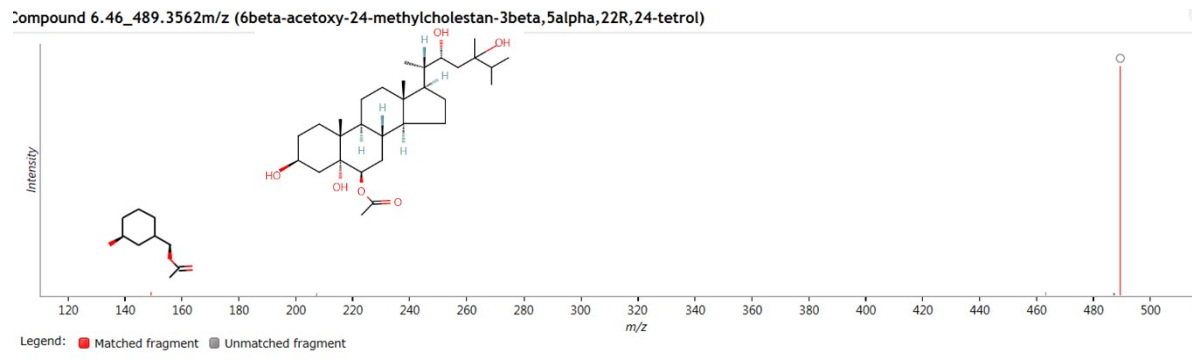


Figure S27 6.59\_344.2306n (Methyl 4,6-O-(10-undecenylidene)hexopyranoside)

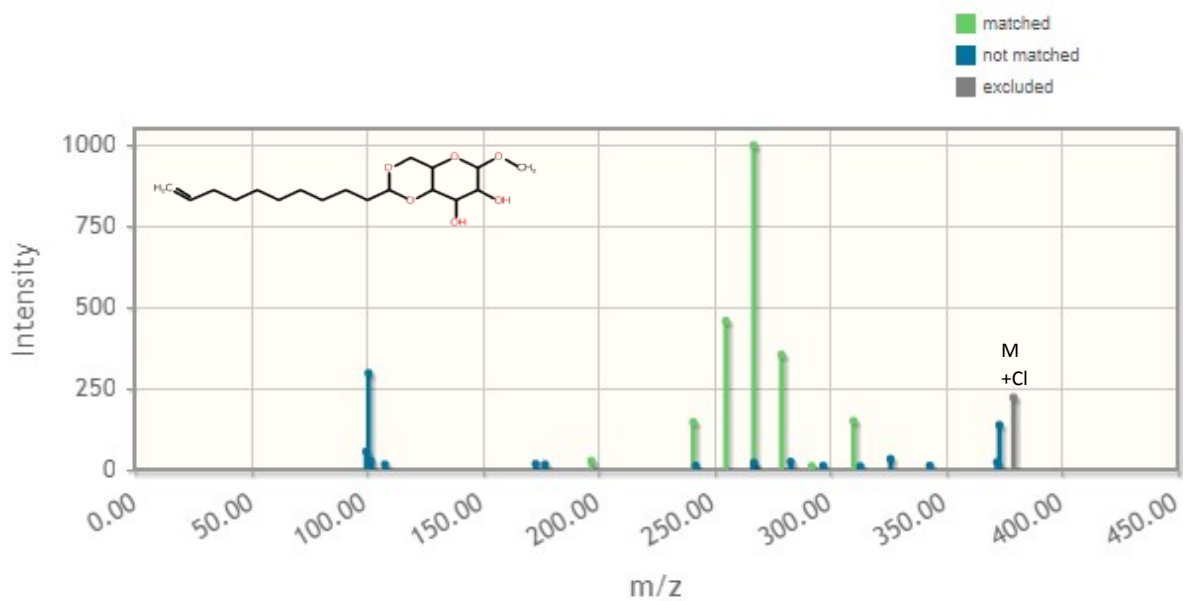
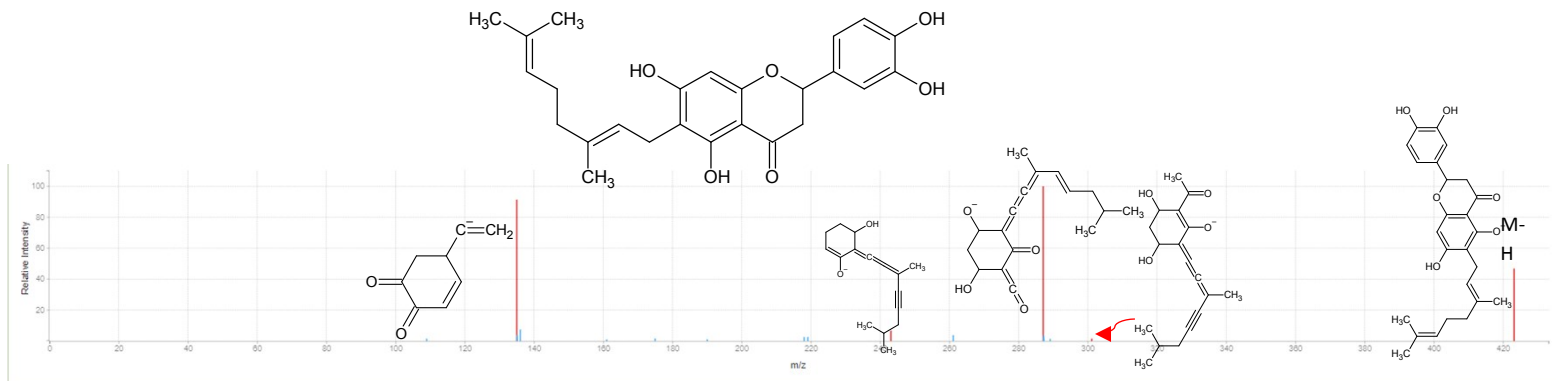


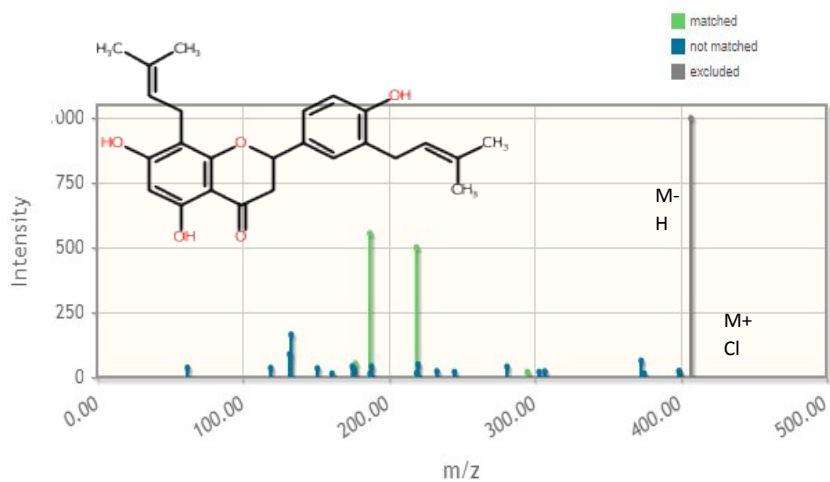
Figure S28 6.94\_424.1860n (Propolin C/D/F)

(Chen, Wu et al. 2004, Kumazawa, Goto et al. 2004, Huang, Huang et al. 2007, Raghukumar, Vali et al. 2010)

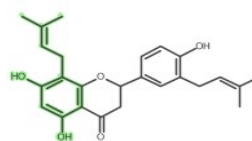




**Figure S30 6.98\_408.1906n (3',8-diprenylnaringenin)**

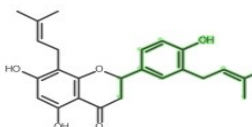


**Fragment 1**



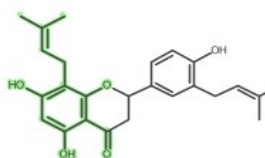
**Formula** [C11H12O2+H]-  
**Mass** 177.09216  
**Peak m/z** 177.0903

**Fragment 2**



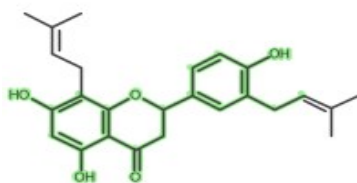
**Formula** [C13H16O]-H-  
**Mass** 187.11291  
**Peak m/z** 187.1111

**Fragment 3**



**Formula** [C12H12O4]-H-  
**Mass** 219.06632  
**Peak m/z** 219.0646

**Fragment 4**



**Formula** [C17H13O5-H]-H-  
**Mass** 295.06123  
**Peak m/z** 295.0595

**Fragment 5** M-H (407.1834m/z)

**Fragment 6** M+Cl (443.1452 m/z)

Figure S31 7.12\_334.2115n (Agathic acid)

(Banskota, Tezuka et al. 1998)

Compound 7.12\_334.2115n

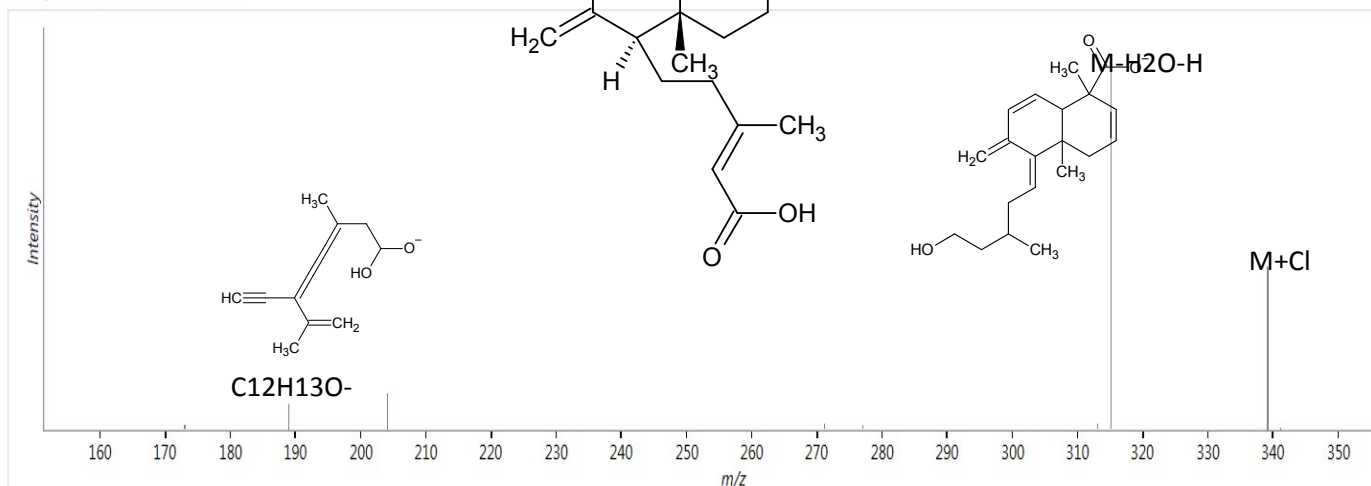


Figure S32 7.37\_337.1057m/z (pinobanksin-3-pentanoate)

(Kumazawa, Hayashi et al. 2002, Usia, Banskota et al. 2002, Alday, Valencia et al. 2015)

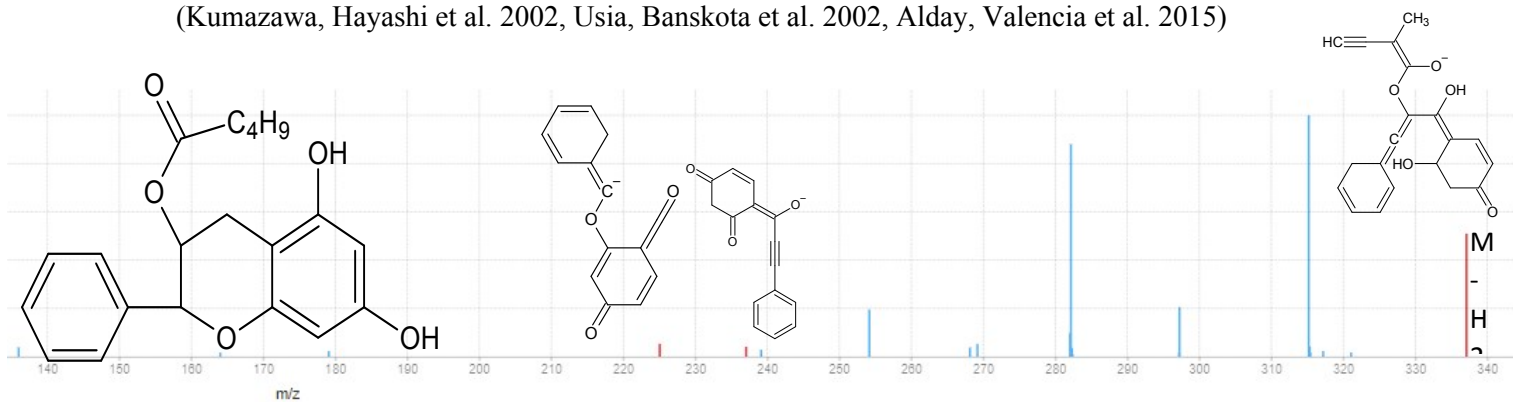
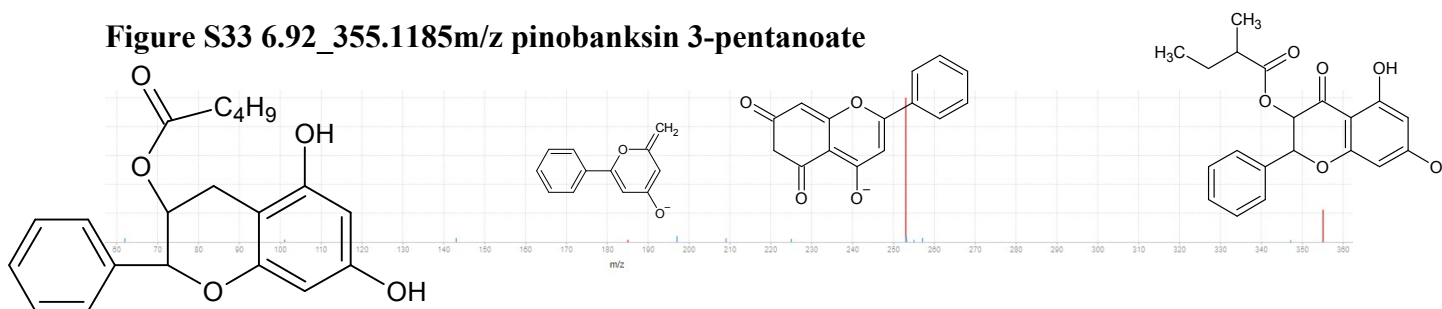
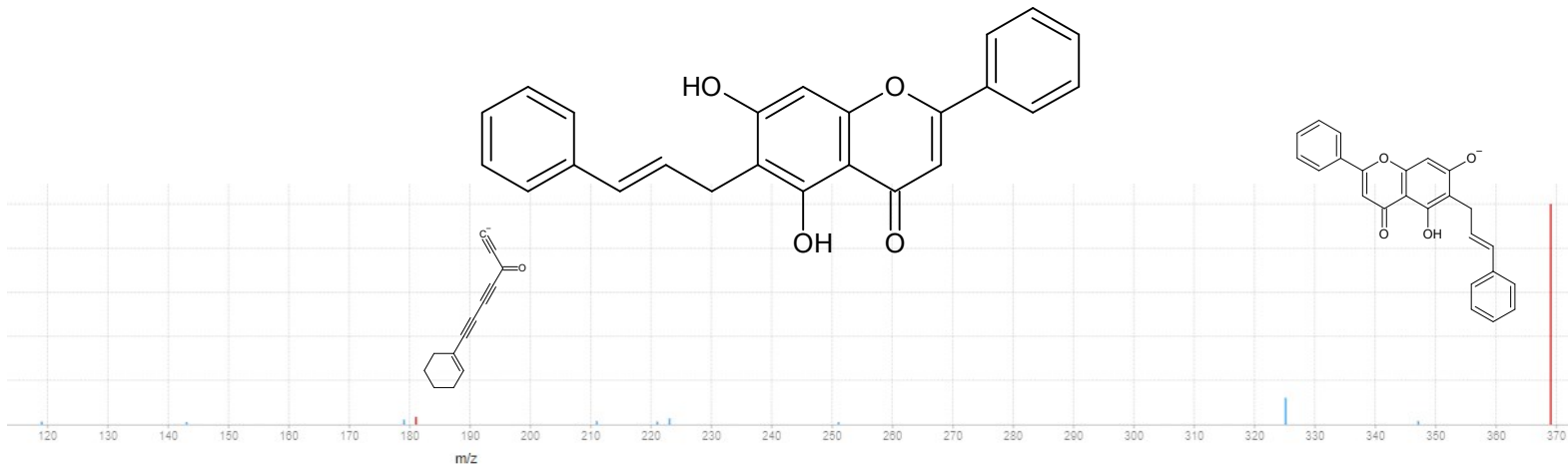


Figure S33 6.92\_355.1185m/z pinobanksin 3-pentanoate



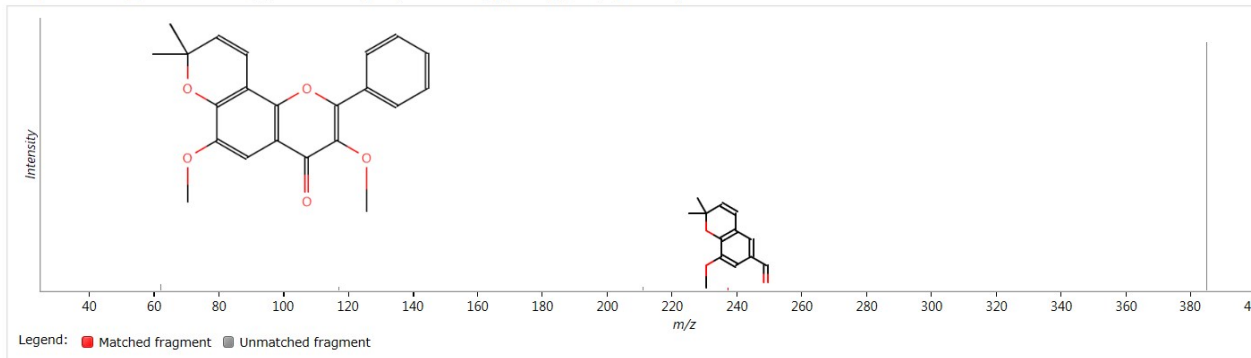
### Figure S34 7.43\_369.1107m/z (6-cinnamylchrysin)

(Usia, Banskota et al. 2002)



### Figure S35 7.45\_385.1056m/z (Dimethoxy-6'',6''-dimethylpyranoflavone)

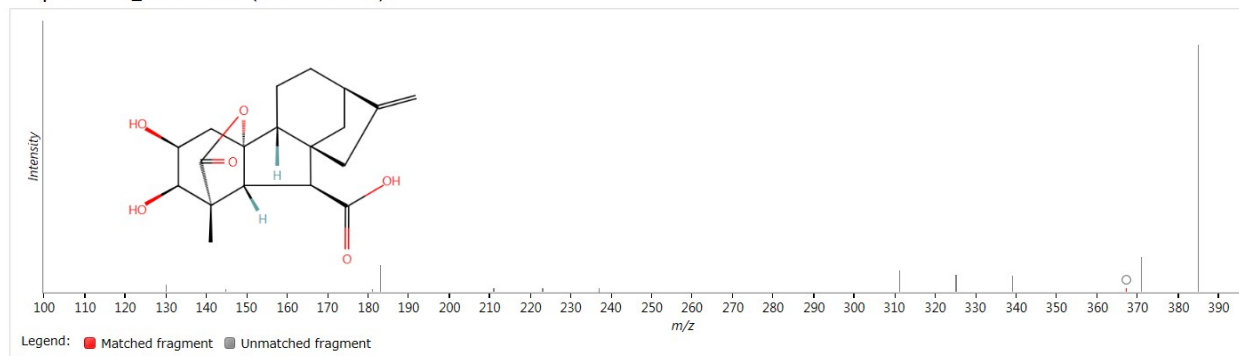
Compound 7.45\_385.1056m/z (3,6-Dimethoxy-6'',6''-dimethylpyrano[2,3:7,8]flavone)



### Figure S36 7.57\_385.1061m/z (Gibberellin A29/A1/A34/A36/A58/A60)

(Kim, Kim et al. 2019, Nani, Sardi et al. 2020)

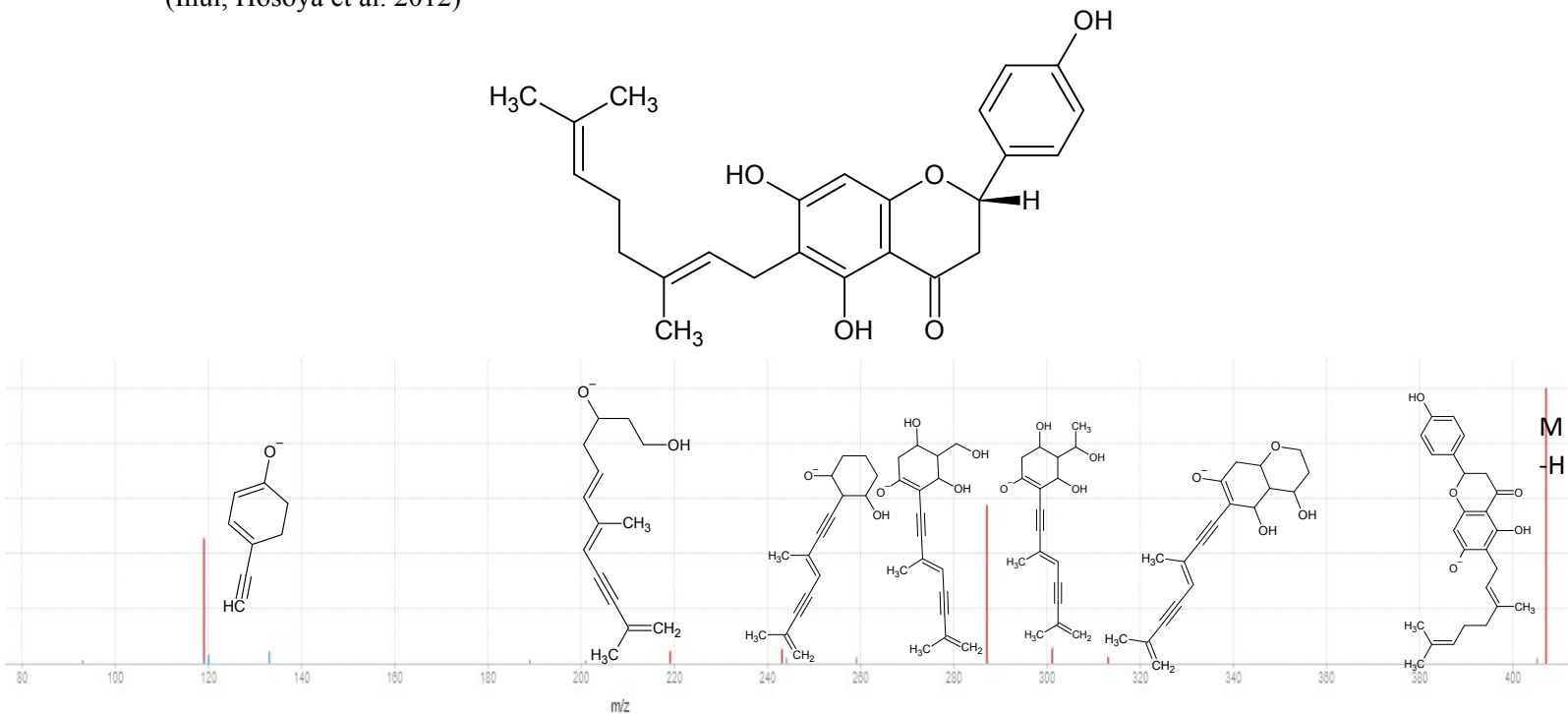
Compound 7.57\_385.1061m/z (Gibberellin A34)





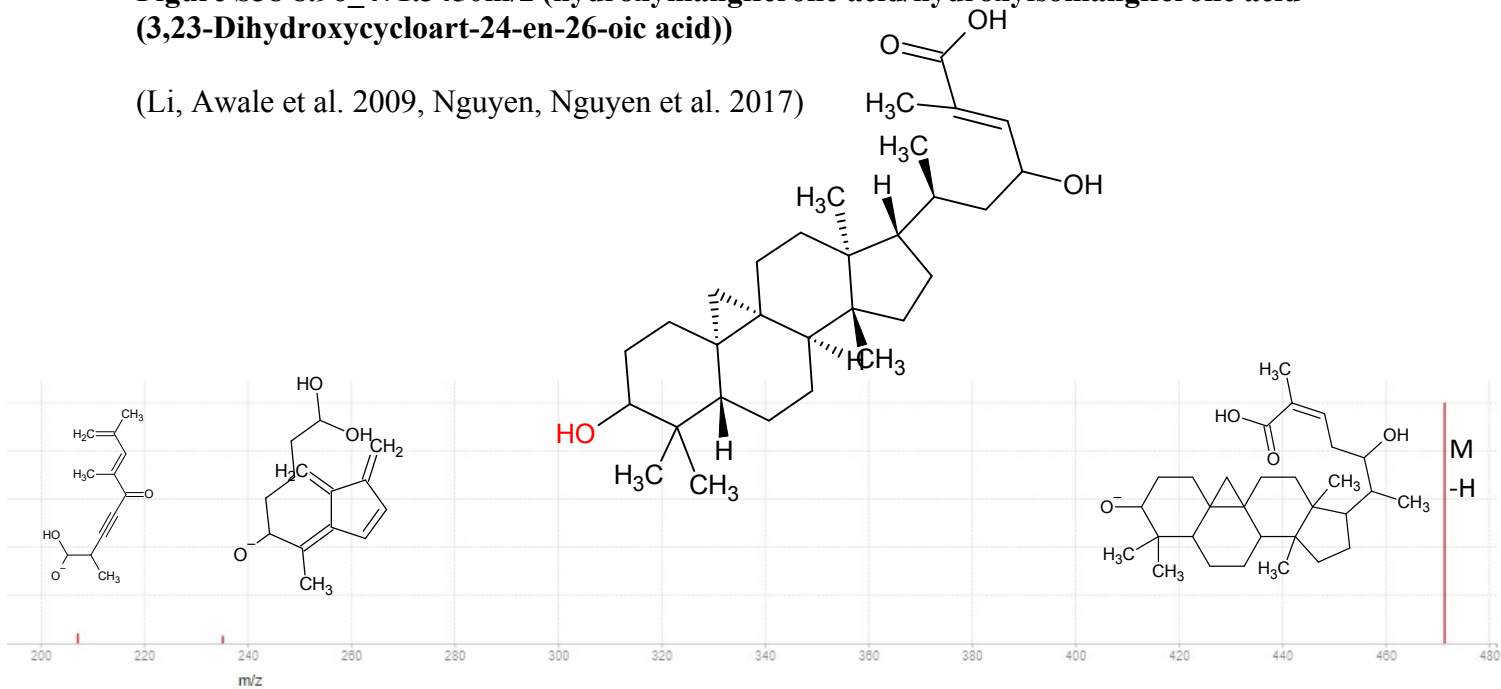
**Figure S37 7.76\_407.1835m/z (8-geranyl naringenin(bonannione A,sophoraflavanone A))**

(Inui, Hosoya et al. 2012)



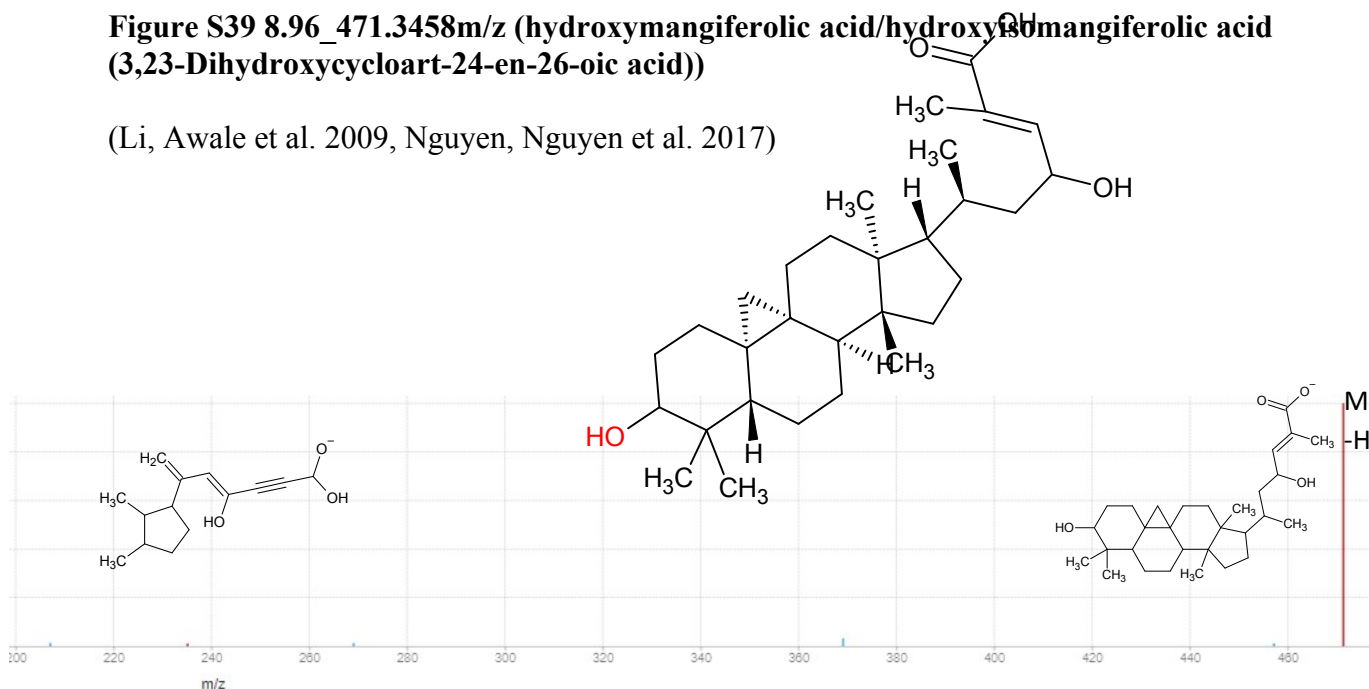
**Figure S38 8.96\_471.3450m/z (hydroxymangiferolic acid/hydroxyisomangiferolic acid (3,23-Dihydroxycycloart-24-en-26-oic acid))**

(Li, Awale et al. 2009, Nguyen, Nguyen et al. 2017)



**Figure S39 8.96\_471.3458m/z (hydroxymangiferolic acid/hydroxyisomangiferolic acid (3,23-Dihydroxycycloart-24-en-26-oic acid))**

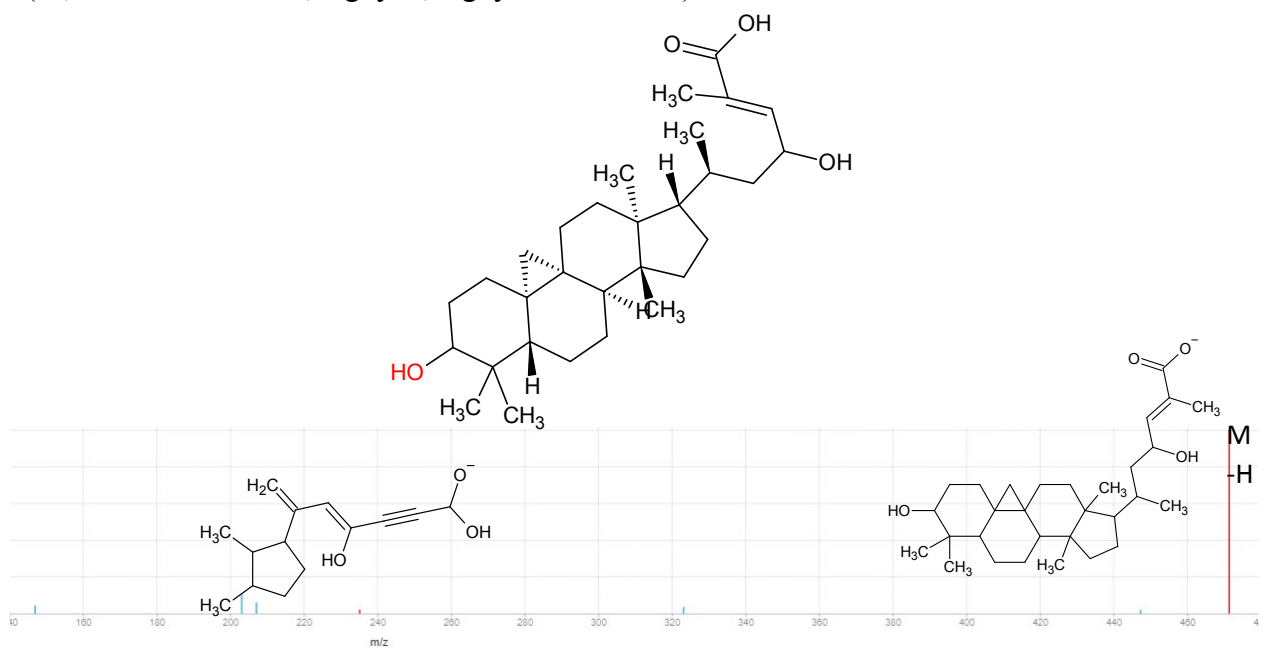
(Li, Awale et al. 2009, Nguyen, Nguyen et al. 2017)



\*Matched fragments colored red

**Figure S40 9.21\_471.3448m/z (hydroxymangiferolic acid/hydroxyisomangiferolic acid (3,23-Dihydroxycycloart-24-en-26-oic acid))**

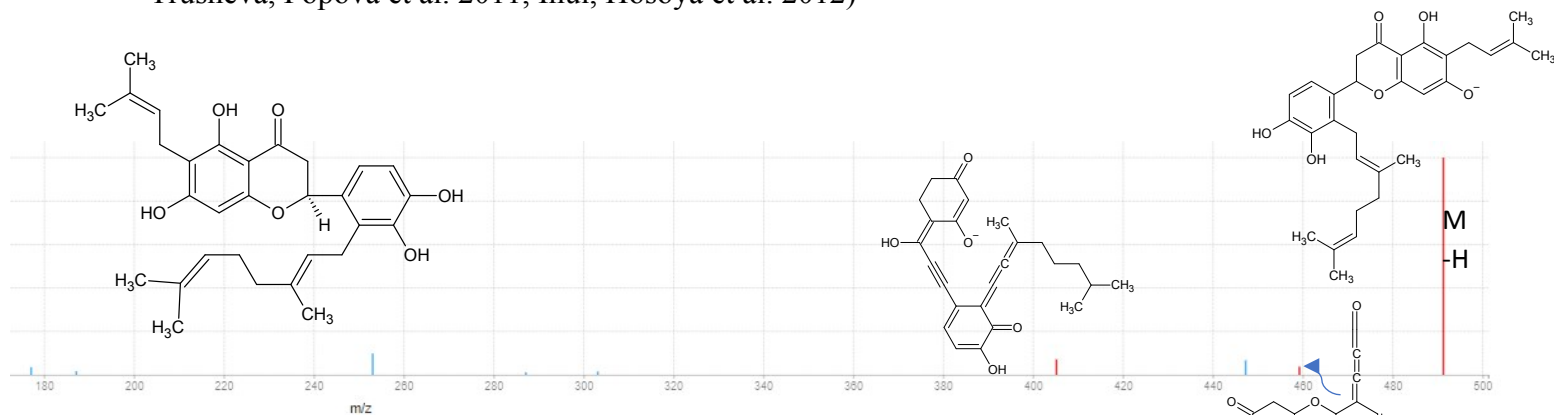
(Li, Awale et al. 2009, Nguyen, Nguyen et al. 2017)



\*Matched fragments colored red

**Figure S41 9.04\_491.2414m/z (Propolin G/Solophenol A/Nymphaeol C (Geranyl-tetrahydroxy-prenylflavanone))**

(Kumazawa, Goto et al. 2004, Huang, Huang et al. 2007, Raghukumar, Vali et al. 2010, Trusheva, Popova et al. 2011, Inui, Hosoya et al. 2012)

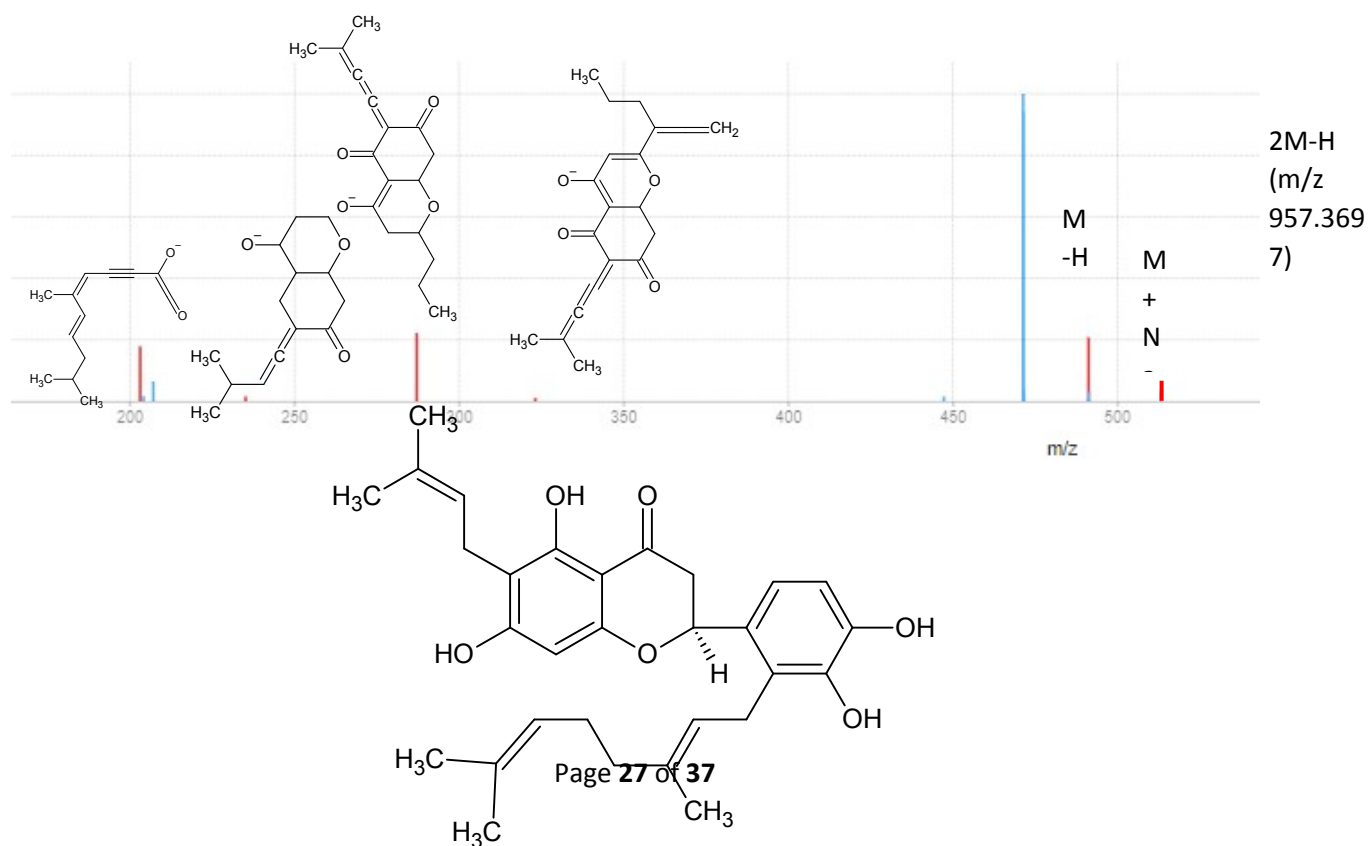


\*Matched fragments colored red

**Figure S42 9.21\_492.2487n (Propolin G/Solophenol A/Nymphaeol C (Geranyl-tetrahydroxy-prenylflavanone))**

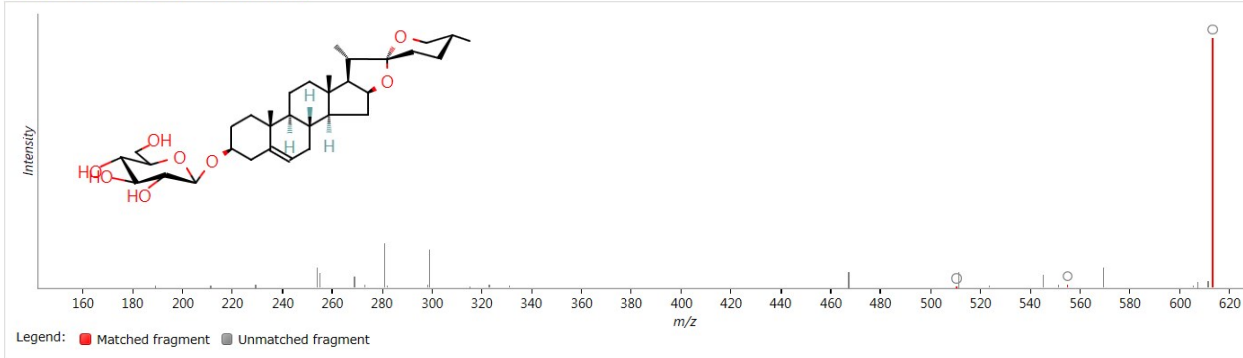
(Kumazawa, Goto et al. 2004, Huang, Huang et al. 2007, Raghukumar, Vali et al. 2010, Trusheva, Popova et al. 2011, Inui, Hosoya et al. 2012)

All adducts



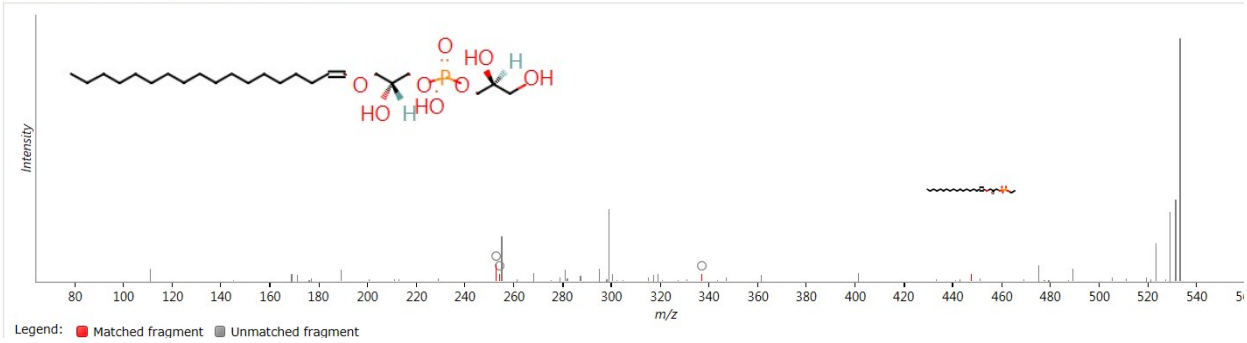
**Figure S43 9.50\_613.3172m/z (Spirostenyl-hexoside)**

Compound 9.50\_613.3172m/z (Trillin)

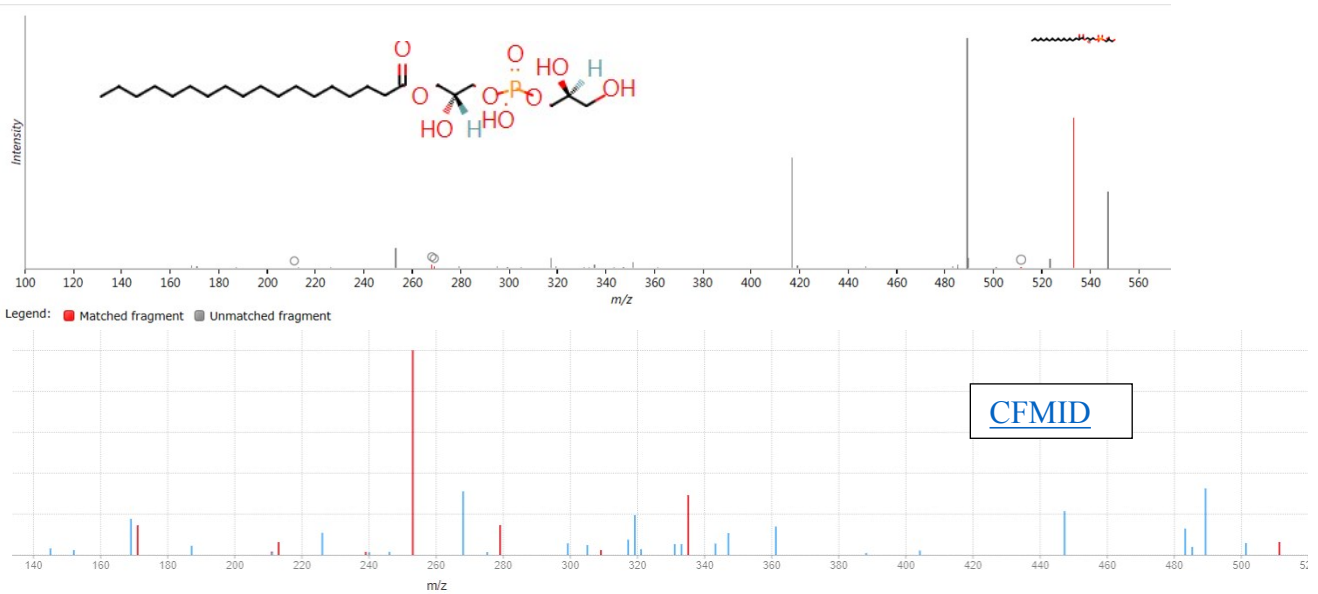


**Figure S44 9.51\_496.3161n (PG(P-18:0/0:0))**

Compound 9.51\_496.3161n (PG(P-18:0/0:0))

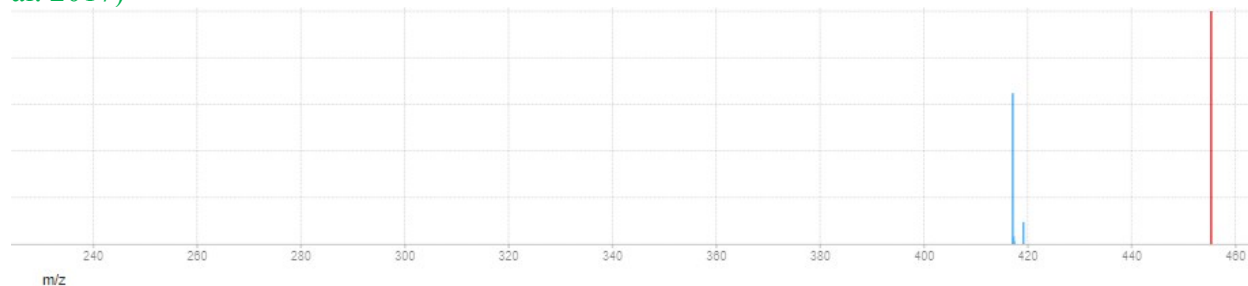


**Figure S45 9.68\_512.3120n (PG(18:0/0:0))**

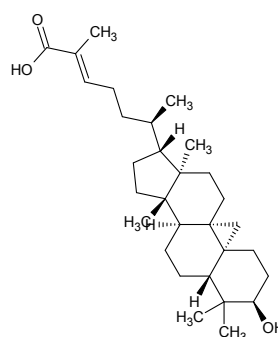
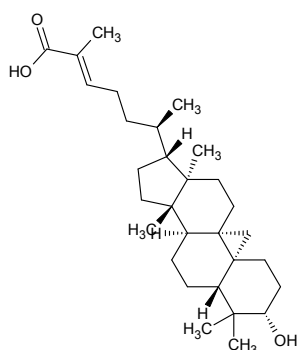


**Figure S46 9.69\_455.3493m/z (Mangiferolic acid/isomangiferolic acid/12-Hydroxy-3,4-seco-cycloarta-4(28),24-dien-3-oic acid)**

(Li, Awale et al. 2009, Popova, Chinou et al. 2009, Kardar, Zhang et al. 2014, Sanpa, Popova et al. 2017)

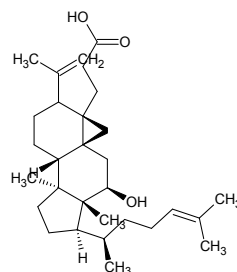
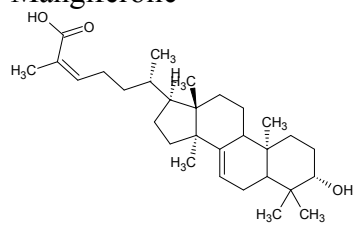


Potential candidate



Mangiferolic

Isomangiferolic

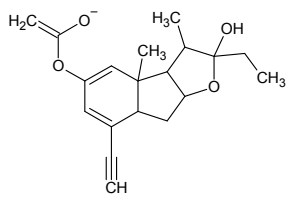
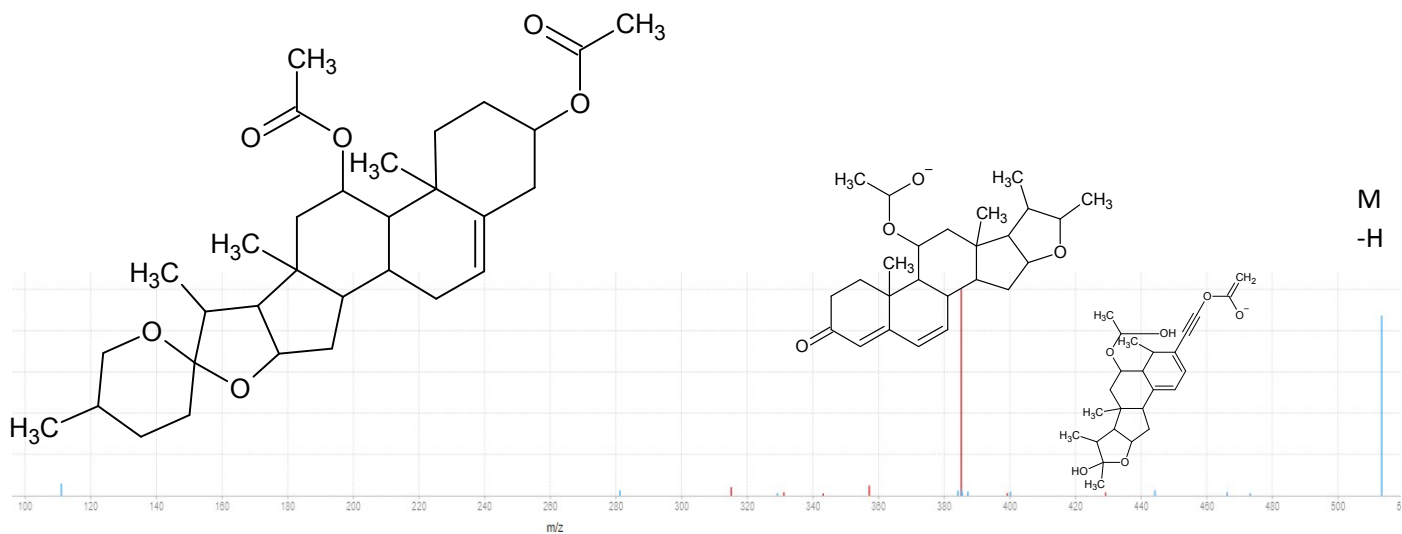


24(Z)-3-hydroxyeupha-7,24-dien-26-oic acid

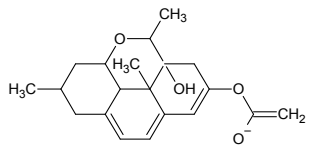
3,4-seco-cycloarta-12-hydroxy-4(28),24-dien-3-oic acid



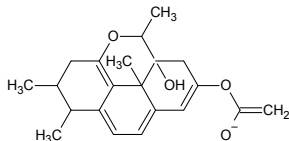
Figure S48 10.38\_514.3308n (Spirost-5-en-3,11-diyl diacetate)



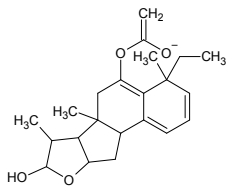
315.1584



331.1899



343.1895

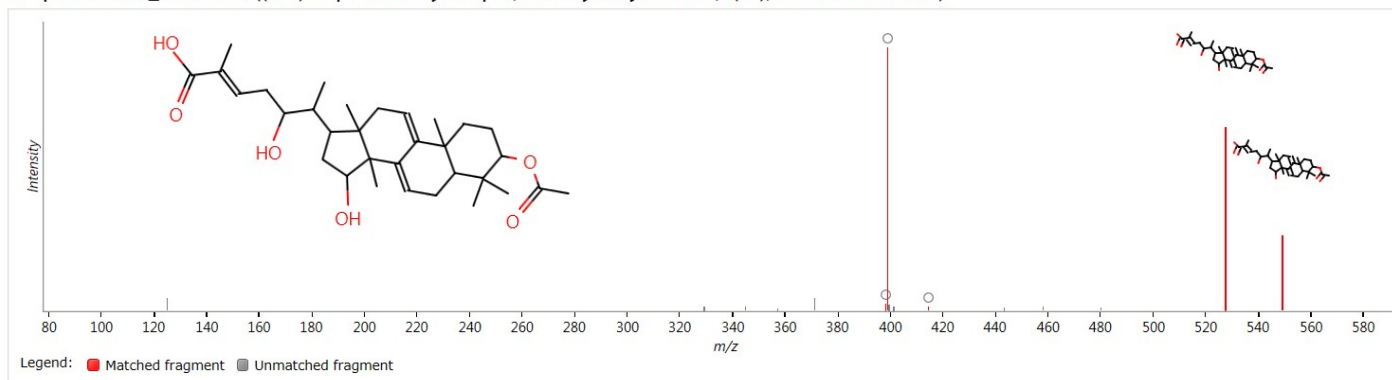


357.2053

**Figure S49 10.65\_528.3449n ((24E)-3alpha-Acetoxy-15alpha,22S-dihydroxylanosta-7,9(11),24-trien-26-oic acid)**

Compound 10.65\_528.3449n ((24E)-3alpha-Acetoxy-15alpha,22S-dihydroxylanosta-7,9(11),24-trien-26-oic acid)

He





**Table S1 UPLC-DAD quantified phenolics in propolis samples (Mean  $\pm$ SD)**

	<b>BP-1</b>	<b>AP-1</b>	<b>CP-1</b>	<b>AP-2</b>
	Concentration mg/g			
<b>CAPE</b>	0.55 $\pm$ 0.01n	1.63 $\pm$ 0.01	1.59 $\pm$ 0.06	1.98 $\pm$ 0.14
<b>Artepellin C</b>	4.27 $\pm$ 0.002	0.5 $\pm$ 0.11	0.39 $\pm$ 0.09	0.59 $\pm$ 0.07
<b>Galagin</b>	0.97 $\pm$ 0.01	11.38 $\pm$ 1.36	1.64 $\pm$ 0.14	6.34 $\pm$ 0.74
<b>Chrysin</b>	2.28 $\pm$ 0.01	1.5 $\pm$ 0.17	4.56 $\pm$ 0.5	5.91 $\pm$ 0.79
<b>Pinocebrim</b>	2.28 $\pm$ 0.01	8.37 $\pm$ 1.14	9.17 $\pm$ 1	26.24 $\pm$ 2.52
<b>Daidzen</b>	3.07 $\pm$ 0.01	5.99 $\pm$ 1.31	6.9 $\pm$ 1.045	7.65 $\pm$ 1.42
<b>Narigenin</b>	1.59 $\pm$ 0.15	3.92 $\pm$ 0.99	6.09 $\pm$ 1.43	1.85 $\pm$ 0.14

<b>Tukey's multiple comparisons test</b>	<b>Mean Diff.</b>	<b>95% CI of diff.</b>	<b>Significant?</b>	<b>Summary</b>
<b>CAPE</b>				
AP-1 vs. AP-2	-0.3437	-2.164 to 1.477	No	ns
AP-1 vs. BP-1	1.083	-0.7379 to 2.904	No	ns
AP-1 vs. CP-1	0.04340	-1.777 to 1.864	No	ns
AP-2 vs. BP-1	1.427	-0.3942 to 3.247	No	ns
AP-2 vs. CP-1	0.3871	-1.434 to 2.208	No	ns
BP-1 vs. CP-1	-1.039	-2.860 to 0.7813	No	ns
<b>Artepellin C</b>				
AP-1 vs. AP-2	-0.08799	-1.909 to 1.733	No	ns
<b>AP-1 vs. BP-1</b>	<b>-3.771</b>	<b>-5.592 to -1.951</b>	<b>Yes</b>	<b>****</b>
AP-1 vs. CP-1	0.1055	-1.715 to 1.926	No	ns
<b>AP-2 vs. BP-1</b>	<b>-3.683</b>	<b>-5.504 to -1.863</b>	<b>Yes</b>	<b>****</b>
AP-2 vs. CP-1	0.1935	-1.627 to 2.014	No	ns
BP-1 vs. CP-1	3.877	2.056 to 5.698	Yes	****
<b>Galagin</b>				
AP-1 vs. AP-2	5.036	3.216 to 6.857	Yes	****
AP-1 vs. BP-1	10.41	8.585 to 12.23	Yes	****
AP-1 vs. CP-1	9.739	7.918 to 11.56	Yes	****
AP-2 vs. BP-1	5.369	3.548 to 7.190	Yes	****
AP-2 vs. CP-1	4.703	2.882 to 6.523	Yes	****
BP-1 vs. CP-1	-0.6664	-2.487 to 1.154	No	ns
<b>Chrysin</b>				
AP-1 vs. AP-2	-4.413	-6.234 to -2.593	Yes	****
AP-1 vs. BP-1	-0.7841	-2.605 to 1.037	No	ns
AP-1 vs. CP-1	-3.060	-4.881 to -1.240	Yes	***
AP-2 vs. BP-1	3.629	1.809 to 5.450	Yes	****
AP-2 vs. CP-1	1.353	-0.4678 to 3.174	No	ns
BP-1 vs. CP-1	-2.276	-4.097 to -0.4556	Yes	**
<b>Pinocebrim</b>				
AP-1 vs. AP-2	-17.87	-19.69 to -16.05	Yes	****
AP-1 vs. BP-1	6.089	4.268 to 7.909	Yes	****
AP-1 vs. CP-1	-0.8055	-2.626 to 1.015	No	ns
AP-2 vs. BP-1	23.96	22.14 to 25.78	Yes	****
AP-2 vs. CP-1	17.07	15.25 to 18.89	Yes	****
BP-1 vs. CP-1	-6.894	-8.715 to -5.073	Yes	****
<b>Daidzen</b>				

AP-1 vs. AP-2	-1.666	-3.487 to 0.1543	No	ns
AP-1 vs. BP-1	2.917	1.096 to 4.737	Yes	***
AP-1 vs. CP-1	-0.9148	-2.736 to 0.9059	No	ns
AP-2 vs. BP-1	4.583	2.762 to 6.404	Yes	****
AP-2 vs. CP-1	0.7516	-1.069 to 2.572	No	ns
BP-1 vs. CP-1	-3.831	-5.652 to -2.011	Yes	****
<b>Narigenin</b>				
AP-1 vs. AP-2	2.076	0.2552 to 3.897	Yes	*
AP-1 vs. BP-1	2.331	0.5103 to 4.152	Yes	**
AP-1 vs. CP-1	-2.169	-3.989 to -0.3479	Yes	*
AP-2 vs. BP-1	0.2551	-1.566 to 2.076	No	ns
AP-2 vs. CP-1	-4.245	-6.065 to -2.424	Yes	****
BP-1 vs. CP-1	-4.500	-6.321 to -2.679	Yes	****

Source of Variation	% of total variation	P value	P value summary	Significant?		Two-way ANOVA, Alpha <sup>a</sup>
Interaction	46.79	< 0.0001	****	Yes		
Row Factor	39.11	< 0.0001	****	Yes		
Column Factor	12.30	< 0.0001	****	Yes		
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value	
Interaction	1038	18	57.68	F (18, 56) = 81.33	P < 0.0001	
Row Factor	867.9	6	144.6	F (6, 56) = 203.9	P < 0.0001	0.05
Column Factor	272.9	3	90.98	F (3, 56) = 128.3	P < 0.0001	
Residual	39.72	56	0.7093			



**Figure S50.** The abundance of Artepillin C among propolis samples (UPLC-qTOF-MS)

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