Transcriptome and Metabolite analysis reveal candidate genes of cardiac glycoside biosynthetic pathway from *Calotropis procera*

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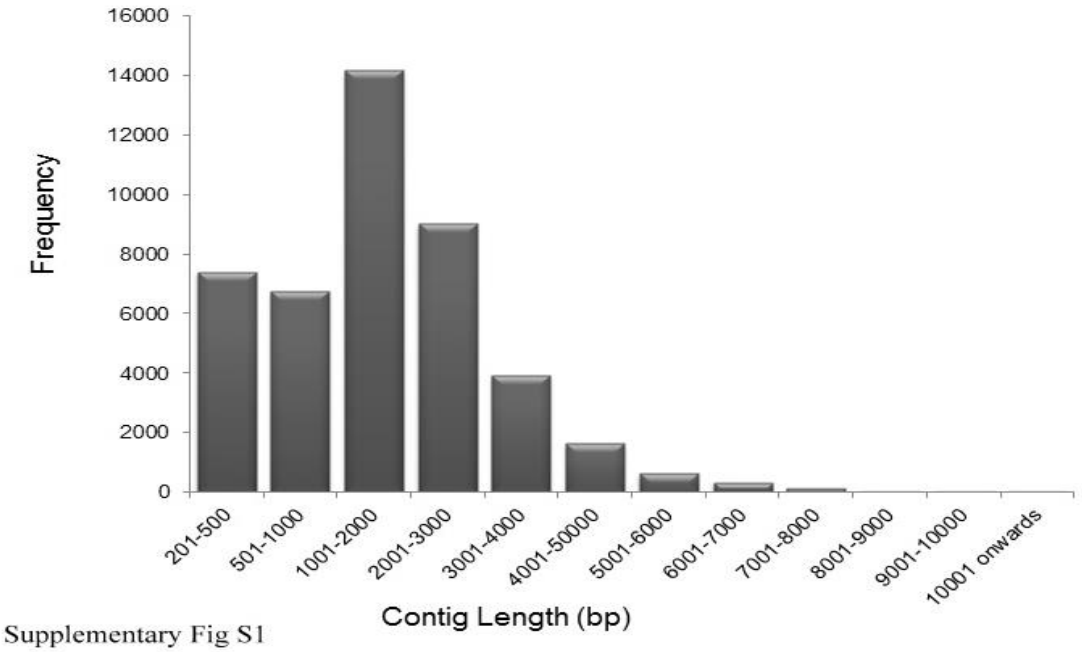
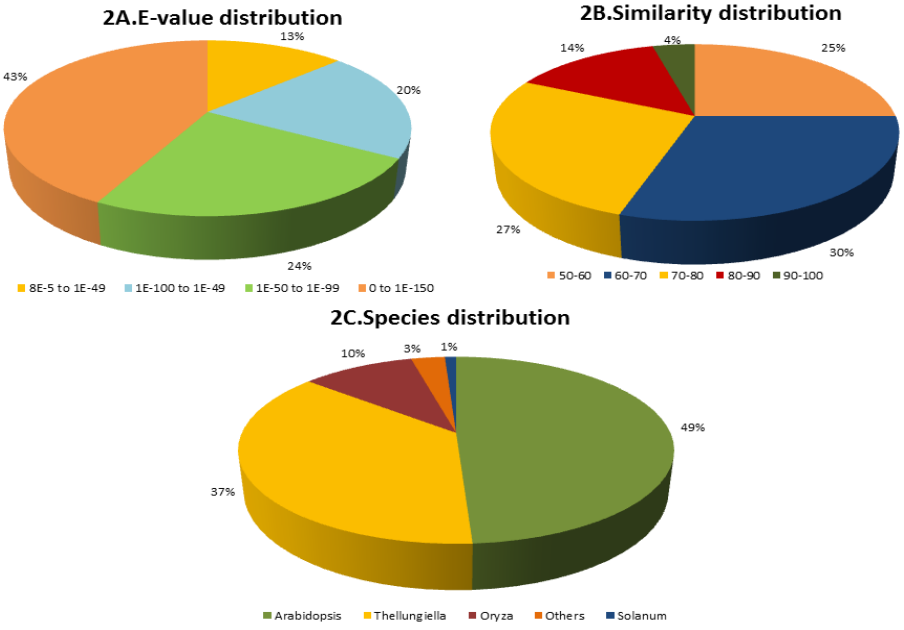
#authors contributed equally

Supplementary Figure S1. Length distribution of contigs assembled in *C. procera.* The number of 12 groups of unigenes with different length is shown.



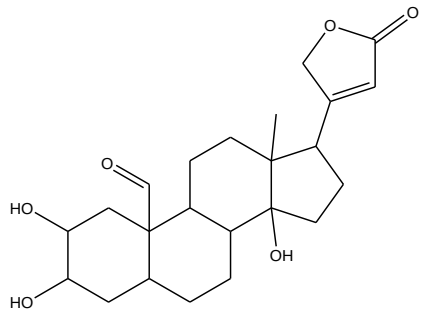
Supplementary Fig S1

Supplementary Figure S2. Characterstic of homolgy search of assembled unigenes.A-E-value distribution of top Blast hits. B- Similarity distribution of unigenes. C-Species distribution of Blast hits.

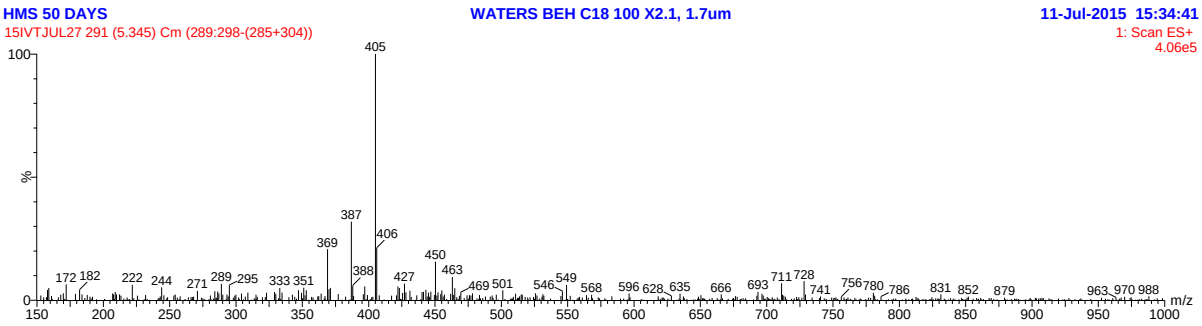


Supplementary Figure S3: Structure and spectra chromatogram of cardiac glycosides and genin units with their proposed fragmentation pattern.

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
01	5.34	404	Calotropagenin	387,369,351,341,333,323,305	A	-



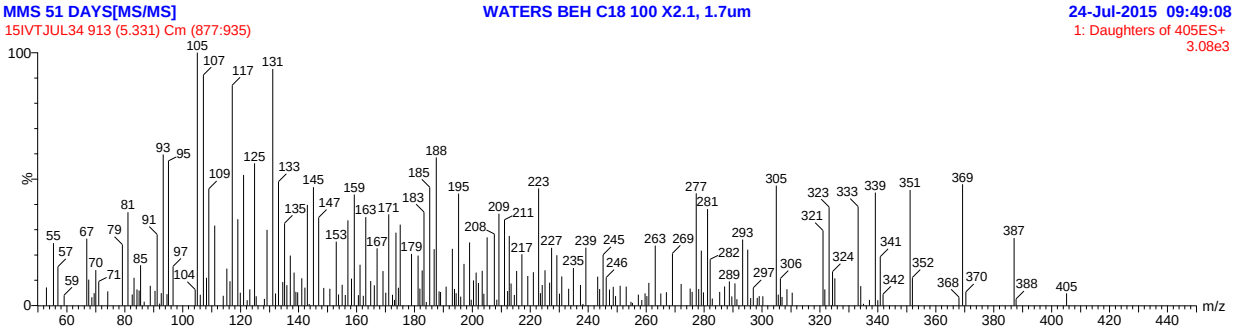
Calotropagenin
Chemical Formula: $C_{23}H_{32}O_6$
Exact Mass: 404.2199
Molecular Weight: 404.4966



LC-ESI-MS Spectrum of Calotropagenin *m/z* 405 $[M+H]^+$

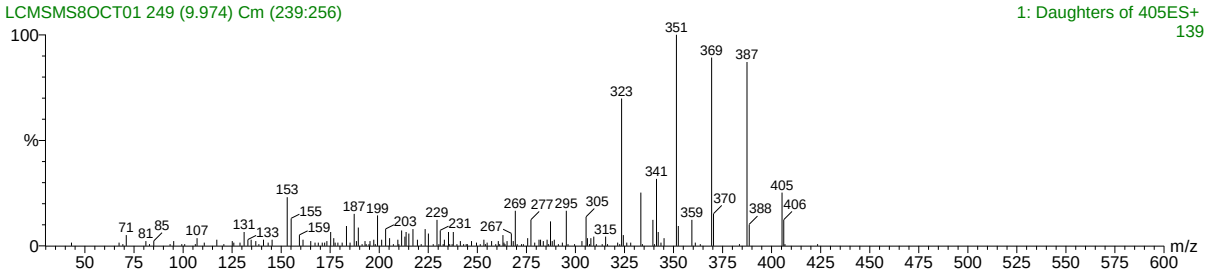
m/z	Annotation	Mass difference	Confirmation remark
405	$[M+ H]^+$	1Da	Molecular weight 404
427	$[M+ Na]^+$	23 Da	Da

Accurate mass observed	Annotation	Calc. mass of Calotropagenin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
405.2270	$[M+ H]^+$	405.2272	0.0002	Molecular formula of the compounds $C_{23}H_{33}O_6^+$



LC-ESI-MS/MS Spectrum of Calotropagenin *m/z* 405 $[M+H]^+$ recorded at 30-20ev collision energy

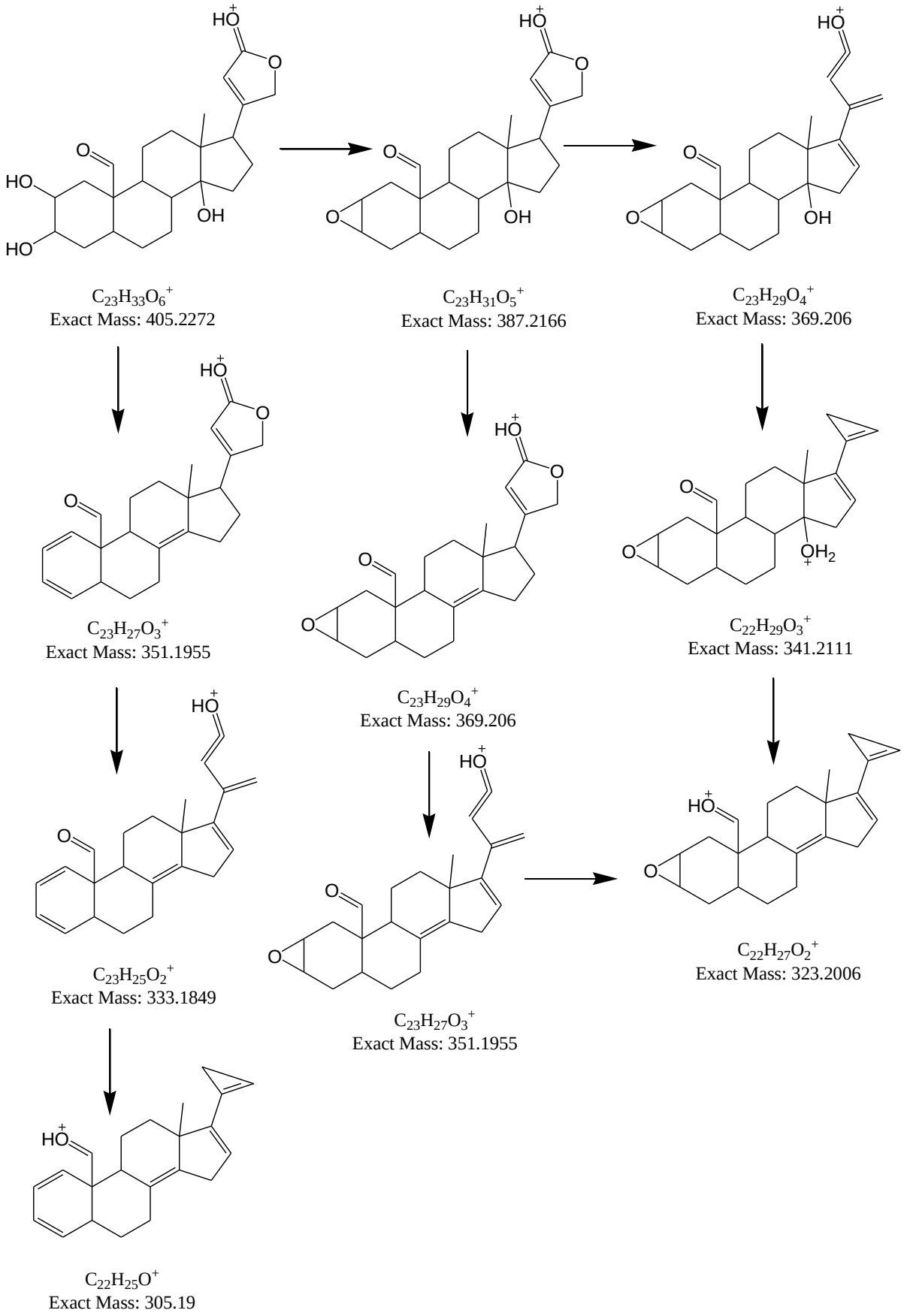
Reference LC-ESI-MS/MS Spectrum (Phytochem Anal, 2012. 23(2): p. 117-25)



Previously published LC-ESI-MS/MS Spectrum of Calotropagenin *m/z* 405 $[M+H]^+$ recorded at 15-5ev collision energy

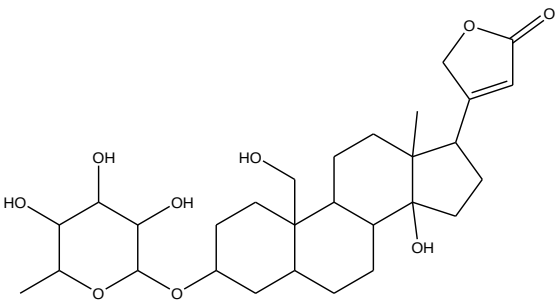
m/z	Annotation	Neutral losses in Da
387	$[M+ H-H_2O]^+$	18
369	$[M+ H-2H_2O]^+$	36
359	$[M+ H-H_2O+CO]^+$	46
351	$[M+ H-3H_2O]^+$	54
341	$[M+ H-2H_2O+CO]^+$	64
333	$[M+ H-4H_2O]^+$	72
323	$[M+ H-3H_2O+CO]^+$	82

All the above neutral losses can be predicted from structure of calotropagenin as proposed in fragmentation pattern.

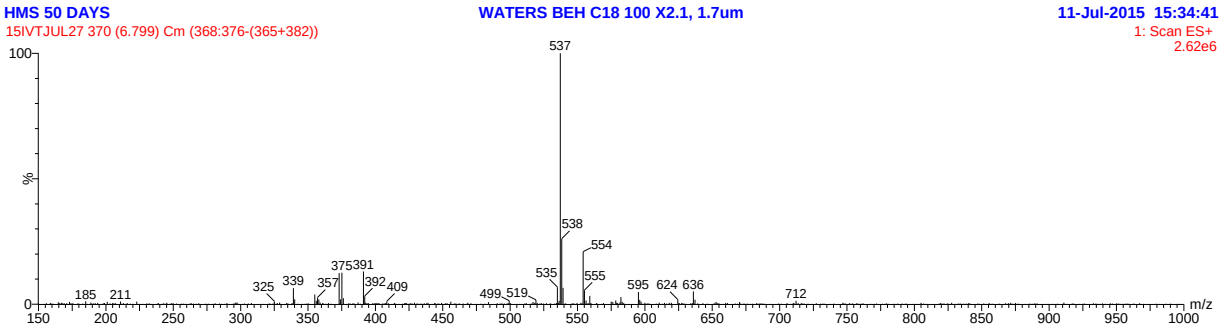


Proposed fragmentation pattern of Calotropagenin *m/z* 405 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
02	6.78	536	Frugoside	391,373,355,339,337,325	C	146



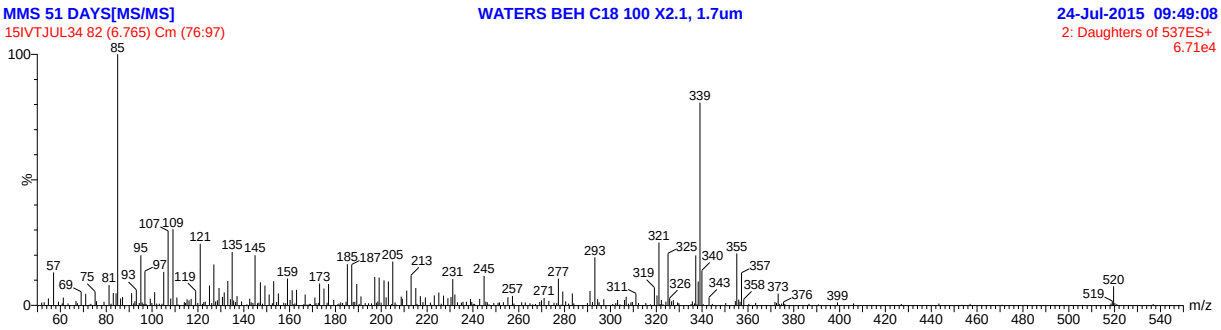
Frugoside
Chemical Formula: $C_{29}H_{44}O_9$
Exact Mass: 536.2985
Molecular Weight: 536.6543



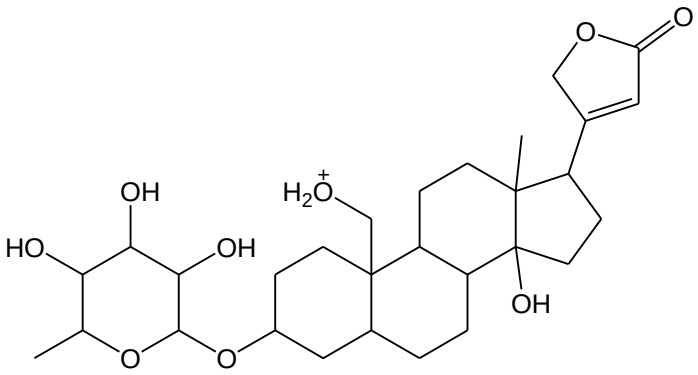
LC-ESI-MS Spectrum of frugoside *m/z* 537 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
537	$[M+ H]^+$	1Da	Molecular weight 536
554	$[M+ NH_4]^+$	18 Da	Da
391	$[M+ H\text{-glycone}]^+$	146 Da	Cleavage of –O-glycoside bond

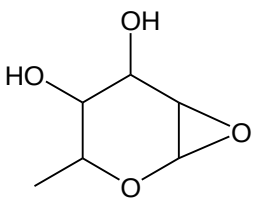
Accurate mass observed	Annotation	Calculated mass of Frugoside $[M+ H]^+$	Mass difference In mmu	Confirmation remark
537.3057	$[M+ H]^+$	537.3058	0.0001	Molecular formula of the compounds $C_{29}H_{45}O_9^+$



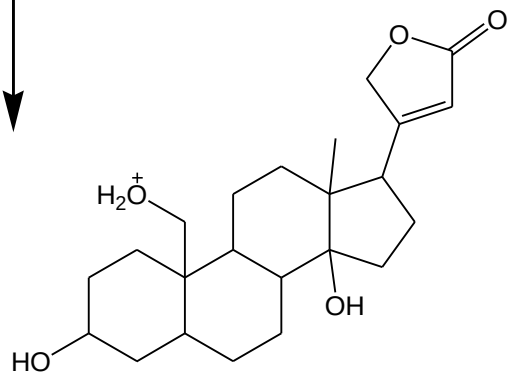
LC-ESI-MS/MS Spectrum of frugoside *m/z* 537 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed *m/z* 373,355,339/337, 325]



$C_{29}H_{45}O_9^+$
Exact Mass: 537.3058



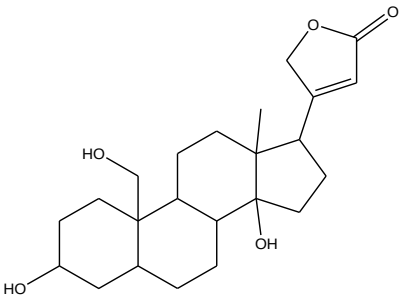
$C_6H_{10}O_4$
Exact Mass: 146.0579



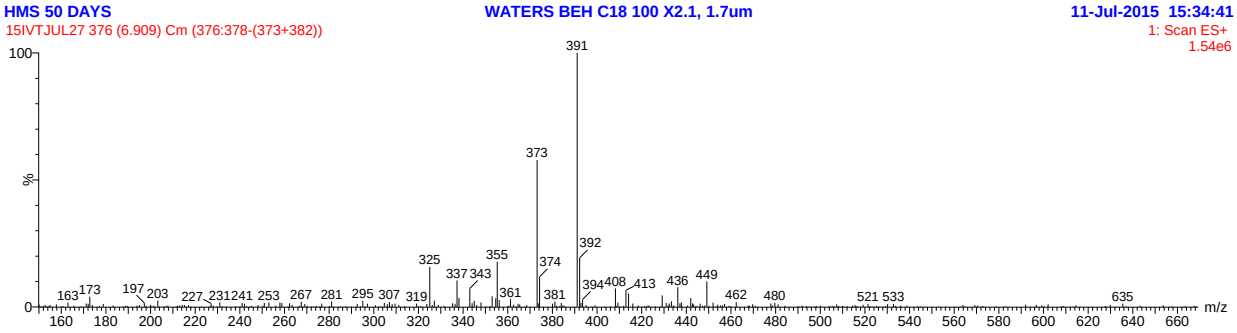
$C_{23}H_{35}O_5^+$
Exact Mass: 391.2479

Proposed fragmentation pattern of Frugoside m/z 537 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
03	6.89	390	Coroglaucigenin	373,355,337, 325	C	-



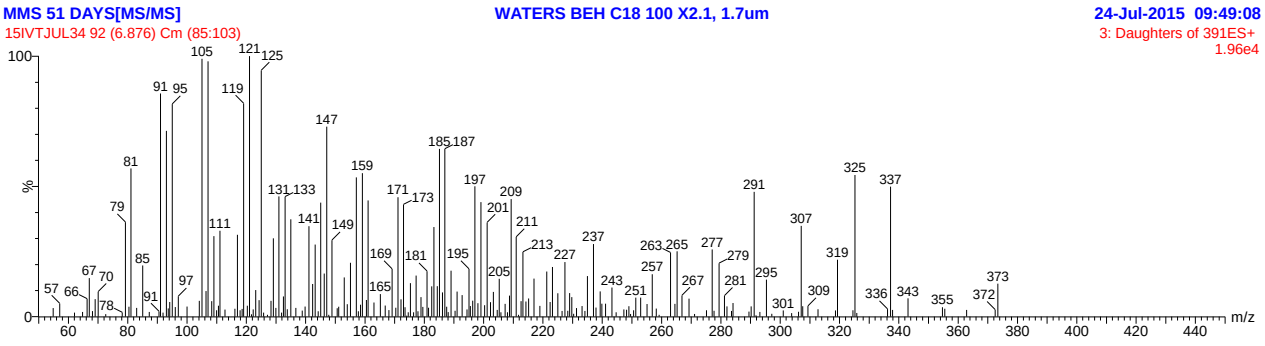
Coroglaucigenin
Chemical Formula: $C_{23}H_{34}O_5$
Exact Mass: 390.2406
Molecular Weight: 390.5131



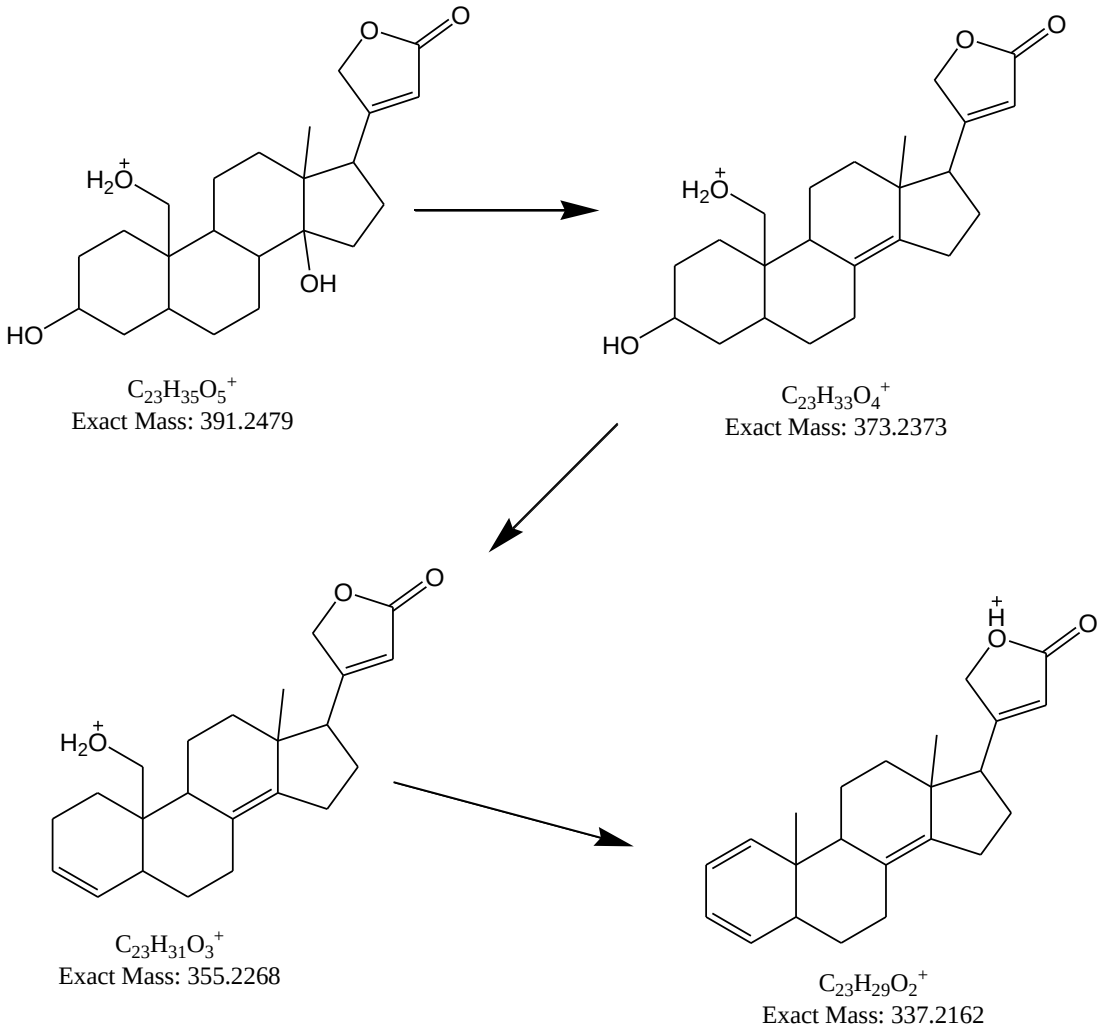
LC-ESI-MS Spectrum of coroglaucigenin *m/z* 391 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
391	$[M+ H]^+$	1Da	Molecular weight 390
408	$[M+ NH_4]^+$	18 Da	Da

Accurate mass observed	Annotation	Calc. mass of coroglaucigenin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
391.2478	$[M+ H]^+$	391.2479	0.0001	Molecular formula of the compounds $C_{23}H_{35}O_5^+$

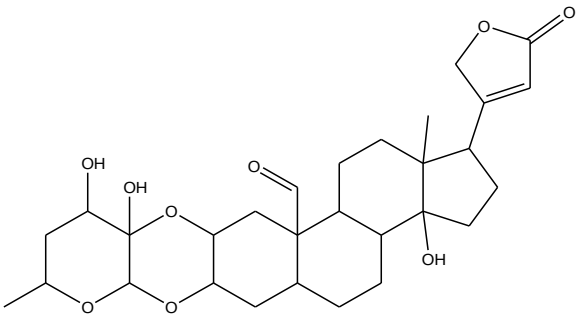


LC-ESI-MS/MS Spectrum of coroglaucigenin *m/z* 391 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed *m/z* 373, 355, 337, 325]

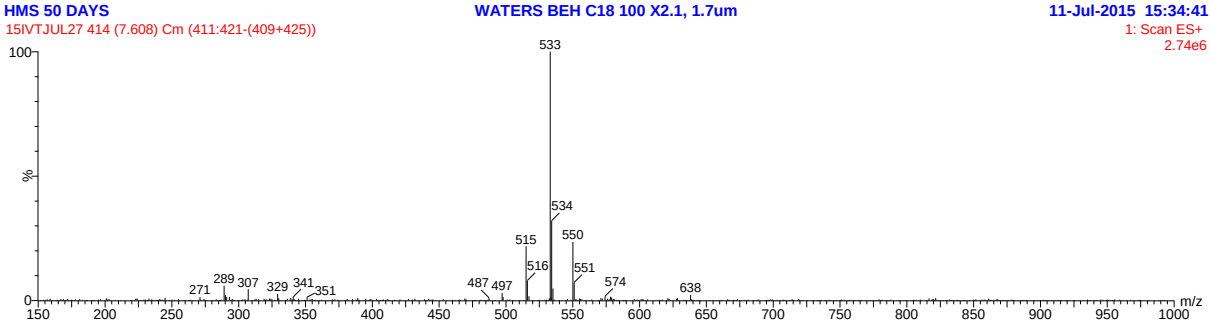


Proposed fragmentation pattern coroglaucigenin *m/z* 391 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
04	7.85	532	Calotropin	387,369,359,351,341,333,323	A	146



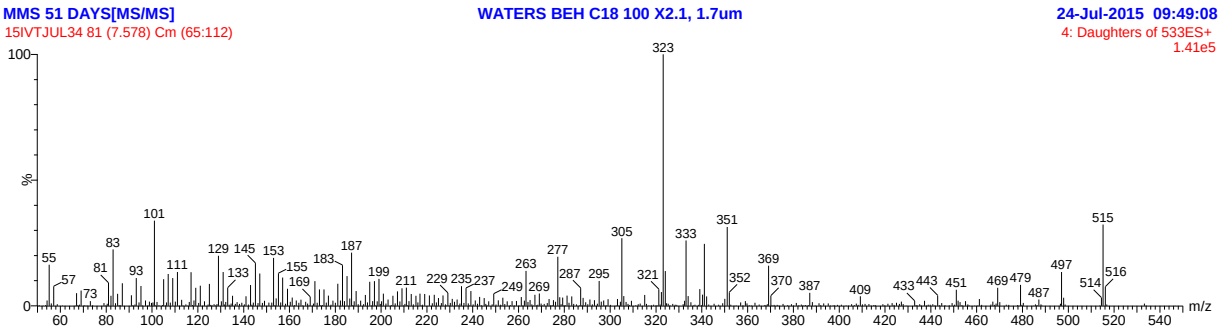
Calotropin
Chemical Formula: $C_{29}H_{40}O_9$
Exact Mass: 532.2672
Molecular Weight: 532.6225



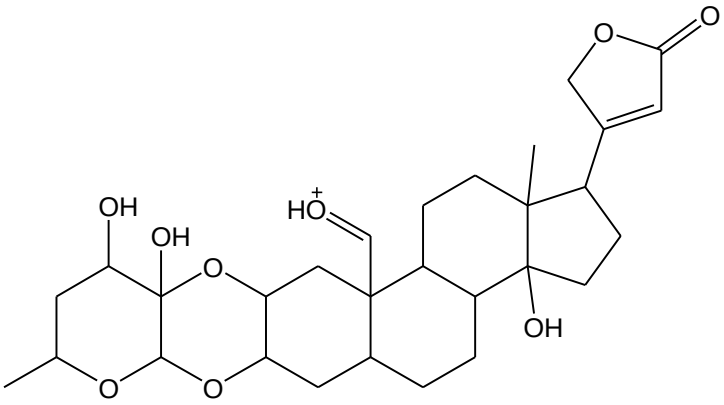
LC-ESI-MS Spectrum of calotropin *m/z* 533 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
533	$[M+ H]^+$	1Da	Molecular weight 532
550	$[M+ NH_4]^+$	18 Da	Da

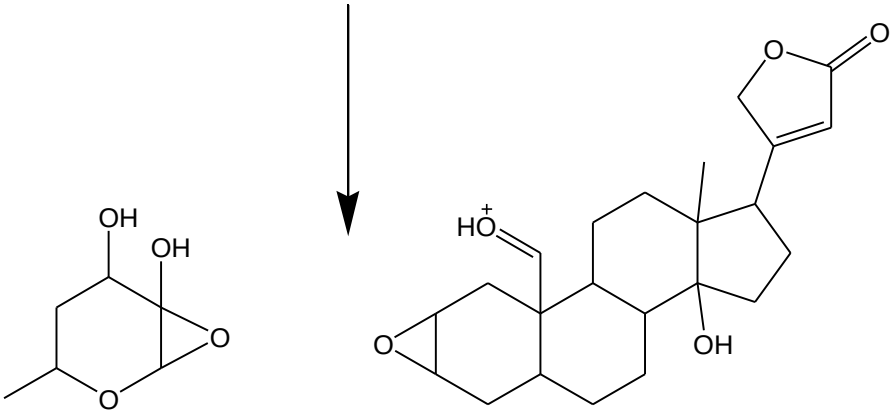
Accurate mass observed	Annotation	Calc. mass of Calotropin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
533.2745	$[M+ H]^+$	533.2745	0.0000	Molecular formula of the compounds $C_{29}H_{41}O_9^+$



LC-ESI-MS/MS Spectrum of calotropin *m/z* 533 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed *m/z* 387,369, 351,341,333,323,305]



$C_{29}H_{41}O_9^+$
Exact Mass: 533.2745

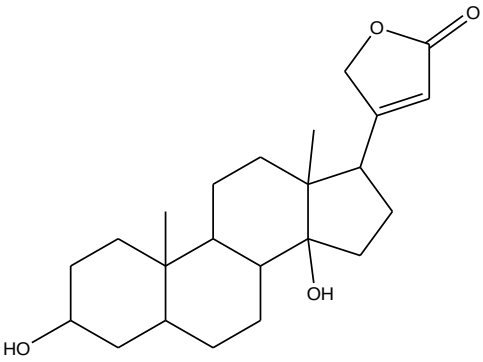


$C_6H_{10}O_4$
Exact Mass: 146.0579

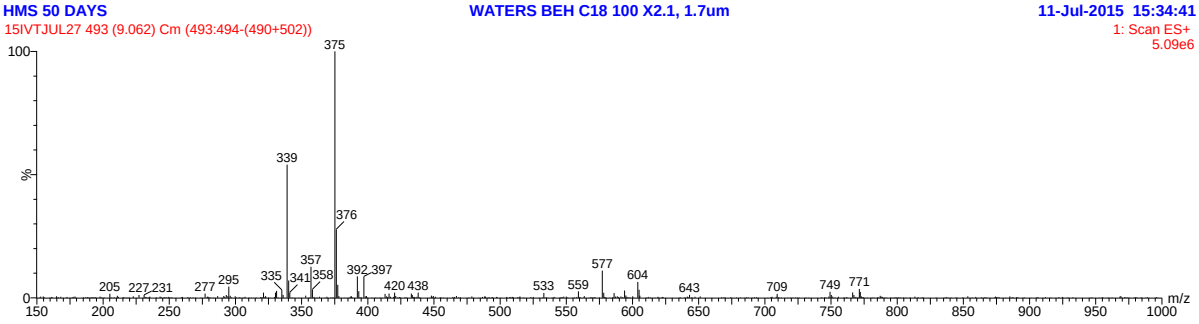
$C_{23}H_{31}O_5^+$
Exact Mass: 387.2166

Proposed fragmentation pattern of calotropin m/z 533 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
05	9.04	374	Uzarigenin	357,339,321,293	B	-



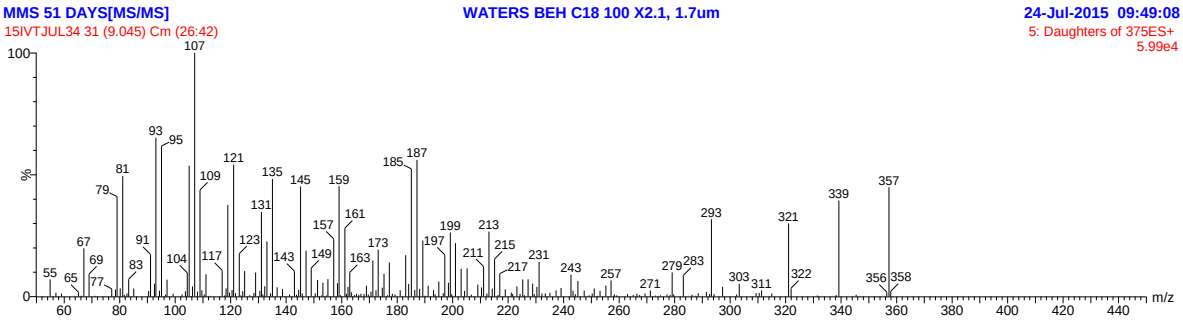
Uzarigenin
Chemical Formula: $C_{23}H_{34}O_4$
Exact Mass: 374.2457
Molecular Weight: 374.5137



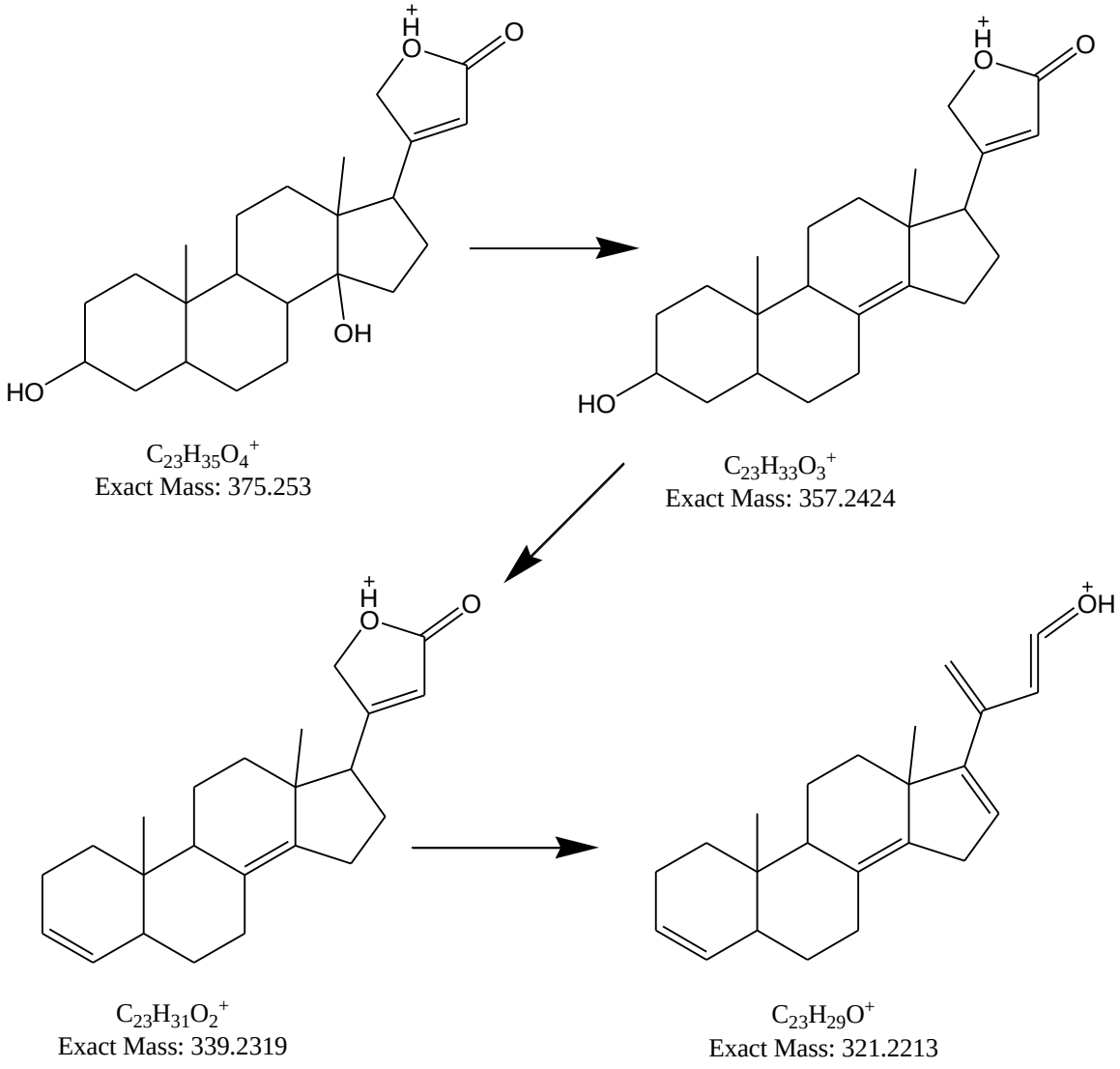
LC-ESI-MS Spectrum of uzarigenin *m/z* 375 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
375	$[M+ H]^+$	1Da	Molecular weight 374
392	$[M+ NH_4]^+$	18 Da	Da
397	$[M+ Na]^+$	23 Da	

Accurate mass observed	Annotation	Calc. mass of uzarigenin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
375.2531	$[M+ H]^+$	375.2530	0.0001	Molecular formula of the compounds $C_{23}H_{35}O_4^+$

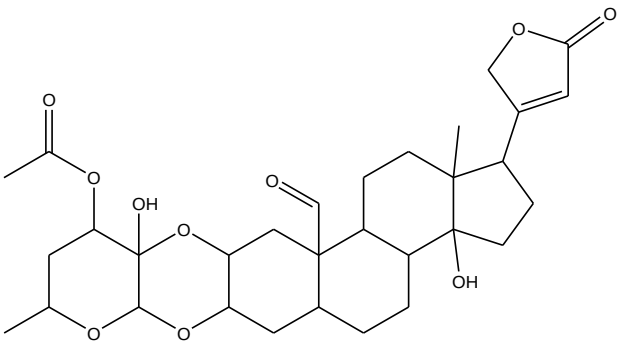


LC-ESI-MS/MS Spectrum of uzarigenin m/z 375 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed *m/z* 357,339,321,293]

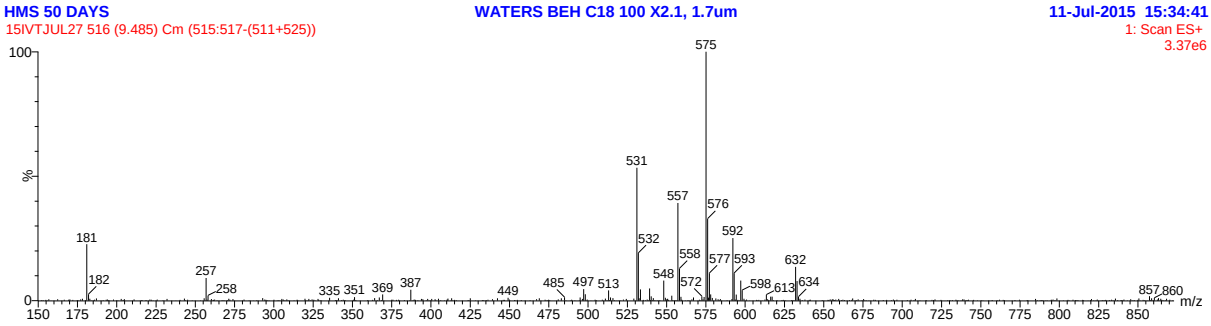


Proposed fragmentation pattern of uzarigenin m/z 375 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
06	9.46	574	Asclepin	387,369,351,341,333,323	A	188



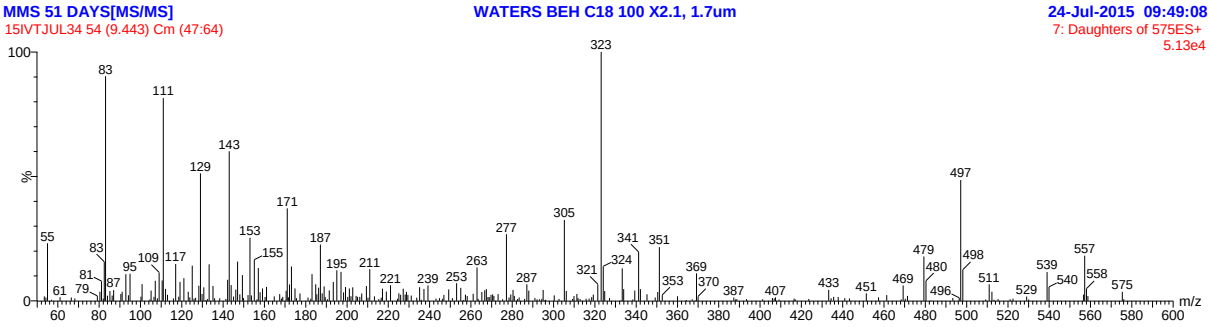
Asclepin
Chemical Formula: $C_{31}H_{42}O_{10}$
Exact Mass: 574.2778
Molecular Weight: 574.6592



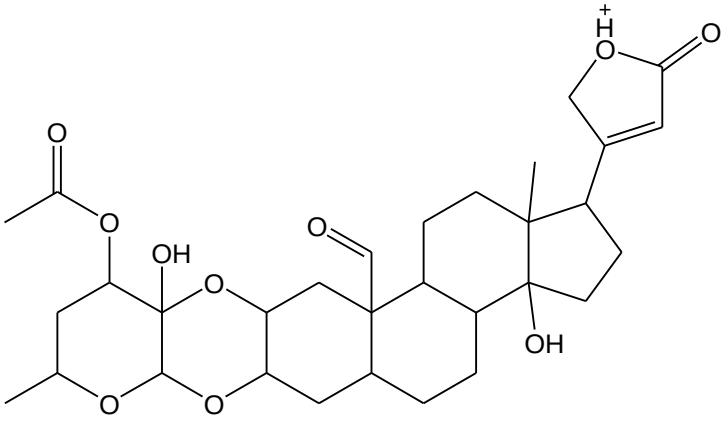
LC-ESI-MS Spectrum of asclepin m/z 575 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
575	$[M+ H]^+$	1Da	Molecular weight 574
592	$[M+ NH_4]^+$	18 Da	Da
597	$[M+ Na]^+$	23 Da	

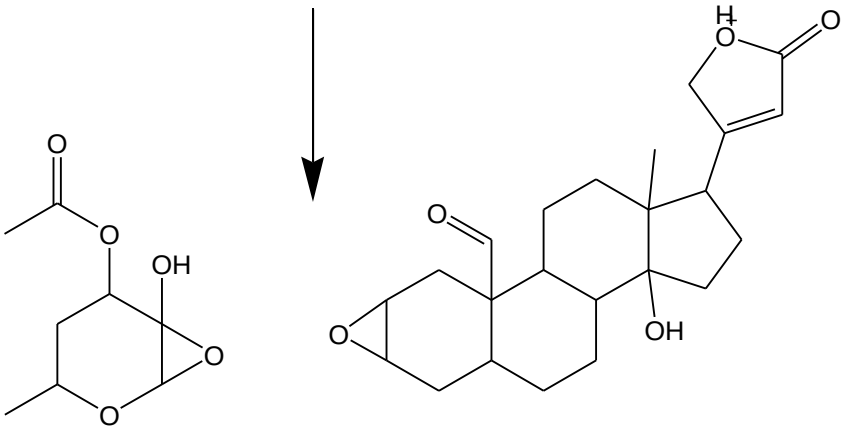
Accurate mass observed	Annotation	Calc. mass of asclepin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
575.2850	$[M+ H]^+$	575.2051	0.0001	Molecular formula of the compounds $C_{31}H_{43}O_{10}^+$



LC-ESI-MS/MS Spectrum of asclepin m/z 575 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed m/z 387,369,351,341,333,323,305]



$C_{31}H_{43}O_{10}^+$
Exact Mass: 575.2851

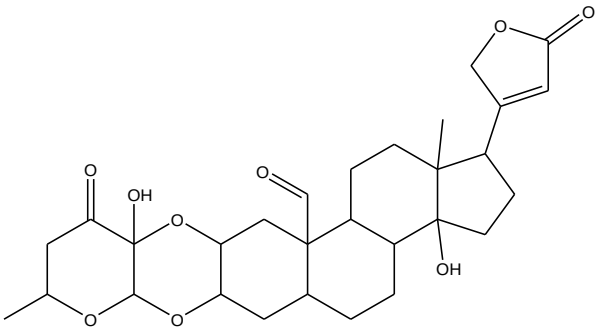


$C_8H_{12}O_5$
Exact Mass: 188.0685

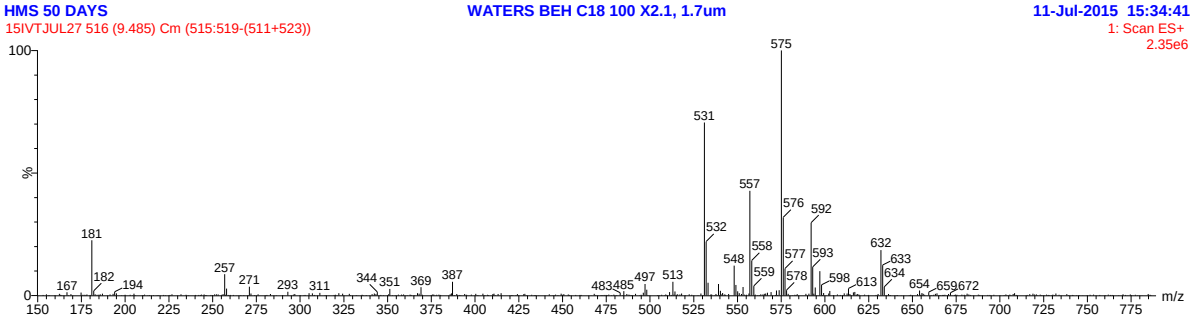
$C_{23}H_{31}O_5^+$
Exact Mass: 387.2166

Proposed fragmentation pattern of asclepin m/z 575 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
07	9.47	530	Uscharidin	369,351,341,333,323,305	A	144



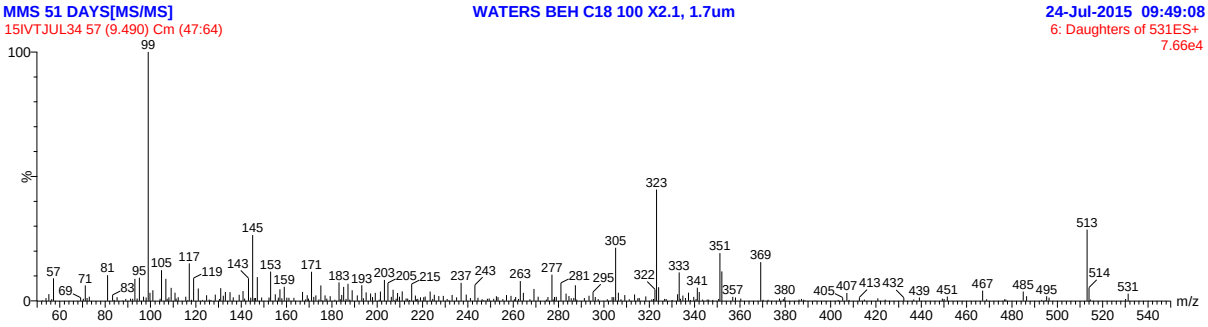
Uscharidin
Chemical Formula: $C_{29}H_{38}O_9$
Exact Mass: 530.2516
Molecular Weight: 530.6066



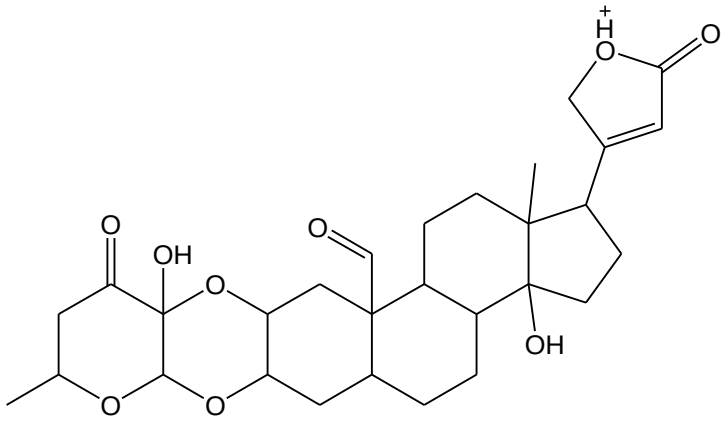
LC-ESI-MS Spectrum of uscharidin m/z 531 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
531	$[M+ H]^+$	1Da	Molecular weight 530
548	$[M+ NH_4]^+$	18 Da	Da
553	$[M+ Na]^+$	23 Da	

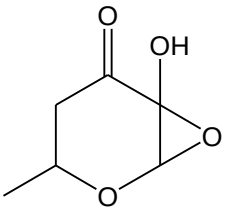
Accurate mass observed	Annotation	Calc. mass of uscharidin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
531.2589	$[M+ H]^+$	531.2589	0.0000	Molecular formula of the compounds $C_{29}H_{39}O_9^+$



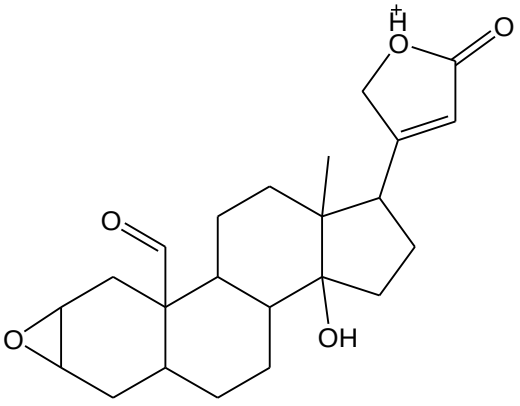
LC-ESI-MS/MS Spectrum of uscharidin m/z 531 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed m/z 369,351,341,333,323,305]



$C_{29}H_{39}O_9^+$
Exact Mass: 531.2589



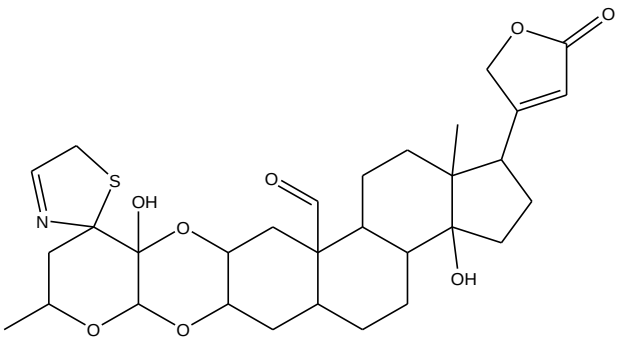
$C_6H_8O_4$
Exact Mass: 144.0423



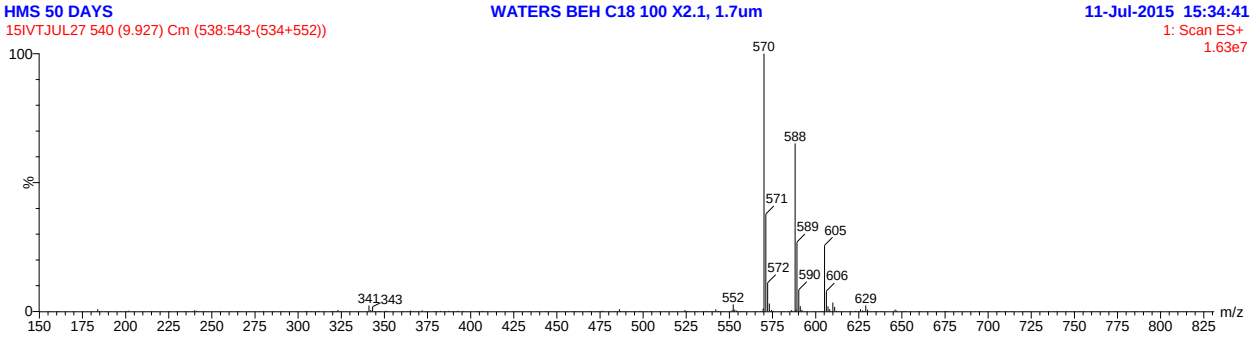
$C_{23}H_{31}O_5^+$
Exact Mass: 387.2166

Proposed fragmentation pattern of uscharidin m/z 531 $[M+H]^+$

S. No.	RT	M.W.	Identified	*m/z* (Characteristic fragment ions of genin unit)	Genin unit	Sugar unit
08	9.90	586	Uscharin	369,351,341,333,323,305	A	201



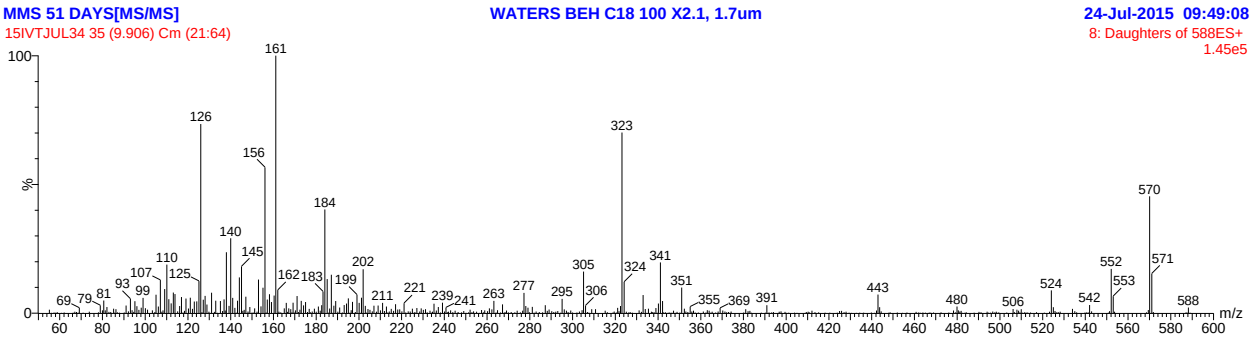
Uscharin
Chemical Formula: $C_{31}H_{41}NO_8S$
Exact Mass: 587.2553
Molecular Weight: 587.7241



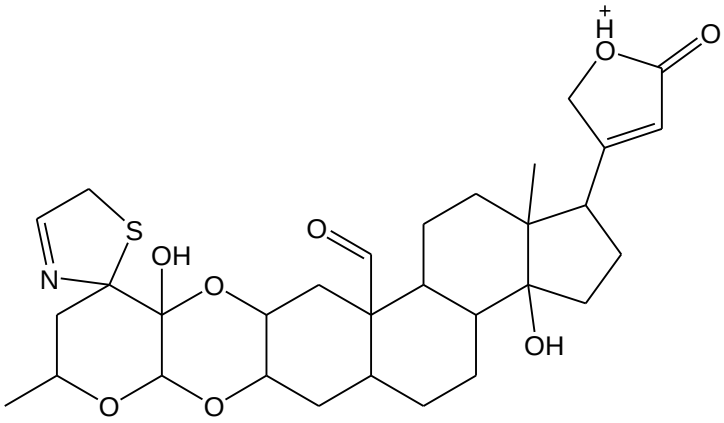
LC-ESI-MS Spectrum of uscharin m/z 588 $[M+H]^+$

m/z	Annotation	Mass difference	Confirmation remark
588	$[M+ H]^+$	1Da	Molecular weight 587
605	$[M+ NH_4]^+$	18 Da	Da

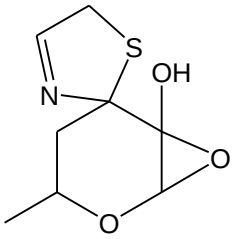
Accurate mass observed	Annotation	Calc. mass of uscharin $[M+ H]^+$	Mass difference In mmu	Confirmation remark
588.2629	$[M+ H]^+$	588.2626	0.0003	Molecular formula of the compounds $C_{31}H_{42}NO_8S^+$



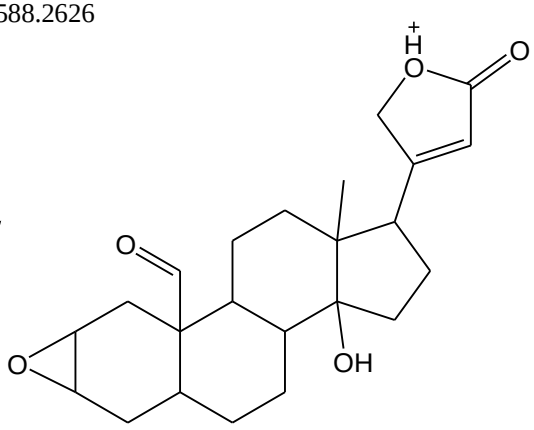
LC-ESI-MS/MS Spectrum of uscharin m/z 588 $[M+H]^+$ recorded at 30-20ev collision energy [characteristic fragment ions from genin observed m/z 369,351,341,333,323,305]



$C_{31}H_{42}NO_8S^+$
Exact Mass: 588.2626



$C_8H_{11}NO_3S$
Exact Mass: 201.046



$C_{23}H_{31}O_5^+$
Exact Mass: 387.2166

Proposed fragmentation pattern of uscharin m/z 588 [M+H]

Supplementary Table 1. Relative peak area intensity of metabolites measured by UPLC/Q-TOF MS.

S.No	Metabolite	Area (Mean+-SD)						
		3 month	6 month	9 month	12 month	Leaf(3 month)	Stem(3 month)	Root(3 month)
1	Uzarigenin	146941±5673	110247±4309	117506±8178	137993±6232	13194±2540	192415±10980	8212±1342
2	Calotropagenin	40729±5601	15062±4442	33236±5463	12365±2343	24302±5608	57545±14327	15615±1450
3	Coroglaucigenin	18768±2567	17318±2678	3998±986	1564±543	5261±634	1282±324	256±99
4	Frugoside	233200±9989	55684±4532	82267±6533	10457±1053	26937±4538	389985±25609	62190±4390
5	Uscharidin	114256±5523	40964±6732	35717±6623	75487±2365	103472±7908	266356±11123	38905±16700
6	Uscharin	1810726+4536	333477±7743	592055±5633	1346303±3783	857564±85750	1500333±15009	952749±98780
7	Ascelpin	113935±2323	47581±4288	61529±6234	88052±7723	59291±5532	135970±43308	73342±8900
8	Calactin	297240±5678	88170±9823	128451±9982	257425±2673	121638±1800	376483±35876	172995±9990

Supplementary Table 2- Plausible Unigenes involved in cardiac glycosides biosynthesis.

S.No.	Name of Enzyme	EC no.	Unigene ID	No. of transcripts
1	DXS, 1-deoxy-D-xylulose-5-phosphate synthase	EC:2.2.1.7	16078,11240	2
2	DXR, 1-deoxy-D-xylulose-5-phosphate reductoisomerase	EC:1.1.1.267	2570	2
3	MCT, 2-C-methyl-D-erythritol 4-phosphate cytidylyltransferase (ISP)	EC:2.7.7.60	3403	1
4	CMK, 4-diphosphocytidyl-2-C-methyl-D-erythritolkinase(4diphosphocytidyl-2C-methyl-D-erythritol synthase)	EC:2.7.1.148	6895	1
5	MDS, 2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase	EC:4.6.1.12	18970	1
6	HDS, 4-hydroxy-3-methylbut-2-en-1-yl diphosphate synthase	EC:1.17.7.1	1922	2
7	HDR, 4-hydroxy-3-methylbut-2-enyl diphosphate reductase	EC:1.17.1.2	1156	1
8	AACT, acetyl-CoA C-acetyltransferase	EC:2.3.1.9	12190	2
9	HMGS, hydroxymethylglutaryl-CoA synthase	EC:2.3.3.10	1140	4
10	HMGR, hydroxymethylglutaryl-CoA reductase	EC:1.1.1.34	1054	4
11	MK, mevalonate kinase	EC:2.7.1.36	8210	3
12	PMK, phosphomevalonate kinase	EC:2.7.4.2	1929	2
13	MPD, diphosphomevalonate decarboxylase	EC:4.1.1.33	2203	5
14	IDI, isopentenyl-diphosphate delta-isomerase	EC:5.3.3.2	6514	7
15	GGPPS1, geranylgeranyl pyrophosphate synthase 1	EC:2.5.1.1/10	568	6
16	FDPS1, farnesyldiphosphate synthase 1	EC:2.5.1.12/10	568	6
17	SQS1, squalene synthase	EC:2.5.1.21	12515	4
18	SMO, squalene monooxygenase	EC 1.14.13.132	3321,811,18064	12
19	CAS1, cycloartenol synthase 1	EC:5.4.99.8	2371,8367	10
20	SMT1, sterol 24-C-methyltransferase	EC:2.1.1.41	7133	2
21	CPI1, cyclopropyl isomerise;CPI1; cycloeucalenol cycloisomerase	EC:5.5.1.9	807	7
22	CYP51G1, cytochrome P450, family 51,subfamily A (sterol 14-demethylase)	EC:1.14.13.70	8978	4
23	FK, delta14-sterol reductase	EC:1.3.1.70	8353	7
24	HYD1, cholestenol delta-isomerase	EC:5.3.3.5	3051	1
25	SMT2, sterol methyltransferase 2	EC:2.1.1.143	2514	1
26	STE1, C-5 sterol desaturase	EC:1.14.2.6	172	4
27	DWF5, sterol delta7 reductase	EC:1.3.1.21	1261	4
28	DWF1, delta24-sterol reductase,(delta14-sterol reductase)	EC:1.3.1.72	2522	1
29	3βHSD, 3-beta-hydroxysteroid-dehydrogenase	-	5463, 14271, 845,303	15
30	5βPOR, progesterone 5β-reductase	-	1572	1
31	GH, glucohydrolase	-	9455,12988	4

32	GT, glycosyltransferase/glucuronosyltransferase UGT,UDPglycosyltransferase/glucuronosyltransferase	-	9455,12988, 16256,889,7 94,2312,682 7,15669,197 1,6604,9044, 14107,16749 ,6297,14001, 3348,11001, 13521,16372 ,2170,8004,5 351,9397,10 21,19905,38 24,4441,968 4,4803,8678, 22663,13316 ,7329,4933,5 124,3223,85 78,9784,441 7,8515,6875, 10638,173,3 747,5219,51 7,7752,1021 7,10597,513 0,2166,1536 6,5087,2314, 4704,4060,5 333,7748,11 734,1133,49 51,7455,165 03,6830	125
33	Monooxygenases	-	248,426,429, 591,619,811, 1466,1647,1 784,2419,29 92,4204,588 0,6582,7188, 13087,14352 ,14542,1671 9,11371,820 6,7319,7565, 7582,2206,8 421,8498,89 14,9235,100 89,10751,11 372,12547,1 2715,12768, 12818,17161 ,18175,1366 6,2994.	90

Supplementary table 3- Primer sequences used in qRT-PCR analysis

Name	Forward Primer	Reverse Primer
ACTIN	GCGTCGGAGGTGAGAGAG	AGAGTGTACGGGCCATGC
DXS	TGCAGCTGCCATAGACGATA	TCCTATCCCATTTCCACGAG
DXR	CCCTGATGCTGTCACTGTTG	CGCTGCTACTGTTGGCTTTA
MCT	TCGTTTATCCAGAAGGCAGTC	TTCACAACAGCACCGGAAG
CMK	TGATCTAGAACATCCTGCTTTTGA	ACACGCTGCTTCAACCTTTT
MDS	TCGTTTATCCAGAAGGCAGTC	TTCACAACAGCACCGGAAG
HDS	ACAATCAGAGTGTCTCTTACTGAACC	TGCTAACCTTCTACAGGGGTCT
HDR	CAGACTCGTCGGTGGTAGC	CGGAAACCTGTGTCTGTACG
AACT	CAGTGCGAATTTAGGCCAAG	TTAGGAATACCAGCGCCAAG
HMGS	TTTCCTCCTACTTGCATCCAG	TTCCCTTTGCTTGCTCCA
HMGR	CCATTTCGCCCTCTCCTAA	CTTCTGAAGAATGCGAGGTGA
MK	ACAAGTTGTCTTCCAAGTTGACTG	TGGCAATAGTGTCAACACACAG
PMK	CCCGTCAATGGTAGGAGCTA	TTCTAGAGAATTTTGGGGGTCA
MPD	TTCCCATCTCTGTACCACCAC	CCACATACGATCCTGCGTAA
IDI	ACCGGCGGTTACACCTATC	GCAGCAACAGAAGAAAAGCA
SQS	TAAGGTTTCGAGGAGCTTTGC	GCGTCCCGAAGATCAGTATC
SMO	AACATGCGCCATCCTTTAAC	GATCACGAAGGACAACAATGTCT
SQE	CTTTTCTTGTTTCTTTATCTGGGTTT	TGGTTCAAATTTAGAAGAAAGCTTAGA
CAS 1	ACTGGCGGAGATCGAAAAG	CGCTGTGCTTTTTCTCGAAT
SMT1	CCTCCGGGAAAGCATTAAG	CCAGGTCTCAGGCCTAGTTG
CPI1	CACAGTTTTGGGTGCTTCCT	TGAGTGAGGAGAAAAGTAGTATGTGG
CYP	GCCGGAGCATTCTCATACAT	TGGCTCTCCAAGACATCCAT
HYD1	GAAAATCTCAAAGTTGGATAGGATTC	CATGTGGGTTAGGCCAGTG
SMT2	AAATGGCCGTGGATCTATTG	CGCATCCAACATCGAGAAT
STE 1	TGCAAATGTCTGTTGCAATG	TCACGTATTCAGAGACTGTAGGAAG
DWF 5	GAAAAAGGGTTGAGGGTCCTA	TGCTTGCAAACCATTAGCC
DWF1	GACAAGGAGAGGATGGTTGC	CCGGGATATCTGACCCATATT
POR	ATGAATCTAGTTGGTACCATTTGTGT	GGAAACTTCAATGGCACTCC
LS	TTTGATCCTAATGCCGGAAC	ATTCCCGGCGAACTCTTT
GH	TTGGTGACGAGAACGAGGTT	ACCAAATTCCCATTGTACGC
GT	CCCTGTAAATTGCATGCTGA	GGAGTGTTAAGGAAAGTGACGTG
MO	TCCCACCAAGAAACTTCCAC	TGTGAATGTGTCCGATGATTG

Supplementary Table no 4- Expanded names of genes for figures 6 and 7.

Abbreviation	Full name
DXS	1-Deoxy-D-xylulose-5-phosphate synthase
DXR	1-Deoxy-D-xylulose-5-phosphate reductoisomerase
MCT	2-C-methyl-D-erythritol4-phosphate cytidylyltransferase
CMK	4-Diphosphocytidyl-2-C-methyl-D-erythritolkinase;
MDS	2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase
HDS	4-Hydroxy-3-methylbut-2-en-1-yldiphosphate synthase
HDR	4-Hydroxy-3-methylbut-2-enyl diphosphate reductase
AACT	AcetylCoAacetyltransferase
HMGS	HydroxymethylglutarylCoAsynthase
HMGR	Hydroxymethylglutaryl-CoA reductase
MK	Mevalonate kinase
PMK	Phosphomevalonate kinase
MPD	Diphosphomevalonate decarboxylase
IDI	Isopentenyl-diphosphate delta-isomerase
GGPPS1	Geranylgeranyl pyrophosphate synthase 1
FDPS1	Farnesyldiphosphate synthase 1
SQS	Squalene synthase
SMO	Squalene monooxygenase
CAS	Cycloartenol synthase
SMT1	Sterol 24-C-methyltransferase
CPI1	Cyclopropyl isomerase
CYP51G1	Cytochrome P450, family 51,subfamily A(sterol14demethylase)
FK	Delta14-sterol reductase
HYD	Cholestenol delta-isomerase
SMT2	Sterol methyltransferase 2
STE	C-5 sterol desaturase
DWF5	Sterol delta7 reductase
DWF1	Delta24-sterolreductase
3βHSD	3beta-hydroxy-steroid-dehydrogenase
POR	Progesterone reductase
OR	Oxidoreductase
MaT	Malonyltransferase
HOX	Hydroxylase
GH	Glucohydrolase
MO	Monooxygenases
GT	Glycosyltransferase/glucuronosyltransferase
UGT	UDP-glycosyltransferase/ glucuronosyltransferase