Electronic Supplementary Material (ESI) for RSC Advances.

Supercritical CO_2 assisted extraction of essential oil and naringin from *Citrus grandis* peels: *in vitro* antimicrobial activity and docking study

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Supplementary Data

Table S1. Physicochemical properties of compound *d*-limonene

Property	Value	Comment
Molecular weight	136.13	Contain hydrogen atoms. Optimal: 100–600
Volume	167.687	Van der Waals volume
nHA	0	Number of hydrogen bond acceptors. Optimal: 0–12
nHD	0	Number of hydrogen bond donors. Optimal: 0–7
nRot	1	Number of rotatable bonds. Optimal: 0–11
nRing	1	Number of rings. Optimal:0~6
MaxRing	6	Number of atoms in the biggest ring. Optimal: 0–18
nHet	0	Number of heteroatoms. Optimal: 1–15
fChar	0	Formal charge. Optimal: −4-~4
nRig	7	Number of rigid bonds. Optimal: 0–30
Flexibility	0.143	Flexibility = nRot/nRig
Stereocenters	1	Optimal: ≤2
TPSA	0	Topological polar surface area. Optimal: 0–140
logS	-4.239	Log of the aqueous solubility. Optimal: −4–0.5 log mol/L
logP	4.368	Log of the octanol/water partition coefficient. Optimal: 0–3
logD	3.469	logP at physiological pH 7.4. Optimal: 1–3

Table S2. Medicinal chemistry compound *d*-limonene.

Property	Value	Comment
QED	0.485	A measure of drug-likeness based on the concept of desirability; attractive: >0.67; unattractive: 0.49~0.67; too complex: <0.34.
SAscore	3.165	Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules. SAscore ≥ 6, difficult to synthesize; SAscore < 6, easy to synthesize.
Fsp^3	0.6	The number of sp^3 hybridized carbons/total carbon count, correlating with melting point and solubility. $Fsp^3 \geq 0.42$ is considered a suitable value.
MCE-18	15.0	MCE-18 stands for medicinal chemistry evolution. MCE-18 ≥ 45 is considered a suitable value.
NPscore	2.359	Natural-product-likeness score. This score is typically in the range of −5 to 5. The higher the score is, the higher the probability is that the molecule is an NP.
Lipinski Rule	Accepted	MW ≤ 500; logP ≤ 5; Hacc ≤ 10; Hdon ≤ 5. If two properties are out of range, a poor absorption or permeability is possible; one property being out of range is acceptable.
Pfizer Rule	Rejected	logP > 3; TPSA < 75; compounds with a high log P (>3) and low TPSA (<75) are likely to be toxic.
GSK Rule	Rejected	MW ≤ 400; logP ≤ 4; compounds satisfying the GSK rule may have a more favorable ADMET profile.
Golden Triangle	Rejected	200 ≤ MW ≤ 500; −2 ≤logD ≤ 5; compounds satisfying the Golden Triangle rule may have a more favorable ADMET profile.
PAINS	0 alerts	Pan-assay interference compounds, frequent hitters, *α*-screen artifacts and reactive compound.
ALARM NMR	0 alerts	Thiol reactive compounds.
BMS	0 alerts	Undesirable, reactive compounds.
Chelator Rule	0 alerts	Chelating compounds.

Table S3. The absorption of compound *d*-limonene.

Property	Value	Comment
Caco-2 Permeability	-4.32	Optimal: higher than −5.15 log unit
MDCK Permeability	1.9e-05	Low permeability: $<2 \times 10^{-6}$ cm/s Medium permeability: $2–20 \times 10^{-6}$ cm/s High passive permeability: $>20 \times 10^{-6}$ cm/s
Pgp-inhibitor	0.002	Category 1: inhibitor; Category 0: non-inhibitor; the output value is the probability of being Pgp-inhibitor
Pgp-substrate	0.0	Category 1: substrate; Category 0: non-substrate; the output value is the probability of being Pgp-substrate
HIA	0.003	Human intestinal absorption; Category 1: HIA+(HIA < 30%); Category 0: HIA-(HIA < 30%); the output value is the probability of being HIA+
$F_{20\%}$	0.818	20% Bioavailability; Category 1: F20%+ (bioavailability < 20%); Category 0: F20%- (bioavailability ≥ 20%); The output value is the probability of being F20% +
$F_{30\%}$	0.798	30% Bioavailability; Category 1: F30% + (bioavailability < 30%); Category 0: F30% - (bioavailability ≥ 30%); The output value is the probability of being F30% +

Table S4. The properties of the drug distribution of compound *d*-limonene.

Property	Value	Comment
PPB	86.38%	Plasma protein binding; optimal: <90%. Drugs with high protein binding may have a low therapeutic index.
VD	86.38%	Volume distribution; optimal: 0.04–20 L/kg.
BBB Penetration	86.38%	Blood–brain barrier penetration; Category 1: BBB+; Category 0: BBB−; the output value is the probability of being BBB+.
Fu	9.244%	The fraction unbound in plasma; low: <5%; middle: 5~20%; high: >20%.

Table S5. The properties of the drug metabolism of compound *d*-limonene.

Property	Value	Comment
CYP1A2 inhibitor	0.678	Category 1: inhibitor; Category 0: non-inhibitor; the output value is the probability of being an inhibitor.
CYP1A2 substrate	0.652	Category 1: substrate; Category 0: non-substrate; the output value is the probability of being a substrate
CYP2C19 inhibitor	0.223	Category 1: inhibitor; Category 0: non-inhibitor; the output value is the probability of being an inhibitor
CYP2C19 substrate	0.834	Category 1: substrate; Category 0: non-substrate; the output value is the probability of being a substrate
CYP2C9 inhibitor	0.06	Category 1: inhibitor; Category 0: non-inhibitor; the output value is the probability of being an inhibitor.
CYP2C9 substrate	0.804	Category 1: substrate; Category 0: non-substrate; the output value is the probability of being a substrate.
CYP2D6 inhibitor	0.02	Category 1: inhibitor; Category 0: non-inhibitor; the output value is the probability of being an inhibitor.
CYP2D6 substrate	0.874	Category 1: substrate; Category 0: non-substrate; the output value is the probability of being a substrate.
CYP3A4 inhibitor	0.057	Category 1: inhibitor; Category 0: non-inhibitor; the output value is the probability of being an inhibitor.
CYP3A4 substrate	0.253	Category 1: substrate; Category 0: non-substrate; the output value is the probability of being a substrate.

Table S6. The properties of the drug excretion of compound *d*-limonene.

Property	Value	Comment
CL	11.517	Clearance; high: >15 mL/min/kg; moderate: 5–15 mL/min/kg; low: <5 mL/min/kg.
T1/2	0.233	Category 1: long half-life; Category 0: short half-life; long half-life: >3 h; short half-life: <3 h; the output value is the probability of having a long half-life.

Table S7. The properties of the drug toxicity of compound *d*-limonene

Property	Value	Comment
hERG Blockers	0.023	Category 1: active; Category 0: inactive; the output value is the probability of being active.
H-HT	0.69	Human hepatotoxicity; Category 1: H-HT positive (+); Category 0: H-HT negative (−); the output value is the probability of being toxic.
DILI	0.037	Drug-induced liver injury. Category 1: drugs with a high risk of DILI; Category 0: drugs with no risk of DILI. The output value is the probability of being toxic.
AMES Toxicity	0.007	Category 1: AMES positive (+); Category 0: AMES negative (−); the output value is the probability of being toxic.
Rat Oral Acute Toxicity	0.017	Category 0: low toxicity; Category 1: high toxicity; the output value is the probability of being highly toxic.
FDAMDD	0.309	Maximum recommended daily dose; Category 1: FDAMDD (+); Category 0: FDAMDD (−); the output value is the probability of being positive.
Skin Sensitization	0.355	Category 1: sensitizer; Category 0: non-sensitizer; the output value is the probability of being a sensitizer.
Carcinogencity	0.992	Category 1: carcinogens; Category 0: non-carcinogens; the output value is the probability of being toxic.
Eye corrosion	0.849	Category 1: corrosive; Category 0: noncorrosive; the output value is the probability of being corrosive.
Eye irritation	0.981	Category 1: irritants; Category 0: non-irritants; the output value is the probability of being an irritant.
Respiratory Toxicity	0.216	Category 1: respiratory toxicants; Category 0: respiratory non-toxicants; the output value is the probability of being toxic.

Table S8. Toxicophore rules of compound *d*-limonene

Property	Value	Comment
Acute Toxicity Rule	0 alerts	20 substructures; acute toxicity during oral administration
Genotoxic Carcinogenicity Rule	0 alert	117 substructures; carcinogenicity or mutagenicity
Nongenotoxic Carcinogenicity Rule	0 alerts	23 substructures; carcinogenicity through nongenotoxic mechanisms
Skin Sensitization Rule	0 alerts	155 substructures; skin irritation
Aquatic Toxicity Rule	1 alerts	99 substructures; toxicity to liquid (water)
Nonbiodegradable Rule	0 alerts	19 substructures; nonbiodegradable
SureChEMBL Rule	0 alerts	164 substructures; MedChem unfriendly status

Table S9. The role results on *in silico* molecular docking model of Naringin and small ligand in receptor, enzyme 2VF5 docked to enzyme 2VF5.

Entry	Active pose	Free Energy of Binding[a]	K_i[b]	The number of hydrogen bonds[c]	The property and bond length[d]
Naringin	60	-5.51	91.22	4	X:Gly301:N - **Naringin** (2.85 Å) X:Lys487:N-**Naringin**:O (2.55 Å) X:Ala496:N-**Naringin**:O (2.82 Å) **Naringin**: H - X:Lys603:O (1.87 Å)
Small ligand	83	-5.38	114	13	X:Thr 302:O–**Small ligand** (2.86 Å) X:Gln 348:N–**Small ligand** (3.11 Å) X:Ser 349:N–**Small ligand** (2.95 Å) X:Ser 349:O–**Small ligand** (2.66 Å) X:Thr 352:O–**Small ligand** (3.00 Å) X:Ser 401:N– **Small ligand** (3.06 Å) **Small ligand**: H–X:Glu 488:O (2.03 Å) **Small ligand**: H–X:Glu 488:O (1.88 Å) **Small ligand**: H–X:Glu 488:O (2.05 Å) **Small ligand**: H–X:Ala 602:O (1.88 Å) **Small ligand**: H–X:Ser 349:O (1.90 Å) **Small ligand**: H– X:Lys 603:O (2.15 Å) **Small ligand**: H–X:Lys 603:O (1.92 Å)
Fluconazole	87	-5.55	86.10	4	X:Thr302:N–**Fluconazole**:O (3.00 Å) X:Ser303:N–**Fluconazole**:O (3.05 Å) X:Ser349:O–**Fluconazole**:N (2.77Å) **Fluconazole**:H–X:Cys300:O (1.94 Å)

Table S10. The values of RMSD of naringin, small ligand in enzyme 2VF5, and Fluconazole, standard drug.

RMSD, Å	Naringin	Small ligand	Fluconazole	Pose 60	Pose 83	Pose 87 (Reference)
Naringin	0	3.911	3.453	6.186	4.254	2.581
Small ligand	3.911	0	2.924	4.331	2.483	2.098
Fluconazole	**3.453**	**2.924**	**0**	**4.463**	**2.453**	**2.370**
Pose 60	6.186	4.331	4.463	0	4.705	2.896
Pose 83	4.254	2.483	2.453	4.705	0	2.453
Pose 87	**2.581**	**2.098**	**2.370**	**2.896**	**2.453**	**0**

Table S11. NMR data of **n**aringin in DMSO-d_6

C	**Naringin**				
	δ_C	**δ_H mult., (*J* in Hz)**	**δ_C**	**δ_H mult., (*J* in Hz)**	**HMBC (H→C)**
	2*S*		**2*R***		
2	78.6	5.49 (1H, *dd*, 13.2; 3.0)	78.8	5.51 (1H, *dd*, 12.6; 3.0)	C-4, C-1’
3	42.0	3.14-3.17 (1H, *m*, H-3eq) 2.72 (1H, *dd*, 13.2; 3.0, H-3ax)	42.1	3.18-3.21 (1H, *m*, H-3ax) 2.73 (1H, *dd*, 13.8; 3.0, H-3eq)	C-4, C-1’
4	197.2		197.3		
5	163.0		163.0		
6	96.3	6.08 (1H, *d*, 2.4)	96.4	6.09 (1H, *d*, 2.4)	C-5, C-7, C-10
7	164.7		164.9		
8	95.1	6.10 (1H, *d*, 2.4)	95.2	6.11 (1H, *d*, 2.4)	C-6, C-7, C-9, C-10
9	162.8		162.9		
10	103.3		103.4		
1’	128.6		128.6		
2’, 6’	128.4	7.32 (1H, *d*, 8.4)	128.5	7.33 (1H, *d*, 8.4)	C-2, C-1’, C-3’, C-4’
3’,5’	115.2	6.79 (1H, *d*, 8.4)	115.2	6.80 (1H, *d*, 8.4)	C-1’, C-2’, C-4’
4’	157.8		157.9		
4’-OH		9.64 (1H, *s*)		9.65 (1H, *s*)	C-4’
5-OH		12.04 (1H, *s*)		12.05 (1H, *s*)	C-5
Glc					
1’’	97.3	5.13 (1H, *d*, 7.8)	97.4	5.14 (1H, *d*, 7.8)	C-7
2’’	77.1	3.39 (1H, *m*)	77.1	3.39 (1H, *m*)	C-1’’
3’’	76.9	3.41 (1H, *m*)	76.8	3.41 (1H, *m*)	C-2’’, C-5’’
4’’	71.8	3.19 (1H, *m*)	71.8	3.19 (1H, *m*)	C-3’’,C-5’’
5’’	76.1	3.40 (1H, *m*)	76.2	3.40 (1H, *m*)	C-4’’, C-6’’
6’’	60.4	3.40 (1H, *m*) 3.65 (1H, *m*)	60.4	3.40 (1H, *m*) 3.65 (1H, *m*)	C-5’’
Rha					
1’’’	100.4	5.09 (1H, *d*, 1.8)	100.5	5.10 (1H, *d*, 1.8)	C-2’’
2’’’	69.6	3.17 (1H, *m*)	69.6	3.17 (1H, *m*)	C-1’’’
3’’’	70.4	3.67 (1H, *m*)	70.4	3.67 (1H, *m*)	C-2’’’, C-4’’’
4’’’	70.5	3.30 (1H, *m*)	70.5	3.30 (1H, *m*)	C-3’’’, C-5’’’
5’’’	68.3	3.69 (1H, *m*)	68.3	3.69 (1H, *m*)	C-4’’’, C-6’’’
6’’’	18.0	1.14 (1H, *d*, 6,0)	18.0	1.15 (1H, *d*, 6,0)	C-5’’’

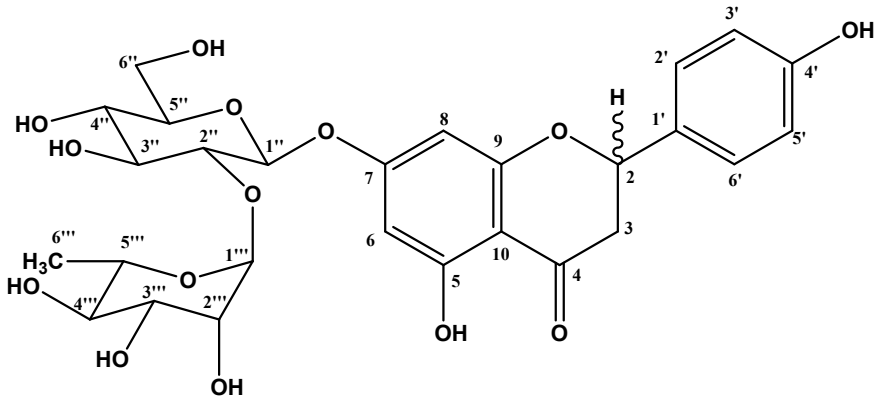


Figure S1. Chemical structure of naringin

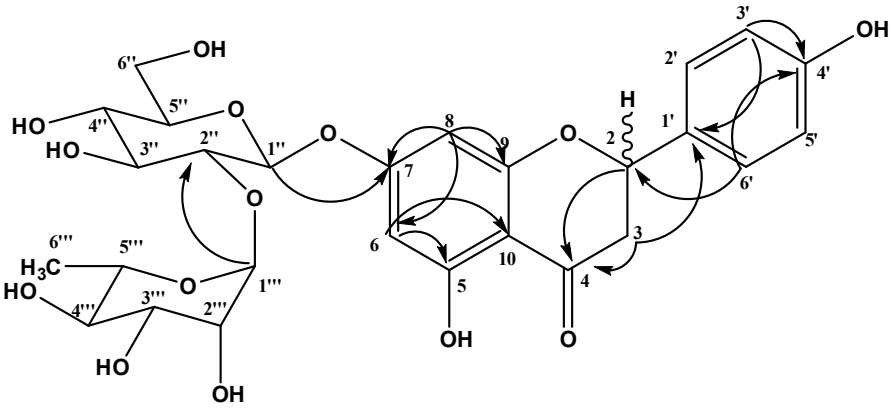


Figure S2. The key HMBC correlations of naringin

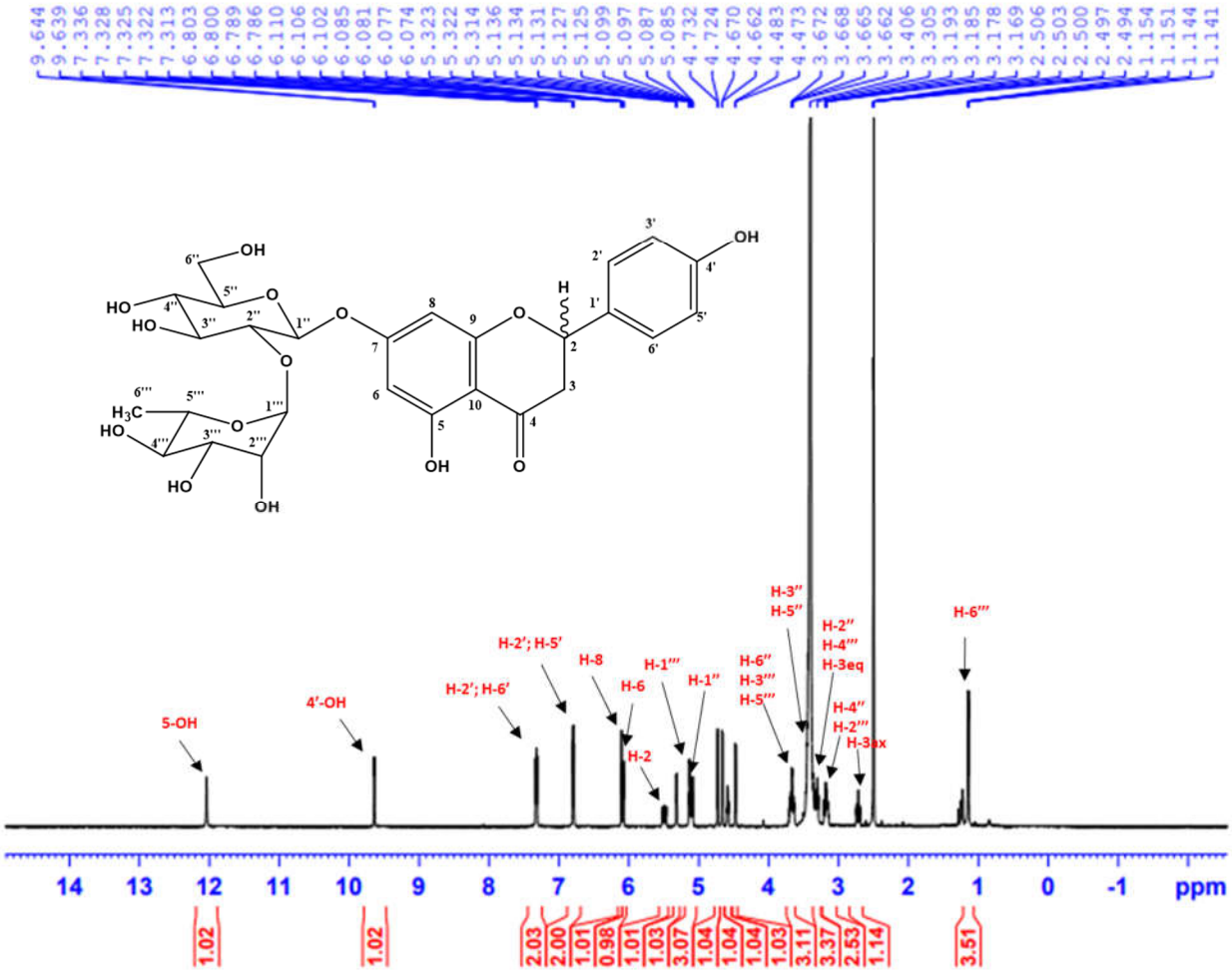


Figure S3. ^{1}H-NMR spectrum copy of naringin

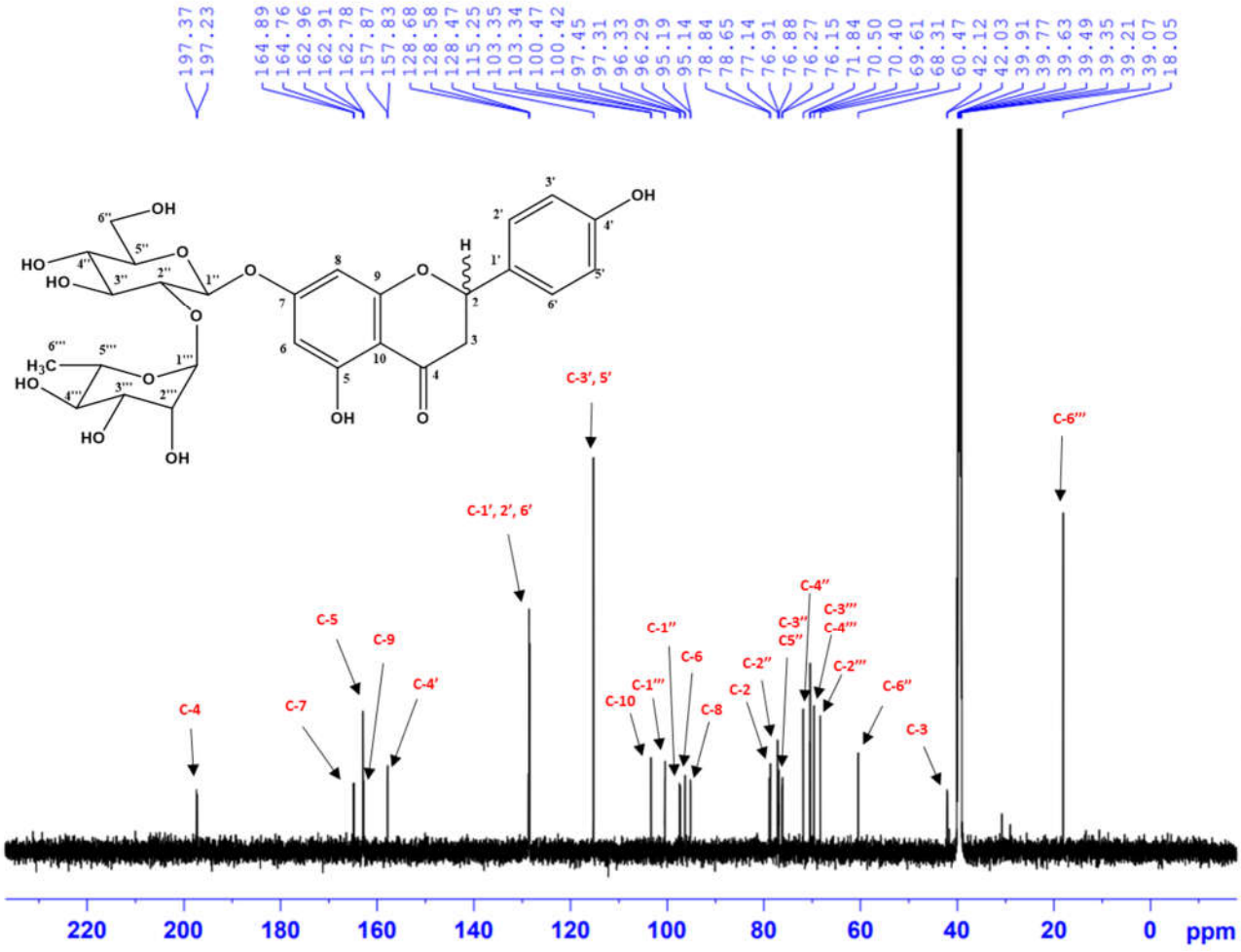


Figure S4. ^{13}C-NMR spectrum copy of naringin

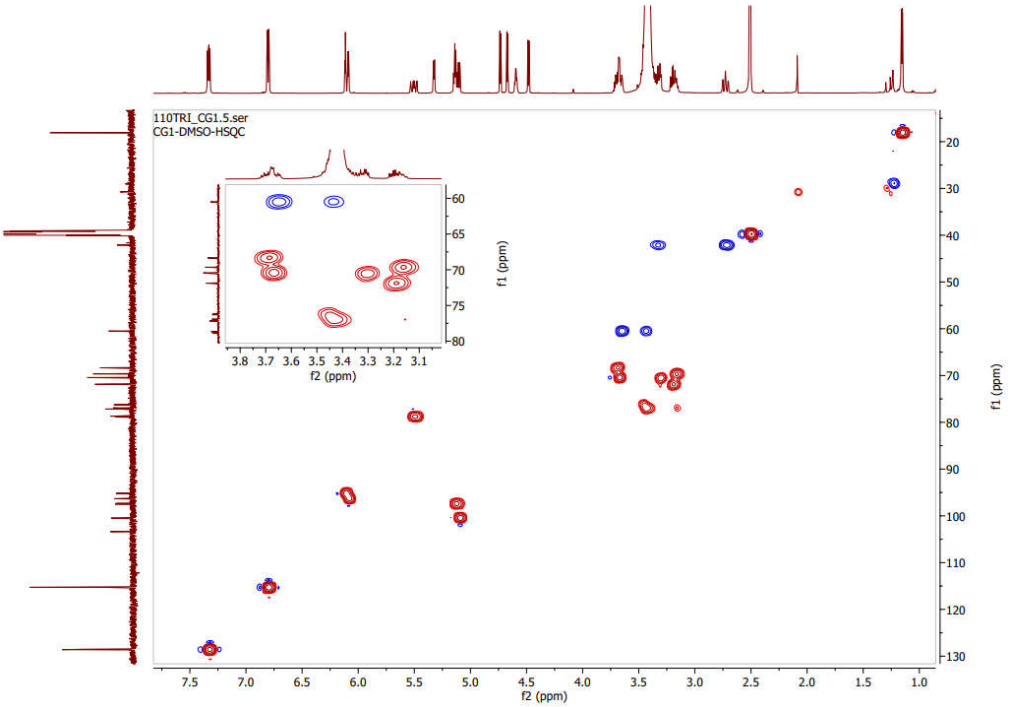


Figure S5. HSQC spectrum copy of naringin

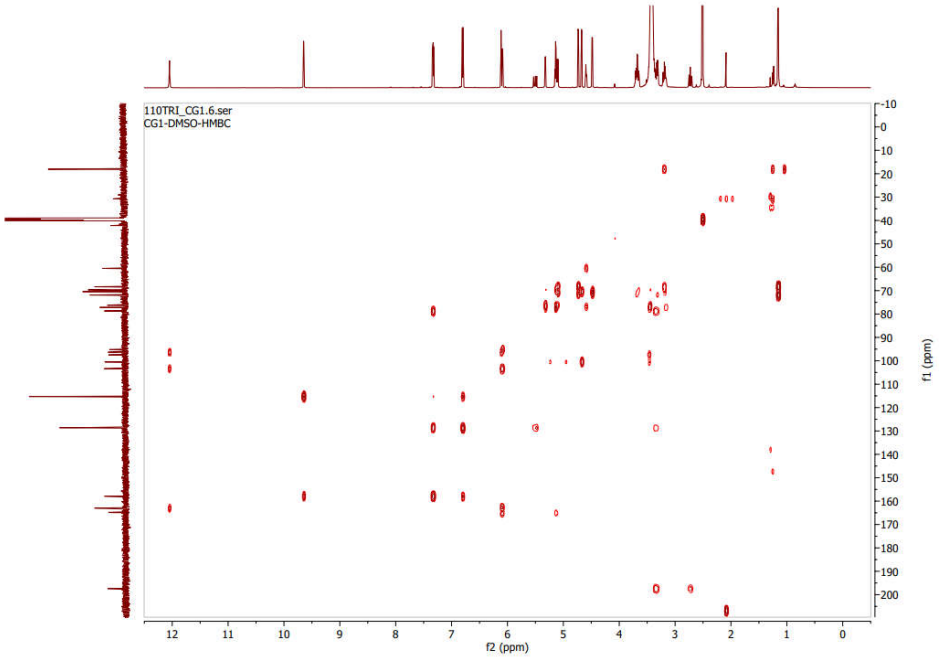
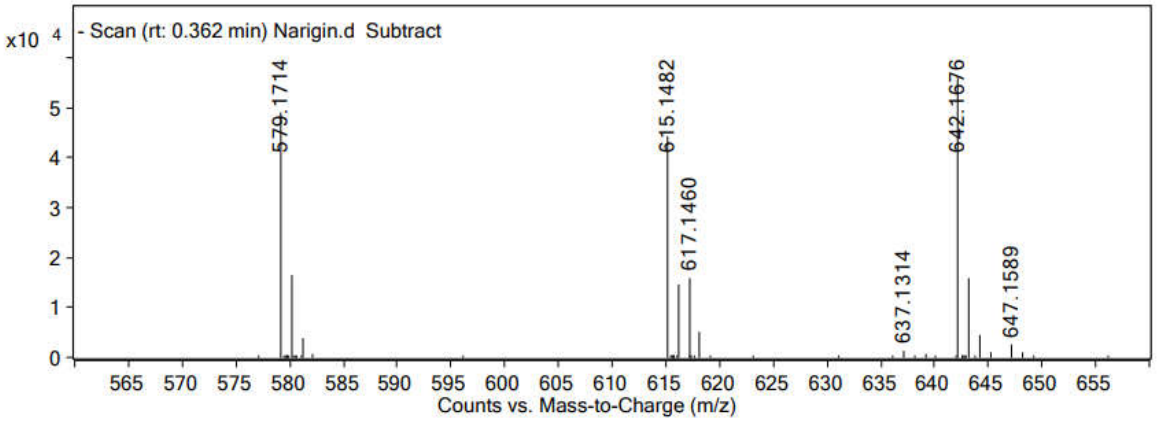


Figure S6. HMBC spectrum copy of naringin

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
140	0	ESI



Peak List

m/z	z	Abund
132.8679		17043.91
134.8655		21154.85
136.8637		6658.37
579.1714	1	49013.24
580.175	1	16525.76
615.1482	1	44263.45
616.1516	1	14580.11
617.146	1	15905.95
642.1676	1	55881.25
643.1701	1	15682.34

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Figure S7. HRMS spectrum copy of naringin

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Operator   :
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Instrument :    Instrumen
Sample Name: TD Buoi hoi nuoc
Misc Info  :
Vial Number: 1
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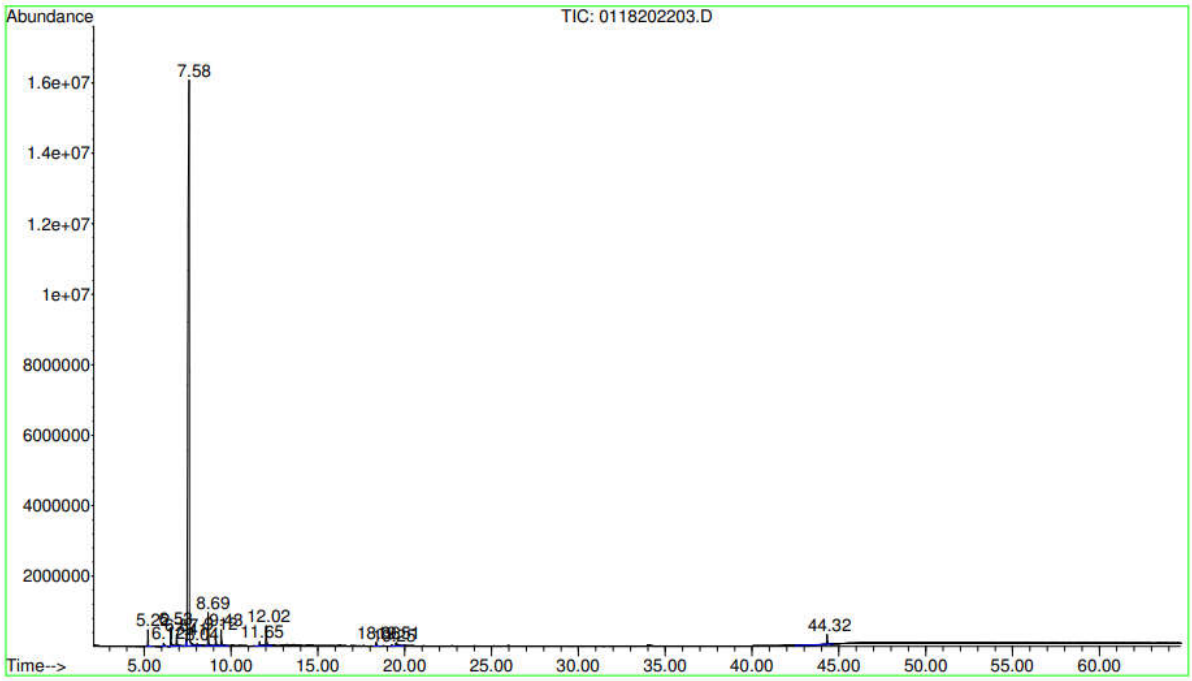

Figure S8. GCMS spectrum copy of HDEO

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Vial Number: 1
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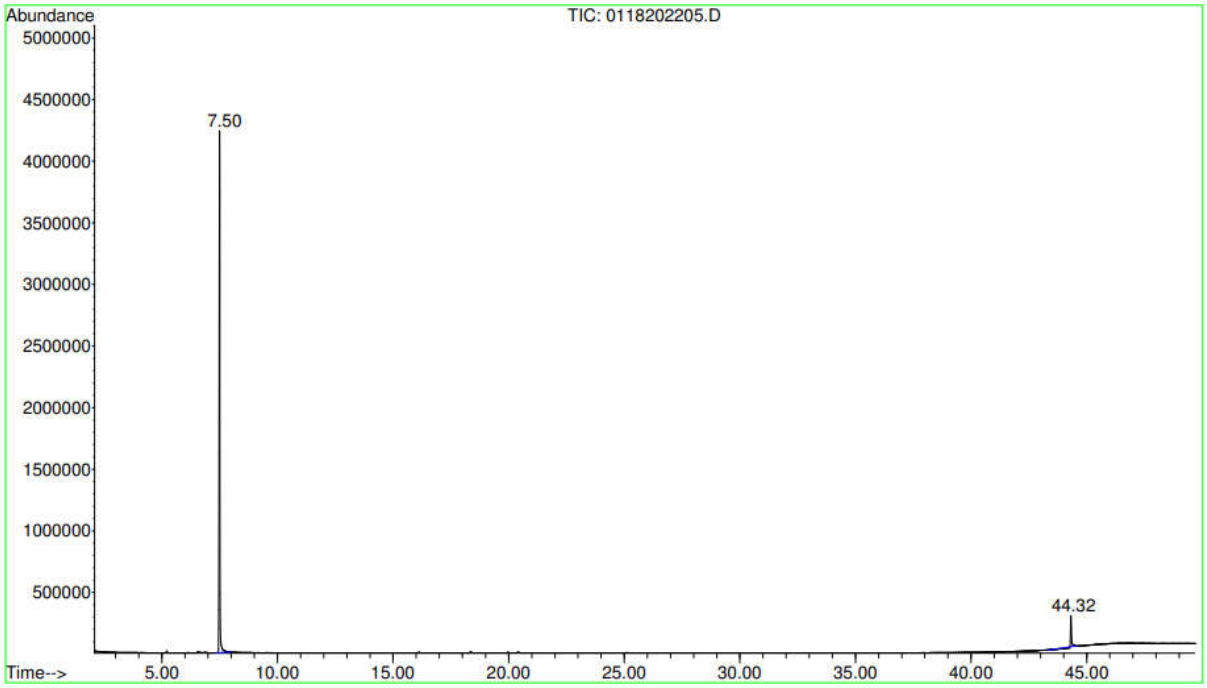

Figure S9. GCMS spectrum copy of SCEO

Figure S10. Supercritical CO_2 instrument made in Institute of Chemical Technology (ICT)-Vietnam Academy of Science and Technology (VAST) - Vietnam