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SUPPLEMENTARY MATERIAL TO

A computational study to identify the metabolites in *Lippia alba* capable of inhibiting gastric cancer through BCL-2 protein inhibition

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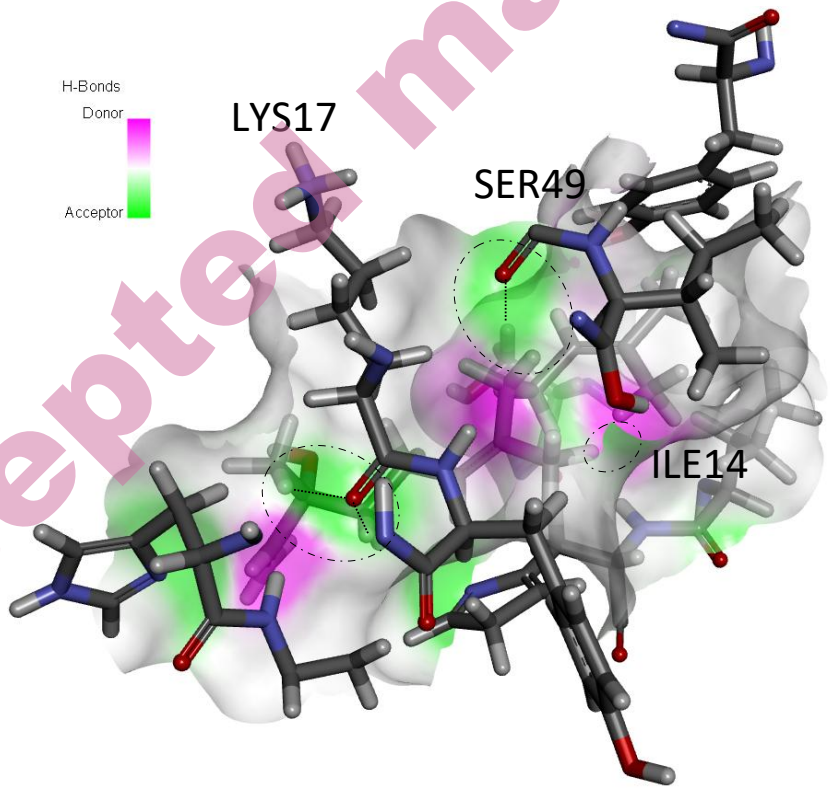

Figure S-1. Predominant molecular interactions between Lys17, Ile14, and Ser49.

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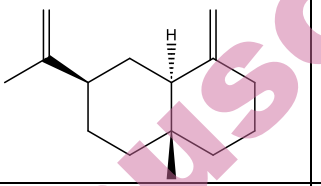
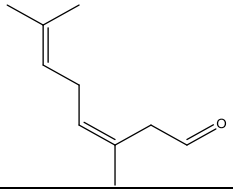
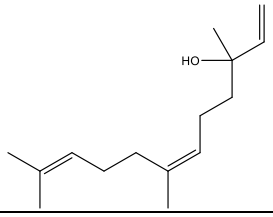
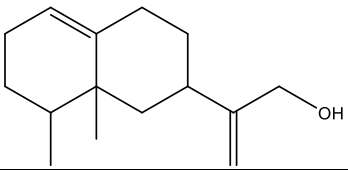
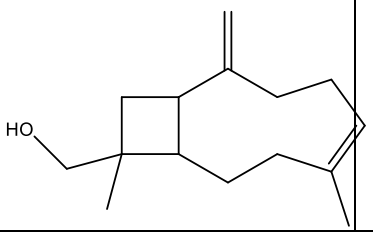
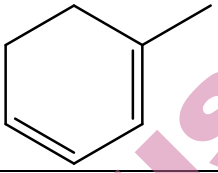
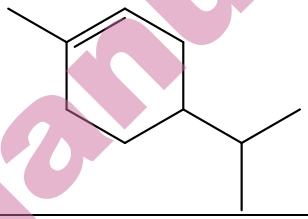
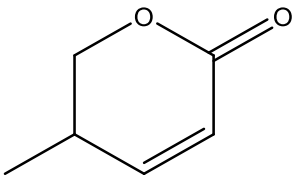
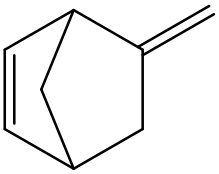
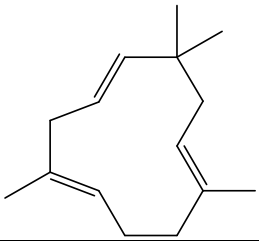
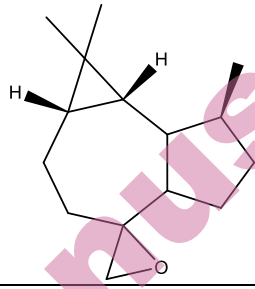
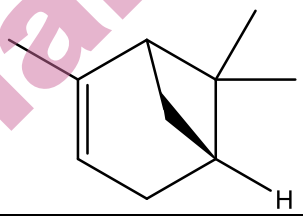
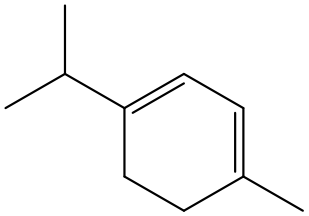
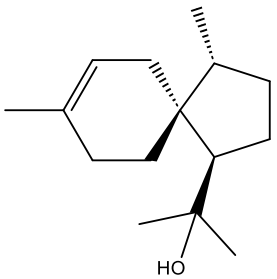
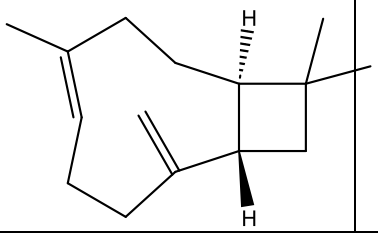
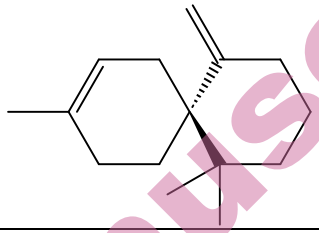
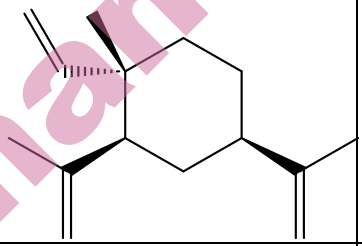
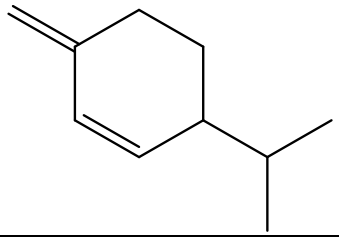
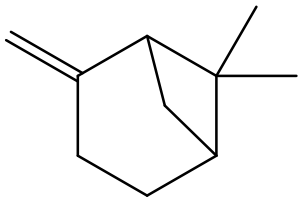
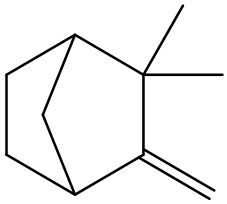
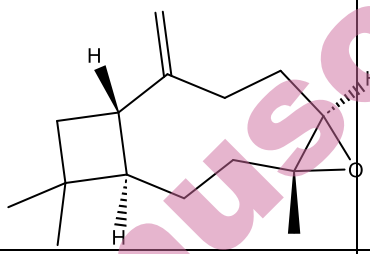
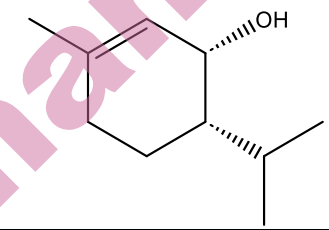
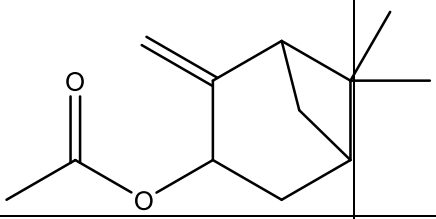
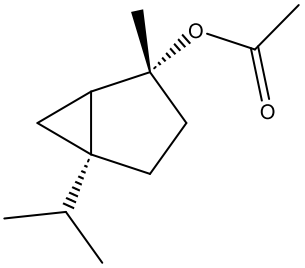
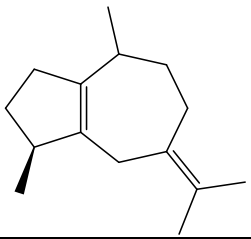
Table 1S. *Lippia alba* metabolites studied and biological properties.[1,2]

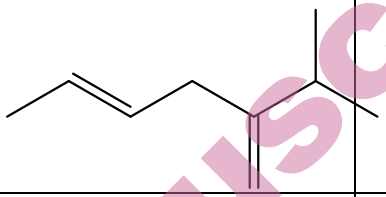
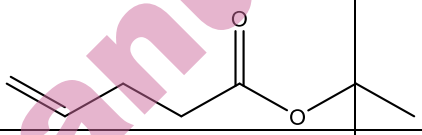
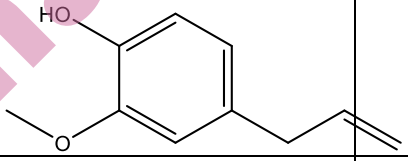
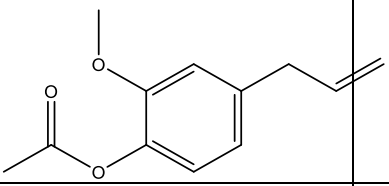
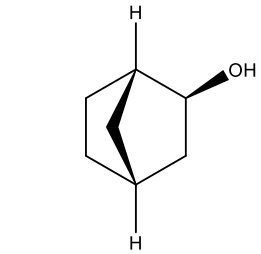
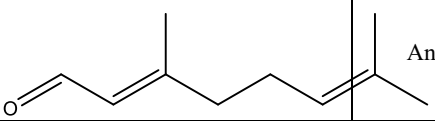
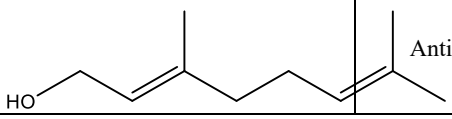
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
1	(3*R*,4a*S*,8a*R*)-8a-methyl-5-methylidene-3-prop-1-en-2-yl-1,2,3,4,4a,6,7,8-octahydronaphthalene	β-selinene		Antifungal, antibacterial and antioxidants
	(*Z*)-hex-3-enal	(3*Z*)-hexenal		-
		(*Z*)-Isocitral		Antispasmodic
4	(6*Z*)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol	(*Z*)-nerolidol		Antioxidant, antibacterial, antimycotic, antitumoral
5	(1*S*,4a*R*,7*S*,8a*S*)-1,4a-dimethyl-7-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalen-1-ol.	13-hydroxy-valencene		Antioxidant, anti-inflammatory
6	[(5*Z*)-6,10-dimethyl-2-methylidene-10-bicyclo[7.2.0]undec-5-enyl]methanol	14-hydroxy-9-epi-(*E*)-Caryophyllene		-

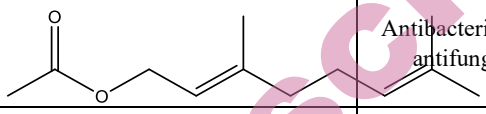
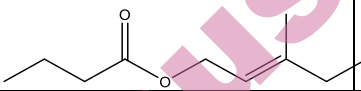
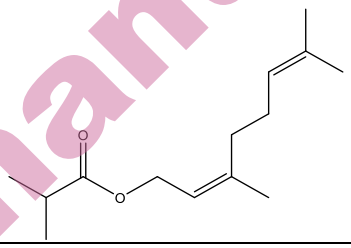
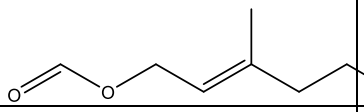
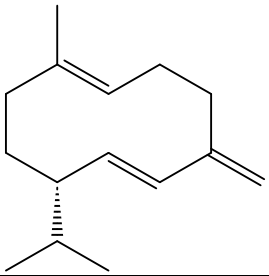
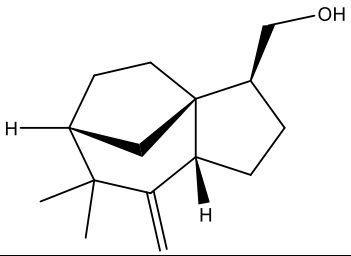
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
7	1-methylcyclohexa-1,3-diene	1-methylcyclohexa-1,3-diene		-
8	p-Menth-1-ene	p-Menth-1-ene		-
9	4-methyl-2,3-dihydro-2H-pyran-6-one	4-methyl-2,3-dihydro-2H-pyran-6-one		-
10	5-methylidenebicyclo[2.2.1]hept-2-ene	5-Methylene-2-norbornene		-
11	(1*Z*,4*Z*,8*E*)-2,6,6,9-tetramethylcycloundeca-1,4,8-triene	α-humulene		Anti-inflammatory

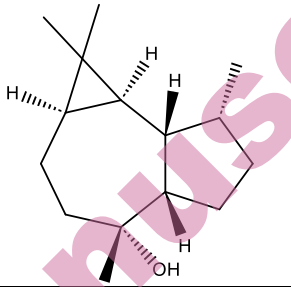
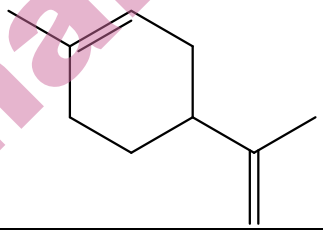
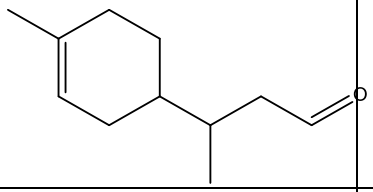
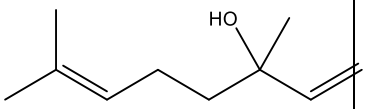
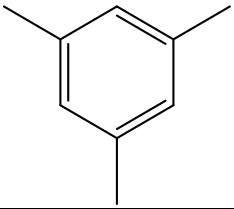
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
12	(1a*S*,7*S*,7b*R*)-1,1,7-trimethylspiro[2,3,4a,5,6,7,7a,7b-octahydro-1aH-cyclopropa[e]azulene-4,2'-oxirane]	Allo-Aromadendrene epoxide		Antiviral
13	(1*R*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene	α-Pinene		Antioxidant, anticancer, genotoxic
14	1-methyl-4-propan-2-ylcyclohexa-1,3-diene	α-terpinene		Antioxidant
15	2-[(1*R*,4*R*,5*R*)-1,8-dimethylspiro[4.5]dec-8-en-4-yl]propan-2-ol	β-acorenol		-
16	(4*E*)-4,11,11-trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene	β-caryophyllene		Anticancer, antioxidant, antimicrobial.

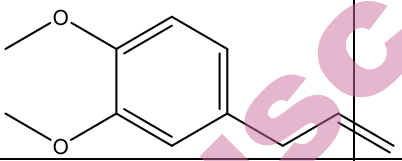
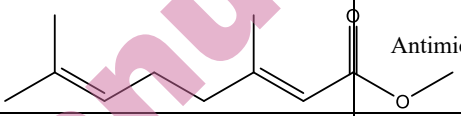
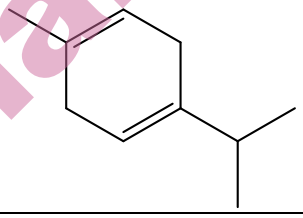
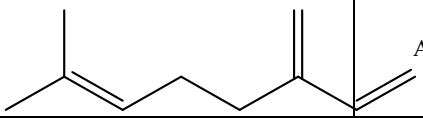
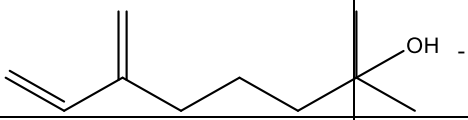
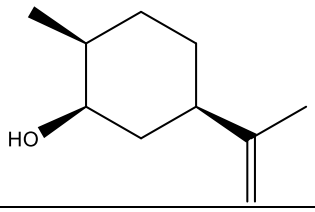
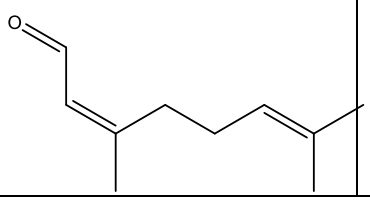
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
17	(6*R*)-5,5,9-trimethyl-1-methylidenespiro[5.5]undec-9-ene	β-chamigrene		-
18	(1*S*,2*S*,4*R*)-1-ethenyl-1-methyl-2,4-bis(prop-1-en-2-yl)cyclohexane	β–elemene		Anticancer
19	3-methylidene-6-(propan-2-yl)cyclohex-1-ene	β-Phellandrene		-
20	6,6-dimethyl-2-methylidenebicyclo[3.1.1]heptane	β-pinene		Anticancer
21	2,2-dimethyl-3-methylidenebicyclo[2.2.1]heptane	Camphene		Antibacterial, antifungal, antioxidant, anticancer

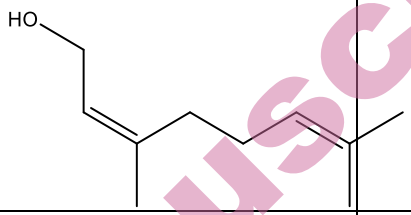
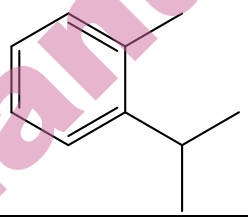
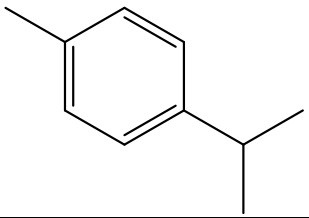
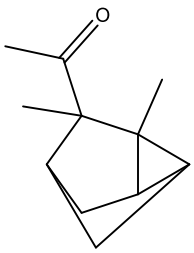
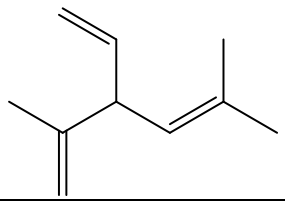
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
22	(1*R*,4*R*,6*R*,10*S*)-4,12,12-trimethyl-9-methylene-5-oxatricyclo[8.2.0.04,6]dodecane	Caryophyllene oxide		Anticancer, analgesic.
23	(1*R*,6*S*)-3-methyl-6-propan-2-ylcyclohex-2-en-1-ol	Cis-piperitol		-
24	1*S*,3*S*,5*S*)-6,6-dimethyl-2-methylidenebicyclo[3.1.1]hept-3-yl acetate	Cis-Pinocarvyl acetate		-
25	[(2*R*,5*S*)-2-methyl-5-propan-2-yl-2-bicyclo[3.1.0]hexanyl] acetate	Cis-sabinene hydrate acetate		-
26	(1*R*,4*R*)-1,4-dimethyl-7-propan-2-ylidene-2,3,4,5,6,8-hexahydro-1H-azulene	Cis-ß-guaiene		-

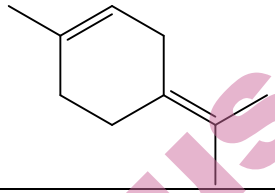
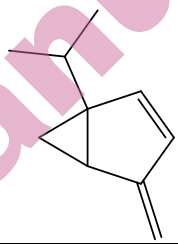
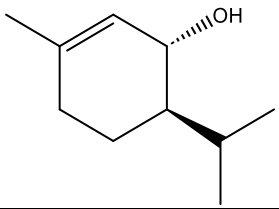
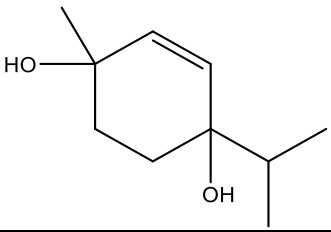
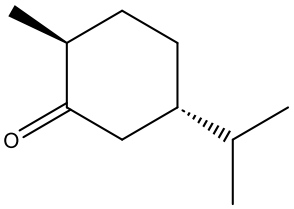
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
27	(2*E*)-6-methyl-5-methylenehept-2-ene	*E*-Salvene		-
28	*E*thyl pent-4-enoate	Ethyl pent-4-enoate		-
29	2-methoxy-4-prop-2-enylphenol	Eugenol		Anticancer
30	(2-methoxy-4-prop-2-enylphenyl) acetate	Eugenol acetate		Anticancer
31	bicyclo[2.2.1]heptan-2-ol	Exo-2-Norborneol		-
32	(2*E*)-3,7-dimethylocta-2,6-dienal	Geranial		Anticancer
33	(2*E*)-3,7-dimethylocta-2,6-dien-1-ol	Geraniol		Anticancer

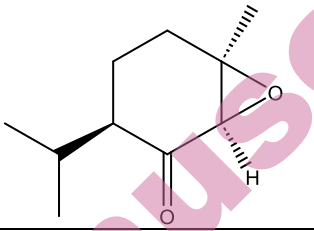
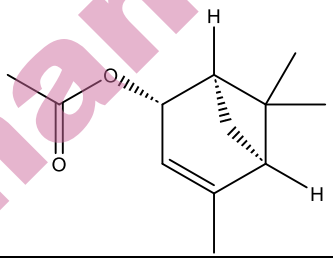
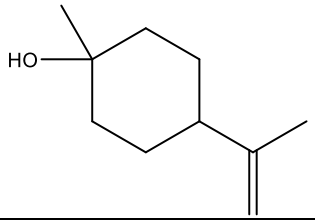
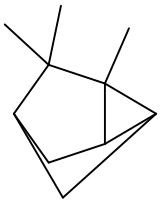
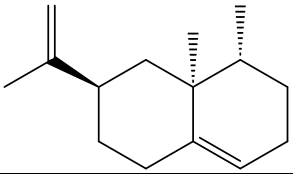
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
34	(2*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate	Geranyl acetate		Antibacterial and antifungal.
35	(2*E*)-3,7-dimethylocta-2,6-dien-1-yl butanoate	Geranyl butanoate		-
36	(2*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-methylpropanoate	Geranyl isobutanoate		-
37	(2*E*)-3,7-dimethylocta-2,6-dien-1-yl formate	Geranyl formate		-
38	(1*E*,6*E*,8*S*)-1-methyl-5-methylidene-8-propan-2-ylcyclodeca-1,6-diene	Germacrene D		Antibacterial, antifungal, anti-inflammatory
39	[(1*R*,2*S*,5*S*,8*R*)-7,7-dimethyl-6-methylidene-2-tricyclo[6.2.1.0^{1,5}]undecanyl]methanol	Khusimol		-

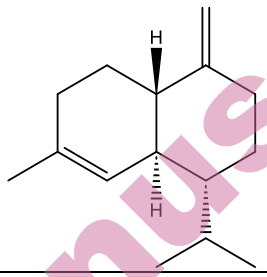
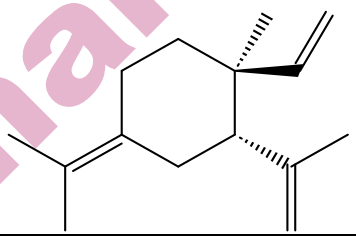
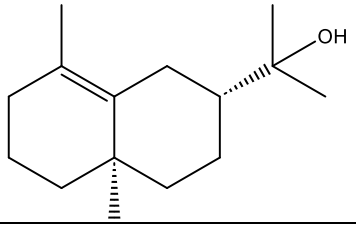
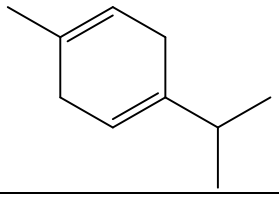
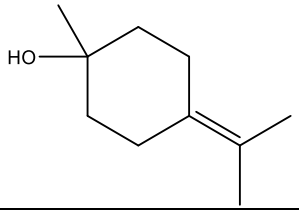
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
40	1,1,4,7-tetramethyl-2,3,4*a*,5,6,7,7*a*,7*b*-octahydro-1*aH*-cyclopropa[e]azulen-4-ol	Ledol		-
41	1-methyl-4-prop-1-en-2-ylcyclohexene	Limonene		Antioxidant, antigenotoxic, anti-inflammatory
42	3-(4-methylcyclohex-3-en-1-yl)butanal	Limonene aldehyde		-
43	(3*R*)-3,7-dimethylocta-1,6-dien-3-ol	Linalool		Anti-inflammatory, anticancer, antimicrobial, contraceptive, analgesic, anxiolytic, antidepressant
44	1,3,5-trimethylbenzene	Mesitylene		-

No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
45	1,2-dimethoxy-4-prop-2-enylbenzene	Methyl eugenol		Anticancer
46	methyl (2*E*)-3,7-dimethylocta-2,6-dienoate	Methyl geranate		Antimicrobial.
47	1-methylcyclohexa-1,4-diene	1-methylcyclohexa-1,4-diene		-
48	7-methyl-3-methyleneocta-1,6-diene	Myrcene		Analgesic
49	2-methyl-6-methylideneoct-7-en-2-ol	Myrcenol		-
50	2-methyl-5-prop-1-en-2-ylcyclohexan-1-ol	Neoisodihydro carveol		-
51	(2*Z*)-3,7-dimethylocta-2,6-dienal	Neral		Anticancer

No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
52	(2*Z*)-3,7-dimethylocta-2,6-dien-1-ol	Nerol		Anticancer
53	1-methyl-2-(propan-2-yl)benzene	o-Cymene		Antimicrobial.
54	1-methyl-4-(propan-2-yl)benzene	p-Cymene		Antimicrobial.
55	1-{2,3-dimethyltricyclo[2.2.1.0^{2,6}]heptan-3-yl}ethan-1-one	Santalone		Analgesic.
56	3-ethenyl-2,5-dimethylhexa-1,4-diene	Santolina triene		Anti-inflammatory, antioxidant y antibacterial

No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
57	1-methyl-4-(propan-2-ylidene)cyclohex-1-ene	Terpinolene		-
58	1-Isopropyl-4-methylenebicyclo[3.1.0]hex-2-ene	Thuja-2,4(10)-diene		-
59	(1*S*,6*S*)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-ol	Trans piperitol		Antifungal
60	2-Cyclohexene-1,4-diol, 1-methyl-4-(1-methylethyl)-	Trans-ascaridol glycol		Antioxidant.
61	(2*R*,5*R*)-2-methyl-5-prop-1-en-2-ylcyclohexan-1-one	Trans-dihydrocarvone		Antioxidant.

No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
62	(1*R*,3*R*,6*R*)-6-methyl-3-propan-2-yl-7-oxabicyclo[4.1.0]heptan-2-one	Trans-Piperitone epoxide		Antioxidant, antibacterial.
63	[(1*R*,2*S*,5*R*)-4,6,6-trimethyl-2-bicyclo[3.1.1]hept-3-enyl] acetate	Trans-verbenyl acetate		-
64	1-Methyl-4-(1-methylvinyl)cyclohexan-1-ol	Trans-β-pterpineol		-
65	1,7,7-trimethyltricyclo[2.2.1.0²,⁶]heptane.	Tricyclene		Antioxidant.
66	(3*R*,4a*S*,5*R*)-4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalene	Valencene		-

No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
67	(1*S*,4a*R*,8a*R*)-7-Methyl-4-methylidene-1-(propan-2-yl)-1,2,3,4,4a,5,6,8a-octahydronaphthalene	γ-Cadinene		Antioxidant.
68	(1*S*,2*S*)-1-ethenyl-1-methyl-4-propan-2-ylidene-2-prop-1-en-2-ylcyclohexane	γ-Elemene		Larvicide.
69	(2-[(2*R*,4*aR*)-4*a*,8-dimethyl-2,3,4,5,6,7-hexahydro-1*H*-naphthalen-2-yl]propan-2-ol	γ-eudesmol		Antioxidant, Antimicrobial.
70	1-methyl-4-propan-2-ylcyclohexa-1,4-diene	γ-terpinene		Anticancer, antibacterial, Antifungal.
71	1-methyl-4-propan-2-ylidenecyclohexan-1-ol	γ-terpineol		Anticancer

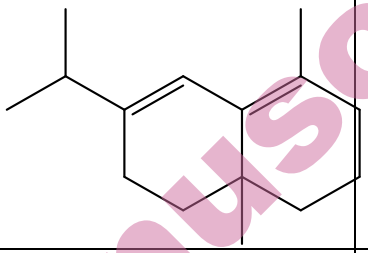
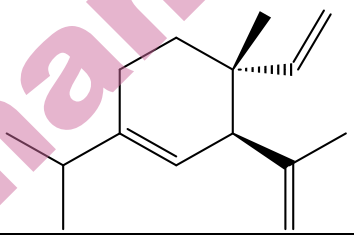
No.	IUPAC Name Metabolite[3]	Common name Metabolite	Structure	Biological properties
72	4,8*a*-dimethyl-6-propan-2-yl-2,3,7,8-tetrahydro-1*H*-naphthalene	δ-selinene		-
73	4-ethenyl-4-methyl-1-propan-2-yl-3-prop-1-en-2-ylcyclohexene	δ-elemene		Anticancer

Table S-2. Nomenclature of terms used in the manuscript

Term	Description
BCL-2	B-cell lymphoma 2
BH3	Bcl-2 Homology 3
BAX	Bcl-2-associated X protein
BH4	Bcl-2 Homology 4
Raf-1	Raf-1 proto-oncogene, serine/threonine kinase
c-Myc	cellular Myelocytomatosis oncogene
IP3R	Inositol 1,4,5-trisphosphate receptor
His20	Histidine at position 20
Tyr21	Tyrosine at position 21
His94	Histidine at position 94
Val93	Valine at position 93
Ile14	Isoleucine at position 14
Tyr9	Tyrosine at position 9
Lys17	Lysine at position 17
Tyr18	Tyrosine at position 18
	Quantum Mechanics / Molecular Mechanics,
IG5M	PDB ID of BCL-2
Ile14	isoleucine amino acid residue at position 14
Tyr9	Tyrosine residue at position 9
Val93	Valine amino acid residue at position 93
His94	Histidine residue at position 94
PM6	Parametric Method 6
DFT	Density Functional Theory
UFF	Universal Force Field (UFF)

Table S-3. Results of Lipinski's Rule of Five Analysis for the 73 Evaluated Metabolites

Compound	PM ≤500	MLOGP ≤ 4.15	N or O ≤ 10	NH or OH ≤ 5
2,3,4,5,6,7,9,10,12,14,15,19,22,23,24,25,26,27,28,29, 30,31,32,33,34,35,36,37,39,40, 41,42,43,45,46,47,48,49,50, 51,52,55,56, 57,58,59,60,61,62,63,64,69,70,71	✓	✓	✓	✓
1,8,11,13,15,16,17,18,20,21,38,44,53,54,65,66,67,68,72,73				✓

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2. P. T. de Souza Silva, L. M. de Souza, M. B. de Morais, M. M. de Moraes, C. A. G. da Camara, C. Ulisses, *South African J. Bot.* **147** (2022) 415–424 (http://dx.doi.org/10.1016/j.sajb.2022.01.042)
3. Lexichem TK 2.7.0, (2025). https://docs.eyesopen.com/toolkits/python/lexichemtk/index.html#. Accessed July 28, 2025.