

Supplementary Materials: Mechanistic Insights into Biological Activities of Polyphenolic Compounds from Rosemary Obtained by Inverse Molecular Docking

Samo Lešnik and Urban Bren

Table S1. Best docking scores of ligands/drugs known to bind to a specific target.

PDB ID with chain	Ligand ID	Predicted ligand docking score (arb. units)
4lucB	M1X	−79,52
3oojA	G6P	−50,66
1kenA	75U	−47,43
4jd6C	TOY	−68,64
3mt7A	16O	−58,29
3rycC	LOC	−41,68
2p2hA	STI	−50,02
2d1jA	D01	−58,50
2jt5A	JT5	−66,79
4jzbA	P2H	−51,53
3qmuB	B1T	−35,91
5fi6A	04A	−61,02

Table S2. Best docking scores for carnosol, carnosic acid and rosmannol.

PDB ID with chain	Ligand	Predicted ligand docking score (arb. units)	Protein name	Organism
5ilhA	carnosol	−70.6	5-epi-aristolochene synthase	<i>Nicotiana tabacum</i>
4lucB*	carnosic acid	−69.9	K-Ras G12C	<i>Homo sapiens</i>
1g0hA	carnosol	−69.0	Inositol monophosphatase	<i>Methanocaldococcus jannaschii</i>
5ilhA	rosmannol	−68.5	5-epi-aristolochene synthase	<i>Nicotiana tabacum</i>
3oojA*	carnosic acid	−68.2	Glucosamine-fructose-6-phosphate aminotransferase	<i>Escherichia coli</i>
3srdD*	carnosic acid	−68.1	Pyruvate kinase M2	<i>Homo sapiens</i>
3bjtC	carnosic acid	−67.6	Pyruvate kinase M2	<i>Homo sapiens</i>
2w27A	rosmannol	−66.9	YKUI protein	<i>Bacillus subtilis</i>
1kenA*	carnosic acid	−66.9	Hemagglutinin HA1	<i>Influenza A virus</i>
4qg8D	carnosic acid	−66.8	Pyruvate kinase M2	<i>Homo sapiens</i>
3oyrB	rosmannol	−66.7	Trans-isoprenyl diphosphate synthase	<i>Caulobacter vibrioides</i>
4lv6B	carnosic acid	−65.7	K-Ras G12C	<i>Homo sapiens</i>
4lltB	carnosic acid	−65.6	Geranyltranstransferase	<i>Roseobacter denitrificans</i>
1pkmA	carnosic acid	−65.3	Pyruvate kinase M2	<i>Felis catus</i>
3srfE	carnosic acid	−65.1	Pyruvate kinase M2	<i>Homo sapiens</i>
3u2zA	carnosic acid	−65.0	Pyruvate kinase M2	<i>Homo sapiens</i>
2hpeA*	carnosic acid	−65.0	HIV-2 protease	<i>Human immunodeficiency virus 2</i>

2uulK	carnosic acid	−65.0	C-phycocyanin	<i>Phormidium sp.</i>
5v6vA	carnosic acid	−64.9	K-Ras G12C	<i>Homo sapiens</i>
4jd6C*	carnosic acid	−64.8	Enhanced intracellular survival protein	<i>Mycobacterium tuberculosis</i>
5u46A*	carnosic acid	−64.7	Peroxisome proliferator activated receptor delta	<i>Homo sapiens</i>
4ffbA	carnosic acid	−64.5	Tubulin	<i>Saccharomyces cerevisiae</i>
3mt7A*	carnosic acid	−64.5	Glycogen phosphorylase	<i>Oryctolagus cuniculus</i>
5x1vA	carnosic acid	−64.2	Pyruvate kinase M2	<i>Homo sapiens</i>
5x1vB	carnosic acid	−64.2	Pyruvate kinase M2	<i>Homo sapiens</i>
3rycC*	carnosic acid	−64.2	Tubulin	<i>Rattus norvegicus</i>
5x1vD	carnosic acid	−64.1	Pyruvate kinase M2	<i>Homo sapiens</i>
4o4lA	carnosic acid	−64.0	Tubulin	<i>Bos taurus</i>
5v0tA	carnosic acid	−63.9	Trehalose-phosphate synthase	<i>Paraburkholderia xenovorans</i>
4wj8A	carnosic acid	−63.9	Pyruvate kinase M2	<i>Homo sapiens</i>
4rppB	carnosic acid	−63.9	Pyruvate kinase M2	<i>Homo sapiens</i>
3cdxE	rosmannol	−63.7	Succinylglutamatedesuccinylase/aspartoacylase	<i>Cereibacter sphaeroides</i>
3cdxE	carnosic acid	−63.6	Succinylglutamatedesuccinylase/aspartoacylase	<i>Cereibacter sphaeroides</i>
4o4iA	carnosic acid	−63.6	Tubulin	<i>Bos taurus</i>
3bjtB	carnosic acid	−63.5	Pyruvate kinase M2	<i>Homo sapiens</i>
2ps1A	carnosic acid	−63.5	Orotate phosphoribosyltransferase 1	<i>Saccharomyces cerevisiae</i>
2j9kB	carnosic acid	−63.5	HIV-1 protease	<i>Human immunodeficiency virus 1</i>
1fxfB*	carnosol	−63.3	Phospholipase A2	<i>Sus scrofa</i>
3ogpA*	carnosic acid	−63.3	FIV protease	<i>Felis catus</i>
4i50C	carnosic acid	−63.2	Tubulin	<i>Bos taurus</i>
3h6oA	carnosic acid	−63.1	Pyruvate kinase M2	<i>Homo sapiens</i>
2p2hA*	carnosic acid	−63.1	Vascular endothelial growth factor receptor 2	<i>Homo sapiens</i>
5ilqC*	carnosic acid	−63.0	Aspartate carbamoyltransferase	<i>Plasmodium falciparum</i>
3h6oC	carnosic acid	−63.0	Pyruvate kinase M2	<i>Homo sapiens</i>
5jqgA	carnosic acid	−63.0	Tubulin	<i>Sus scrofa</i>
3h6oB	carnosic acid	−63.0	Pyruvate kinase M2	<i>Homo sapiens</i>
4iv5A*	carnosic acid	−62.8	Aspartate carbamoyltransferase	<i>Trypanosoma cruzi</i>
1mrxB	carnosic acid	−62.8	Hiv-1 protease	<i>Human immunodeficiency virus 1</i>
3fpfA	carnosic acid	−62.8	Uncharacterized protein	<i>Methanothermobacter thermoautotrophicus</i>

* Is described in the main text.

Table S3. Best docking scores for rosmarinic acid.

PDB ID with chain	Predicted lig- and docking score (arb. units)	Protein name	Organism
2d1jA*	−86.1	Factor Xa	<i>Homo sapiens</i>
1fxfB*	−84.8	Phospholipase A2	<i>Sus scrofa</i>
2jt5A*	−84.5	Matrix metalloproteinase 3	<i>Homo sapiens</i>
4jzbA*	−83.2	Farnesyl pyrophosphate synthase	<i>Leishmania major</i>
2w27A	−80.9	YKUI protein	<i>Bacillus subtilis</i>

3qmuB*	-80.2	Glutamate dehydrogenase 1	<i>Bos taurus</i>
3qxB	-79.3	Inorganic pyrophosphatase	<i>Bacteroides thetaiotaomicron</i>
4jzxA	-79.1	Farnesyl pyrophosphate synthase	<i>Leishmania major</i>
3m1rC	-78.8	Formimidoylglutamase	<i>Bacillus subtilis</i>
5fi6A*	-78.6	Glutaminase	<i>Homo sapiens</i>

* Is described in the main text.

Table S4. Interactions of carnosic acid with K-Ras.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Glu62-A	3.81
Tyr96-A	3.29
Gln99-A	2.74
<i>Hydrogen bonds</i>	
Thr58-A	3.45
Ala59-A	3.86
Gly60-A	3.52
<i>Salt bridge</i>	
Arg68-A	4.10

Table S5. Interactions of carnosic acid with glucosamine/fructose-6-phosphate aminotransferase.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Val399-A	3.87
Leu601-A	3.69
Val605-A	3.92
<i>Hydrogen bonds</i>	
Thr302-A	3.01
Ser303-A	3.23
Ser401-A	2.73
<i>Salt bridge</i>	
Lys603-A	2.96

Table S6. Interactions of carnosic acid with Pyruvate kinase 2 – muscle isoform.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Phe-26-B	3.78
Asn-350-B	3.90
Leu-353-B	3.55
Leu353-D	3.84
Ile389-D	3.79
Tyr390-D	3.72
Leu394-D	3.71
<i>Hydrogen bonds</i>	
Asn350-B	3.38
Asp354-D	2.49
<i>Salt bridge</i>	

Lys311-D	3.42
<i>π-stacking</i>	
Phe26-B	5.10

Table S7. Interactions of carnosic acid with Hemagglutinin HA1.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Val55-D	3.92
Trp92-D	3.69
Glu97-B	3.73
Leu99-D	3.70
Pro293-C	3.53
Phe294-C	3.52
Lys307-C	3.96
<i>Hydrogen bonds</i>	
Thr59-D	3.33
Lys307-C	2.86
Lys310-A	2.91

Table S8. Interactions of carnosic acid with HIV-2 protease.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Ala28-A	3.63
Ala28-B	3.98
Ile32-A	3.77
Val47-A	3.71
<i>Hydrogen bonds</i>	
Ile50-A	3.20

Table S9. Interactions of carnosic acid with enhanced intra-cellular survival protein.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Phe24-C	3.83
Ile28-C	3.74
Trp36-C	3.85
Phe84-C	3.61
Val85-C	3.92
Leu118-C	3.76
<i>Hydrogen bonds</i>	
His119-C	3.05

Table S10. Interactions of carnosic acid with Peroxisome proliferator-activated receptor δ .

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Phe190-A	3.83
Met192-A	3.74
Thr252-A	3.90
Glu255-A	3.94

Met293-A	3.77
Ile297-A	3.71
<i>Hydrogen bonds</i>	
Asn191-A	2.98
Met192-A	2.88
Glu259-A	3.20

Table S11. Interactions of carnosic acid glycogen phosphorylase.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Leu139-A	3.61
Asp283-A	3.53
Val455-A	3.25
Arg569-A	3.80
<i>Hydrogen bonds</i>	
Lys574-A	2.75
Thr676-A	4.10

Table S12. Interactions of carnosic acid with tubulin.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Gln247-D	3.80
Thr325-D	3.98
<i>Hydrogen bonds</i>	
Pro175-C	2.73
Ser178-C	3.59

Table S13. Interactions of carnosic acid with HIV-1 protease.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Ala28-B	3.78
Ile48-B	3.53
Ile50-A	3.95
<i>Hydrogen bonds</i>	
Asp25-A	4.04
Asp29-B	3.18
<i>Salt bridge</i>	
Arg8-A	3.99

Table S14. Interactions of carnosol with Phospholipase A2.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Leu18-A	3.79
Leu2-B	3.24
Phe5-B	3.73
Arg6-B	3.90
Pro18-B	3.17
Leu19-B	3.56

Phe22-B	3.95
Leu31-B	3.78
Tyr69-B	3.77
<i>Hydrogen bonds</i>	
Tyr69-B	2.89

Table S15. Interactions of carnosic acid with FIV protease.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Ile57-B	3.82
Ile59-B	3.73
<i>Hydrogen bonds</i>	
Asp29-B	2.80

Table S16. Interactions of carnosic acid vascular endothelial growth factor receptor 2

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Ile1025-A	2.94
His1026-A	2.74
Asp1028-A	3.57
Leu1049-A	3.08
Ala1050-A	3.42
<i>Salt bridges</i>	
Arg1027-A	4.37

Table S17. Interactions of carnosic acid with aspartate carbamoyltransferase (P. falciparum).

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Lys138-A	3.99
<i>Hydrogen bonds</i>	
Ser107-C	3.08
Arg109-C	2.72
110-C	2.73
<i>Salt bridges</i>	
Arg159-C	3.15
His187-C	5.16
<i>π-cation interaction</i>	
Arg109-C	4.81

Table S18. Interactions of carnosic acid with aspartate carbamoyltransferase (T. cruzi).

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Arg64-A	3.96
Asp169-A	3.71
Thr175-A	3.71
Arg242-A	3.84
Pro288-A	3.62
<i>Hydrogen bonds</i>	

Arg113-A	2.85
Arg174-A	3.49
<i>Salt bridges</i>	
Lys92-B	5.00
Arg242-A	3.57

Table S19. Interactions of rosmarinic acid with coagulation factor X.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Tyr99-A	3.62
Gln192-A	3.49
Trp215-A	3.37
Cys220-A	3.47
Tyr228-A	4.66
<i>π-stacking</i>	
Phe174-A	3.84

Table S20. Interactions of rosmarinic acid with phospholipase A2.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Leu2-A	3.92
Phe5-A	3.90
Asn23-A	3.89
Leu31-A	3.97
Asp49-A	3.68
Tyr52-A	3.73
Tyr69-A	3.88
<i>Hydrogen bonds</i>	
Pro18-A	2.71
Gly30-A	2.97
Asp49-A	2.99
Arg53-A	3.49
Tyr-69-A	2.93
<i>Salt bridges</i>	
His48-A	3.61

Table S21. Interactions of rosmarinic acid with matrix metalloproteinase-3.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Leu197-A	3.79
Tyr220-A	4.00
Tyr223-A	3.83
<i>Hydrogen bonds</i>	
Asn162-A	2.94
Ala165-A	3.19
Tyr223-A	2.92
Thr215-A	4.59

Table S22. Interactions of rosmarinic acid with farnesyl pyrophosphate synthase.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Phe94-A	3.55
Leu95-A	3.62
Asp98-A	3.78
Thr163-A	3.44
Gln167-A	3.41
Lys207-A	3.74
Phe246-A	3.82
<i>Hydrogen bonds</i>	
Lys48-A	3.75
Arg51-A	3.84
Asn126-B	3.25
Gln247-A	2.24
<i>Salt bridges</i>	
Arg51-A	4.75
Lys207-A	4.83
<i>π-stacking</i>	
Phe94-A	4.25
<i>π-cation interactions</i>	
Lys264	4.53

Table S23. Interactions of rosmarinic acid with glutamate dehydrogenase 1.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Ile65-B	3.81
Arg66-B	3.85
Lys143-B	3.96
Lys143-C	3.65
Arg146-C	3.80
Arg147-B	3.66
Phe500E	3.53
<i>Hydrogen bonds</i>	
Arg66-B	2.91
Glu142-C	2.74
Lys143-C	2.74
Arg146-C	3.07
Arg147-C	2.88
Thr501-E	2.70
<i>π-stacking</i>	
Phe500-E	4.13

Table S24. Interactions of rosmarinic acid with glutaminase.

Contact residue	Closest contact distance (Å)
<i>Hydrophobic interactions</i>	
Lys319-A	3.60
Lys319-B	3.70
Leu320-A	3.53
Phe321-A	3.75
Leu322-A	3.81
Tyr393-A	3.47
<i>Hydrogen bonds</i>	
Phe321-B	2.77
Leu322-A	3.95
Leu322-B	2.80
Glu324-B	4.08
Asp326-A	3.56
Asp326-B	2.59
Tyr393-B	4.10
<i>π-cation interactions</i>	
Lys319-A	4.59