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Latin american phytochemical derivatives as promising candidates for gallstone disease therapy: insights from Molecular Screening, Molecular Docking, Density Functional Theory, and Molecular Dynamics studies

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Around 15% of latin american adult population suffers from biliary lithiasis.

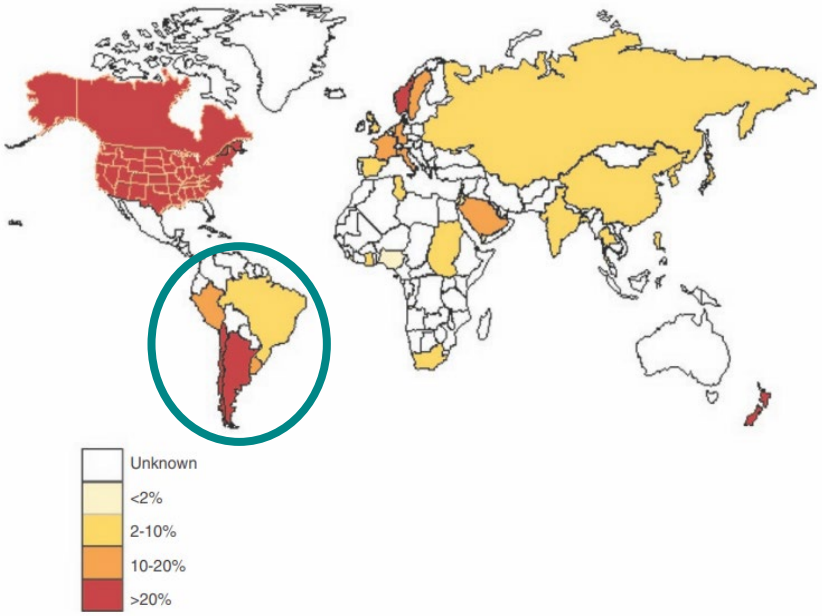


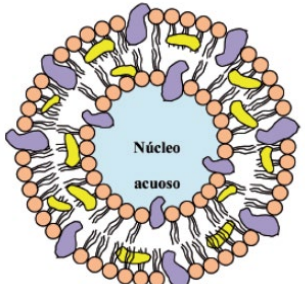
Fig. 3.1 Prevalence of gallstone disease

Continent	Population	Prevalence (%)			Number of participants (*n*)	Study
		Overall	Female	Male		
South America						
	Mapuche Indians		49.4	12.6		Covarrubias 1984[a] [18]
	Argentina	21.9	25.0	18.2	1875	Palermo 2013 [19]
	Peru	14.3	16.0	10.7	1534	Moro 2000 [20]
	Chile	28.0	37.4	14.5	1699	Covarrubias 1995 [21]
	Uruguay	10.4	–	–	693	Cohen 1992 [22]

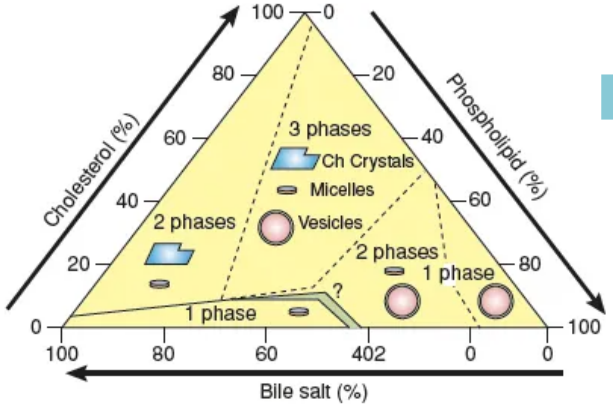
PURPOSE

In Latin american, ancestral knowledge about the natural treatment of diseases involves the use of medicinal plants. However, studies are needed to identify the phytochemicals present in these plants capable of interacting with the agents related to gallstone formation.

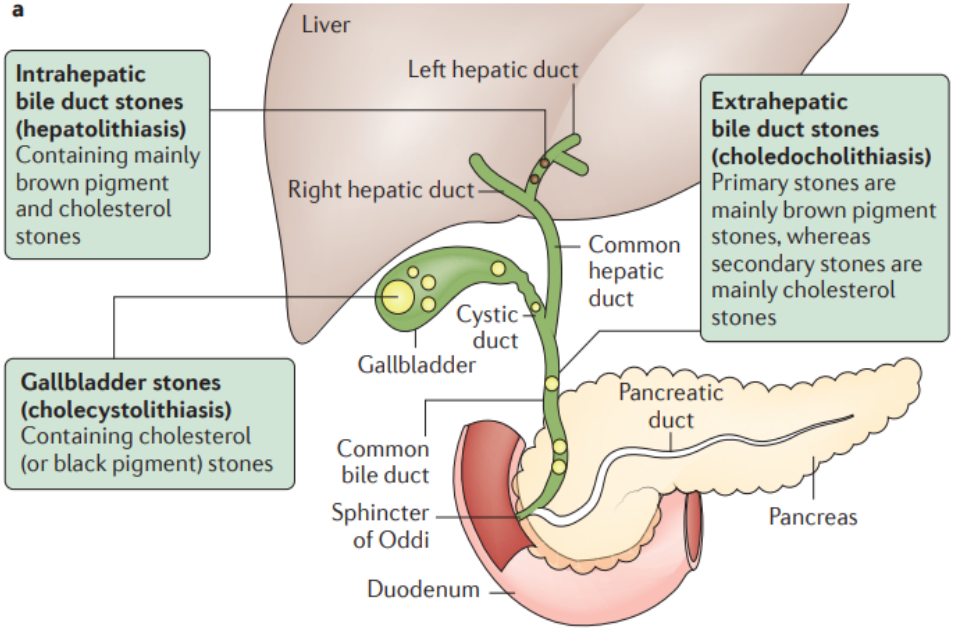
Bile crystallizes when there is an imbalance in the amount of its components, forming gallstones.



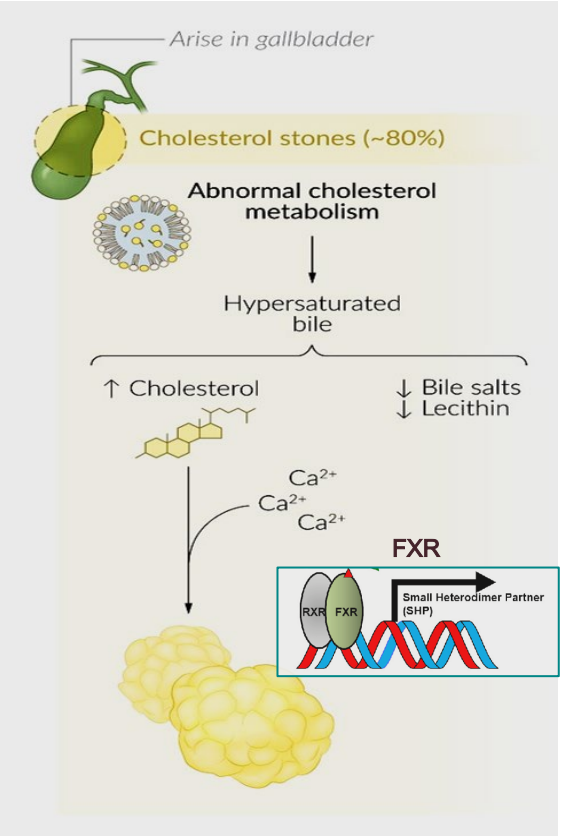
bile salts
phospholipids
cholesterol

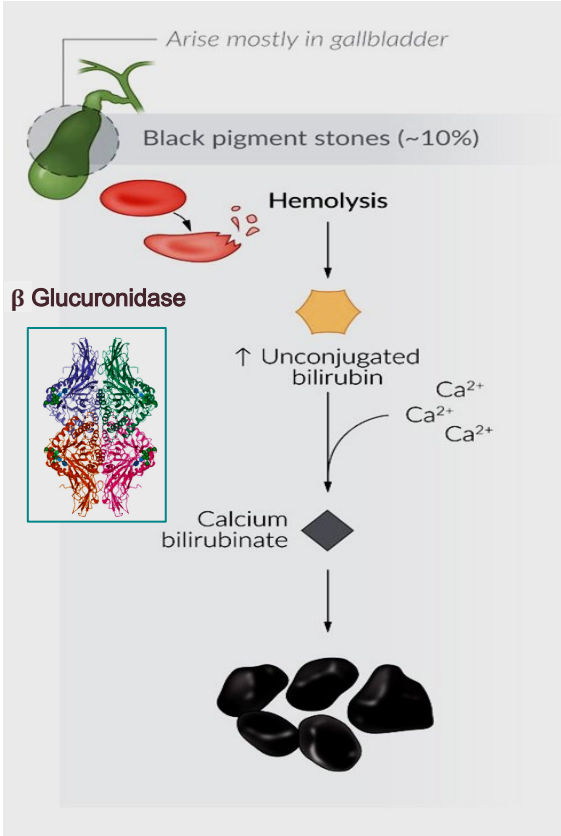


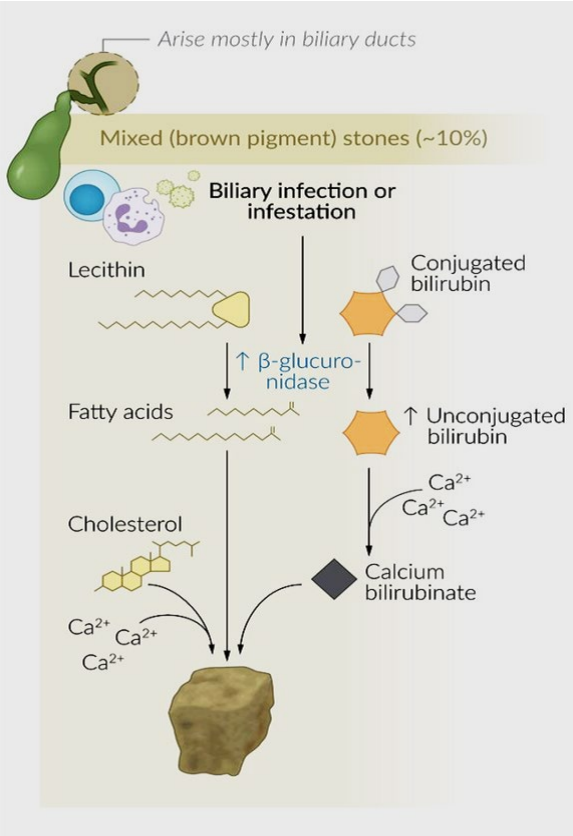
imbalance



FXR receptor modulates yellow stones and β Glucuronidase black stones







Conformations of FXR receptor

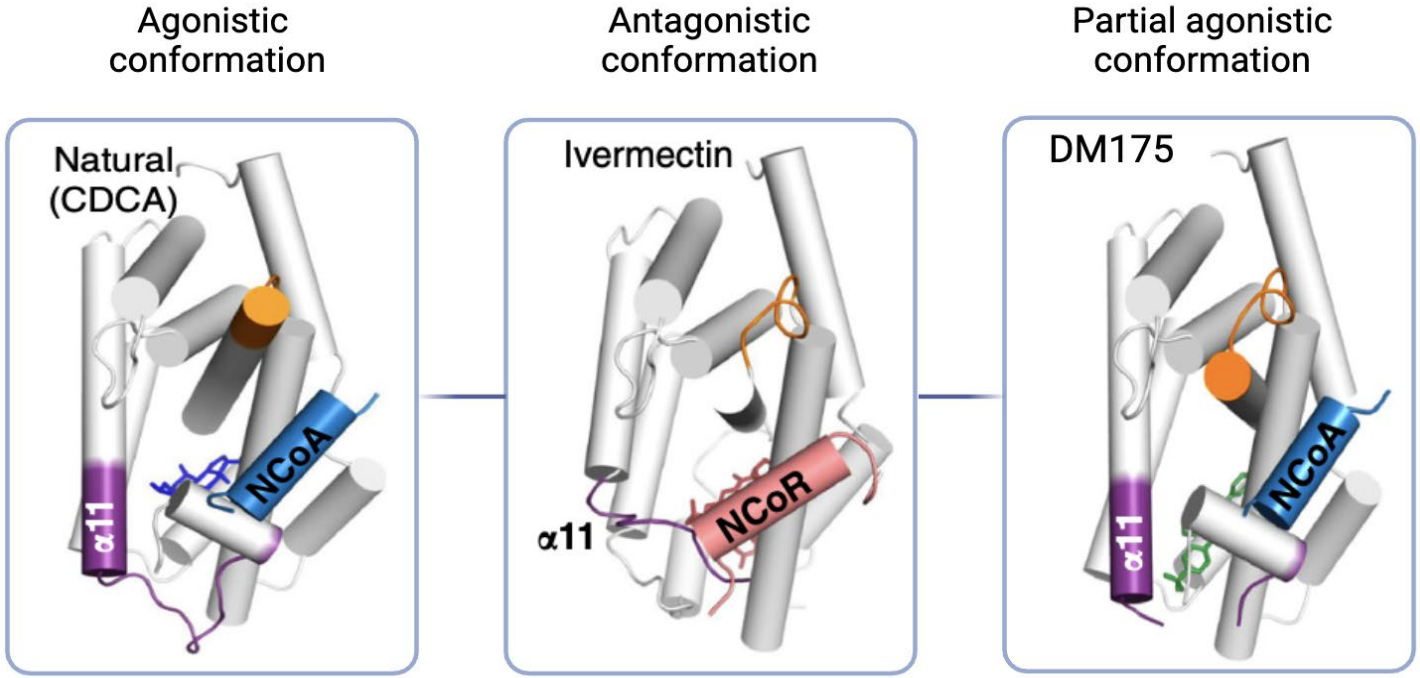
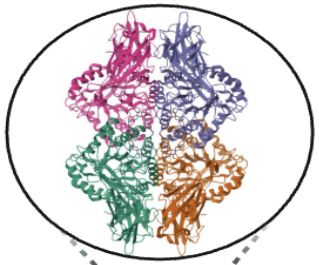
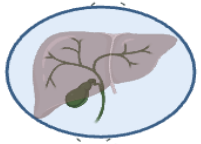


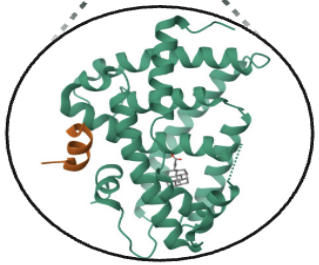
Image taken from: Merk, D., 2019, fig 3. https://doi.org/10.1038/s41467 -019-10853-2

β Glucuronidase Receptor



Cholelithiasis





FXR Receptor

Virtual Molecular Screening

Stage 1
Latin american phytochemical database

NaturAr · PERUNPDB · NuBBE · SISTEMAT · DIFACQUIM · UNIIQUIM

Stage 2
Bioactivity filter

PASS · molinspiration

Stage 3
Molecular docking

fastDRH · NCIPLOT-4.2

Stage 4
Toxicity and pharmacokinetics

ADMETlab 2.0 · PreADMET · SIB · pkCSM

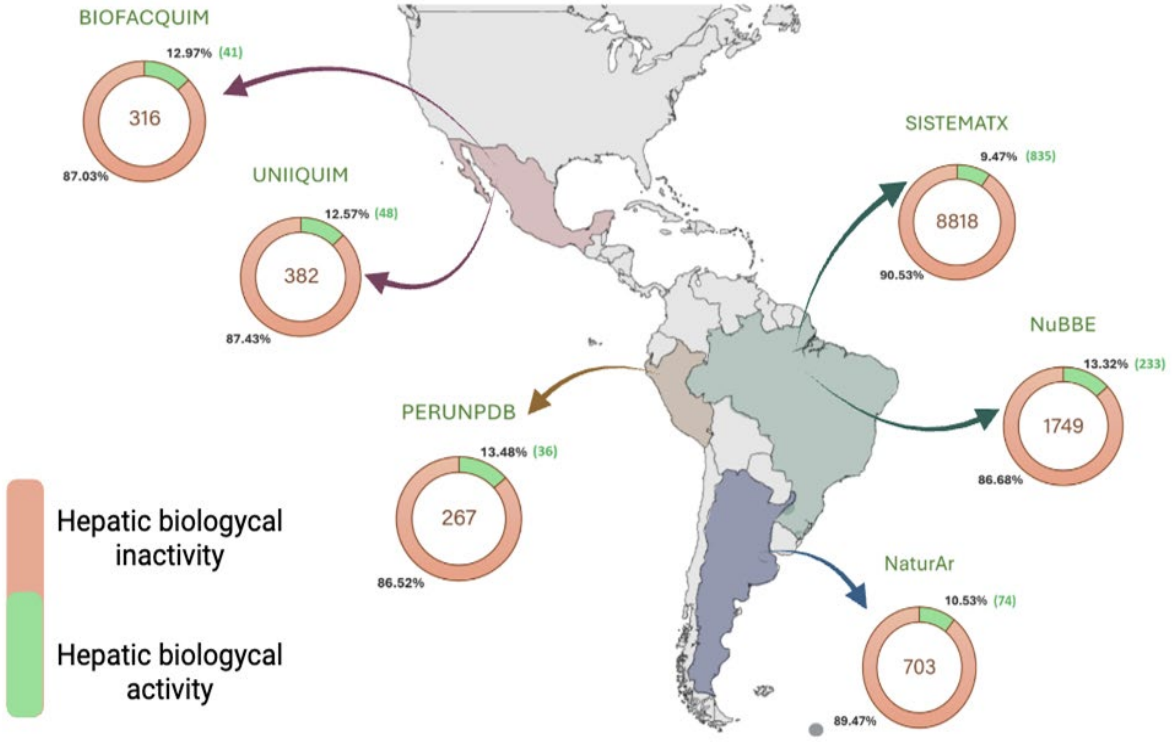
Stage 5
DFT and molecular dynamics

GROMACS · VMD

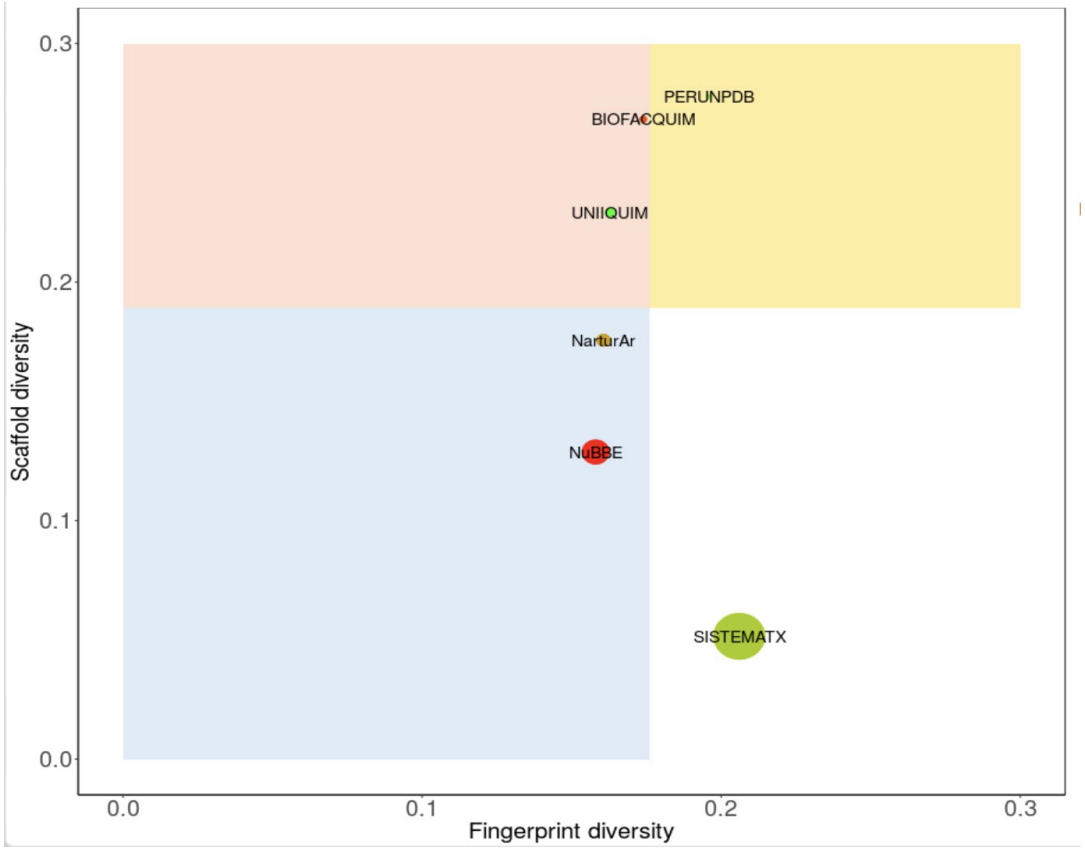
Overal 12 thousand compounds were analyzed

From 9% to 14% of compounds had Hepatic active biological properties

Way2drug	Molinspiration
• Beta glucoronidase inhibitor • Hepatic disorder treatment • Hepatoprotectant	• Nuclear Receptor Ligand
Activity > 0.5 Activity > inactivity	Score > - 0.5



Diversity of compounds with hepato -active biological response



Euclidean distances

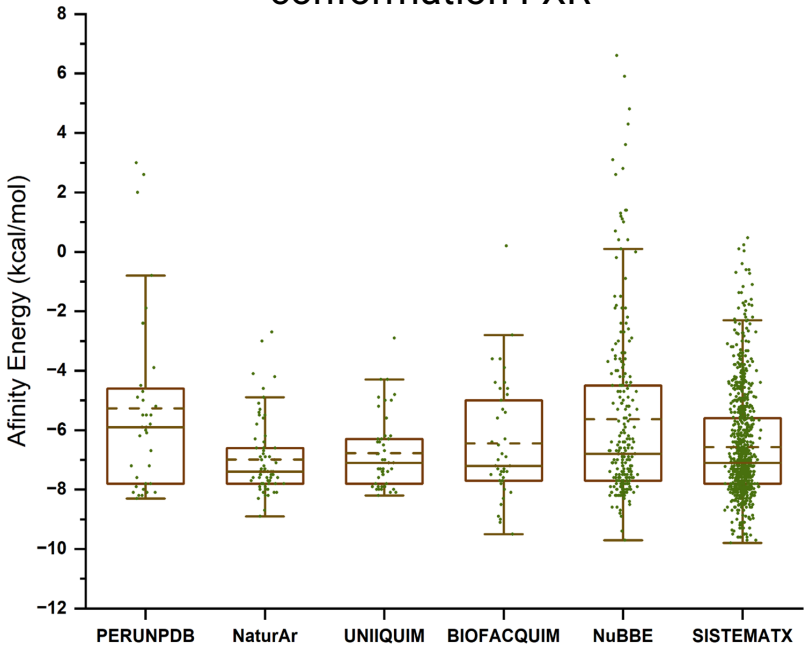
2.6 2.8 3.0 3.2 3.4

Liver Bioactive Phytochemicals Database Size

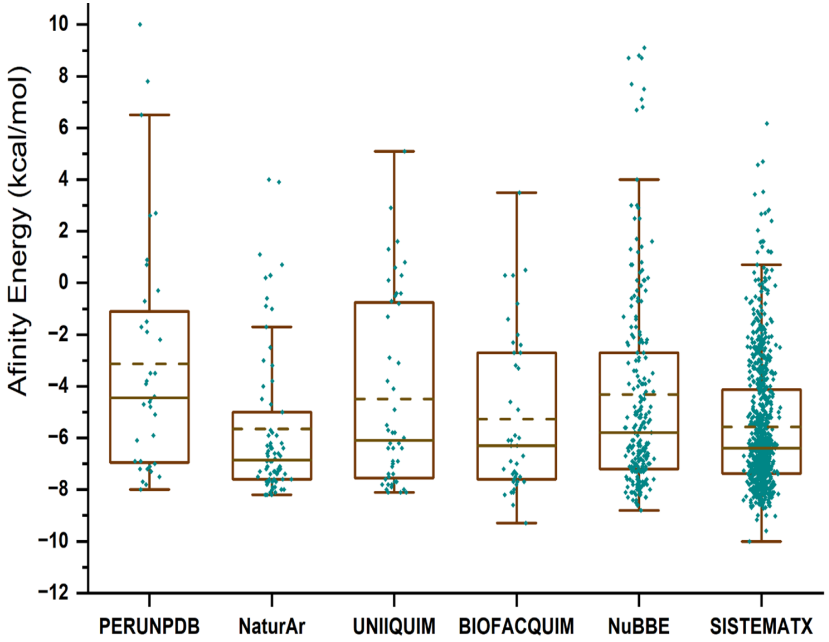
36
41
48
74
233
835

Energetic distribution of compounds per dataset for the FXR receptor

database sets vs **agonist** conformation FXR

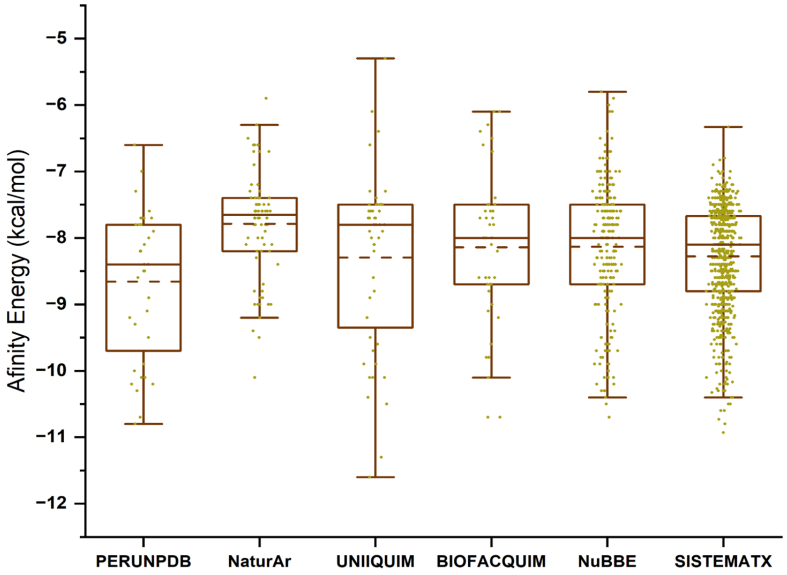


database sets vs **partial agonist** conformation FXR



Energetic distribution of compounds per dataset for the FXR receptor

database sets vs **antagonist**
conformation FXR



Top 10 potential phytochemical agonists

	Phytochemical	FXR in agonistic conformation	FXR in partial agonistic conformation	FXR in antagonistic conformation	B-glucuronidase	FXR agonistic conformation and B-glucuronidase
		Mean AE (kcal/mol)	Mean AE (kcal/mol)	Mean AE (kcal/mol)	Mean AE (kcal/mol)	Sum of AE (kcal/mol)
	CDCA	-11.5	-6.9	-8.3	-7.5	-19.0
1	NuBBE_1313	-8.6	-8.1	-8.2	-9.5	-18.1
2	SISTEMATX_15470	-9.6	-9	-8.7	-8.2	-17.8
3	SISTEMATX_549	-8.9	-6.9	-8.1	-8.6	-17.5
4	SISTEMATX_16776	-9.8	-7.3	-7.8	-7.6	-17.4
5	FQNP354	-9.5	-6.9	-7.9	-7.9	-17.4
6	SISTEMATX_13206	-9.6	-7.7	-8.8	-7.7	-17.3
7	SISTEMATX_14687	-9.3	-5.5	-8.6	-7.9	-17.2
8	FQNP108	-8.9	-8.1	-8.5	-8.3	-17.2
9	SISTEMATX_17444	-9.0	-2.1	-8.7	-8.2	-17.2
10	SISTEMATX_14474	-8.7	-4.5	-8.1	-8.5	-17.2

Top 10 potential phytochemical as partial agonists

	Phytochemical	FXR in agonistic conformation	FXR in partial agonistic conformation	FXR in antagonistic conformation	B-glucuronidase	FXR agonistic conformation and B-glucuronidase
		Mean AE (kcal/mol)	Mean AE (kcal/mol)	Mean AE (kcal/mol)	Mean AE (kcal/mol)	Sum of AE (kcal/mol)
	DM175	-8.7	-8.9	-8.5	-8.1	-17.0
1	SISTEMATX_14736	-9.3	-9.6	-9.1	-9	-18.6
2	SISTEMATX_15108	-6.2	-8.5	-8.3	-9.5	-18.0
3	SISTEMATX_15178	-6.4	-8.6	-8.5	-8.9	-17.5
4	SISTEMATX_19255	-9	-10	-8.3	-7.4	-17.4
5	SISTEMATX_15370	-7.8	-8.4	-7.7	-8.7	-17.1
6	SISTEMATX_14651	-8.6	-9	-8.1	-7.9	-16.9
7	NuBBE_1305	-8.7	-8.8	-8.2	-8.1	-16.9
8	NuBBE_2395	-8.6	-8.6	-8.4	-8.2	-16.9
9	NuBBE_1323	-8.4	-8.6	-8.4	-8.2	-16.8
10	SISTEMATX_16701	-8.6	-9.2	-7.8	-7.4	-16.6

Top 10 potential phytochemical derivatives as agonists/partial agonists

Class	Derivative ID	FXR in agonistic conformation	FXR in partial agonistic conformation	FXR in antagonistic conformation	B-glucuronidase	FXR agonistic conformation and B-glucuronidase
		Mean AE (kcal/mol)	Mean AE (kcal/mol)	Mean AE (kcal/mol)	Mean AE (kcal/mol)	Sum of AE (kcal/mol)
Potential FXR agonist	CDCA	-11.5	-6.9	-8.3	-7.5	-19.0
	A_23	-9.80	-8.43	-8.70	-8.98	-18.8
	A_31	-10.00	-7.70	-7.90	-8.53	-18.5
	A_37	-9.33	-8.10	-8.70	-8.71	-18.0
	A_8	-9.20	-7.20	-8.20	-8.20	-17.4
	A_85	-9.03	-7.23	-8.50	-8.26	-17.3
Potential FXR partial agonist	DM175	-8.7	-8.9	-8.5	-8.1	-17.0
	A_79	-8.70	-10.20	-8.30	-9.07	-19.3
	A_14	-8.60	-10.00	-8.50	-9.03	-19.0
	A_65	-9.03	-9.43	-8.80	-9.09	-18.5
	A_83	-8.20	-9.40	-8.73	-8.78	-18.2
	A_10	-8.80	-9.10	-8.70	-8.87	-18.0

Ligand efficiency table of the phytochemical derivatives as potential agonists/partial agonists

Derivative ID	Name_File	Ebind (kcal/mol)	Kd	LE (kcal/mol)	BEI (kDa)	LLE	MM/PB(GB)SA (kcal/mol)	
							PB4	GB8
Potential FXR agonist	A_31	-10.0	4.69E-08	0.40	21.03	2.62	-52.16	-52.6
	A_23	-9.8	6.57E-08	0.35	18.54	3.90	-46.64	-50.5
	A_37	-9.5	1.09E-07	0.34	18.21	4.44	-37.97	-43.15
	A_8	-9.2	1.81E-07	0.38	20.47	3.61	-39.24	-42.49
	A_85	-9	2.54E-07	0.32	17.20	3.34	-43.85	-48.44
Potential FXR partial agonist	A_79	-10.2	3.35E-08	0.39	20.62	2.81	-47.94	-49.78
	A_14	-10.0	4.69E-08	0.43	23.39	5.33	-36.27	-39.66
	A_65	-9.4	1.29E-07	0.36	19.55	4.76	-39.71	-43.72
	A_83	-9.4	1.29E-07	0.35	18.65	3.50	-51.42	-53.24
	A_10	-9.1	2.14E-07	0.40	21.15	3.48	-42.41	-44.34

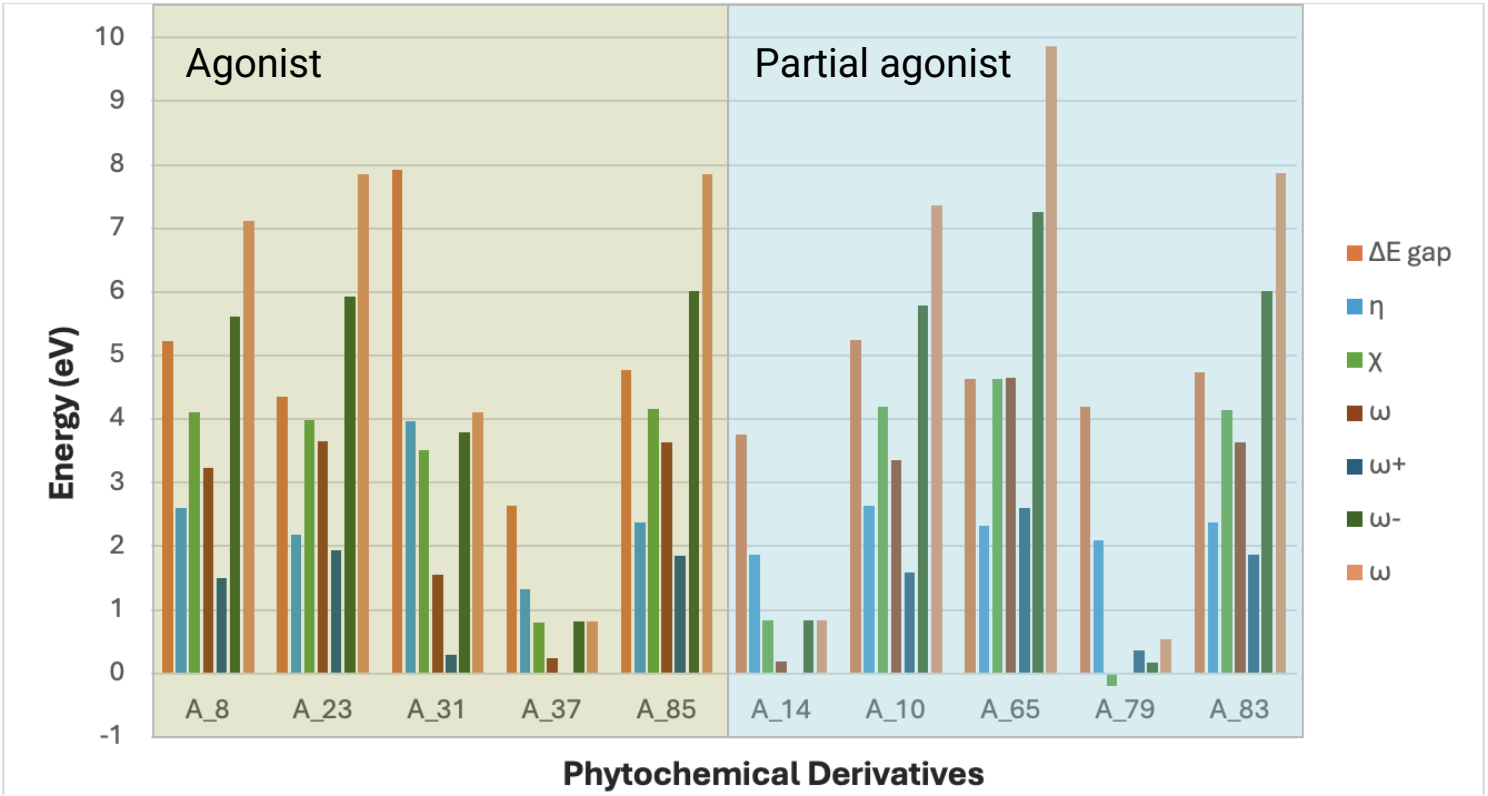
Pharmacokinetics of Top 10 derivatives

Class	Derivative ID	Absorption			Distribution			Metabolism					Excretion	
		HI (%)	Pgp Inhibitor	Caco-2 (nm/sec)	%PPB	BBB (C.brain/ C.blood)	VD (L/Kg)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	CL (mL/min/Kg)	T1/2 (min)
Potential FXR agonist	A_8	98.48	Non	22.06	88.02	0.26	1.742	No	No	No	No	No	3.91	308.83
	A_23	95.49	Non	22.14	57.36	0.01	1.449	No	No	No	No	No	2.53	397.06
	A_31	95.33	Yes	24.48	97.00	2.51	0.938	No	No	Yes	No	No	3.90	166.63
	A_37	84.69	Non	20.54	76.76	0.02	0.629	No	No	No	No	No	0.97	450.31
	A_85	96.71	Non	19.10	64.41	0.01	1.548	No	No	No	No	No	2.31	464.20
Potential FXR partial agonist	A_10	94.77	Non	12.84	46.16	0.01	1.358	No	No	No	No	No	2.08	452.67
	A_14	89.94	Non	0.57	74.10	0.01	0.532	No	No	No	No	No	1.17	314.30
	A_65	92.07	Non	14.36	88.74	0.11	0.419	Yes	No	No	No	No	8.74	33.21
	A_79	98.00	Yes	21.61	95.94	0.07	0.521	No	No	Yes	No	No	1.21	297.90
	A_83	96.24	Non	21.38	59.82	0.02	1.396	No	No	No	No	No	2.13	454.40

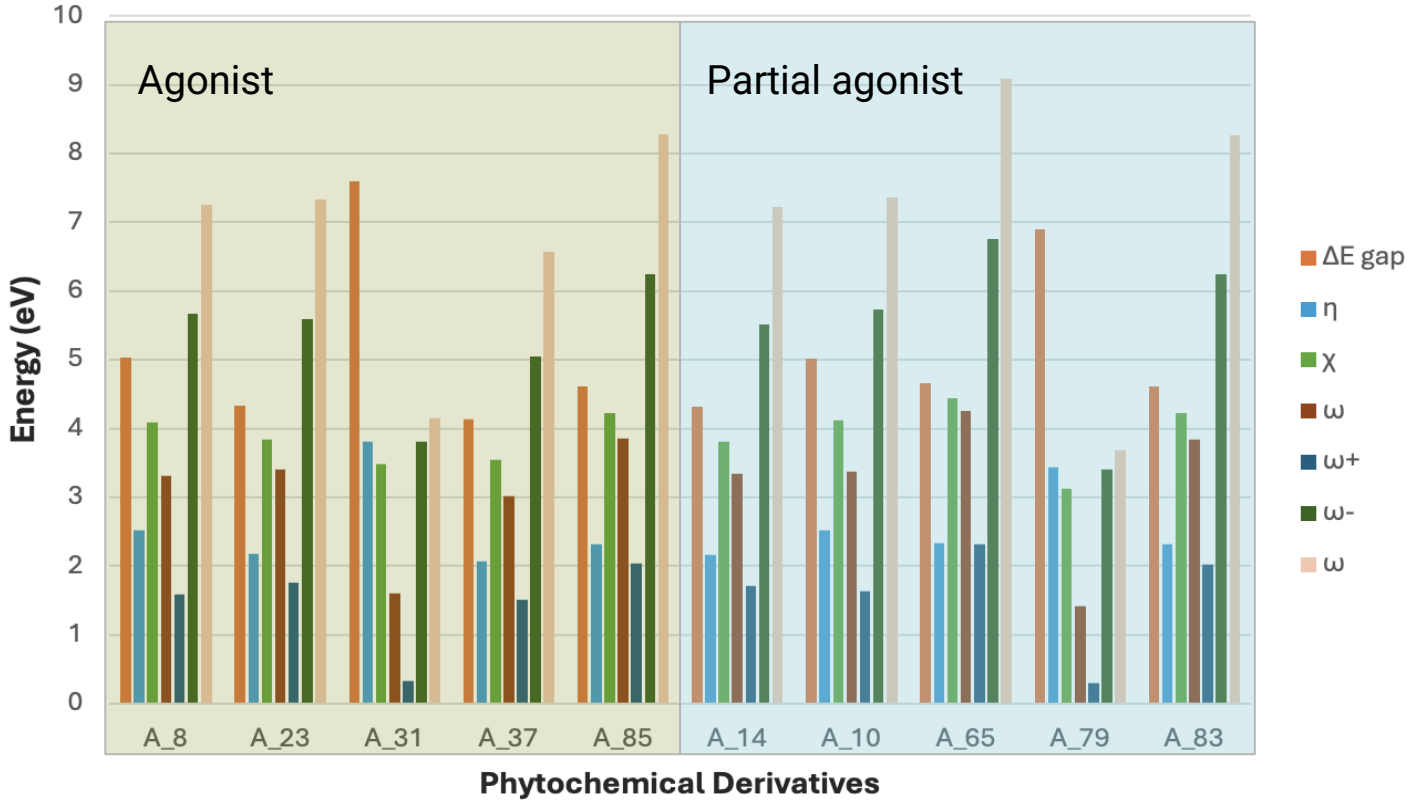
Toxicity of Top 10 derivatives

Class	Derivative ID	Mutagenic	Tumorigenic	Reproductive Effective	Irritant	hERG I inhibitor	hERG II inhibitor	Skin Sensitisation	Max. tolerated dose (log(mg/Kg/day))	T.Pyriformis toxicity (log µg/L)	Minnow toxicity (Log LC50)
Potential FXR agonist	A_8	none	none	none	none	No	No	No	0.229	0.285	1.753
	A_23	none	none	none	none	No	No	No	0.51	0.285	1.738
	A_31	none	none	none	none	No	No	No	-0.659	0.655	-0.451
	A_37	none	none	none	none	No	No	No	0.64	0.285	1.497
	A_85	none	none	none	none	No	No	No	0.21	0.285	1.045
Potential FXR partial agonist	A_10	none	none	none	none	No	No	No	-0.409	0.392	0.846
	A_14	none	none	none	none	No	Yes	No	0.509	0.286	2.004
	A_65	none	none	none	none	No	No	No	0.948	0.285	-1.251
	A_79	none	none	none	none	No	No	No	0.429	0.285	0.13
	A_83	none	none	none	none	No	No	No	1.125	0.285	0.995

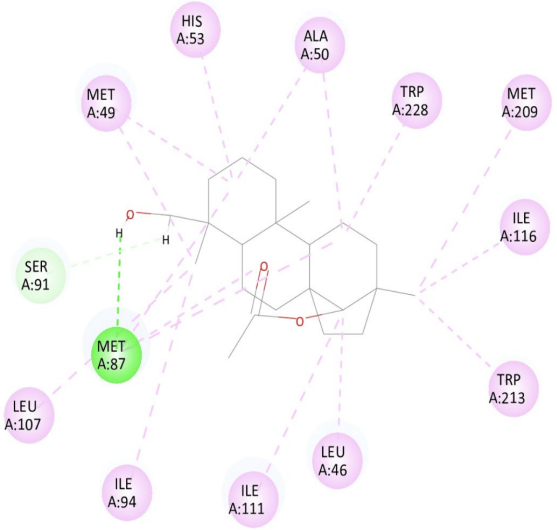
Reactivity index for the best derivatives in vacuum

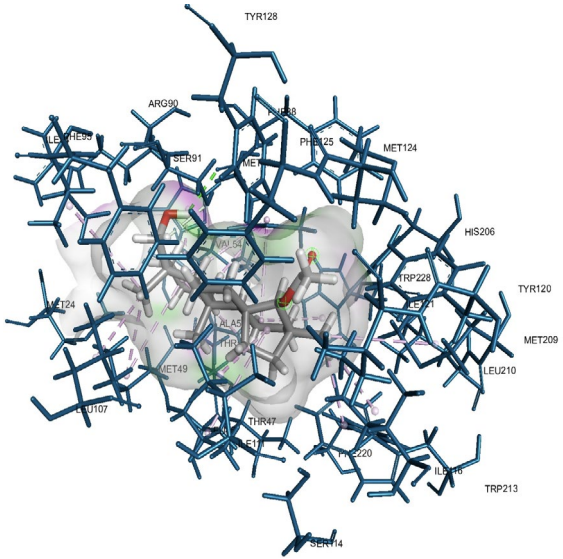


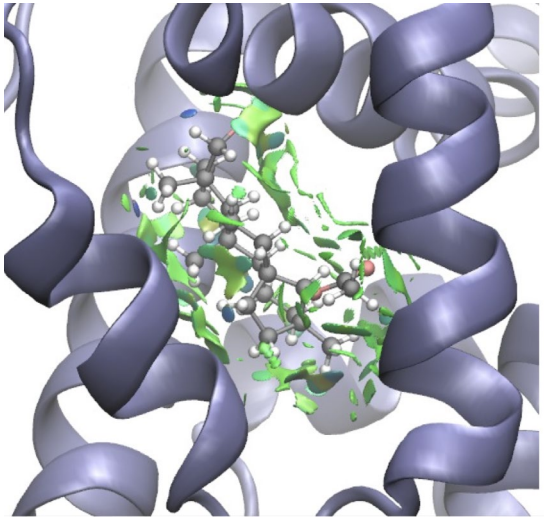
Reactivity index for the best derivatives in water



2D, 3D interactions and NCI of the potential agonist A_31



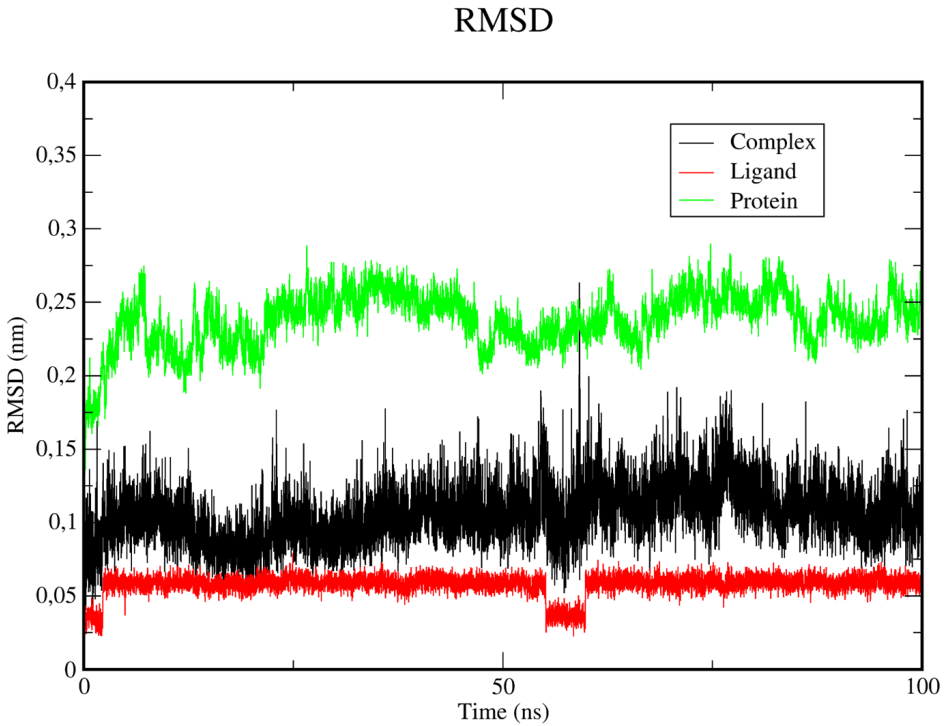




Interactions

- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Alkyl
- Pi-Alkyl

RMSD of the molecular dynamics of the potential agonist A_31



Summary

- From all compounds, only 10% (1200) presentes favourable biological hepatic according to way2drug and molinspiration
- PERUNPDB presents the highest diversity, although it was the smallest database
- the SISTEMTIX database contains phytochemicals with an overall low affinity energy
- top 10 potential natural products and top 5 derivatives come from SISTEMATX, NuBBE and BIOFACQUIM
- The compounds analyzed are stable in vacuum and water
.
- Non polar interactions are more abundant in agonist.
- The complex analyzed showed better stability than the ligand at 100 ns

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XXX Symposium on Bioinformatics
and Computer-Aided Drug Discovery

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