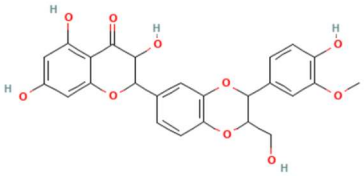
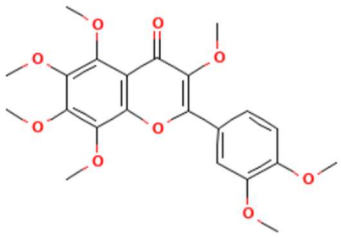
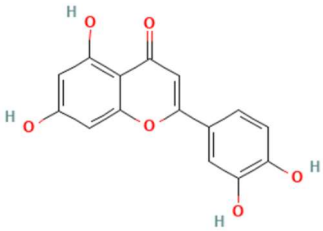
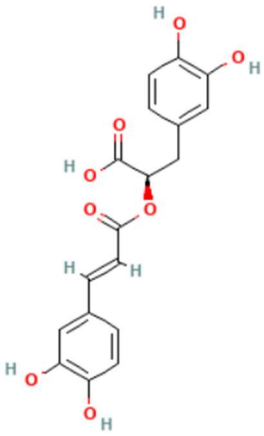
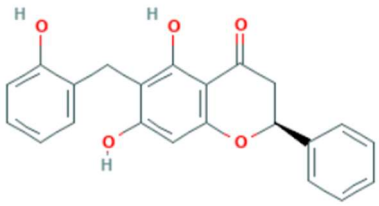
Supplementary Material

Table 1. List of protein targets for docking analysis

PDB ID	Protein description	Protein function	Protein	Resolution (Å)	References
1CM8	Proline-directed serine/threonine kinase	MAP kinases are pivotal in regulating embryogenesis, cellular differentiation, proliferation, and apoptosis.	MAP kinase	2.40	(Berman et al., 2000)
2AR9	Cysteine proteases	The caspase-9 function is vital for apoptosis during the normal development of the central nervous system	Caspase 9	2.80	(Kuida, 2000)
4LQM	Family of receptor tyrosine kinases	EGFR belongs to the ErbB family of proteins, playing a role in cell proliferation, survival, differentiation, migration, and continued existence	EGFR	2.50	(Janani et al., 2022)
5CT7	Kinase	BRAF is the most prevalent form of serine-threonine protein kinase, playing a critical role in regulating intracellular signal transduction from RAS to MEK, thereby influencing processes such as cellular proliferation, differentiation, and survival.	BRAF in complex with RAF265	3.17	(Gnoni et al., 2019; Maji et al., 2024)
5G4N	Tumour-suppressor protein	The function of p53 in orchestrating glycolysis and autophagy, facilitating the repair of genotoxic damage, promoting cell survival, modulating oxidative stress, influencing invasion and motility, regulating cellular senescence, driving angiogenesis, governing differentiation, and overseeing bone remodeling.	p53	1.35	(George, 2011)
6HH1	Receptor tyrosine kinase	The mutated variant of c-Kit and its associated intracellular signaling mechanisms are critically involved in the development of certain cancers.	c-Kit with allosteric inhibitor 3G8	2.25	(Sangwan & Park, 2006)

TABLES. 2.

List of phytochemicals used in this study.

Ligand	Chemical Formula	Chemical structure	Molecular weight	Category
Silymarin	$C_{25}H_{22}O_{10}$		482.4	Dihyroflavonols
Heptamethoxy flavone	$C_{22}H_{24}O_9$		432.4	Polymethoxyflavone
Luteolin	$C_{15}H_{10}O_6$		286.4	Tetrahydroxyflavone
Rosmarinic acid	$C_{18}H_{16}O_8$		360.3	Polyphenol
Isochamanetin	$C_{22}H_{18}O_5$		362.4	Diarylheptanoid

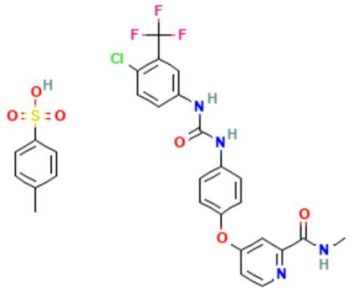
Sorafenib tosylate (Positive control)	$C_{28}H_{24}ClF_3N_4O_6S$		637.0	P-toluene sulfonic acid

Table 3. The list of the target proteins of HCC, along with their PDB ID, chain ID, and chain length

Proteins	PDB id	Chains	Chain length
Phosphorylated MAPK P38-GAMMA	1CM8	A, B	367
Dimeric Caspase-9	2AR9	A,B,C,D	278
Epidermal Growth Factor Receptor	4LQM	A	331
BRAF in Complex with RAF265	5CT7	A, B	281
p53 Y220C	5G4N	A,B	219
Receptor tyrosine kinase	6HH1	A	303

Table 4. ADME/T Properties of the phytochemicals used in this study

Compound Name	Lipinski Rule of Five		TPSA (Bhowmik et al., 2020)	AB% (Bhowmik et al., 2020)	Solubility
	Properties	Values			
Silymarin	Molecular weight(g/mol)	482.44	155.14	1.82	Moderately Soluble
	Lipophilicity	1.595			
	Hydrogen Bond Donors	5			
	Hydrogen Bond Acceptors	10			
	Molar Refractivity	120.55			
	Lipinski's Violations	0			
Heptamethoxyflavone	Molecular weight(g/mol)	432.42	94.82	0.55	Moderately Soluble
	Lipophilicity	3.040			
	Hydrogen Bond Donors	0			
	Hydrogen Bond Acceptors	9			

	Molar Refractivity	113.36			
	Lipinski's Violations	0			
Luteolin	Molecular weight(g/mol)	286.24	111.13	68.21	Moderately Soluble
	Lipophilicity	1.73			
	Hydrogen Bond Donors	4			
	Hydrogen Bond Acceptors	6			
	Molar Refractivity	76.01			
	Lipinski's Violations	0			
Rosmarinic acid	Molecular weight(g/mol)	360.31	144.52	75.19	Moderately Soluble
	Lipophilicity	1.52			
	Hydrogen Bond Donors	5			
	Hydrogen Bond Acceptors	8			
	Molar Refractivity	91.40			
	Lipinski's Violations	0			
Isochamanetin	Molecular weight(g/mol)	362.38	86.99	75.19	Moderately Soluble
	Lipophilicity	3.40			
	Hydrogen Bond Donors	3			
	Hydrogen Bond Acceptors	5			
	Molar Refractivity	101.02			
	Lipinski's Violations	0			

Table 5. Toxicity profile

Ligands	Toxicity class	LD50 (mg/kg)	Cyto toxicity	Immuno toxicity	Carcino genicity	Mutagen icity	Hepato toxicity	Nepro toxicity
Silymarin	4	1190	Inactive	Active	Inactive	Inactive	Active	Inactive
Heptamethoxy flavone	5	5000	Inactive	Inactive	Inactive	Inactive	Inactive	Active

Luteolin	4	1190	Inactive	Active	Inactive	Inactive	Active	Inactive
Rosmarinic acid	5	5000	Inactive	Active	Inactive	Inactive	Inactive	Active
Isochamanetin	4	1190	Inactive	Active	Inactive	Inactive	Active	Inactive
Control	5	3000	Inactive	Active	Inactive	Inactive	Active	Inactive

Table 6. Grid box parameters were selected for the target enzyme based on the binding site residues.

Protein	PDB ID	Center Coordinates	Grid Box Dimensions (Å)	Active Site Residues
EGFR	4LQM	x: -52.286, y: 0.242, z: -24.291	26 × 36 × 31	ALA52, ARG150, ASP109, ASP164, CYS106, GLN100, GLU71, GLY105, ILE53, ILE98, LEU101, LEU153, LEU27, LEU97, LYS54, MET102, THR163, THR99, VAL35
Caspase-9	2AR9	x: 21.017, y: 37.430, z: -15.036	22 × 16 × 19	SER 353, TRP 354, ARG 355, ASP 356, Pro 357
Kinase	5CT7	x: -8.025, y: -3.703, z: 10.225	26 × 30 × 32	ALA39, ASP152, CYS90, GLN88, GLU59, GLU91, GLY151, GLY92, HIS132, ILE130, ILE150, ILE21, ILE71, ILE85, LEU125, LEU63, LEU72, LYS41, PHE141, PHE153, THR66, THR87, TRP89, VAL29, VAL40, VAL62
Receptor tyrosine kinase	6HH1	x: -1.132, y: 21.587, z: -15.574	52 × 39 × 32	ALA57, ASP225, CYS109, GLU107, GLU235, GLU76, GLY246, ILE89, LEU31, LEU80, LEU83, LYS59, MET247, PRO245, SER224, THR106, TYR244, VAL219, VAL226, VAL39, VAL79, VAL90
P53 inhibitor	5G4N	x: -9.603, y: -2.170, z: 11.775	23 × 25 × 25	ASP135, CYS127, CYS136, GLU128, LEU164, LEU52, PHE16, PRO129, PRO130, PRO58, THR137, THR57, TRP53, VAL54, VAL64
Phosphorylated MAP kinase p38	1CM8	x: -6.331, y: -1.121, z: -6.035	49 × 38 × 37	ALA160, ALA40, ALA54, ARG152, ARG176, ARG192, ARG70, ARG73, ASN158, ASP115, ASP153, ASP171, ASP230, GLU181, GLY157, GLY184, HIS231, ILE87, LEU170, LYS118, LYS155, LYS56, LYS69, MET109, MET112, MET182, MET201, PHE111, PRO110, SER180, THR114, TRP200, TYR203, VAL186, VAL187, VAL33, VAL41

Table 7: Binding affinity scores for each protein candidate.

Ligand Name	EGFR	Caspase-9	BRAF	RTK	P53	MAPk

SA	-8.7	-7.6	-9.2	-9.9	-7	-9.6
HMF	-6.8	-6.6	-7.2	-6.6	-5.6	-7.3
LU	-7.5	-7	-8.2	-8.6	-6.6	-8.6
RA	-7	-6.2	-8.6	-8.8	-6.4	-8.3
IC	-8.2	-6.7	-9	-8.9	-7.4	-8.9
Sorafenib	-8.5	-7.3	-10.3	-10.6	-7.4	-9.7

Table 8. Hydrogen bond interaction against each protein candidate.

Ligand Name	EGFR	Caspase-9	BRAF	RTK	P53	MAPk
SILYMARIN	2	0	1	1	1	1
Heptamethoxy flavone	1	4	1	0	1	0
Luteolin	0	3	0	1	1	0
Rosmarinic acid	3	4	2	1	2	2
Isochamanetin	1	0	2	1	0	0
Sorafenib Tosylate	0	3	0	0	0	2

Table. 9. Interaction table for 4LQM with phytocompounds

S.no	*Phytocompounds*	*Hydrogen bond*	*Hydrophobic*	*Polar*	*Glycine*
1.	Silymarin	ALA52 & CYS106	ALA52, CYS106, ILE53, VAL35 &PHE104	THR163 & THR99	GLY105
2.	Heptamethoxy flavone	THR854	LEU792, MET793, ILE789,CYS797 & LEU788	THR854,GLN791, THR790&ASN842	
3.	Luteolin		LEU101,PRO103 & PRO50		GLY38
4.	Rosmarinic acid	GLU71 & ASP164	PHE165,CYS106, MET102,LEU101,LEU97 & CYS84	THR163,THR99 & GLN100	GLY105
5.	Isochamanetin	PRO301	LEU101,PRO103 & LEU39	THR156	GLY38
6.	Positive control		ALA64,LEU97,ILE53,ALA52,ILE60,PHE32 & VAL35	THR99 & THR163	

Table. 10. Interaction table for 2AR9 with phytocompounds

S.no	*Phytocompounds*	*Hydrogen bond*	*Hydrophobic*	*Polar*	*Glycine*
1.	Silymarin		ALA148,ILE258,TYR259	SER215,+GLN147 & SER149,HIS99	GLY100
2.	Heptamethoxy flavone	ARG355 & THR181	PRO357,TRP354,VAL352 & ALA286	SER361,GLN285,HIS237,SER287,THR 181 & SER236	GLY238
3.	Luteolin	ARG42,LYS154 & GLN147	ALA148,TRP216 & VAL 214	SER223,GLN147,SER215,HIS99 & SER98	
4.	Rosmarinic acid	SER215,ARG42 & ARG217	VAL234 & TRP216	GLN147, SER149 & HIS99	
5.	Isochamanetin		VAL214 & TRP216	SER215	
6.	Positive control	ARG217,SER149 & ARG42	ALA148,TRP216, ILE258 & TYR259	HIS99,SER149,GLN147 & SER215	GLY257

Table 11. Interaction table for 5CT7 with phytocompounds

S.no	*Phytocompounds*	*Hydrogen bond*	*Hydrophobic*	*Polar*	*Glycine*
1.	Silymarin	ASN138	ILE21,PHE26,VAL 29,PHE141,CYS90 & TRP89	SER25,ASN138 & ASN139	GLY24 & GLY27
2.	Heptamethoxy flavone	THR87	ILE85,TRP89,CYC 90,PHE141 & ALA39	ASN138,SER93SEER94 & HIS97	GLY92
3.	Luteolin		TRP89 & CYS90	THR87 & GLN88	GLY24 & GLY92
4.	Rosmarinic acid	ASP134, SER25	LEU72, ALA39,TRP89,ILE 21,PHE26 & VAL29	SER25,SER23,ASN139 & GLN88	GLY24 & GLY27
5.	Isochamanetin	GLY92	PHE141, TRP89 & CYS90	THR87 & SER93	GLY92
6.	Positive control		ALA39,CYS90,TRP89,ILE85,PHE153 & ILE85	THR87 & SER98	GLY92 & GLY151

Table. 12. Interaction table for 6HH1 with phytocompounds

S.no	*Phytocompounds*	*Hydrogen bond*	*Hydrophobic*	*Polar*	*Glycine*
1.	Silymarin	ILE182 & GLU76	CYS183,ILE182,ILE89,VAL90,CYS162 & ILE163	THR106, HIS164 &ASN161	

2.	Heptamethoxy flavone		ALA72,LEU12,LEU157,CYS162,ILE163 & PHE185	SER75,ASN161 & HIS164	GLY186
3.	Luteolin	LEU31	VAL39,PHE185,ALA57,		GLY112
4.	Rosmarinic acid	CYS109	ALA57,TYR106,CYS183,ILE162,PHE185 & CYS109	THR106	
5.	Isochamanetin	CYS109	PHE185, CYS110,CYS109 & LEU173	THR106	GLY112
6.	Positive control		CYS109,TYR108,PHE185,CYS183,ILE182 & LEU80	THR106	GLY112

Table. 13. Interaction table for 5G4N with phytocompounds

S.no	***Phytocompounds***	***Hydrogen bond***	***Hydrophobic***	***Polar***	***Glycine***
1.	Silymarin	GLY133	CYS127,PRO126, VAL125,VAL132 & ILE139	THR137,THR138,HID140 & ASN107	GLY133
2.	Heptamethoxy flavone		PHE20,LEU18,TYR33,PRO35,ALA36 & LEU37	SER176, THR9,HID22 & GLN51	GLY19
3.	Luteolin	GLU105	CYS136	SER134,THR138,HID140 & ASN107	GLY106
4.	Rosmarinic acid	CYS136	ILE139,CYS136,PRO130 & PRO129	ASN107, THR138,HID140 & SER134	
5.	Isochamanetin		ILE139,CYS136,PRO130 & VAL125	HID140,THR138, SER134,ASN107 & THR137	GLY106
6.	Positive control		PRO126, CYS136 & ILE139	SER134,THR138 & GLN51	

Table 14. Interaction table for 1CM8 with phytocompounds

S.no	***Phytocompounds***	***Hydrogen bond***	***Hydrophobic***	***Polar***	***Glycine***
1.	Silymarin	ASP171	VAL41,TYR38,VAL33,MET112,PHE111,PRO110,MET109 & LEU170	THR114	GLY36 & GLY 113
2.	Heptamethoxy flavone	LYS56	ALA54,LEU170,TYR38,MET112,PHE111,PRO110 & MET109	SER35	GLY39,GLY36 & GLY157

3.	Luteolin		LEU170,ALA54,ILE87,MET109,PRO110,PHE111 & MET112	THR114	GLY113
4.	Rosmarinic acid	ASP171& ASP115	MET109,PRO110, PHE111,MET112 & LEU170	THR114	GLY157
5.	Isochamanetin		PRO110,MET112, LEU170,TYR38 & VAL41	ASN158	GLY36
6.	Positive control	ASN158	ALA160,MET112, PHE111,PRO110, MET109,VAL187, VAL186 & LEU174	ASN158 & THR114	GLY113

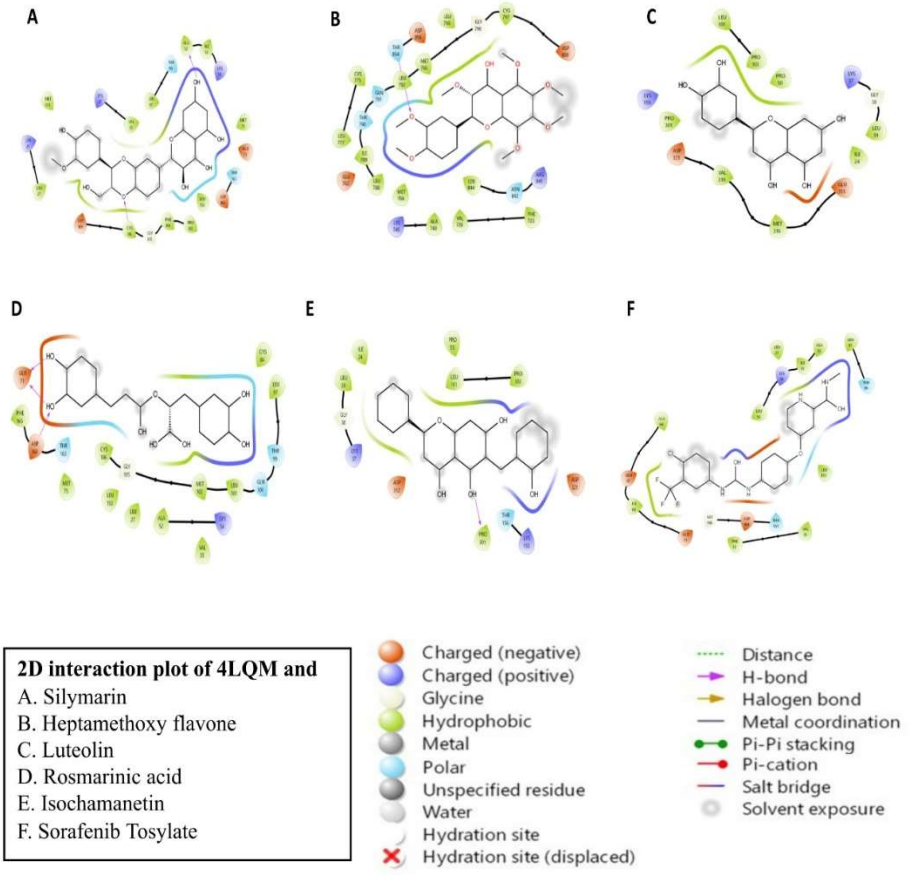


Fig. 1. 2D interaction plot of the interaction site of docking between 4LQM (EGFR) and the phytochemicals A. SA, B. Heptamethoxy flavone, C. LA, D. Rosmarinic

acid, E. Isochamanetin, F. Sorafenib. The various interaction schemes are displayed using different color schemes in the bottom right corner of the figure.

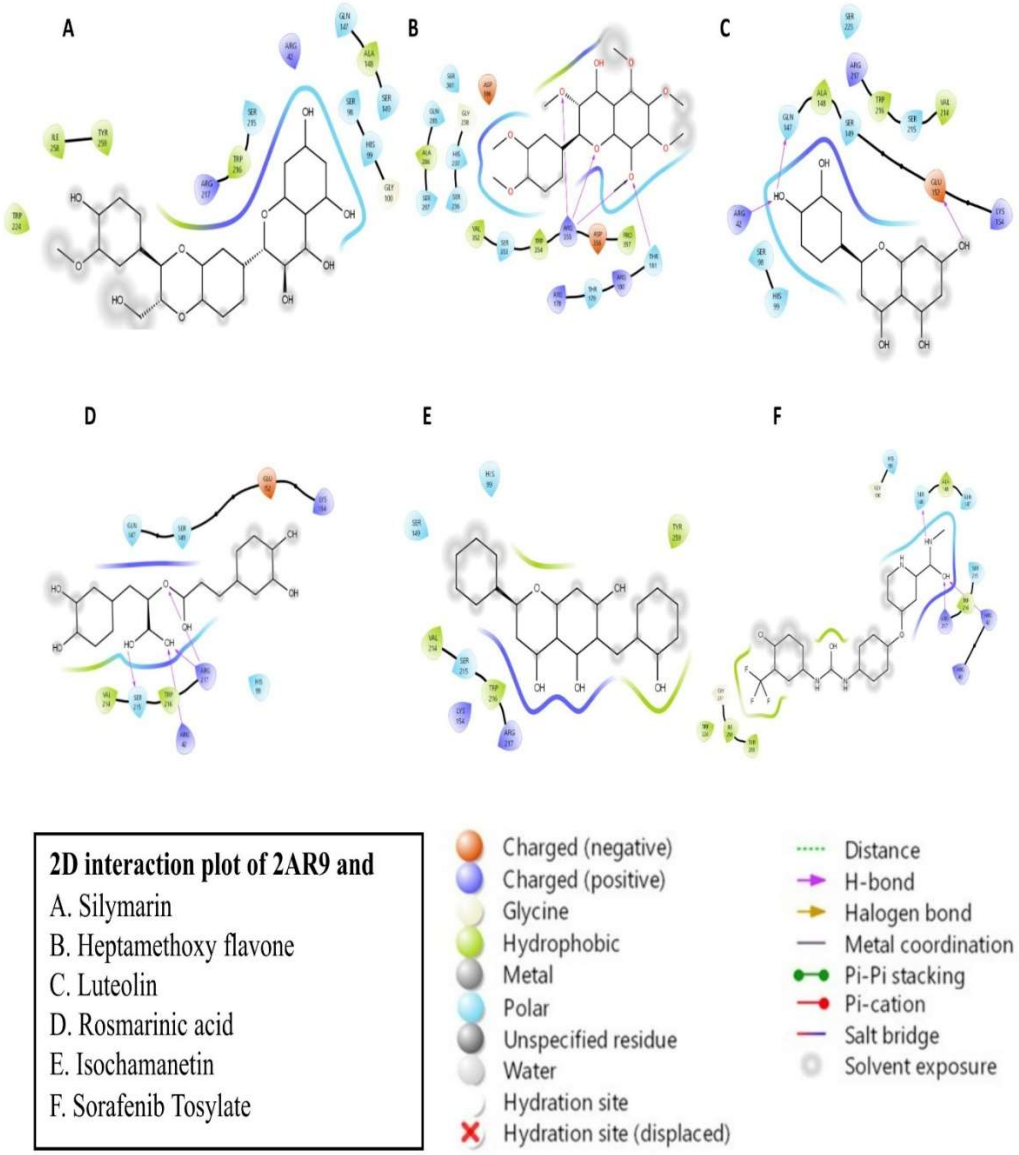


Fig. 2. 2D interaction plot of the interaction site of docking between 2AR9 (Dimeric Caspase-9) and the following phytochemicals: A. SA, B. Heptamethoxy flavone, C. LA, D. Rosmarinic acid, E. Isochamanetin, F. Sorafenib. The various interaction schemes are displayed using different color schemes in the bottom right corner of the figure.

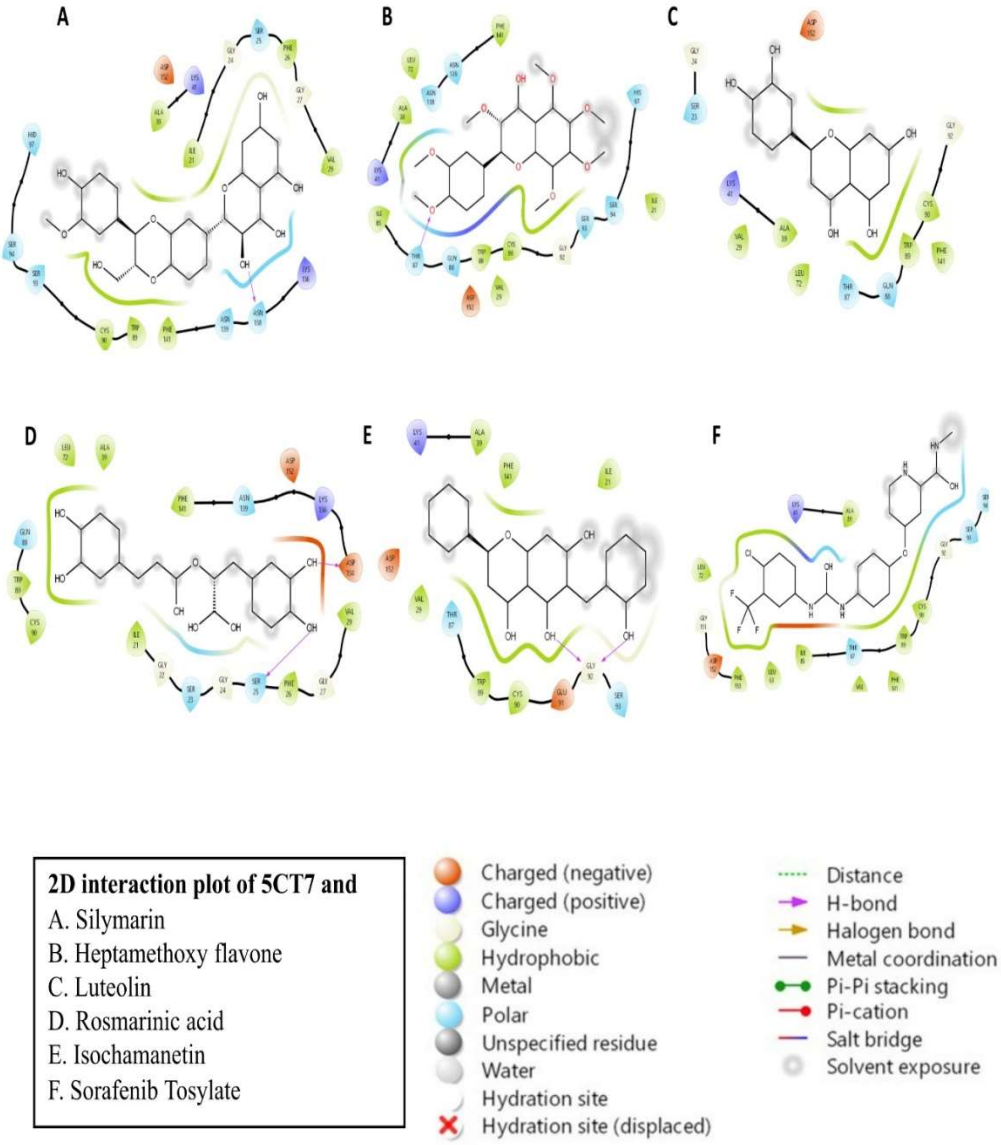


Fig. 3. 2D interaction plot of the interaction site of docking between 5CT7 (B-RAF Kinase) and the following phytochemicals: A. SA, B. Heptamethoxy flavone, C. LA, D. Rosmarinic acid, E. Isochamanetin, F. Sorafenib. The various interaction schemes are displayed using different color schemes in the bottom right corner of the figure.

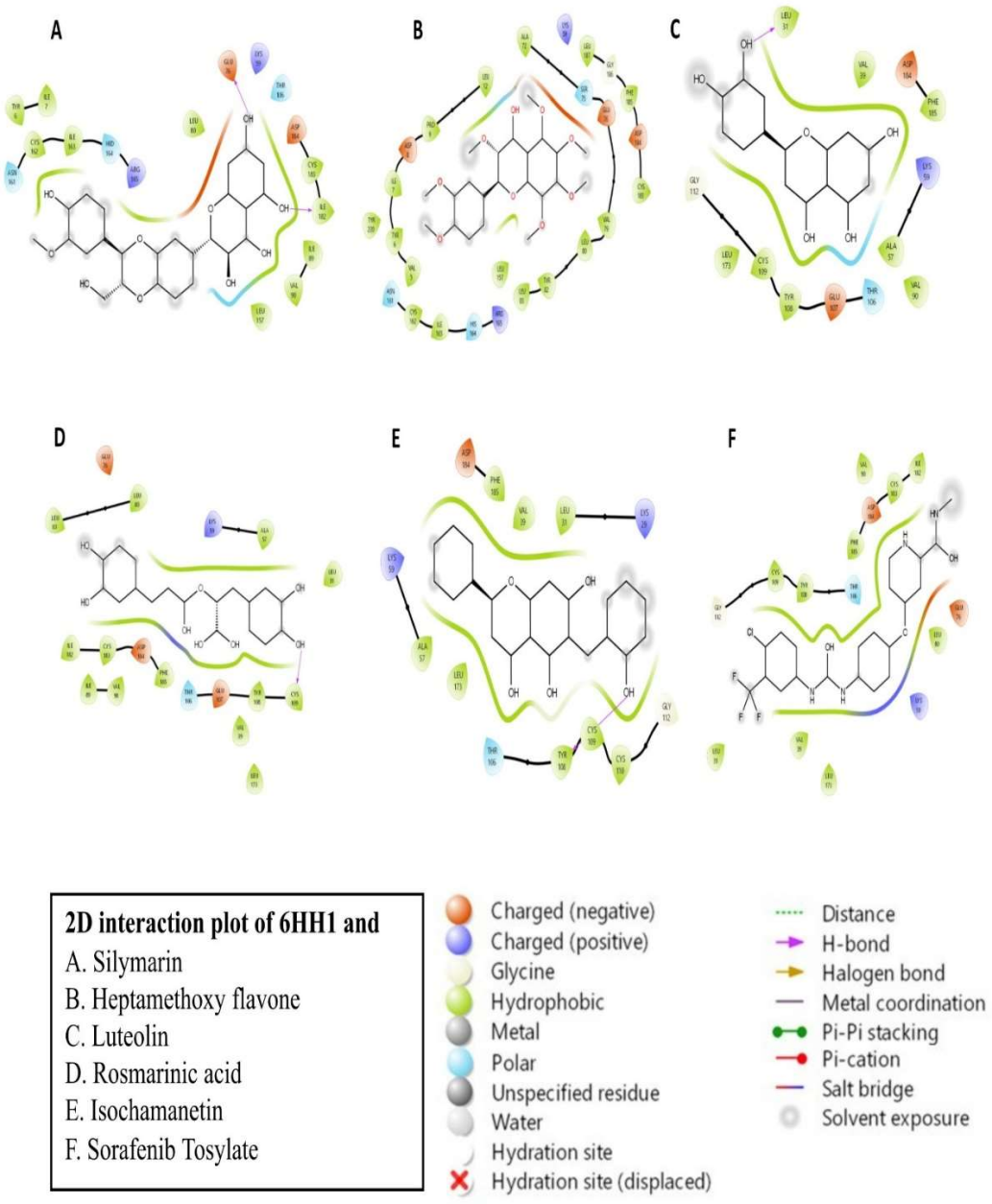


Fig. 4. 2D interaction plot of the interaction site of docking between 6HH1 (c-Kit with allosteric inhibitor 3G8) and the phytochemicals A. SA, B. Heptamethoxy flavone, C. LA, D. Rosmarinic acid, E. Isochamanetin, F. Sorafenib. The various interaction schemes are displayed using different color schemes in the bottom right corner of the figure.

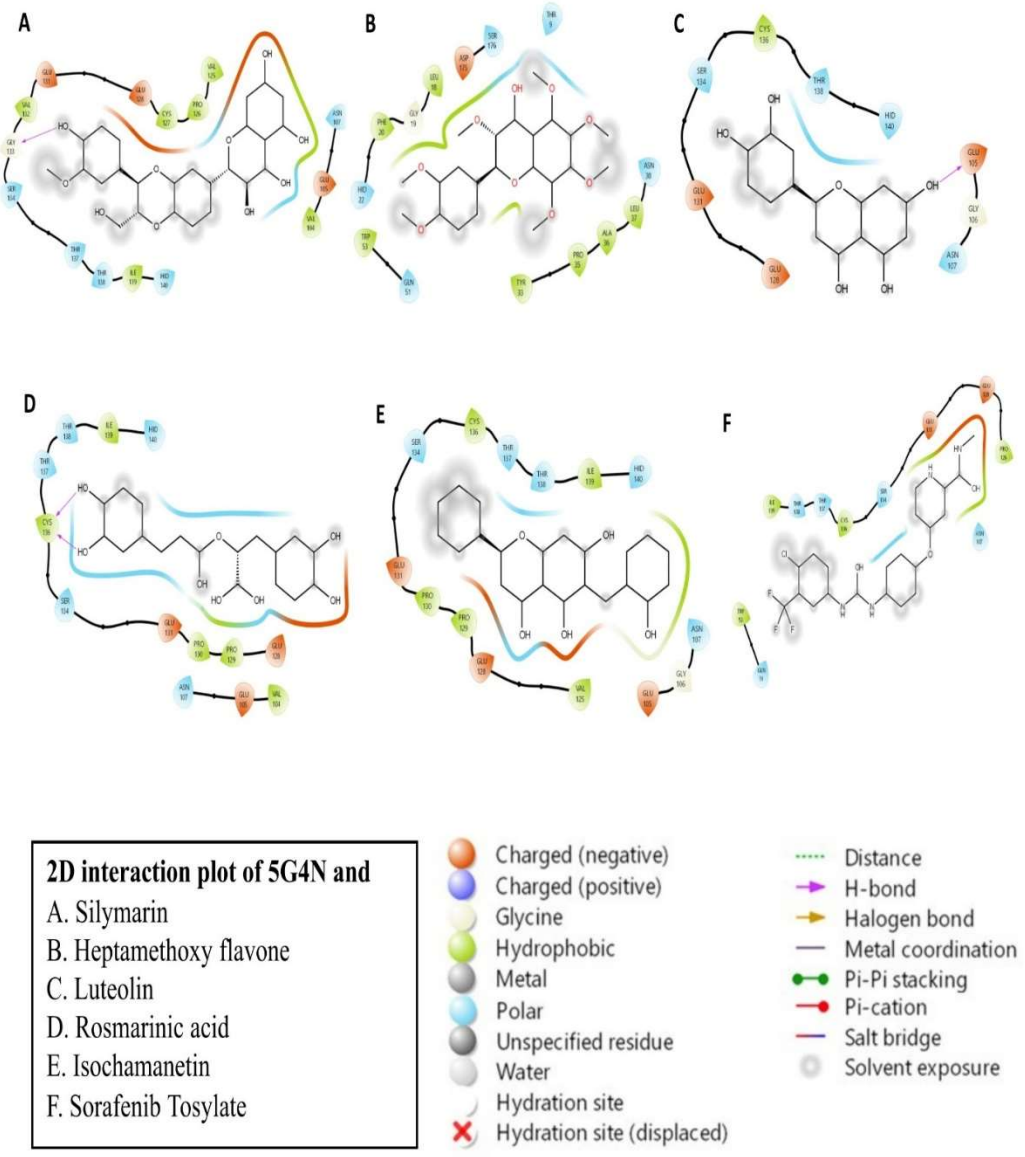


Fig. 5. 2D interaction plot of the interaction site of docking between 5G4N (P53 Mutant Y220C) and the following phytochemicals: A. SA, B. Heptamethoxyflavone, C. LA, D. Rosmarinic acid, E. Isochamanetin, F. Sorafenib. The various interaction schemes are displayed using different color schemes in the bottom right corner of the figure.

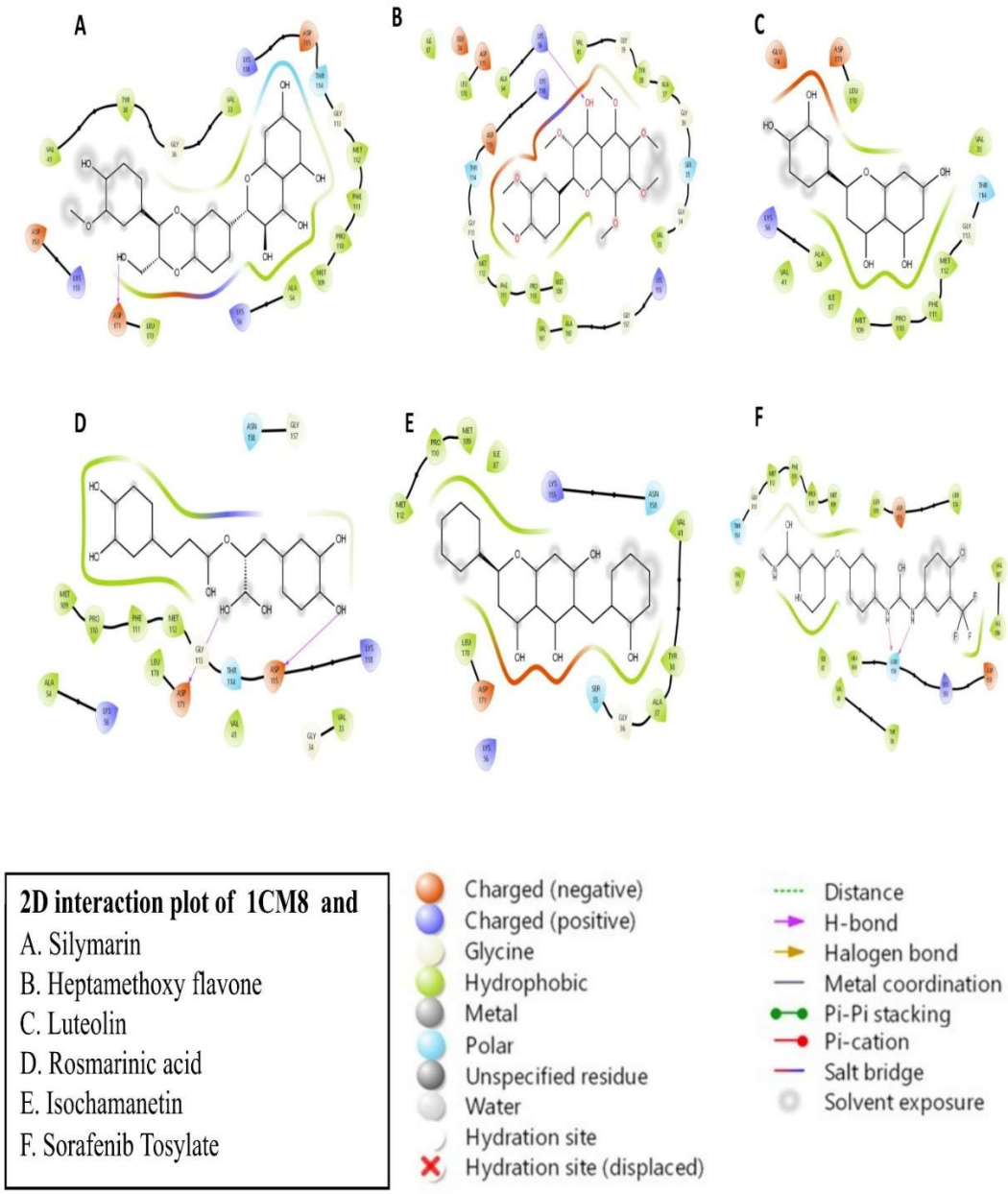


Fig. 6. 2D interaction plot of the interaction site of docking between 1CM8 (MAP kinase) and the phytochemicals A. SA, B. Heptamethoxy flavone, C. LA, D. Rosmarinic acid, E. Isochamanetin, F. Sorafenib. The various interaction schemes are displayed using different color schemes in the bottom right corner of the figure.