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Multi-Targeting Potential of Flavonol Glycosides from *Ginkgo biloba* Leaves against Colorectal Cancer Mutations

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pharmaceuticals MDPI

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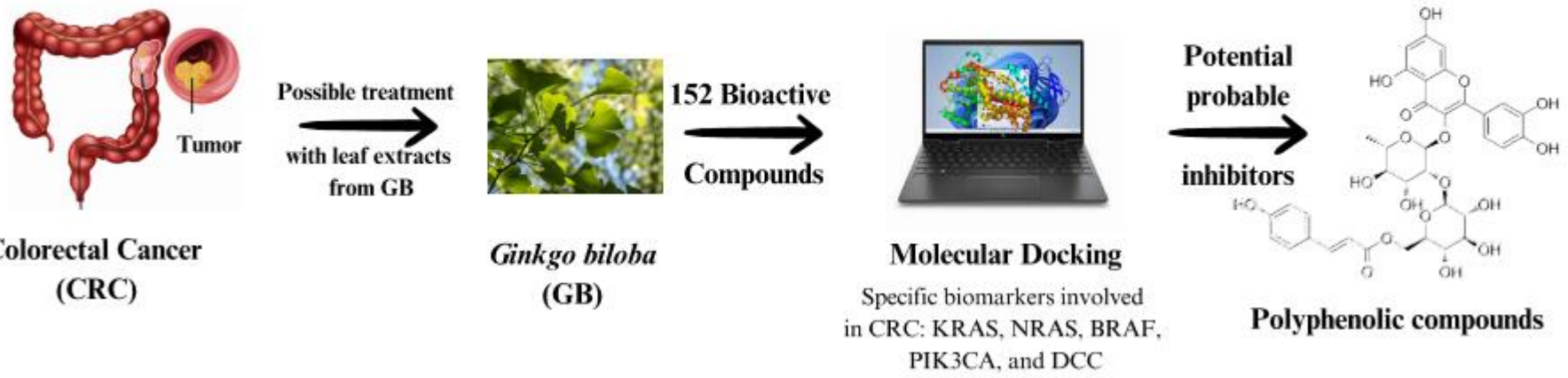
Multi-Targeting Potential of Flavonol Glycosides from *Ginkgo biloba* Leaves against Colorectal Cancer Mutations

Molecules extracted from *Ginkgo biloba* are currently under investigation for their ability to inhibit key colorectal cancer biomarkers (BRAF, KRAS, NRAS, PIK3CA, DCC) through the application of molecular docking techniques. Notably, flavonol compounds such as quercetin-3-O-6''-rhamnosyl-2''-(6''' p-coumaroylglucosyl)glucoside, among others, exhibit promising potential as formidable anticancer agents in this context.



Abstract

This study aimed to evaluate the inhibitory potential of *Ginkgo biloba* polyphenols against colorectal cancer biomarkers through in-silico analysis. The biomarkers investigated included KRAS-G12D, BRAF-V600E, PIK3CA-E545K, NRAS-Q61K, and DCC-T315I, which are commonly associated with colorectal cancer. In-silico docking simulations were conducted using the MOE software to assess the affinity of *Ginkgo biloba* polyphenols for the active sites of the mutant codons. A total of 152 ligands were docked, and their interactions and docking scores were analyzed. The results revealed significant inhibitory potential of *Ginkgo biloba* polyphenols against the mutant codons under investigation. Ligands such as quercetin-3-O-6''-rhamnosyl-2''-(6'''-p-coumaroylglucosyl)glucoside (L15), quercetin 3-O-[2-{6'-(7''''-O-glucosyl)-trans-p-coumaroyl)}-glucosyl]-rhamnoside (L17), and isorhamnetin-3-O-alpha-L-rhamnosyl-2''-(6'''-p-coumaroyl)-beta-D-glucoside (L47) demonstrated promising therapeutic potential. These ligands exhibited multi-targeting effects by interacting with multiple mutant codons simultaneously. L15 interacted with BRAF-V600E and PIK3CA-E545K, L17 targeted BRAF-V600E and DCC-T315I, and L47 showed affinity for both KRAS-G12D and PIK3CA-E545K. The findings suggest that *Ginkgo biloba* polyphenols, including L15, L17, and L47, have potential as therapeutic agents against colorectal cancer mutant codons. Their multi-targeting effects offer new opportunities for therapeutic development. Further investigations are needed to fully explore the therapeutic potential of these natural compounds and their application in cancer treatment. Overall, this in-silico study provides valuable insights into the inhibitory potential of *Ginkgo biloba* polyphenols against colorectal cancer biomarkers. The findings contribute to the field of natural compound-based cancer therapeutics and highlight the significance of multi-targeting approaches in developing effective treatments for complex diseases.

Keywords: Colorectal cancer; *Ginkgo biloba;* in-silico analysis; mutant codons; multi-targeting effects; polyphenols.

Introduction

Colorectal cancer (CRC) represents a significant global health challenge, with substantial morbidity and mortality rates [1]. It stands as the third most prevalent cancer globally, comprising 10% of all cancer cases, and is the second leading cause of cancer-related fatalities, responsible for 9.4% of such deaths [2,3].

In the year 2020, there were recorded more than 1.9 million newly diagnosed cases of CRC, resulting in 935,000 fatalities [4,5].

Taking into account forecasts that consider the effects of aging, population expansion, and advancements in human development, it is anticipated that the incidence of new CRC cases will rise to 3.2 million by the year 2040 [6].

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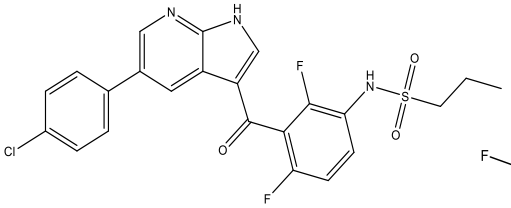
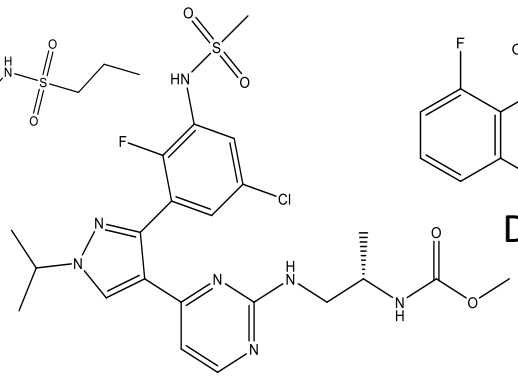
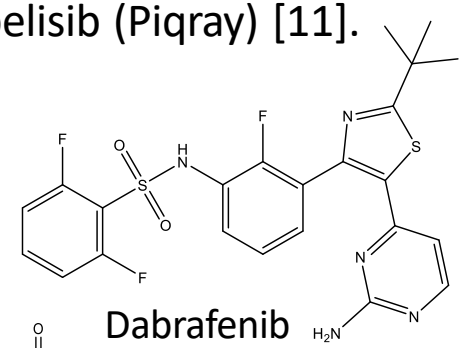
- Several medications are presently authorized and employed in the treatment of CRC, including Vemurafenib (Zelboraf) [7], Encorafenib (Braftovi) [8], Dabrafenib (Tafinlar) [9], Cobimetinib (Cotellic) [10], and Alpelisib (Piqray) [11].



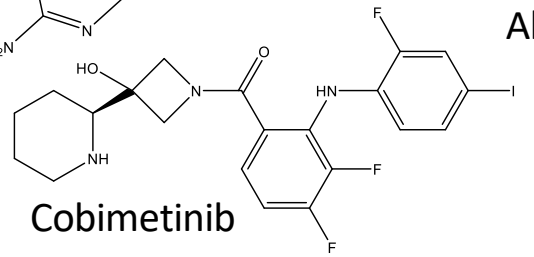
Vemurafenib



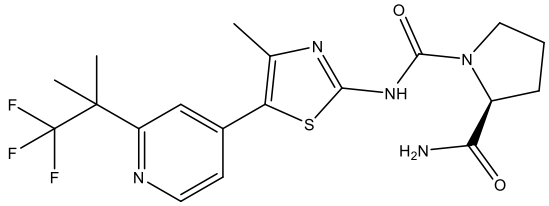
Encorafenib



Dabrafenib



Cobimetinib



Alpelisib

These medications effectively slow down cancer progression and metastasis [12]. Nevertheless, despite their effectiveness in treating CRC, they come with adverse side effects.

- Polyphenols, recognized for their versatile applications, antioxidant capabilities, and intriguing properties, are secondary metabolites.

[7] Car I, Dittmann A, Klobučar M, Grbčić P, Kraljević Pavelić S, Sedić M. Secretome screening of BRAFV600E-mutated colon cancer cells resistant to Vemurafenib. Biology 2023; 12(4):608. doi: 10.3390/biology12040608.
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- The quest for natural-based molecules devoid of adverse effects as potential drugs to combat CRC is underway.

- Among the array of plants renowned for their therapeutic potential, *Ginkgo biloba* stands out due to its wealth of polyphenols, endowing it with anticancer, antimicrobial, antidiabetic, and antioxidant attributes [13–15].

- These polyphenols exhibit promise in their capacity to interact with key biomarkers implicated in colorectal cancer.

- Noteworthy biomarkers with significant exploitable implications include mutations in KRAS (Kirsten rat sarcoma virus) and NRAS (Neuroblastoma RAS) [16], BRAF (serine/threonine-protein kinase B-Raf) [17], PIK3CA (phosphatidylinositol 3'-kinase) [18], and DCC (Deleted Colorectal Cancer) [19], all of which serve as potential therapeutic targets.

[13] Cháirez-Ramírez MH, de la Cruz-López KG, García-Carrancá A. Polyphenols as antitumor agents targeting key players in cancer-driving signaling pathways. Front Pharmacol 2021 Oct 20;12:710304. doi: 10.3389/fphar.2021.710304.
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- The presence of these mutated genes facilitates unchecked tumor cell proliferation, thereby playing a significant role in the development of cancer.
- Contemporary cancer research primarily concentrates on the malfunction of regulatory genes and their potential influence on molecular pathways.
- The adoption of computational techniques not only economizes time and resources but also enhances the accessibility of discovering bioactive compounds.
- In this particular investigation, we utilized molecular docking to explore the interaction between over a hundred polyphenolic compounds sourced from *Ginkgo biloba* and a range of biomarkers implicated in colorectal cancer treatment. The objective was to pinpoint the most promising candidate molecules as potential novel therapeutic avenues.

Results and discussion

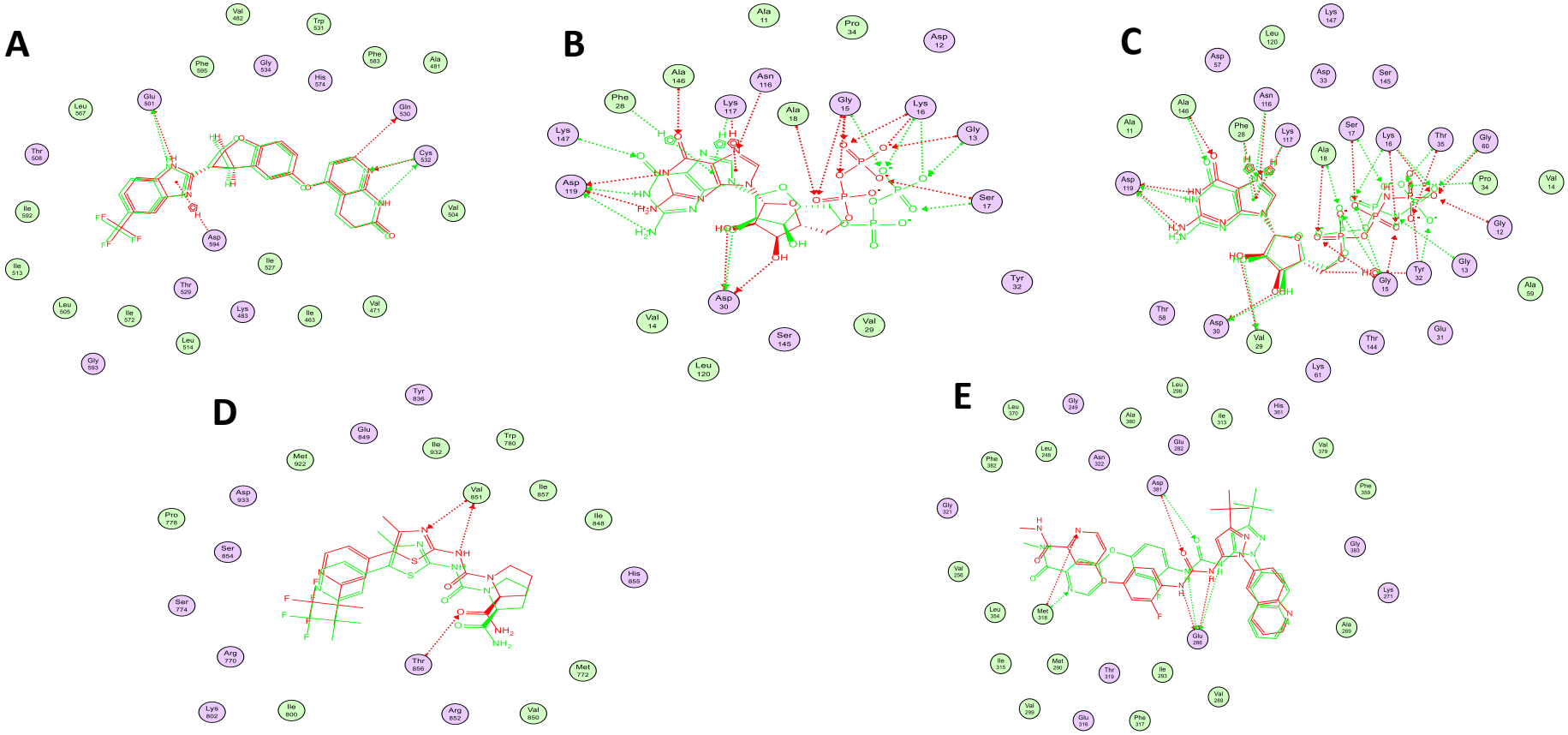

Fig. 1. Superposition of the co-crystallized ligand in the active site of the : (A) BRAF-V600E codon (PDB ID 4R5Y); (B) KRAS-G12D codon (PDB ID 5US4); (C) NRAS-Q61K codon (PDB ID 2RGB); (D) PIK3CA-E545K codon (PDB ID 8GUD) and (E) DCC-T315I codon (PDB ID 3QRJ).

Results and discussion

Table 1 Docking scores of reference ligands and polyphenols with colorectal cancer biomarkers of 5 mutant codons

BRAF- V600E (4R5Y)		KRAS - G12D (5US4)		NRAS- Q61K (2RGB)		PIK3CA- E545K (8GUD)		DCC- T315I (3QRJ)	
Ligands	Score (kcal/mol)	Ligands	Score (kcal/mol)	Ligands	Score (kcal/mol)	Ligands	Score (kcal/mol)	Ligands	Score (kcal/mol)
Ref1.	-9.89756584	**Ref2.**	-8.76872444	**Ref3.**	-10.7470617	**Ref4.**	-6.87398672	**Ref5**	-11.7703533
L15.	-9.67522621	**L47.**	-8.54082775	**L90.**	-8.94333172	**L47.**	-10.0770941	**L17**	-9.50224495
L17.	-9.36398029	**L55.**	-8.34138775	**L120.**	-8.81506538	**L15.**	-9.93335533	**L18**	-9.29626369
L76.	-9.15793896	**L98.**	-8.32394028	**L46.**	-8.6382246	**L30.**	-9.88699722	**L14**	-9.10843468

Results and discussion

Table 2 Physicochemical properties of the selected top ligands after docking

Compounds	Tocixity	Weight (g/mol)	LogP	LogS	H-bonds donor	H-bonds acceptor	TPSA Å²
L14	NO	756.67	0.09	-5.31	10	16	291.82
L15	NO	918.81	-2.08	-5.02	13	21	370.97
L17	NO	918.81	-2.44	-5.08	13	21	370.97
L18	NO	918.81	-2.44	-5.08	13	21	370.97
L30	NO	756.66	-3.76	-2.86	12	19	324.44
L46	NO	770.69	-2.72	-3.44	11	19	313.44
L47	NO	770.69	0.39	-5.72	9	16	280.82
L55	NO	772.66	-0.20	-4.95	11	17	312.05
L76	NO	492.43	-0.09	-3.34	6	11	184.60
L90	NO	582.56	5.91	-8.19	3	9	140.98
L98	NO	728.66	2.90	-8,57	7	13	231.13
L120	NO	594.52	2.89	-3.37	11	13	240.99

Results and discussion

Interactions of polyphenols with BRAF V600E (PDB ID 4R5Y)

Table 3 Docking scores and interaction types of the top 3 ligands docked in the active site of colorectal cancer biomarker BRAF-V600E (PDB ID 4R5Y)

Ligands	Score (kcal/mol)	Bonds between atoms of compounds and residues of the active site					
		Atom of compound	Involved receptor atoms	Involved receptor residues	Type of interaction bond	Distances (Å)	Energy (kcal/mol)
L15	-9.67522621	O 7	OD2	ASP 594	H-donor	2.74	-3.3
		O 16	OE1	GLU 501	H-donor	2.93	-3.2
		O 4	NE	ARG 575	H-acceptor	2.68	-2.5
		O 4	NH2	ARG 575	H-acceptor	2.79	-1.7
		O 13	N	ASP 594	H-acceptor	2.80	-2.7
L17	-9.36398029	O 4	O	PHE 595	H-donor	2.74	-2.6
		O 97	5-ring	HIS 574	H-pi	4.21	-0.6
L76	-9.15793896	O 3	O	GLN 530	H-donor	3.17	-1.3
		O 4	O	CYS 532	H-donor	3.00	-0.9
		O 3	N	CYS 532	H-acceptor	2.88	-2.4

Results and discussion

Interactions of polyphenols with BRAF V600E (PDB ID 4R5Y)

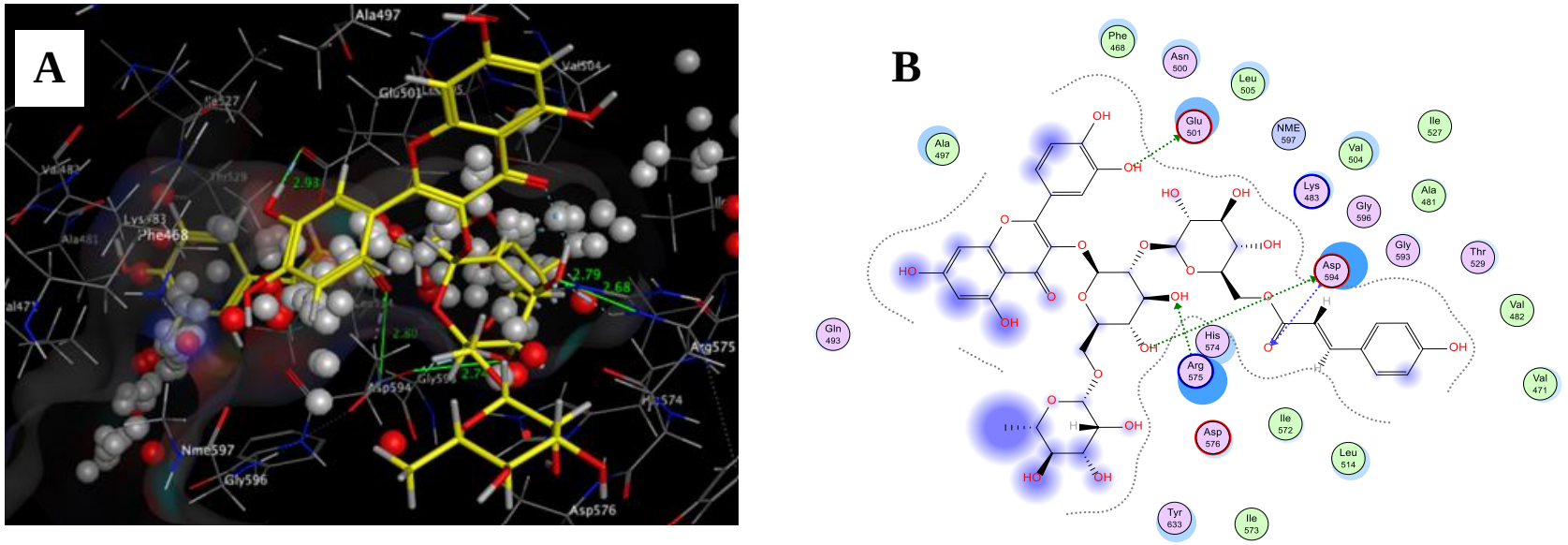

Fig. 2. 3D(A) and 2D(B) interactions between Quercetin-3-O-6''-rhamnosyl-2''-(6'''-p-coumaroylglucosyl)glucoside (L15) and BRAF-V600E.

Results and discussion

Interactions of polyphenols with KRAS-G12D (PDB ID 5US4)

Table 4 Docking scores and interaction types of the top 3 ligands in the active site of the colorectal cancer biomarker KRAS-G12D (PDB ID 5US4)

Ligands	Score (kcal/mol)	Bonds between atoms of compounds and residues of the active site					
		Atom of compound	Involved receptor atoms	Involved receptor residues	Type of interaction bond	Distances (Å)	Energy (kcal/mol)
L47	-8.54082775	O 9	O	ASP 30	H-donor	3.19	-0.9
		O 13	OD1	ASP 119	H-donor	3.04	-3.4
		C 35	OD2	ASP 119	H-donor	3.50	-0.7
		O 11	NZ	LYS 117	H-acceptor	3.27	-3.2
		6-ring	NZ	LYS 147	pi-cation	4.71	-1.3
L55	-8.34138775	O 18	OD1	ASP 119	H-donor	3.21	-2.3
L98	-8.32394028	O 8	OD1	ASP 119	H-donor	3.28	-2.1
		O 74	O	ASP 30	H-donor	2.89	-0.7
		O 74	OD1	ASP 30	H-donor	3.02	-1.3
		O 9	ND2	ASN 116	H-acceptor	3.27	-0.7

Results and discussion

Interactions of polyphenols with KRAS-G12D (PDB ID 5US4)

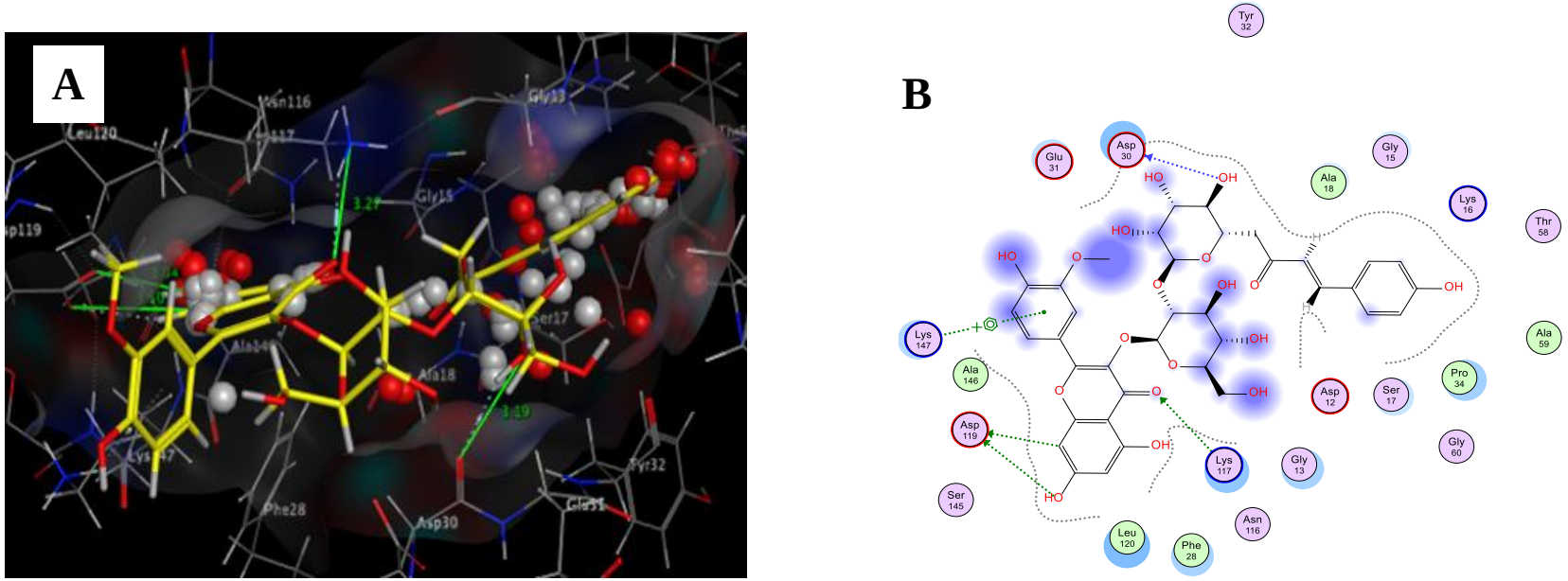

Fig. 3. 3D(A) and 2D(B) interactions between Isorhamnetin-3-O-alpha-L-rhamnosyl-2''-(6'''-p-coumaroyl)-beta-D-glucoside (L47) and KRAS-G12D.

Results and discussion

Interactions of polyphenols with NRAS-Q61K (PDB ID 2RGB)

Table 5 Docking scores and interaction types of the top 3 ligands docked in the active site of colorectal cancer biomarker NRAS-Q61K (PDB ID 2RGB)

Ligands	Score (kcal/mol)	Bonds between atoms of compounds and residues of the active site					
		Atom of compound	Involved receptor atoms	Involved receptor residues	Type of interaction bond	Distances (Å)	Energy (kcal/mol)
L90	-8.94333172	O 5	O	ASP 33	H-donor	3.09	-1.0
L120	-8.81506538	O 4	O	VAL 29	H-donneur	3.18	-1.9
		O 8	OD1	ASP 119	H-donneur	2.74	-4.0
		O 10	OD1	ASP 30	H-donneur	3.18	-2.7
		O 12	O	ASP 30	H-donneur	3.17	-1.3
L46	-8.6382246	O 11	OD1	ASP 119	H-donor	3.20	-2.7
		O 45	O	ASP 30	H-donor	2.86	-2.4
		6-ring	CE	LYS 117	pi-H	3.76	-1.3

Results and discussion

Interactions of polyphenols with NRAS-Q61K (PDB ID 2RGB)

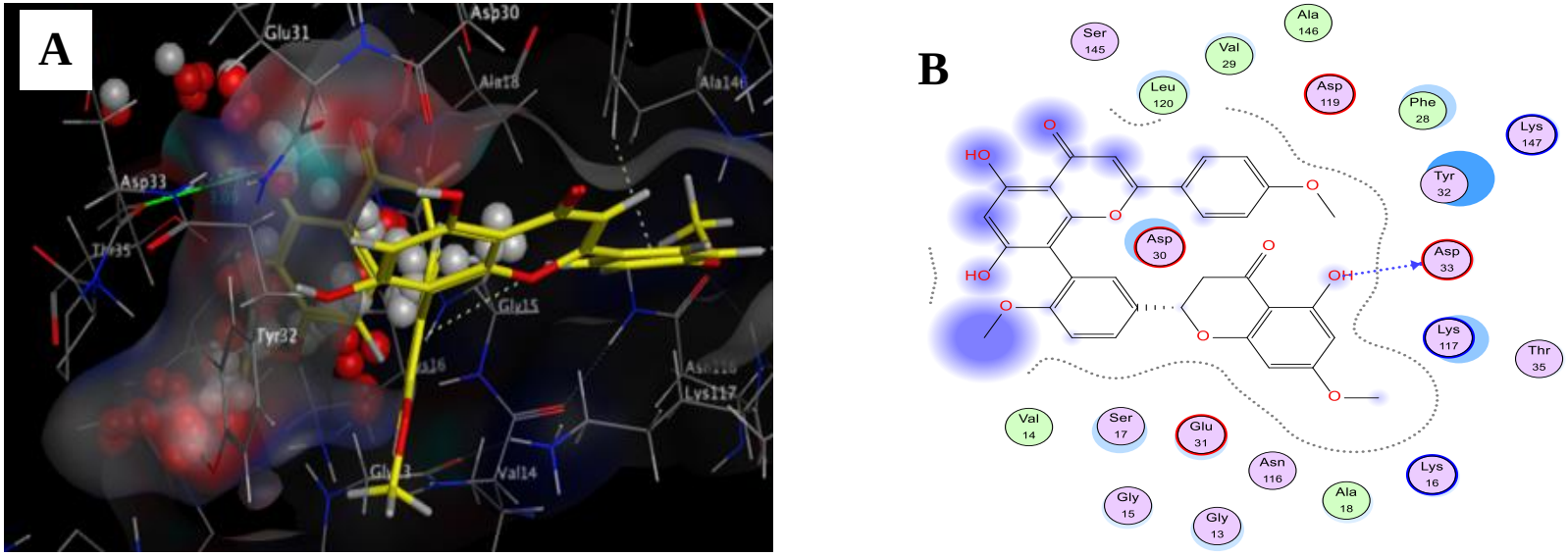

Fig. 4. 3D(A) and 2D(B) interactions between 2,3-Dihydrosciadopitysin (L90) and NRAS-Q61K.

Results and discussion

Interactions of polyphenols with PIK3CA-E545K (PDB ID 8GUD)

Table 6 Docking scores and interaction types of the top 3 ligands docked in the active site of colorectal cancer biomarker PIK3CA-E545K (PDB ID 8GUD)

Ligands	Score (kcal/mol)	Bonds between atoms of compounds and residues of the active site					
		Atom of compound	Involved receptor Atoms	Involved receptor residues	Type of interaction bond	Distances (Å)	Energy (kcal/mol)
L47	-10.0770941	O 15	OD2	ASP 810	H-donor	3.07	-1.3
		O 8	NH1	ARG 770	H-acceptor	3.32	-1.6
		O 9	NH2	ARG 770	H-acceptor	2.78	-3.8
		O 65	OG	SER 774	H-acceptor	2.78	-1.7
		O 67	CA	THR 856	H-acceptor	3.44	-0.6
		O 13	6-ring	TYR 836	H-pi	4.29	-1.1
L15	-9.93335533	O 17	OD1	ASP 933	H-donor	3.02	-3.4
		C 89	OD2	ASP 933	H-donor	3.47	-0.6
		O 2	NH1	ARG 770	H-acceptor	3.25	-1.8
		O 13	N	SER 773	H-acceptor	3.16	-4.0
L30	-9.88699722	O 5	OD2	ASP 933	H-donor	2.90	-4.2
		O 7	OD2	ASP 933	H-donor	2.71	-2.1
		O 13	OD1	ASP 933	H-donor	2.93	-2.5
		O 82	SD	MET 922	H-donor	3.67	-0.8
		O 9	NH1	ARG 770	H-acceptor	3.09	-1.0
		O 9	NH2	ARG 770	H-acceptor	2.96	-1.9
		O 10	NH1	ARG 770	H-acceptor	2.66	-0.3

Results and discussion

Interactions of polyphenols with PIK3CA-E545K (PDB ID 8GUD)

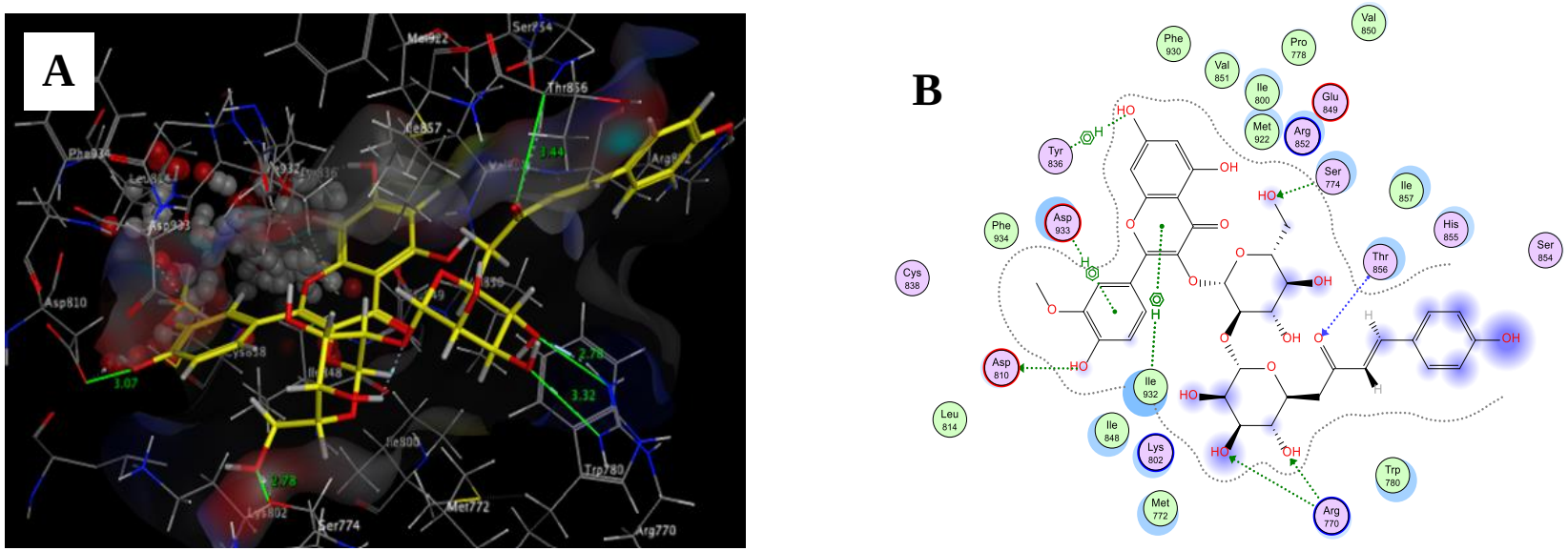

Fig. 5. 3D(A) and 2D(B) interactions between Isorhamnetin-3-O-alpha-L-rhamnosyl-2''-(6'''-p-coumaroyl)-beta-D-glucoside (L47) and PIK3CA-E545K.

Results and discussion

Interactions of polyphenols with DCC-T315I (PDB ID 3QRJ)

Table 7 Docking scores and interaction types of the top 3 ligands docked in the active site of colorectal cancer biomarker DCC-T315I (PDB ID 3QRJ)

Ligands	Score (kcal/mol)	Bonds between atoms of compounds and residues of the active site					
		Atom of compound	Involved receptor atoms	Involved receptor residues	Type of interaction bond	Distances (Å)	Energy (kcal/mol)
L17	-9.50224495	O 7 O 8	OE2 OD2	GLU 282 ASP 381	H-donor H-donor	2.92 3.11	-1.6 -2.9
L18	-9.29626369	O 15 O 7 O 9 O 15	O NE NZ NZ	PHE 382 ARG 362 LYS 285 LYS 271	H-donor H-acceptor H-acceptor H-acceptor	3.01 2.79 2.96 2.82	-1.3 -3.6 -5.1 -5.7
L14	-9.10843468	O 4 O 15 C 47	O OE2 OE2	ILE 360 GLU 282 GLU 286	H-donor H-donor H-donor	3.15 2.93 3.16	-0.7 -2.7 -1.0

Results and discussion

Interactions of polyphenols with DCC-T315I (PDB ID 3QRJ)

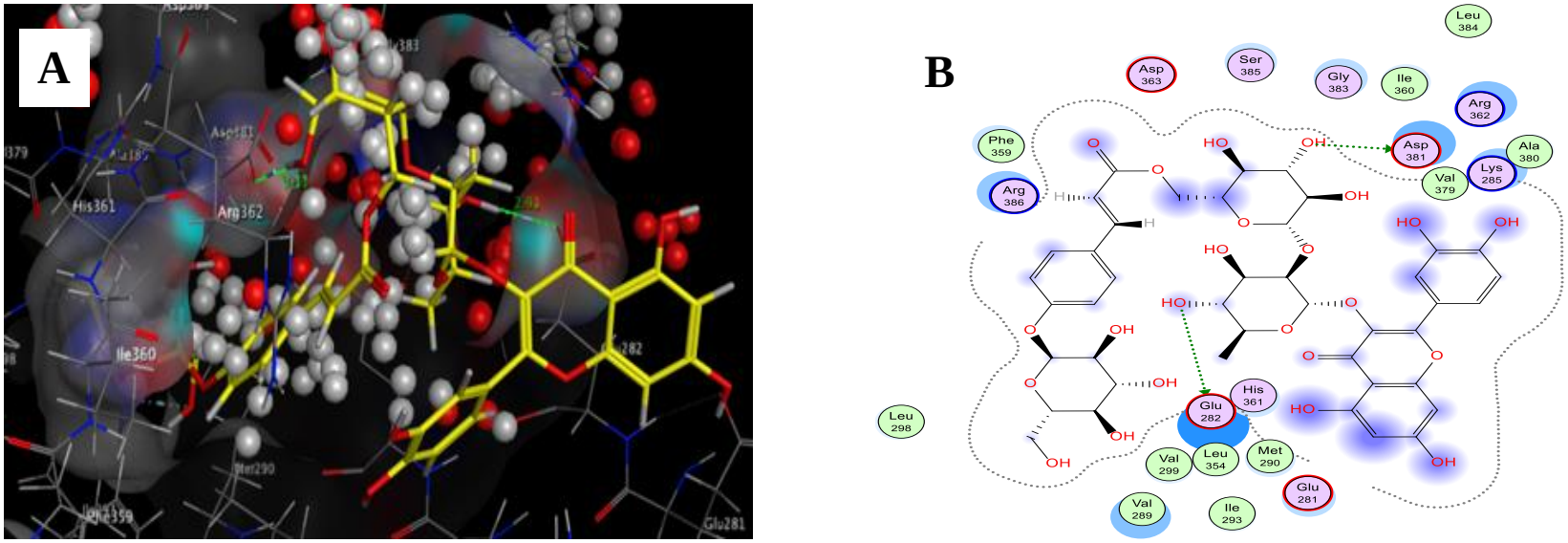

Fig. 6. 3D(A) and 2D(B) interactions between Quercetin 3-O-[2-{6'-(7''''-O-glucosyl)-trans-p-coumaroyl)}-glucosyl]-rhamnoside (L17) and DCC-T315I.

Results and discussion

In our research, we identified a significant likelihood of anticancer therapeutic effectiveness within the group of ligands detailed in Table 1. Particularly noteworthy were the glycosides, quercetin, and isorhamnetin, specifically L15, L17, and L47. These compounds exhibited the ability to simultaneously interact with two mutant codon genes, suggesting promising anticancer potential.

- Quercetin-3-O-6''-rhamnosyl-2''-(6'''-p-coumaroylglucosyl) glucoside (L15) demonstrates its ability to target both BRAF-V600E and PIK3CA-E545K gene mutations simultaneously.

- Quercetin 3-O-[2-{6'-(7''''-O-glucosyl)-trans-p-coumaroyl)}-glucosyl]-rhamnoside (L17) likewise exhibits multi-targeting, interacting with both BRAF-V600E and DCC-T315I.

- The ligand isorhamnetin-3-O-alpha-L-rhamnosyl-2''-(6'''-p-coumaroyl)-beta-D-glucoside (L47) also exhibits a strong affinity for the mutant KRAS-G12D and PIK3CA-E545K genes, suggesting its multi-targeting potential. However, further exploration of the other ligands under investigation is warranted.

Conclusions

- ✓ This study enabled us to identify multiple ligands demonstrating significant inhibitory potential against the codon genes associated with cancer cell proliferation in colorectal cancer (CRC).

- ✓ In this investigation, it is evident from the docking results that the studied ligands exhibit substantial potential for effectively deactivating the KRAS-G12D, BRAF-V600E, PIK3CA-E545K, NRAS-Q61K, and DCC-T315I mutant codons.

Conclusions

- ✓ The polyphenolic compounds identified in our study, particularly flavonol glycosides such as quercetin-3-O-6''-rhamnosyl-2''-(6'''-p-coumaroylglucosyl) glucoside, quercetin 3-O-[2-{6'-(7''''-O-glucosyl)-trans-p-coumaroyl)}-glucosyl]-rhamnoside, and isorhamnetin-3-O-alpha-L-rhamnosyl-2''-(6'''-p-coumaroyl)-beta-D-glucoside, demonstrate potential as valuable therapeutic agents for retarding the progression of CRC.

- ✓ The outcomes of this investigation not only validate the traditional therapeutic application of *Ginkgo biloba* as an anticancer agent but also underscore its potential for extensive exploration in modern medicine and research.

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