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Colorectal Cancer Vrs Glycyrrhiza glabra - Computational Docking & DFT Analysis vis-à-vis TNIK Receptor Protein

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Abstract:- Colorectal cancer (CRC) is a type that develops in the colon to anus segment of the elementary canal. Is painful; acutely debilitating & fatality becausing. Age; diet, lifestyle habits; occupational stress; agrometeorology; bacteriums; virus have been adduced as risk factors and a small percentage being attributed to genetics etc.,. CRC is now a global threat. However, physiologically the protein TNIK (TRAF2 And NCK Interacting Kinase) is found to be widely associated with CRC and is also over expressed. *Glycyrrhizaglabra* is an herbal plant with lots of known medicinal properties. *Glycyrrhizaglabra* has 45 known phyto-compounds (PCs). In the present investigation all the 45 PCs have been put to in silico processes including docking and DFT (Density Functional Theory) analysis to find out the PCs that best stop over-expression of the TNIK protein in colorectal cancer. Glabroiso-flavanone B and Glabridin are found to be champion molecules of this plant against CRCs. Phytos are natural source hence are peerless in drug discovery; functional food and in synergistic therapeutics.

Keyword:- *TNIK (TRAF2 And NCK Interacting Kinase), Docking, DFT, in silico, Wnt pathway.*

I. INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of morbidity and fatality in the globe. It is the second most common cancer in women and the third most common cancer in men (1).In status CRC, the Wnt (Wingless-related integration site) signaling pathway plays a critical role. Because of the functional deletion of the adenomatous polyposis coli (APC) tumor suppressor gene, which results in the constitutive activation of Wnt signaling. In the physiology of healthy humans the Wntpathway occur sporadically (specially in the abdomen organs\cell lines); it however is abnormally active in 90% of CRC malignancies (2). Colorectal cancer genetic and epigenetic variants have been studied extensively in the past. The most striking discovery is that colorectal tumors have mutations in genes involved in the canonical Wnt/β-catenin signaling pathway (3). T-cell factors 3 and 4 (TCF3/4) (TCF7L1/2), axis inhibitor 2 (AXIN2), and APC membrane recruitment protein1 (AMER1, WTX or FAM123B) are all altered often in CRCs (4). By nuclear translocation and subsequent phosphorylation of the transcription factor TCF4, TNIK mediates proliferative Wnt signals in crypts of the small intestine and colorectal cancer cells (5).TNIK is an important regulator of Wnt signaling, and colorectal cancer cells rely heavily on TNIK expression and catalytic activity

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for proliferation (6). TNIK has also been identified as a potential new therapeutic target in a variety of cancer studies. TNIK expression has been linked to the survival of human cancer cells, including colorectal, gastric, liver, colovesical fistula, recto-urethral fissures\lesions, and hematological cancer cells, etc.,(7). Pan globally, CRC combat is done primarily with mono chemo viz., Taxens; (other) multi drug CTs; Repurposed; RT; Surgery; Target therapy and variable admixture(s). Yet prognosis remains poor to grave. And, end of life stage palliative (8,9)cum intensive nursing (10) remain important. Therefore, utilizing molecular docking models it is possible to design and create effective inhibitors of the TNIK ~ TRAF2 And NCK Interacting Kinase (note-i) protein target to interdict Wnt signaling pathways in the setting of CRC. Needed.

Nature with its wide range of medicinal plants available is thought to be a reservoir of therapeutic elements\sources. They have been used to treat & to cure many a diseases for centuries past and have been of great use to humanity. Recently Tripathy, et.al.,(11) used Computational Modeling using PCs from known non-toxic medical phytos to indicate likeness for drug discovery candidates vis-a-visSoriasis. Although conspicuous by absence in the Sino-Nipponese ancient texts (12), the Indian folklore cum traditional medicinal (13) the plant *Glycyrrhiza glabra* Linn., has a wide range of therapeutic properties under official seal (14,15). It's a Leguminosae (legume family) perennial herbaceous plant. It stands around 1.5m tall and has wrinkled woody, dark roots with a delicious taste. In subtropical and warm temperate climates, the leaves are unequally branched in 4-7 pairs. Flowers are violet in hue, with 3-5 brown seed pods. "Liquorice" or "sweet wood" (Jastimadhu) are frequent names for it. This plant's parts contain anti-inflammatory compounds along with expectorant, carminative, anticancer, hypolipidemic, anti-viral, hypotensive, expectorant, carminative, hypolipidemic, hypotensive, anti-diuretic, anti-mutagenic, hepato-protective, spasmolytic antipyretic, antiulcer, anxiolytic, antioxidant, and aphrodisiac are some of the properties of this plant. And have also been used to treat hyperdipsia, cough, and other ailments like bronchitis, urinary tract ulceration, pharyngitis, epilepsy, anaemia, expectorant and in wound healing. It cleanses and safeguards the liver (16). Looking into such medicinal properties, in the current investigation, an *in silico* approach was carried out to explore the anti-cancerous property of the PCs from *Glycyrrhiza glabra* against TNIK (TRAF2 And NCK Interacting Kinase) protein, which world wide is considered to be potential therapeutic target in CRCs. This study lays the groundwork for innovative anti-cancer medications against CRCs; make it easier for drug discoverers; Corporates; to develop and market more effective medications and help clinicians in CRC treatment.

II. MATERIAL AND METHOD

A. *Gene target selection of Colorectal cancer*

In colorectal cancer cell lines the TNIK (TRAF2 And NCK Interacting Kinase)protein (gene name) is frequently found. The best human derived protein X-ray crystallographic structure is obtained from PDB database (17) with PDB Id 6RA7 having a resolution of 1.20 Å combined with nucleic acids, according to a search in the UniProt database (18) with the entry id Q9UKE5, of 1,360 base pairs length, mass 154,943Da.This is the protein that is chosen for this in silico study. The TNIK protein's 3D structure was viewed using Discovery studio visualizer version 2019 (19). The structure's chain A was chosen for the research.

B. *Prediction of binding sites of the TNIK protein*

The active sites of the molecules, where small molecules will attach are defined by the binding sites of a protein. As a result, the CastP website (20) was used to predict the binding sites of the TNIK protein that are used for the investigation.

C. *Reported phytocompounds from Glycyrrhizaglabra (Liquorice)*

Glycyrrhizaglabra contains a number of phytochemicals that have therapeutic effects. The PubChem database (21) was employed to retrieve the details information about the phytocompounds.

D. *Lipinski rule of five – Ro5*

Any oral active medicine should satisfy the requirements of Molecular mass (=500 D), logP (=5), Hydrogen bond donor (=5), Hydrogen bond acceptors (=10), and Molar refractivity (in *in silico* research) (40-130). This rule of 5 (RO5) (22) is the most important criterion for selection. The candidate compound is disqualified as a potential source if any of the rules is not met. The RO5 for all of the phytochemicals utilized in the study was predicted using the TargetNet web server (23) (http://targetnet.scbdd.com/calcnet/calc rule text/#). Protox-II server (24) and Toxicity checker server under mcule environment (25) program were used to check the harmful nature of the substances that pass through the RO5.

E. *Molecular docking of selected compounds from Glycyrrhizaglabra against the colorectal cancer protein TNIK(TRAF2 And NCK Interacting Kinase).*

Glycyrrhizaglabra compounds that follow the RO5 and are non-toxic in nature were further processed for a molecular docking investigation against the TNIK (TRAF2 And NCK Interacting Kinase) protein. The widely accepted software called Autodock 4.2 tool (26) was utilized in the investigation to verify the efficiencies of the ligands chosen for examination in order to undertake molecular docking studies. Based on binding energy values, ligand efficiency, inhibition constant and intermolecular hydrogen (H)-bonds, the best-docked complexes were described and processed for further computational study. In this work, a commonly used medicine in colorectal cancer, Capecitabine (27), was employed in a comparison trial with the TNIK protein.

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F. DFT (Density Functional Theory) analysis

A quantum computational analysis was conducted using the notion of Density Functional Theory (DFT) to determine the reactivity and efficacy of the possible ligands used in this investigation. The Becke, 3-parameter, LeeYang-Parr (B3LYP) density functional theory (DFT) (28) correlation function was used to investigate the reactivity and efficiency. DFT analysis was used to estimate the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy respectively of the two ligand molecules with the best docking score and one commercially marketed medication (namely: Capecitabine as standard) having inhibitory activity against TNIK protein of colorectal cancer. The energy was calculated using the ORCA Program version 4.0 (29). Potential medicines' electronic energy, HOMOs, LUMOs, gap energy, and dipole moment were all measured.

III. RESULTS

A. Selected gene

In research studies relating to CRCs consistent high expression of TNIK (TRAF2 And NCK Interacting Kinase)has been reported. The detail information of this protein is obtained from UniProt database. The 3D-structure of TNIK protein is obtained from PDB database with PDB Id 6RA7. Here the chain A of the structure selected for the investigation.

B. Binding sites of TNIK protein

Using the CastP server, the active sites of the TNIK (TRAF2 And NCK Interacting Kinase) protein obtained. The predicted bindingof TNIK protein are GLU29,VAL31,GLY32,ASN33,THR35,TYR36,VAL39,LYS41,LEU50,ALA52,LYS54,GLU69,LEU73,ILE82,ALA83, MET105,GLU106,PHE107,CYS108,GLY109,ALA110,GLY111,SER112,THR114,ASP115,LEU116,LYS118,ASN119 ,GLN157,ASN158,LEU160,LEU161,GLU163,LEI169,VAL170,PHE172,HIS305,ILE306,THR309,LYS310,ARG313and GLY314. These are the obtained binding sites of TNIK protein.

C. Phyto compounds of Glycyrrhiza glabra

Glycyrrhiza glabra is a traditional medicinal plant. Its therapeutic properties are still being researched. The PCs from *Glycyrrhiza glabra* were acquired from numerous research publications in the current investigation. The 45 PCs as in Table 1 have been obtained from literature (30,31,32,33) and co-verified with PubChem database.

SL. No.	Chemical name	Molecular formula	PMID	SMILE ID
1.	Liquiritin	$C_{21}H_{22}O_9$	503737	C1C(OC2=C(C1=O)C=CC(=C2)O)C3=CC=C(C=C3)OC4C(C(C(C(O4)CO)O)O)O
2.	Glycyrrhizin	$C_{42}H_{62}O_{16}$	14982	CC1(C2CCC3(C(C2(CCC1OC4C(C(C(C(O4)C(=O)O)O)O)O)OC5C(C(C(C(O5)C (=O)O)O)O)O)C)C(=O)C=C6C3(CCC7(C6CC(CC7)©C(=O)O)C)C)C)C
3.	Liquiritigenin	$C_{15}H_{12}O_4$	114829	C1C(OC2=C(C1=O)C=CC(=C2)O)C3=CC=C(C=C3)O
4.	Neoliquiritin	$C_{21}H_{22}O_9$	51666248	C1C(OC2=C(C1=O)C=CC(=C2)OC3C(C(C(C(O3)CO)O)O)O)C4=CC=C(C=C4)O
5.	Isoliquiritigenin	$C_{15}H_{12}O_4$	638278	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2)O)O)O
6.	Neoisoliquiritin	$C_{21}H_{22}O_9$	5320092	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2)OC3C(C(C(C(O3)CO)O)O)O)O)O
7.	Licuraside	$C_{26}H_{30}O_{13}$	14282455	C1C(C(C(O1)OC2C(C(C(OC2OC3=CC(=C(C=C3)C(=O)C=CC4=CC=C(C=C4)O)O)CO)O)O)O)(CO)O
8.	Glabrolide	$C_{30}H_{44}O_4$	90479675	CC1(C2CCC3(C(C2(CCC1O)C)C(=O)C=C4C3(CCC5(C4CC6(CC5OC6=O)C)C)C)C)C
9.	Licoflavonol	$C_{20}H_{18}O_6$	5481964	CC(=CCC1=C(C2=C(C=C1O)OC(=C(C2=O)O)C3=CC=C(C=C3)O)O)C
10.	Glychionide A	$C_{21}H_{18}O_{11}$	11597485	C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C(=C(C=C3O)OC4C(C(C(C(O4)C(=O)O)O)O)O)O
11.	Glychionide B	$C_{22}H_{20}O_{11}$	3084961	COC1=C(C=C(C2=C1OC(=CC2=O)C3=CC=CC=C3)O)OC4C(C(C(C(O4)C(=O)O)O)O)O
12.	Glabridin	$C_{20}H_{20}O_4$	124052	CC1(C=CC2=C(O1)C=CC3=C2OCC(C3)C4=C(C=C(C=C4)O)O)C
13.	Glabrone	$C_{20}H_{16}O_5$	5317652	CC1(C=CC2=C(O1)C=CC(=C2O)C3=COC4=C(C3=O)C=CC(=C4)O)C
14.	Shinpterocarpin	$C_{20}H_{18}O_4$	10336244	CC1(C=CC2=C(O1)C=CC3=C2OCC4C3OC5=C4C=CC(=C5)O)C
15.	Glyzarin	$C_{18}H_{14}O_4$	44257206	CC1=C(C(=O)C2=C(O1)C(=C(C=C2)O)C(=O)C)C3=CC=CC=C3

16.	Kumatakenin	**$C_{17}H_{14}O_6$**	5318869	COC1=CC(=C2C(=C1)OC(=C(C2=O)OC)C3=CC=C(C=C3)O)O
17.	Hispaglabridin A	**$C_{25}H_{28}O_4$**	4484221	CC(=CCC1=C(C=CC(=C1O)C2CC3=C(C4=C(C=C3)OC(C=C4)(C)C)OC2)O)C
18.	Hispaglabridin B	**$C_{25}H_{26}O_4$**	15228661	CC1(C=CC2=C(O1)C=CC(=C2O)C3CC4=C(C5=C(C=C4)OC(C=C5)(C)C)OC3)C
19.	Glycyrrhetic acid	**$C_{30}H_{46}O_4$**	10114	CC1(C2CCC3(C(C2(CCC1O)C)C(=O)C=C4C3(CCC5(C4CC(CC5)(C)C(=O)O)C)C)C)C
20.	Isoliquiritin	**$C_{21}H_{22}O_9$**	5318591	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2)O)O)OC3C(C(C(C(O3)CO)O)O)O
21.	Glabrene	**$C_{20}H_{18}O_4$**	480774	CC1(C=CC2=C(C=CC(=C2O1)C3=CC4=C(C=C(C=C4)O)OC3)O)C
22.	Liquiritinapiioside	**$C_{26}H_{30}O_{13}$**	10076238	C1C(OC2=C(C1=O)C=CC(=C2)O)C3=CC=C(C=C3)OC4C(C(C(C(O4)CO)O)O)OC5C(C(CO5)(CO)O)O
23.	Glabrol	**$C_{25}H_{28}O_4$**	11596309	CC(=CCC1=C(C=CC(=C1)C2CC(=O)C3=C(O2)C(=C(C=C3)O)CC=C(C)C)O)C
24.	3-hydroxyglabrol	**$C_{25}H_{28}O_5$**	480854	CC(=CCC1=C(C=CC(=C1)C2C(C(=O)C3=C(O2)C(=C(C=C3)O)CC=C(C)C)O)O)C
25.	Licochalcone C	**$C_{21}H_{22}O_4$**	9840805	CC(=CCC1=C(C=CC(=C1OC)C=CC(=O)C2=CC=C(C=C2)O)O)C
26.	Formononetin	**$C_{16}H_{12}O_4$**	5280378	COC1=CC=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3)O
27.	Glabroisoflavanone A	**$C_{20}H_{18}O_5$**	11221431	CC1(C=CC2=C(O1)C=CC3=C2OCC(C3=O)C4=C(C=C(C=C4)O)O)C
28.	Glabroisoflavanone B	**$C_{21}H_{20}O_5$**	11405466	CC1(C=CC2=C(O1)C=CC3=C2OCC(C3=O)C4=C(C=C(C=C4)OC)O)C
29.	Kanzonol Y	**$C_{25}H_{30}O_5$**	10001604	CC(=CCC1=CC(=C(C=C1O)O)C(=O)C(CC2=CC(=C(C=C2)O)CC=C(C)C)O)C
30.	Paratocarpin B	**$C_{25}H_{26}O_4$**	42607541	CC(=CCC1=C(C=CC(=C1)C=CC(=O)C2=C(C3=C(C=C2)OC(C=C3)(C)C)O)O)C
31.	Mannopyranosyl-D-glucitol	**$C_{12}H_{24}O_{11}$**	129816843	C(C1C(C(C(C(O1)C(C(C(C(C(CO)O)O)O)O)O)O)O)O)O
32.	Hemileiocarpin	**$C_{21}H_{20}O_4$**	70995758	CC1(C=CC2=C(O1)C=CC3=C2OCC4C3OC5=C4C=CC(=C5)OC)C
33.	Glycyrrhizic acid	$C_{42}H_{62}O_{16}$	14982	CC1(C2CCC3(C(C2(CCC1OC4C(C(C(C(O4)C(=O)O)O)O)O)OC5C(C(C(C(O5)C(=O)O)O)O)O)O)C)C(=O)C=C6C3(CCC7(C6CC(CC7)©C(=O)O)C)C)C)C
34.	Licocoumarin A	$C_{25}H_{26}O_5$	5324358	CC(=CCC1=C(C=CC(=C1O)C2=CC3=C(C(=C(C=C3)O)CC=C(C)C)OC2=O)O)C
35.	18 beta-Glycyrrhetinic acid	$C_{30}H_{46}O_4$	44435791	CC1(C2CCC3(C(C2(CCC1O)C)C(=O)C=C4C3(CCC5(C4CC(CC5)(C)C(=O)O)C)C)C)C
36.	Prenyllicoflavone A	$C_{25}H_{26}O_4$	11349817	CC(=CCC1=CC2=C(C=C1O)OC(=CC2=O)C3=CC(=C(C=C3)O)CC=C(C)C)C
37.	Alpha-terpineol	$C_{10}H_{18}O$	17100	CC1=CCC(CC1)C(C)(C)O
38.	Glisoflavone	$C_{21}H_{20}O_6$	5487298	CC(=CCC1=C(C(=CC(=C1)C2=COC3=C(C2=O)C(=CC(=C3)O)OC)O)O)C
39.	Isoangustone A	$C_{25}H_{26}O_6$	21591148	CC(=CCC1=C(C(=CC(=C1)C2=COC3=C(C2=O)C(=C(C(=C3)O)CC=C(C)C)O)O)O)C
40.	1-methoxyficifolinol	$C_{26}H_{30}O_5$	480872	CC(=CCC1=CC2=C(C=C1O)OC3C2COC4=C3C(=C(C(=C4)O)CC=C(C)C)OC)C
41.	Licoriphenone	**$C_{21}H_{24}O_6$**	21591149	CC(=CCC1=C(C=C(C(=C1OC)CC(=O)C2=C(C=C(C=C2)O)O)O)OC)C
42.	Semilicoisoflavone B	**$C_{20}H_{16}O_6$**	5481948	CC1(C=CC2=C(O1)C(=CC(=C2)C3=COC4=CC(=CC(=C4C3=O)O)O)O)C
43.	Licoarylcoumarin	$C_{21}H_{20}O_6$	10090416	CC(C)(C=C)C1=C2C(=C(C=C1O)OC)C=C(C(=O)O2)C3=C(C=C(C=C3)O)O

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44.	Licopyranocoumarin	$C_{21}H_{20}O_7$	122851	CC1(CCC2=C(O1)C=C3C(=C2OC)C=C(C(=O)O3)C4=C(C=C(C=C4)O)O)CO
45.	Tetramethylpyrazine	$C_{12}H_{12}N_2O_8$	291621	COC(=O)C1=C(N=C(C(=N1)C(=O)OC)C(=O)OC)C(=O)OC

Table 1: Description of Phytochemical compounds present in *Glycyrrhiza glabra*

D. Lipinsk's rule of 5 and Toxicity

Lipinski's Rule of 5 plays a significant role in drug development. This rule is commonly used to determine if compounds (are likely to) display the requisite pharmacokinetic properties, hence qualifying them as potential candidates for orally active systemic drugs (candidate moieties) consonant with anthropo-homeo physiology. The Rule-5 through its parametric distribution and mathematical evaluation it also contains the ADME (Absorption, Distribution, Metabolism, and Excretion) features. As a result, Lipinsk's 5 has become crucial. Therefore, the45 PCs from *Glycyrrhiza glabra*, have under gone testing using the TarGetNet server against Lipinsk's rule of five. Table 2 summarizes the findings.

E. Finding :

The Lipinsk's rule of 5 is violated by 23 PCs out of 45.As a result, these 23PCs were discarded. The remaining 22 compounds were processed for toxicity.To check the toxicity of the PCs, two web servers were used, namely:ProTox-II server and Toxicity Checker Tool. Only 11 PCs passed the Toxicity test/s. The findings are listed in Table 3. These 11 compounds were selected for the docking study and analysis against the TNIK protein of CRCs along with the reported drug Capecitabine having PubChem ID 60953; molecular formula $C_{15}H_{22}FN_3O_6$., and MW359). The 3D-structures of the PCs and the reported drug were downloaded from the PubChem database in .SDF format and converted into .pdb format using the Discovery studio tool.

SL. NO	PHYTOCHEMICALS NAME	TPSA (Topological polar surface area) (<140)	MR (Molar Refractivity) (40-130)	MOLECULAR WEIGHT (<=500 D)	HBD-Hydrogen bond donor (<=5)	HBA1-Hydrogen bond acceptors (<=10)	LogP (<=5)	Lipinski rule of five
1.	Liquiritin	145.91	101.6697	418.39398	5.0	9.0	0.2774	75%
2.	Glycyrrhizin	267.04	202.8404	822.93208	8.0	16.0	2.2456	25%
3.	Liquiritigenin	66.76	69.5475	256.25338	2.0	4.0	2.8043	100%
4.	Neoliquiritin	145.91	101.6697	418.39398	5.0	9.0	0.2774	75%
5.	Isoliquiritigenin	77.76	72.3175	256.25338	3.0	4.0	2.6995	100%
6.	Neoisoliquiritin	156.91	104.4397	418.39398	6.0	9.0	0.1726	75%
7.	Licuraside	215.83	130.8923	550.5086	8.0	13.0	-1.3625	25%
8.	Glabrolide	63.6	134.2528	468.66796	1.0	4.0	5.8633	75%
9.	Licoflavonol	111.13	99.732	354.35332	4.0	5.0	3.7911	100%
10.	Glychionide A	187.12	106.7212	446.36102	6.0	10.0	0.1422	50%
11.	Glychionide B	176.12	111.1902	460.3876	5.0	10.0	0.4452	50%
12.	Glabridin	58.92	93.247	324.3704	2.0	4.0	4.0007	100%
13.	Glabrone	79.9	96.087	336.33804	2.0	4.0	4.0554	100%
14.	Shinpterocarpin	47.92	90.795	322.35452	1.0	4.0	4.1861	100%
15.	Glyzarin	67.51	85.1035	294.30136	1.0	3.0	3.6766	100%
16.	Kumatakenin	89.13	84.95	314.28946	2.0	5.0	2.8884	100%
17.	Hispaglabridin A	58.92	116.967	392.48742	2.0	4.0	5.5094	75%
18.	Hispaglabridin B	47.92	115.345	390.47154	1.0	4.0	5.4793	75%
19.	Glycyrrhetic acid	74.6	136.8536	470.68384	2.0	4.0	6.4126	75%
20.	Isoliquiritin	156.91	104.4397	418.39398	6.0	9.0	0.1726	75%
21.	Glabrene	58.92	94.357	322.35452	2.0	4.0	4.215	100%
22.	Liquiritinapioside	204.83	128.1223	550.5086	7.0	13.0	-1.2577	25%
23.	Glabrol	66.76	116.9875	392.48742	2.0	4.0	5.8217	75%
24.	3-hydroxyglabrol	86.99	118.149	408.48682	3.0	5.0	4.7925	100%
25.	Licochalcone C	66.76	100.5065	338.39698	2.0	4.0	4.5112	100%
26.	Formononetin	59.67	76.435	268.26408	1.0	3.0	3.1742	100%
27.	Glabroisoflavanone A	75.99	93.6685	338.35392	2.0	5.0	3.6409	100%
28.	Glabroisoflavanone B	64.99	98.1375	352.3805	1.0	5.0	3.9439	100%
29.	Kanzonol Y	97.99	120.6013	410.5027	4.0	5.0	4.6071	100%
30.	Paratocarpin B	66.76	118.1355	390.47154	2.0	4.0	5.6868	75%
31.	Mannopyranosyl-D-glucitol	211.53	70.387	344.31236	10.0	11.0	-6.3744	50%
32.	Hemileiocarpin	36.92	95.264	336.3811	0.0	4.0	4.4891	100%

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33.	Glycyrrhizic acid	267.04	202.8404	822.93208	8.0	16.0	2.2456	25%
34.	Licocoumarin A	90.9	121.429	406.47094	3.0	4.0	5.5942	75%
35.	18 beta-Glycyrrhetinic acid	74.6	136.8536	470.68384	2.0	4.0	6.4126	75%
36.	Prenyllicoflavone A	70.67	119.406	390.47154	2.0	3.0	5.8886	75%
37.	Alpha-terpineol	20.23	48.7958	154.24932	1.0	1.0	2.5037	100%
38.	Glisoflavone	100.13	104.201	368.3799	3.0	5.0	4.0941	100%
39.	Isoangustone A	111.13	123.452	422.47034	4.0	5.0	5.2998	75%
40.	1-methoxyficifolinol	68.15	122.629	422.5134	2.0	5.0	5.7335	75%
41.	Licoriphenone	96.22	103.8965	372.41166	3.0	6.0	3.7547	100%
42.	Semilicoisoflavone B	100.13	98.11	352.33744	3.0	5.0	3.761	100%
43.	Licoarylcoumarin	100.13	104.084	368.3799	3.0	5.0	4.049	100%
44.	Licopyranocoumarin	109.36	103.4228	384.3793	3.0	6.0	2.9558	100%
45.	Tetramethylpyrazine	130.98	67.15	312.23228	0.0	10.0	-0.377	75%

Table 2: Lipinski's RO5 study was using TargetNet server

S.N.	Phytocompound	Tool	Toxic/Non-Toxic
1.	Liquiritigenin	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
2.	Isoliquiritigenin	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
3.	Licoflavonol	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
4.	Glabridin	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
5.	Glabrone	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
6.	Shinpterocarpin	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
7.	Glyzarin	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
8.	Kumatakenin	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
9.	Glabrene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
10.	3-hydroxyglabrol	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
11.	Licochalcone C	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
12.	Formononetin	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
13.	Glabroisoflavanone A	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
14.	Glabroisoflavanone B	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
15.	Kanzonol Y	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
16.	Hemileiocarpin	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
17.	Alpha-terpineol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
18.	Glisoflavone	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
19.	Licoriphenone	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
20.	Semilicoisoflavone B	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
21.	Licoarylcoumarin	ProTox-II	Non-Toxic

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		Toxicitychecker	Toxic
22.	Licopyranocoumarin	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic

Table 3: Toxicity Checking The Phycompounds Using Protox-II Tool and Toxicity checker tool

F. Molecular docking.

The Autodock 4.2 has been used for the docking of the molecules. The grid box value taken for the study is for X-dimension = 82, Y-dimension = 96 and Z-dimension =66 with 0.375 Angstrom spacing. In the docking study, it was found that,the PCs namely Glabroisoflavanone β shows the highest binding affinity of -8.93 kcal/mol, with an ligand efficiency of-0.34, inhibition constant 286.82 µm and forms conventional hydrogen bond with MET105 with average distance of 2.70951 Å vis-à-vis the TNIK protein of Colorectal cancer. Glabridin shows the second highest binding affinity of -8.39 kcal/mol, with an ligand efficiency of -0.35, inhibition constant 703.39 µm and forms an conventional hydrogen bond with LYS54 with an Average Distance of 2.72686Å and other 9 (of the 11) follow. Table 4 summarizes the docking results in descending order. Figure 1 and 2 represents 2D and 3D interaction of TNIK protein of Colorectal cancer with Glabroisoflavanone B. Our Figure 3 and 4 represents 2D and 3D interaction of TNIK (TRAF2 And NCK Interacting Kinase) protein of the CRC with Glabridin. On the other hand, the reported drug Capecitabine showed a very less binding affinity of -4.57 kcal/mol against the TNIK protein of the Colorectal cancer. Table 5 represents the other docking parameters result of the reported drug.

Sl. No.	Phytocompound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	Glabroisoflavanone B	-8.93	-0.34	286.82	1	MET105	2.70951
2.	Glabridin	-8.39	-0.35	703.39	1	LYS54	2.72686
3.	Hemileiocarpin	-8.27	-0.33	864.82	N/A	N/A	N/A
4.	Formononetin	-8.19	-0.41	987.75	1	CYS108	2.11168
5.	Shinpterocarpin	-7.93	-0.33	1.54	N/A	N/A	N/A
6.	Liquiritigenin	-7.82	-0.41	1.86	3	LYS54,CYS108,ASP115	2.865643333
7.	Kumatakenin	-7.81	-0.34	1.87	3	CYS108,ASP115,GLU106	2.37921
8.	Glabrene	-7.42	-0.31	3.61	2	GLU106,ASP115	2.19543
9.	Glabrone	-7.07	-0.28	6.62	2	ASN119,ASP115	2.092135
10.	Glabroisoflavanone A	-6.38	-0.26	21.21	2	TYR36,CYS108	2.15856
11.	Alpha-terpineol	-5.19	-0.47	157.66	N/A	N/A	N/A

Table 4: Docking of screened Compounds from *Glycyrrhiza glabra* against TNIK protein of Colorectal cancer

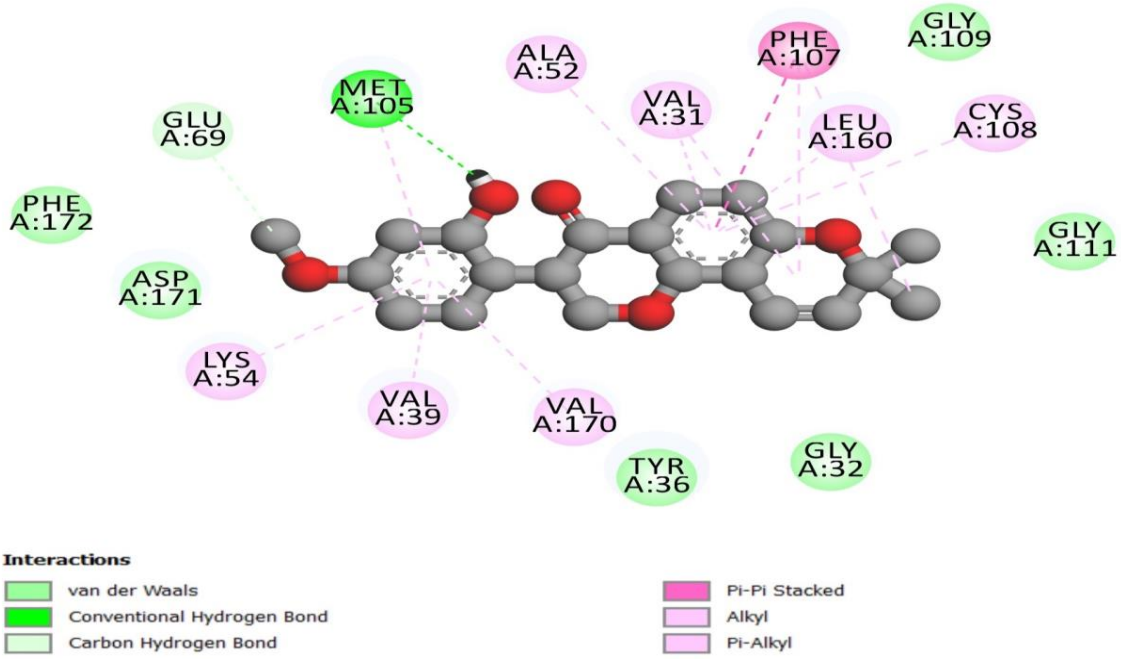

Fig. 1: 2D interaction of TNIK protein of Colorectal cancer with Glabroiso flavanone B

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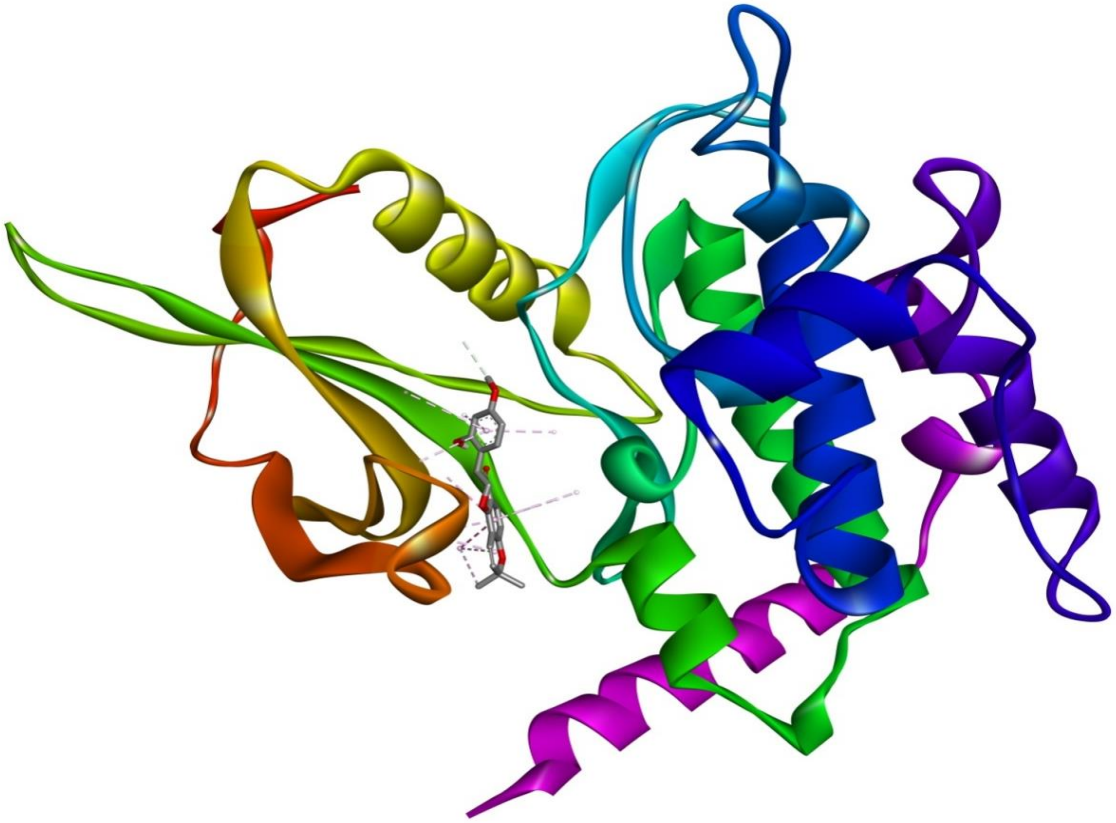

Fig. 2: 3D interaction of TNIK protein of Colorectal cancer with Glabroisoflavanone B

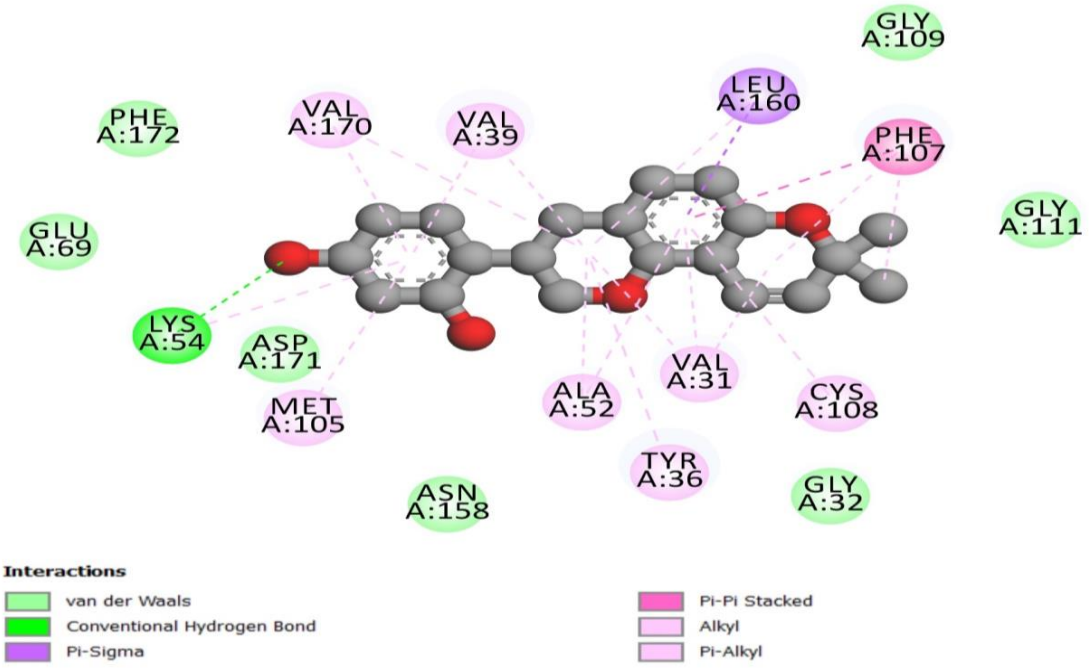

Fig. 3: 2D interaction of TNIK protein of Colorectal cancer with Glabridin.

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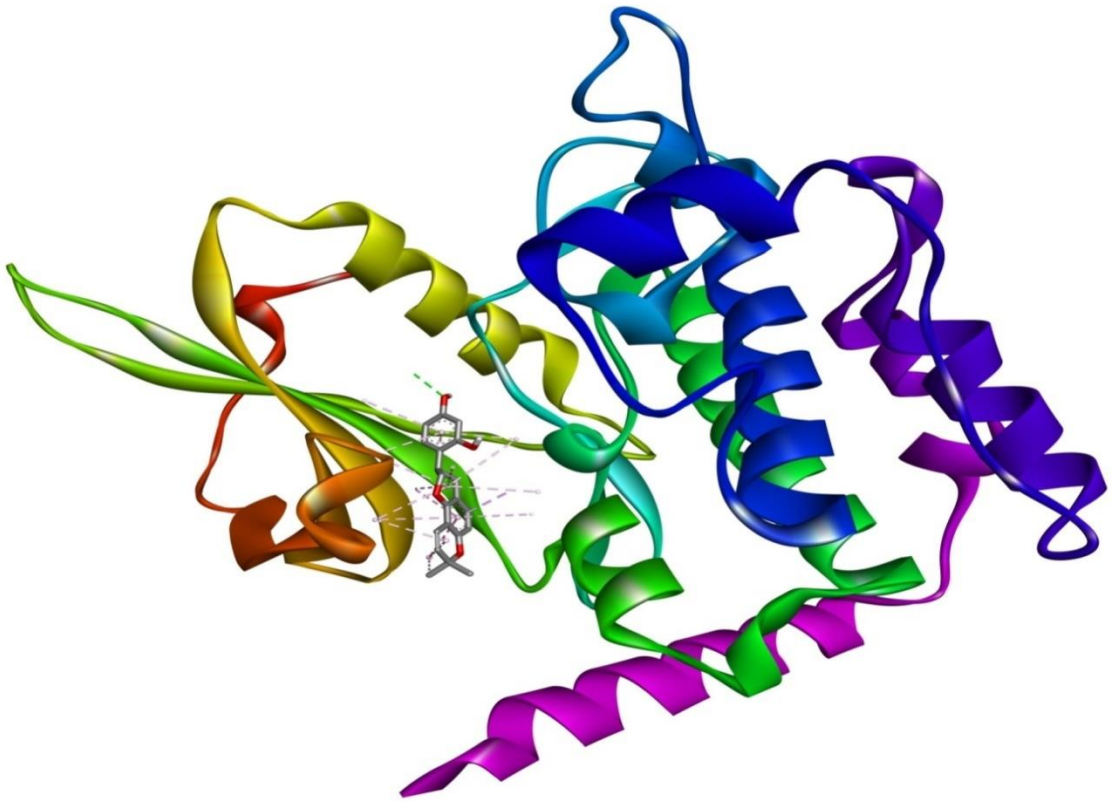

Fig. 4: 3D interaction of TNIK protein of Colorectal cancer with Glabridin

Sl. No.	Phytocompound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (μm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	Capecitabine	-4.57	-0.18	444.7	5	TYR36,LYS41,ASP115, GLU29	2.390316

Table 5: Docking of reported drug used against TNIK protein of Colorectal cancer

IV. QUANTUM CHEMICAL CALCULATION

Due to the relevance of quantum computation, quantum chemistry was utilized to explore the frontier molecular descriptors of Glabroisoflavanone B, Glabridin, and Capecitabine (reported drug), such as HOMO and LUMO, gap energy, and dipole moment (Table 6).The effective reactivity for each compound with a band energy gap (E), i.e. the difference between LUMO and HOMO, was 10.366 eV, 10.563 Ev and 11.649 eV, respectively. Glabroisoflavanone B has a higher reactivity than Glabridin based on its lowest band energy gap. HOMO energy values were -8.101eV for Glabroisoflavanone B, -7.635eV for Glabridin, and -9.795eV for Capecitabine. LUMO energy values were 2.265eV for Glabroisoflavanone B, 2.928eV for Glabridinand1.854eV for Capecitabine. Figure 5 represents the LUMO and HOMO of GlabroisoflavanoneB.Figure 6 represents the LUMO and HOMO of Glabridin.Figure 7 represents the LUMO and HOMO of Capecitabine (for comparison).

This apart, DFT, HUMO, LUMO etc., parameters are all ion mediated. Now, ions have been indicated as be causing therapeutic potency, reactivity & spectrum of any moieties's efficacy (34). And, ions are entirely para-magnetism dependant including (super-para magnetism) in the kinetic pathways of therapeutics (35). The less be the eV value the small be the corresponding distance between the anti-body & the antigen which sums as 'firmness of the docking vestibule' clinically measurable as greater drug delivery in lesser time and (may be) also the copulation period. The end results are of vital importance at clinical level; specially to a conservative clinician.

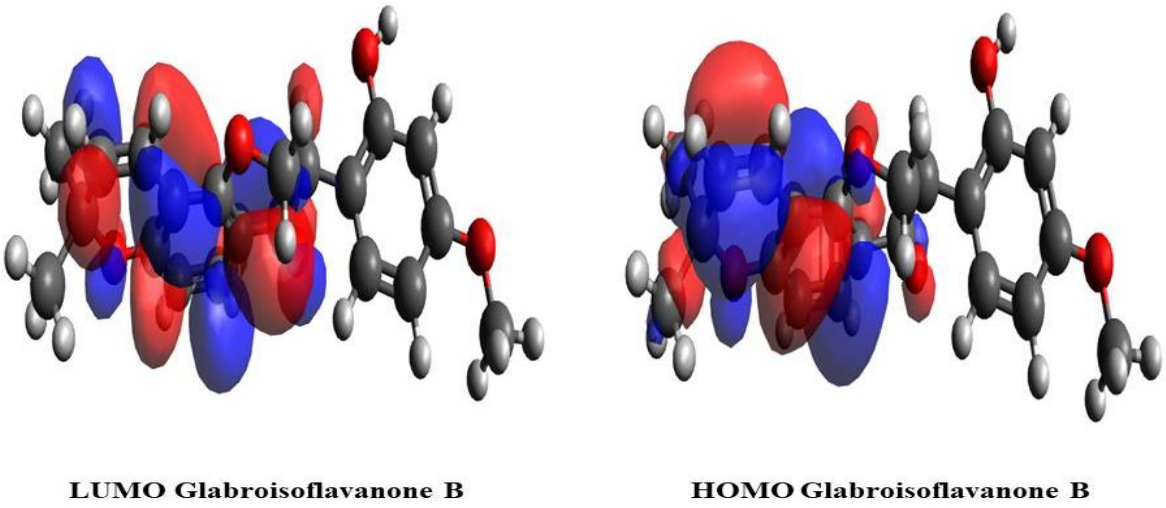

Fig. 5: Represents the LUMO and HOMO of Glabroisoflavanone B

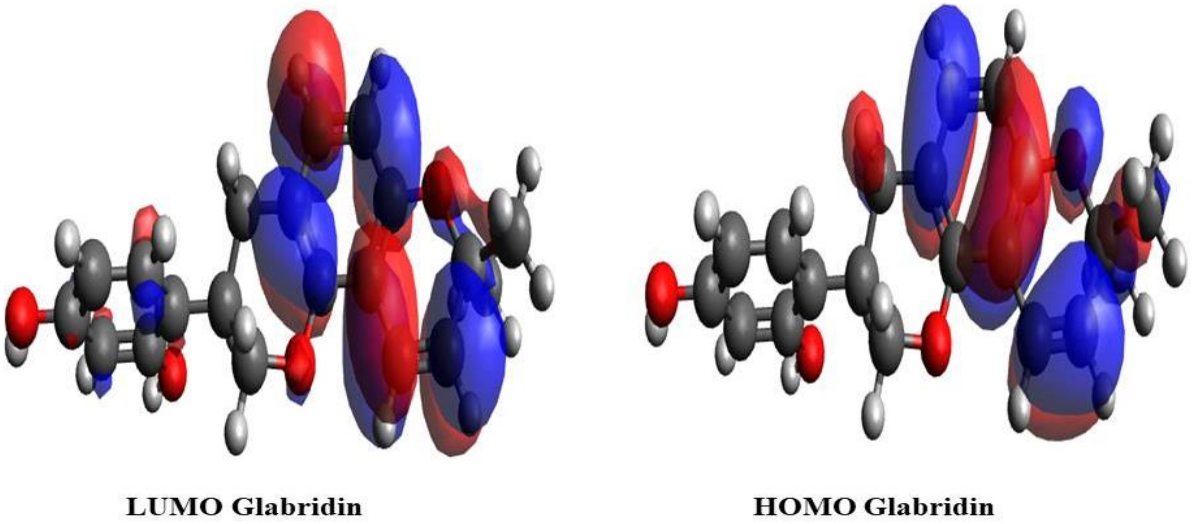

Fig.6: Represents the LUMO and HOMO of Glabridin

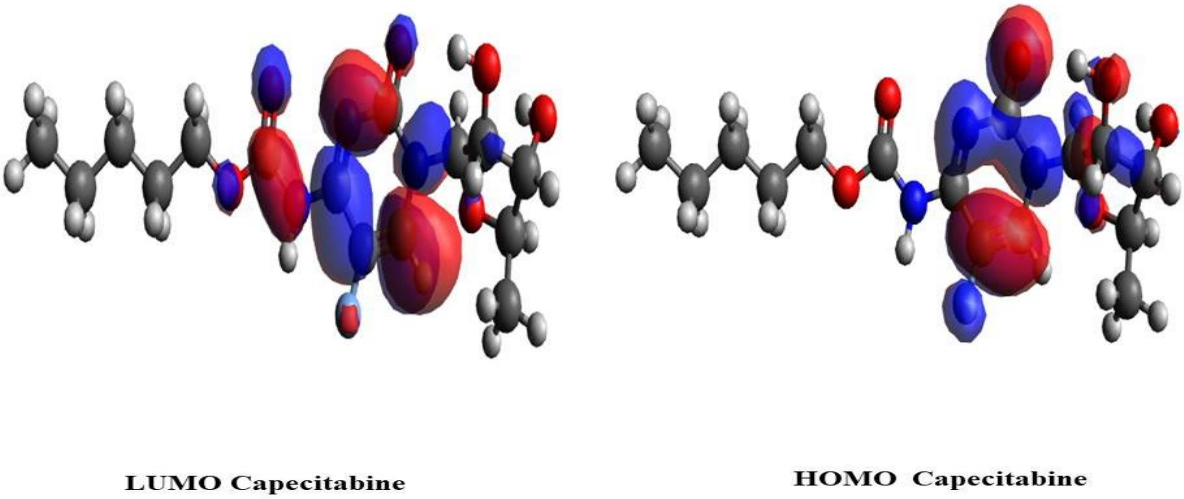

Fig.7: Represents the LUMO and HOMO of Capecitabine

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Sr. No.	Phytochemical name	Electronic Energy(eV)	LUMO(eV)	HOMO(eV)	GAP Energy(eV)	Dipole Moment(Debye)
1.	Glabroisoflavanone B	-92808.83369	2.265	-8.101	10.366	3.54071
2.	Glabridin	-82437.97684	2.928	-7.635	10.563	3.57601
3.	Capecitabine (Reported Drug)	-96037.39031	1.854	-9.795	11.649	8.45606

Table 6: HOMO-LUMO of selected phytochemical compounds from *Glycyrrhiza glabra* and Capecitabine

V. DISCUSSION

A large number of *in silico* studies have recently been undertaken in order to find natural chemicals as lead molecules against various diseases. *Glycyrrhiza glabra* is a medicinal plant that contains numerous bioactive components. Which is why this plant (whole\part) is used to treat various maladies. Colorectal cancer is a threat for the entire human society. CRCs is a threat for the entire human society. The protein TNIK plays the lead role in CRC neoplasogenesis. It is expressed extensively in CRCs. So, in the current *in silico* investigation, the protein TNIK (TRAF2 And NCK Interacting Kinase) is being targeted. Data pertaining to 45 PCs of the *Glycyrrhiza glabra* were collected from various research papers. Each molecule was put to in silico investigation. In this study TargetNet webserver used to check the Lipinsk's rule of 5, in which only 22 PCs out of 45PCs of *Glycyrrhiza glabra* passed the rule of 5. After that, the remaining 22 PCs were put to toxicity testing by the web servers like ProTox II server and Toxicity checker tool and only 11 PC swere found to be non-toxic (fit for human use). These 11 have been computationally assayed. Autodock 4.2 tool used to dock these 11 PCs against the TNIK protein. Furthermore, the reported drug namely Capecitabine which is commonly used as an effective frontline drug by clinicians (worldwide) has taken studied & presented for topical compare & contrast objectives ***(note-i).*** In the docking analysis it was found that (out of the 11 compounds of the *Glycyrrhiza glabra* selected for the docking analysis) the PC Glabroisoflavanone B shows the highest binding affinity of -8.93 kcal/mol against the TNIK (TRAF2 And NCK Interacting Kinase) protein of the CRC followed by Glabridin with second highest binding affinity of -8.39 kcal/mol. And whereas the reported drug Capecitabine showed binding affinity of -4.57 kcal/mol, which is less by an order of 50%.

In computational studies 'Reactivity' of any drug moiety indicates the efficiency of the said candidate drug in becoming blood borne and thereafter being bio-available in the central-peripheral circulation in physiological uptake form and in wash out (overall pharmacokinetics). DFT analysis is done to ascertain such 'reactivity' of any compound (36). This is energy band gap dependant. In our DFT analysis which was carried out to monitor the 'reactivity' of Glabroisoflavanone B, Glabridin, and Capecitabine towards TNIK (TRAF2 And NCK Interacting Kinase) protein of Colorectal cancer. In this analysis, Glabroisoflavanone B showed higher reactivity due to lowest energy band gap (10.366 eV) than Glabridin, and Capecitabine.

In addition, the HOMO and LUMO values of these 3 molecules Glabroisoflavanone B transpires to be most reactive molecule towards the protein (37). So, these two natural compounds can be used to **(i)** drug discovery **(ii)** designing and whereas the whole plant *Glycyrrhiza glabra* and or its parts can be used to treat CRCs as**(iii)** herbal and or holistic medicament **(iv)** functional food, etc. while **(i)** and **(ii)** is well educated employment friendly No., **(iii)** and **(iv)** is rural and low educated segment employment friendly. All being ecologically friendly & symbiotic too.

(note-i): TRAF2 is the 2nd member of the TNF receptor associated factor's family of the human physiology that are associated with systemic defense (specially versus neoplasogenesis). And, NCK1 is a Cytoplasmic (adopter) protein that encodes human genes; wherein NCK = non-catalytic kinase related with the tyrosine region of such adaptor protein. Hence, it is attractive in Drug delivery gateway and as therapeutic target.

(note-ii): In an separate communication we shall present comparative data using Paclitaxel; Carboplatin/Oxy; Irnotecam; 5FLU;etc.

VI. CONCLUSION

Taking into account the combinatorial approaches of various in-silico analyses, the current study may be able to reveal the substances Glabroisoflavanone B and Glabridin's optimal inhibitory affinity against the important protein TNIK (TRAF2 And NCK Interacting Kinase) involved in colorectal cancer. The drugability, molecular docking, and quantum computational (DFT) tests of these screened compounds were all positive. According to the findings, these chemicals may give new routes and methodologies for the development of therapeutic medication candidates for colorectal cancer. As a result of the findings, it is recommended that candidate compounds be isolated and a lead molecule be synthesised from *Glycyrrhiza glabra.* These lead compounds can also be processed for in-vitro and in-vivo studies to establish their efficacy and assess their anti-cancer potency before moving forward with clinical trials.

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Ethical issues: None.

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