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Normal cells' genomic identity is protected by telomeres and sometimes chromosomal instability was observed due to shortening of telomerase because of successive cell divisions. Reports indicate that telomerase length is crucial in determining telomerase activity which in turn leads to cancer initiation. It is reported that telomere length regulation has been identified as a plausible strategy for cancer diagnostics and treatment. In the present MS, we explored the telomerase inhibitory activity of catechin analogues and its oligomers using computational methods. The structural properties of different ligands discussed in the MS were computed using density functional theory. Conformational effect of different chromene subunit such as 2R, 3R conformations were explored using computational methods. The stereochemical contributions to receptor binding such as intra ligand π -interactions of these ligands were also investigated. We herein propose that these stereochemical aspects of catechins and their oligomers as the most vital factor deciding the effective binding with the N-terminal domain of telomerase which is an efficient strategy in cancer therapy.

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Molecular Docking and Dynamics Simulation Study of Telomerase Inhibitors as Potential Anti-cancer Agents

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ABSTRACT: Normal cells' genomic identity is protected by telomeres and sometimes chromosomal instability was observed due to shortening of telomerase because of successive cell divisions. Reports indicate that telomerase length is crucial in determining telomerase activity which in turn leads to cancer initiation. It is reported that telomere length regulation has been identified as a plausible strategy for cancer diagnostics and treatment. In the present MS, we explored the telomerase inhibitory activity of catechin analogues and its oligomers using computational methods. The structural properties of different ligands discussed in the MS were computed using density functional theory. Conformational effect of different chromene subunit such as 2R, 3R conformations were explored using computational methods. The stereochemical contributions to receptor binding such as intra ligand π -interactions of these ligands were also investigated. We herein propose that these stereochemical aspects of catechins and their oligomers as the most vital factor deciding the effective binding with the N-terminal domain of telomerase which is an efficient strategy in cancer therapy.

KEYWORDS: Catechins, cancer, telomerase, docking, dynamics

1. Introduction

Regulation of telomere length in replicative senescence by inhibiting telomerase has currently been highlighted as a potential strategy for cancer diagnostics as well as chemotherapeutics.¹⁻³ Telomerase is a ribonucleoprotein reverse transcriptase, composed of an RNA template (TER or hTR) and a catalytic protein subunit (TERT), which in turn is formed by the alignment of four major functional domains- the TERT N-terminal domain (TEN), the TERT RNA

binding domain (TRBD), the reverse transcriptase domain (RT) and the C-terminal extension (CTE).⁴⁻⁷ Inhibition of telomerase is also effective in regulating proliferation of endometriosis and has been considered as a potential non-hormonal curative strategy in the pathology of endometriosis.⁸⁻¹¹ Telomerase inhibition by amyloid beta (A β) binding has been reported to play a crucial role in cellular senescence and thereby fighting against Alzheimer's disease (AD).¹² Thus telomerase is an important target for unwanted cellular growth, age related diseases such as AD, endometriosis as well as in cancer therapy.¹³⁻¹⁶

The most promising methods for telomerase inhibition involve the direct disruption of capping telomeres using telomerase inhibitors along with conventional chemotherapeutics.¹⁷⁻²⁰ Talari et al. reported a molecular docking approach in pharmacophore based virtual screening of new telomerase inhibitors and suggested that the TEN domain anchor site is a useful template in rational inhibitor design.²¹ Chen et al. demonstrated the importance of major natural products in telomerase maintenance.²² Our survey of literature revealed that role of flavanoids as telomerase inhibitors were discussed recently, but not specifically investigated.²³⁻²⁸ Catechins, a series of low molecular weight polyphenols that primarily consist of flavan-3-ol monomers, are present in leaves, fruits and vegetables. Takanshi et al. recently reported the anticancer activity of epicatechin oligomers longer than trimers. This will inflame us to think about the anticancer activity, especially by telomerase inhibition of catechinsuptotrimers.²⁹ In the present work, we have explored the scope of inhibiting human telomerase TEN domain effectively by catechins. The stereochemistry and mechanistic aspects of the interaction between catechin ligands and telomerase has also been investigated. Computational simulations based on virtual screening, molecular dynamics and electronic structural methods were carried out to find out an effective output from the various conformers of catechin.

2. Materials and methods

2.1. Preparation of protein and active site identification

The crystallized TEN domain of telomerase with 2.22Å resolution (PDB ID:2B2A) was obtained from RCSB Protein Data Bank.⁶ It was optimized and minimized using protein preparation wizard of Maestro, v10.1, Schrodinger suite, LLC, New York, NY, 2015.³⁰ Sitemap, v3.4, Schrodinger, LLC, New York, NY, 2015 was used to identify active site of 2B2A receptor. The grid was generated for cleaned PDB file using the module available with Glide v6.6, Schrodinger, LLC, New York, NY, 2015.³¹ The dimensions of the grid box for 2B2A were kept around the centroid of active site of workspace ligand (X= 61.61, Y= 61.12, Z= 13.61).

2.2. Molecular docking

The 3D structure of selected catechins-monomers, dimers and trimers were downloaded from PubChem open chemistry database (<https://pubchem.ncbi.nlm.nih.gov>). Different conformational catechins were optimized at B3LYP/6-311++G** level (Supporting Information, S5-S17) of Density functional Theory (DFT). These optimized geometries were loaded into workspace of Maestro project and all the possibleconformers were generated using LigPrep module of Schrodinger 2015 under OPLS-2005 forcefield. *In silico* screening and docking studies of the most stable conformers of 22 ligands on the 2B2A receptor was carried out in the active site of TEN domain of telomerase. Docking of ligands with prepared PDB file was carried out using Glideprogramme of Schrodinger suite. The interaction of the ligands with receptors were analysed on the basis of scoring functions- G-score(Glide score) and D-score (Dock score) through XP-visualizer and interaction diagrams.

2.3. ADMET studies

The ligands were screened by qikproptool of Schrodinger 2015 and the data were analysed for the suitability on the basis of ADME/T (adsorption, distribution, metabolism and excretion/toxicity) and Ro5. The values are compared

with the range obtained from QikProp manual. All the monomers and dimers with appreciable range of pharmacokinetic parameters interpreted by qikprop values are assigned for further studies.

2.4. MM-GBSA for Binding Free Energy prediction

The relative binding affinity of ligands (kcal/mol) were calculated by MM-GBSA, which may not in agreement with experimental values. A more negative value denotes stronger binding. It generates a lot of energy properties like that of the ligand, receptor, and complex structures as well as energy differences relating to strain and binding, and are divided into contributions from various terms in the energy expression.

Prime MMGBSA DG bind, the binding free energy, is calculated with the equation:

$$\Delta G(\text{bind}) = E_{\text{complex}(\text{minimized})} - (E_{\text{ligand}(\text{minimized})} + E_{\text{receptor}(\text{minimized})})$$

2.5. Molecular dynamics

To envisage the firmness and fitness of binding of the ligands inside the active site of 2B2A, we carried out MD simulations of three ligands, selected on their scoring functions, through Desmond module of Schrodinger 2015. The simulations were carried out under OPLS-2005 forcefield for 50ns.³² The solvation of the systems were done in orthorhombic boxes with explicit TIP4P water. Counter ions were added to neutralize the systems and simulations were performed under isothermal isobaric ensemble (NPT)³³ having default temperature of 300K and pressure of 1.013 bar.³⁴ RMSD plots for both the protein and the ligands reveals the relative stability of the lead inside its binding pocket of the target 2B2A. The Protein-Ligand (P-L) interaction histogram represents the interacting residues and their suitable interactions, which favours the binding.

3. Results and discussion

3.1. Molecular Docking analysis against 2B2A receptor

A series of catechin conformers and oligomers available from natural dietary sources were selected for the present study (Supporting Information, S2-S4). Monomers investigated include (+)-catechin (**1**), (-)-catechin (**2**), (+)-epicatechin (**3**), (-)-epicatechin (**4**), (+)-gallocatechin (**5**), (-)-gallocatechin (**6**), (+)-epigallocatechin (**7**), (-)-epigallocatechin (**8**), (+)-leucocyanidin (**9**) and (+)-leucopelargonidin (**10**). When subjected to virtual screening (2R,3S,4R)-2-[3,4-bis(oxidanyl)phenyl]-3,4-dihydro-2H-chromene-3,4,5,7-tetraol (**9**) depicted better docking with D-Score/G-Score of -7.2, with six hydrogen bond donors and seven hydrogen bond acceptors. Compounds **1-8** possess only two stereocenters at 2C and 3C whereas in compounds **9** and **10**, there is an additional stereocentre at 4C with R-configuration of 2H-chromene. This additional stereocentre generated by the introduction of an -OH group eventually increases the binding affinity (Supporting Information, S18). As evident from the interaction diagram, the newly introduced -OH (R) in **9** acts as hydrogen donor site, thereby coordinating with the negatively charged glutamic acid residue [Glu162] in the telomerase site. In addition, compound **9** exhibits a π -stacking interaction between its benzene ring and the positively charged arginine [Arg128]. The newly introduced -OH (S) group of **10** resulted in a slightly reduced specific hydrogen donating tendency since the interaction involved a

polar glutamine [Gln168] . Interestingly compounds **7** and **5** with only two stereo centers showed better D-score/G-score compared to **10**. This observation suggests that the introduction of a hydroxy group enhances the ligand protein interaction while the stereochemistry of the chromene dictates specificity in binding (Supporting Information, S18).

It has recently been reported that artemisinin-derived dimers have better inhibiting capacity than the corresponding monomers. However, the exact mechanism of inhibition remains elusive till date.³⁵ Since catechin oligomers are present in dietary sources, we next explored the potential of these compounds in telomerase inhibition. Of particular interest were the compounds having appreciable molecular weight range which may result in better docking due to the presence of multiple -OH groups. Interestingly, all except four (**13**, **14**, **17** and **20**) of the ten compounds **11-20** exhibited strong binding. Optimized geometries all the six ligands are depicted in Fig.1 and important interactions are noted in **Table1**. ProcyanidinA1(**11**) with twelve H-bond acceptors and 10 H-bond donors was found to be superior (G-score/D-score of -10.1.) to other compounds. This is in agreement with the recent reports on Cocoa procyanidins which showed selective cytotoxicity against epithelial ovarian cancer.³⁶ It was observed that all the six dimers with five stereocentres showed better scores than the corresponding monomers, which may be attributed to the better suitability of the ligands in the pocket. It was also intriguing to find that the compounds **11**, **19** and **12** with better scores share a common tendency of linking of two H-donor site -OH to the negatively charged glutamic acid [Glu162]. These results suggest that the effective binding demands the interaction of negatively charged glutamic acid [Glu162] with a H-donor of the ligand. Asn105 and Gln109 are the other two important aminoacids to which the high scored ligands show interaction by H-bond. Investigating the stereochemical aspects of the interaction diagrams (**Fig.2**), it is evident that the 2R, 3R configuration of chromene from epicatechin unit is significant for deciding both the effective binding with negatively charged glutamic acid as well as autofit of the ligand in the pocket.

15 (Procyanidin B3)

16 (Procyanidin B4)

18 (Procyanidin B6)

19 (Procyanidin B7)

Fig.1. Optimized geometries (B3LYP/6-311++G**) of high scored ligands

12

11

Fig.2. 11, 12, 15, 16, 18 and 19 in the binding site of 2B2A

Studies were further extended to analyse the properties of trimers using procyanidin C1 (**21**) and procyanidin C2 (**22**). Even though these compounds gave better score of -7.7 and -7.6 compared to monomers, the higher molecular weights make them less attractive drug candidates. Another aspect which renders these compounds unappealing is their inability to fit into the binding site due to their bulky size. In spite of the proximity of the two –OH in compound **22** to the glutamic acid residue, it was observed that the 2R, 3S configuration of the chromene hinders its effective binding, which confirms our finding that the stereochemistry of the ligand plays a critical role in its binding efficiency. The binding affinity were compared with the standard telomerase inhibitors: BIBR-1532 (**a**) and MST-312 (**b**)³⁷ and it was found that the D-score/G-score values are very low in **a** (-3.9/-3.9kcal/mol). **b** is sometimes better than **a**, but not as good as catechin dimers with a value of -6.6/-7.1 kcal/mol.

It has been reported elsewhere that parameters such as enthalpic and entropic components, hydrogen bond interactions, π -stacking interactions, etc. play a pivotal role in determining the binding efficiency between the ligand and receptor.³⁸ In the present study we explored the contribution of 3D-positioning of intra ligand π -interaction between the monomers, in defining the binding of the dimers with the receptor. As the vertical alignment between

the two aromatic systems gets perfected, the D-score also increases. It was observed that in the case of compound **11** with D-score and G-score of -10.1, the two π -systems are almost in perpendicularly eclipsed alignment to each other, resulting in an angle 0.0 between the centres of two systems. This increased the delocalisation leading to an increase in the electron density on terminal oxygens which was further supported by Natural Bond Orbital (NBO) analysis on terminal oxygens of the dimers (**Fig.3, Table 1**). NBO analysis revealed that the charge contribution from terminal oxygens is greatest in the case of **11**, which increased the H-donating capacity. Eventually this adds to the superiority of **11** (procyanidin A1) as the hydrogen donor potential of the molecule has been enhanced. This property can be defined as "doppleganger effect". The word "doppelgänger" is often used in a more general sense to describe any person who physically or behaviorally resembles another person or shadow. In this context one of the aromatic systems stay behind the another as its shadow. Therefore it can be established that the stereochemical positioning of the two π -systems plays a major role in determining the binding affinity values.

Fig.3. The alignment of two intra ligand π -systems in procyanidin A1

(11)

Table 1. The alignment angle and NBO analysis on terminal oxygens

Entry	11	12	13	14	15	16	17	18	19	20
Alignment of two π -systems (in terms of angle)	0.0	0.5	-9.3	-5.5	2.7	-1.8	7.6	-0.6	-0.3	4.0
Dihedral angle	94.9	99.9	-152.1	-164.2	-44.8	-54.2	128.7	82.6	125.3	-158.5
Natural charge on terminal oxygens	-0.72486	-0.72399	-0.75323	-0.69940	-0.72052	-0.71178	-0.69779	-0.70334	-0.75585	-0.69871
	-0.75258	-0.75244	-0.71757	-0.69921	-0.70564	-0.69880	-0.69819	-0.70232	-0.71964	-0.69977

3.2. Analysis of ADME/T properties

The ADME/T properties are also well suited for a drug as per pharmacokinetic parameters (**Table 2**). The molecular weights (M.W.) for the monomers and dimers are well within the range (130.0 to 725.0) with central nervous system toxicity (CNS) value of -2. In the case of trimers the molecular weight is quite high with CNS of safe value (-2). All

the monomers and dimers acts as drug like with #stars of zero while that of trimers were found to be 2, which means the drug likeness is less for them. The hydrogen bond donors (HBD) are within 6 for monomers and dimers and the hydrogen bond acceptors (HBA) are less than 20 for all the three categories. The hydrophilic component of solvent accessible surface area (FISA) is well within the range (7.0 to 330.0) for the first two categories. The values for octanol/water partition coefficient (QlogPo/w = -2.0 to 6.5), aqueous solubility (QlogS = -6.5 to 0.5) and binding to human serum albumin (QlogKhsa = -1.5 to 1.5) are within the range shows the binding and solubility features of all the ligands inside the blood circulation system. All the monomers and dimers are seem to be good candidates with Ro5 value of 0 or 1 and 100% HOA(Human Oral Absorption). In the case of references **a** and **b**, the MW, #stars, CNS, FISA, HBA, HBD, QlogPo/w, QlogS and QlogKhsa are well within the range with minimum deviation from Ro5.

3.3. MM-GBSA analysis and binding free energy prediction

The free energy of binding (B.E.), $\Delta G(\text{bind})$, shows the interaction of the ligands within the binding pocket of 2B2A (Table2). As the value becomes more negative the complex is more stable. The B.E. is maximum (-52.321kcal/mol) for procyanidin A1(**11**) with high score of -10.2kcal/mol. The other ligands 19, 12 and 15 also shows better B.E. compared to the standard MST-312 and all the ligands exhibit better B.E. compared to BIBR-1532. The calculations shows that the B.E. is directly related to scoring function as expected.

Table 2. Pharmacokinetic parameters and G/D-Scores of 1-22

No.	G-Score	D-Score	ΔG_{Bind}	M.W.	#stars	CNS	FISA	HBA	HBD	QlogPo/w	QlogS	QlogKhsa	Ro5
1	-5.5	-5.5	-34.6	290.27	0	-2	239.25	5.45	5	0.481	-2.609	-0.41	0
2	-4.4	-4.4	-22.7	290.27	0	-2	239.25	5.45	5	0.481	-2.609	-0.41	0
3	-5.4	-5.4	-32.5	290.27	0	-2	237.71	5.45	5	0.494	-2.587	-0.405	0
4	-5.0	-5.0	-30.7	290.27	0	-2	237.71	5.45	5	0.494	-2.587	-0.405	0
5	-6.2	-6.2	-38.9	306.27	0	-2	285.87	6.2	6	-0.179	-2.381	-0.549	1
6	-5.5	-5.5	-34.8	306.27	0	-2	285.87	6.2	6	-0.179	-2.381	-0.549	1
7	-6.3	-6.3	-39.5	306.27	0	-2	284.09	6.2	6	-0.17	-2.356	-0.546	1
8	-3.0	-3.0	-17.5	306.27	0	-2	284.09	6.2	6	-0.17	-2.356	-0.546	1
9	-7.2	-7.2	-46.2	306.27	0	-2	273.30	7.15	6	-0.317	-2.297	-0.605	1
10	-5.9	-5.9	-36.7	290.27	0	-2	223.86	6.4	5	0.322	-2.466	-0.488	0
11	-10.1	-10.1	-75.6	592.51	0	-2	330.08	11.65	5	-0.054	-4.384	-0.378	1
12	-8.2	-8.2	-73.9	576.51	0	-2	382.95	10.9	5	0.638	-4.665	-0.208	1
13	-4.4	-4.4	-22.3	578.53	0	-2	321.15	10.9	6	0.199	-3.697	-0.231	1
14	-4.8	-4.7	-25.6	578.53	0	-2	321.19	10.9	5	0.244	-3.76	-0.218	1
15	-8.0	-6.2	-56.7	578.53	0	-2	311.05	10.9	5	0.634	-4.574	-0.189	1
16	-8.2	-8.1	-65.1	578.53	0	-2	309.58	10.9	5	0.619	-4.587	-0.201	1
17	-4.2	-4.2	-21.4	578.53	0	-2	313.57	10.9	5	0.584	-4.829	-0.232	1
18	-7.5	-7.5	-48.5	578.53	0	-2	304.41	10.9	5	0.668	-4.872	-0.229	1
19	-8.5	-8.5	-74.3	578.53	0	-2	315.02	10.9	5	0.574	-4.86	-0.236	1
20	-4.9	-4.9	-26.5	578.53	0	-2	302.54	10.9	5	0.681	-4.848	-0.225	1
21	-7.6	-7.2	-49.6	866.78	2	-2	566.90	16.35	15	-0.063	-4.236	-0.241	2
22	-7.7	-7.0	-47.4	866.78	2	-2	570.98	16.35	15	0.571	-6.093	-0.201	3

ΔG_{Bind} (kcal/mol); M.W.(Molecular Weight):130.0-725.0; #stars (few stars-more drug-like): 0-5; CNS (Central Nervous System activity): -2 to +2; FISA(Hydrophilic component of total solvent accessible area): 7.0-333.0; HBA(Hydrogen bond acceptor): 2.0-20.0; HBD(hydrogen bond donor): 0.0-6.0; QlogPo/w(octanol/water partition coefficient): -2.0-6.5; QlogS(Aqueous solubility): -6.5-0.5; QlogKhsa(binding to human serum albumin): -1.5-1.5; Ro5(Number of violations of Lipinski's rule of five): maximum is 4.

3.4. MD simulation analysis

The flexibility in conformation and stability of the ligands inside the active site of the receptor (with **11**, **12** and **19**) were established by molecular dynamics (MD) analysis under OPLS2005 force field at 50 nanosecond (ns). To resolve the stability and conformational flexibility of the protein-ligand interactions, Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), Protein-Ligand (P-L) contacts, ligand torsion profile of the protein-ligand complex of highest scores were determined. **Fig.4** & **5** shows the average RMSD of the C α atoms of the protein 2B2A(left Y-axis) and the ligand (right Y-axis). RMSD of the ligand heavy atoms is measured by aligning the protein-ligand complex on the receptor backbone of the reference. The magnitude of fluctuations indicates that the complexes attained stable conformations after equilibration and how stable the ligands are with refer to the

active
in **11,12**
values

lower than
the
denotes
are
to the
site even

protein and its
binding pocket
and **19**. The
predicted are
significantly
the RMSD of
protein, which
the ligands
strongly bind
initial binding
after 50ns.

Fig.4. RMSD plots of C α of 2B2A and ligands **11**, **19** and **12**

Fig.5. P-L interactions of **11**, **12** and **19**

P-L interactions throughout the simulations can be categorized and summarised in **Fig.5**. The stacked bar charts for hydrogen bonds, hydrophobic, ionic and water bridges are normalized over the course of the trajectory. H-bond play a significant role in ligand binding because of their strong influence on drug specificity, metabolism and absorption. H-bonds predominates and most of them last for more than 80% time of simulation. In **11**, there are six H-bond donors and two H-bond acceptors. Among these H-bond with E162 lasts for 100%, 98% and 86%; N105 lasts for 98% and T112 lasts for 98% of simulation time. While in **19**, there are 5 H-donors and only two H-acceptors, among these H-bond with Q109 (88%), N105 (90%), Q12(80%), Q168 (92%), N175 (84%), Q163 (96%) last for the starting to end of the simulation time. But in **12**, there are only two H-donors to E162 last for 96% and Y106 for 95%. The contacts confirmed the interaction with glutamate moiety, E162 and Q163 upto 100% of simulation time and gives the stability to P-L complex. In order to generate new chemotypes that are able to make similar interactions, we have done 3D pharmacophore model for dimers (**11-20**) using seven-point hypothesis based on best alignment and common features (**Fig.6**). The hypothesis includes two donors, three acceptors and two rings in common to fit all the 10 ligands (**11-20**). This data is helpful design new inhibitors for telomerase more accurately.

Fig.6. 3D pharmacophore model generated for the ligands 11-20

4. Conclusion

In summary, we investigated the stereochemical aspects of telomerase inhibition by Catechin analogues and its oligomers. It was found that the catechin ligands bind effectively to the negatively charged glutamic acid residue present in the binding site of the TEN domain of telomerase. Among the various compounds studied, those with H-donors which interacted strongly with this glutamic acid residue were found to exhibit strong binding. This observation ascertains the fact that the ligand binding to this glutamic acid ensures better interaction with the protein. The catechin dimers having 2R, 3R configuration in the chromene ring were found to have strong interaction with telomerase, which was exemplified by the superiority of the dimer procyanidin A1 (**11**) in the binding with the protein. Molecular dynamics simulations prove the stability of protein-ligand complex. RMSD, RMSF and P-L contacts supports the stability of P-L complex. We envisage that these stereochemical and mechanistic revelations regarding the binding interactions of catechin ligands and the corresponding dimers with telomerase could open up new avenues in chemotherapy.

Conflict of interest

There is no conflict of interest

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