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Docking Studies and ADMET Profile of Streblusol E, Anti-Hepatitis B viral Agent of Streblus Asper

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Abstract: Background: Streblusol E, a phenolic phytoconstituents of Streblus asper is a potential antihepatitis B viral agent. Objective: Current study is to mechanistically analyze the probable site of action for streblusol E. Material and methods: Streblusol E has been docked with EF3-CaM adenylyl cyclase(1PK0), deoxycytidine kinase(2NOA), human nucleoside diphosphate kinase(3FKB), human Hepatitis B Viral Capsid(1QGT) and hepatitis B X-interacting protein(3MSH) proteins using GRIP docking methodology. Results: Results revealed its preferential intractability towards 1PK0 i.e. EF3-CaM adenylyl cyclase and 1QGT i.e. human hepatitis B viral capsid(HBCAG) compared with reference ligand like adefovir diphosphate(active metabolite of adefovir), lamivudine, tenofovir monophosphate(active metabolite of tenofovir) and tenofovir diphosphate(active metabolite of tenofovir). Drug metabolism and pharmacokinetics studies did affirm that Streblusol E possessed all the desired drug Likeness potential. According to Derek Nexus predictions, Streblusol E did not carry potential toxicities like carcinogenicity, mutagenicity genotoxicity and developmental toxicity, providing further impetus for discovery and clinical development of semi-synthetic analogs of Streblusol E. Conclusion: The present study successfully denotes the docking studies and ADMET profile of streblusol E from Streblus asper.

Keywords: Streblus asper; Streblusol E; Antihepatitis B Viral Activity; GRIP Docking; Viral Receptors.

1. Introduction

Traditional medicinal plants have been recognized for their therapeutic benefits for centuries. However, there is still lack of the evidence for the clarification of their typical mechanism of action (Sripanidkulchai et al., 2009). Streblus asper, family Moraceae, commonly known as Sihora, is a rigid shrub or medium sized tree distributed in South China and South Asia (Aeri et al., 2012; Jun et al., 2012). S. asper was used by traditional healers as remedy for hepatitis B virus in South China.

Streblusol E (Fig. 1), a phenolic phytoconstituent of S. asper was proved to have potential anti-hepatitis B viral activity (anti-HBV activity), but its mechanism is still unknown for the world. Anti-HBV activity was evaluated in HepG2.2.15 cell line stably transfected with the HBV genome. Test concentrations were 4, 20, 100 and 200 μM. The levels of HBV surface antigen (HBsAg) and HBV e antigen (HBeAg) were assayed with ELISA.IC50 value reported was 153.7 μM for HBsAg while for HBeAg, it is 23.1 μM (Jun et al., 2012). In purview of this, we tried to mechanistically analyze the probable site of anti-HBV action and to find out the pharmacophores present.

So aim of current study was to dock streblusol E with specific protein responsible for the virulence of HBV and analyze the site of action and also to evaluate its drug likeness by calculating drug metabolism, pharmacokinetics and toxicity by in silico route.

2. Results and Discussion

Literature revealed the potential of Streblusol E, a phytoconstituent of Streblus asper as anti-hepatitis B viral agent. In purview of this, we tried to mechanistically analyze the probable site of anti-HBV action using various proteins like EF3-CaM adenylyl cyclase(1PK0), deoxycytidine kinase (2NOA), human nucleoside diphosphate kinase (3FKB), human Hepatitis B viral capsid (1QGT), Hepatitis B X-interacting protein(3MSH) and compared it with standard antiviral agents like adefovir diphosphate(active metabolite of adefovir), lamivudine, tenofovir monophosphate (active metabolite of tenofovir) & tenofovir diphosphate (active metabolite of tenofovir)(Table 1). Docking studies revealed that streblusol E of streblus asper have significant anti-hepatitis B viral activity and preferentially interacting with EF3-CaM adenylyl cyclase and human hepatitis B viral capsid protein. In case of EF3-CaM adenylyl cyclase (1PK0), Streblusol E have vanderwaal's interactions with Lys346A, Leu348A, Val350A, His351A, Lys353A, Asp493A, Gly547A, Thr548A, His577A, Thr579A, Glu580A and Asn583A amino acid residues while having hydrophobic interactions with Leu348A and Gly547A amino acid residues of 1PK0. Along with this, streblusol E also have aromatic interactions (Fig. 2) with His351A & His577A and hydrogen bonding with Lys346A. Similarly, reference ligand, Adefovir diphosphate have vanderwaal's interactions with Arg329A, Lys346A, Leu348A, Lys353A, Ser354A, Lys372A, Ala490A, Asp493A, Gly547A, Thr548A, His577A, Gly578A, Thr579A, Glu580A and Asn583A amino acid residues while having hydrophobic interactions with Leu348A, Gly547A, Thr548A, His577A,

Gly578A and Asn583A amino acid residues of 1PK0. Along with these, Adefovir diphosphate do exert charge effect with Asp493A, aromatic interactions with His577A and hydrogen bonding with Arg329A, Lys346A, Ser354A, Lys372A and Thr548A amino acid residue of 1PK0. In case of deoxycytidine kinase(2NOA), Streblusol E have vanderwaal's interactions with Ile30A, Glu53A, Val55A, Trp58A, Met85A, Tyr86A, Phe96A, Gln97A, Arg104A, Arg128A, Asp133A, Phe137A, Leu141A, Arg192A, Arg194A, Glu197A and Tyr204A amino acid residues while having hydrophobic interactions with Met85A, Phe137A and Leu141A amino acid residues of 2NOA. In addition to these, Streblusol E also have aromatic interactions (Fig. 3) with Phe96A & Phe137A and hydrogen bonding with Arg104A & Arg194A amino acid residues of 2NOA i.e. deoxycytidine kinase. Similarly, reference ligand, Lamivudine have vanderwaal's interactions with Ile30A, Glu53A, Val55A, Trp58A, Leu82A, Met85A, Tyr86A, Phe96A, Gln97A, Arg104A, Arg128A, Asp133A, Phe137A and Arg194A amino acid residues while having hydrophobic interactions with Ile30A, Val55A, Leu82A, Met85A, Ala100A, Asp133A and Phe137A amino acid residues of 2NOA. Along with these, lamivudine do have charge effect with Asp133A and hydrogen bonding with Gln97A and Arg128A amino acid residues of 2NOA i.e. deoxycytidine kinase. In case of human nucleoside diphosphate kinase(3FKB), Streblusol E have vanderwaal's interactions with Lys16D, Arg92D, Thr98D, Arg109D, Val116D, Gly117D, Asn119D, Gly122D and Gly123D amino acid residues while having hydrophobic interactions with Val116D and Gly117D amino acid residues of 3FKB. In addition to these, streblusol E do exert hydrogen bonding (Fig. 4) with Arg92D, Thr98D, Arg109D and Gly123D amino acid residues of 3FKB i.e. human nucleoside diphosphate kinase. Similarly, reference ligand, tenofovir diphosphate have vanderwaal's interactions with Lys16D, Tyr56D, His59D, Arg62D, Phe64D, Leu68D, Arg92D, Thr98D, Arg109D, Val116D, Gly117D, Asn119D and Gly122D amino acid residues while having hydrophobic interactions with Phe64D, Leu68D, Thr98D, Val116D and Gly117D amino acid residues of 3FKB. Along with these, tenofovir do have charge effect with Glu58D and hydrogen bonding with Lys16D, His59D and Arg92D amino acid residues of human nucleoside diphosphate kinase. In case of human hepatitis B viral capsid(HBCAG)(1QGT), Streblusol E have vanderwaal's interactions with Gln57B, Ala58B, Leu60B, Cys61B, Glu64B, Gln57A, Ala58A, Cys61A, Lys96A, Ile97A and Leu100A amino acid residues while having hydrophobic interactions with Gln57B, Ala58B, Cys61B, Ala58A and Cys61A amino acid residues of 1QGT. In addition to these, streblusol E do have hydrogen bonding (Fig. 5) with Lys96A of human hepatitis B viral capsid. In case of hepatitis B X-interacting protein(3MSH), Streblusol E have vanderwaal's interactions with Glu40A, His41A, Val44A, Ile45A, Leu48A, Leu67A, Ile74A and Ile76A amino acid residues while having hydrophobic interactions with, His41A, Val44A, Ile45A, Leu48A and Ile74A amino acid residues of 3MSH. Along with these, streblusol E do exert aromatic interactions/pi-staking (Fig. 6) with His41A of hepatitis B X-interacting protein. In case of human hepatitis B viral capsid protein, the active site for streblusol E consist amino acid residues of chain A and chain B of this capsid. It has been found that both the aromatic rings played a great role in pi-pi staking, while the three hydroxyl groups possess hydrogen bonding with the amino acids of target proteins.

It was well emphasized in this present study that the crystal structure of the EF3-CaM complexed with PMEApp(1PK0) was docked with various drugs along with streblusol E, adefovir diphosphate, lamivudine, tenofovir mono phosphate and tenofir diphosphate. Interestingly, it was notable that streblusol E could bind with the EF3-CaM significantly like the standard drug adefovir diphosphate. It did dock evidently with other proteins like deoxycytidine kinase complexed with Lamivudine & ADP (2NOA), NDPK H122G and Tenofovir-diphosphate (3FKB), Hepatitis B Viral Capsid (HBCAG) (1QGT), crystal structure of Hepatitis B X-interacting protein at high resolutions (3MSH) (Table 1). From the previous literature, it was well identified that EF3-CaM was well related to viral hepatitis B [14]. The molecular docking of sreblusol E in the present study was cohesive to this protein and it is thus evident that the action against hepatitis B protein can be possible by streblusol E.

As per the Lipinski rule of five, Streblusol E stands a good chance to be drug (Table 2). Further the logs of 3.244 and logP of 2.664 made it a good molecule which will be having better dissolution and bioavailability because of its absorption via human intestine also. hERG channel inhibition is also below 5, which is good signal. As plama protein binding is high, so the half life of the drug, Streblusol E is expected to be high and have a longer duration of action. Streblusol E will not be able to cross blood brain barrier, so side effect will not be related to that of brain like nausea etc. As this molecule is not a P-gp substrate, so likeliness of resistance will be minimal.

Moreover, as per the data of Derek Nexus, Streblusol E doesn't have potential toxicities like carcinogenicity, mutagenicity, genotoxicity and developmental toxicity, but found to be possible hepatotoxic, skin sensitizer and can damage chromosome Table 3).

These results will certainly attract the attention of researchers worldwide to derivatize streblusol E and clinically developed this class to reach bedside as alternative and complementary medicine for the treatment of acute or chronic hepatitis B viral infection.

Table 1. Docking studies of streblusol E and reference ligands with various targeted proteins.

Proteins under Docking Study	**Dock Score**				
	Streblusol E	**Adefovir Diphosphate**	**Lamivudine**	**Tenofovir Mono Phosphate**	**Tenofovir Diphospha-te**
Crystal Structure of the EF3-CaM complexed with PMEApp(**1PK0**)	-68.075706	-85.297596	-	-	-
The structure of deoxycytidine kinase complexed with Lamivudine & ADP(**2NOA**)	-36.970556	-	-79.054872	-	-
Structure of NDPK H122G and Tenofovir-diphosphate(**3FKB**)	-54.745946	-	-	-76.971639	-75.772605
Human Hepatitis B Viral Capsid(HBCAG)(**1QGT**)	-59.566571	-	-	-	-
Crystal structure of Hepatitis B X-interacting protein at high resolution(**3MSH**)	-47.307476	-	-	-	-

Table 2. ADME profile prediction of Streblusol E.

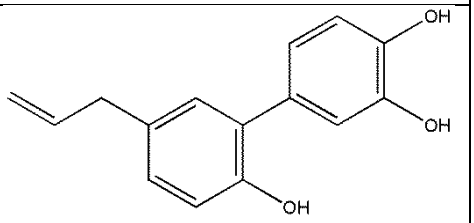
ID	Streblusol E
Structure	
MW	242.3
HBD	3
HBA	3
TPSA	60.69
Flexibility	0.1579
Rotatable Bonds	3
P450_3A4_CSL	0.9901
LogS	3.244
logS @ pH7.4	3.244
logP	2.664
logD	2.664
2C9 pKi	5.039
hERG pIC50	4.867
BBB log([brain]:[blood])	-0.3491
BBB category	-
HIA category	+
P-gp category	no
2D6 affinity category	medium
PPB90 category	high

Table 3. Toxicity Profile Prediction of Streblusol E

Carcinogenicity	No report
Photocarcinogenicity	No report
Hepatotoxicity	**Plausible**
Genotoxicity in vitro	No report
Genotoxicity in vivo	No report
Photogenotoxicity in vitro	No report
Photogenotoxicity in vivo	No report
Chromosome damage in vitro	**Plausible**
Chromosome damage in vivo	No report
Photo-induced chromosome damage in vitro	No report
alpha-2-mu-Globulin nephropathy	No report

Anaphylaxis	No report
Bladder urothelial hyperplasia	No report
Cardiotoxicity	No report
Cerebral oedema	No report
Chloracne	No report
Cholinesterase inhibition	No report
Cumulative effect on white cell count and immunology	No report
Cyanide-type effects	No report
High acute toxicity	No report
Methaemoglobinaemia	No report
Nephrotoxicity	No report
Neurotoxicity	No report
Oestrogenicity	No report
Peroxisome proliferation	No report
Phospholipidosis	No report
Phototoxicity	No report
Pulmonary toxicity	No report
Uncoupler of oxidative phosphorylation	No report
Irritation (of the eye)	No report
Irritation (of the gastrointestinal tract)	No report
Irritation (of the respiratory tract)	No report
Irritation (of the skin)	No report
Lachrymation	No report
HERG channel inhibition in vitro	No report
Thyroid toxicity	No report
Photoallergenicity	No report
Skin sensitisation	**Plausible**
Occupational asthma	No report
Respiratory sensitisation	No report
Developmental toxicity	No report
Teratogenicity	No report
Testicular toxicity	No report
Ocular toxicity	No report
Mutagenicity in vitro	No report
Mutagenicity in vivo	No report
Photomutagenicity in vitro	No report

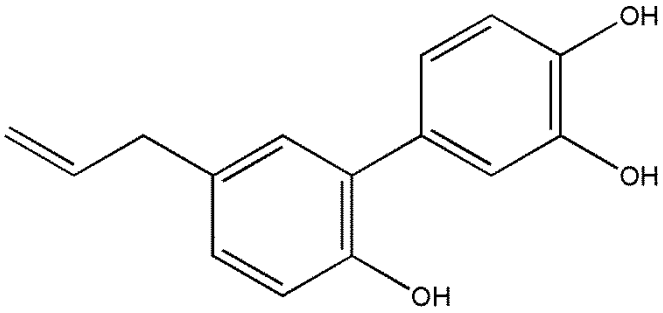


Figure 1. Structure of Streblusol E

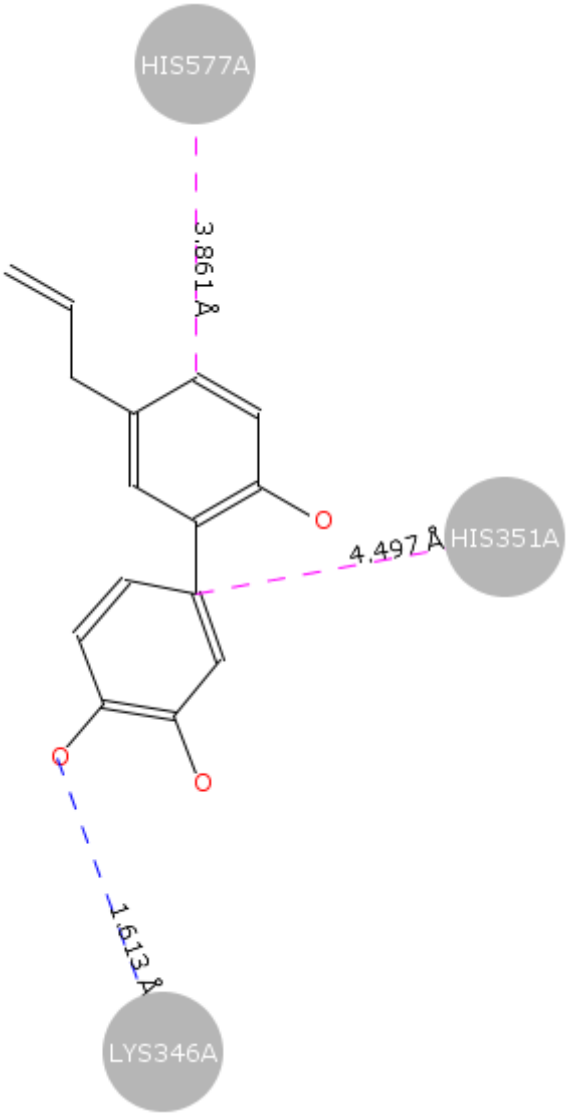


Figure 2. Hydrogen bonding and aromatic interactions of Streblusol E with EF3-CaM adenylyl cyclase(1PK0); Blue Broken Line- Hydrogen Bonding; Pink Broken Line: Aromatic/pi-pi staking.

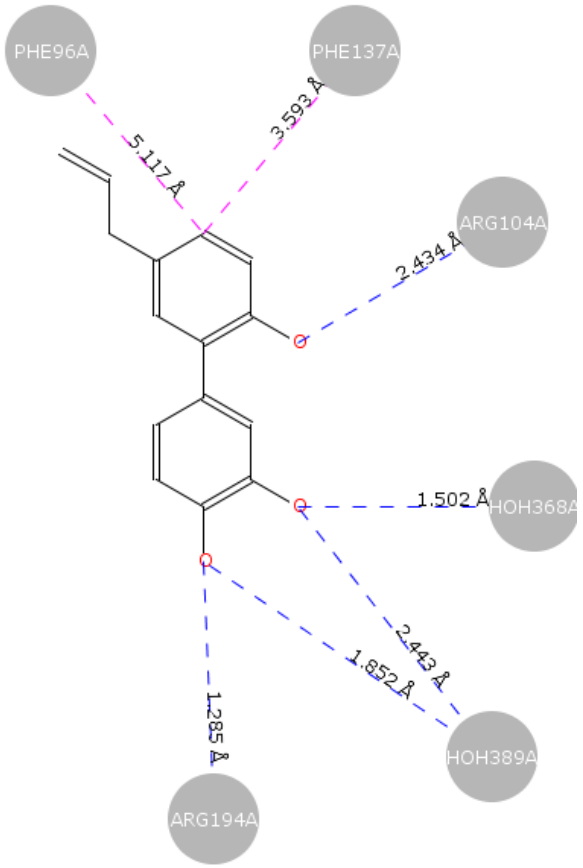


Figure 3. Hydrogen bonding and aromatic interactions of Streblusol E with deoxycytidine kinase(2NOA); Blue Broken Line- Hydrogen Bonding; Pink Broken Line: Aromatic/pi-pi staking.

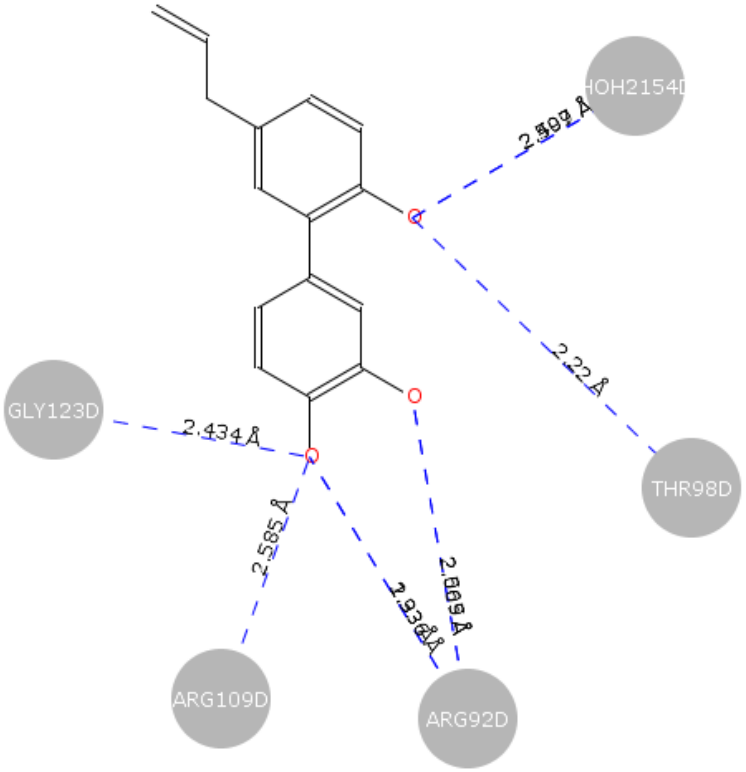


Figure 4. Hydrogen bonding of Streblusol E with human nucleoside diphosphate kinase(3FKB) ; Blue Broken Line- Hydrogen Bonding.

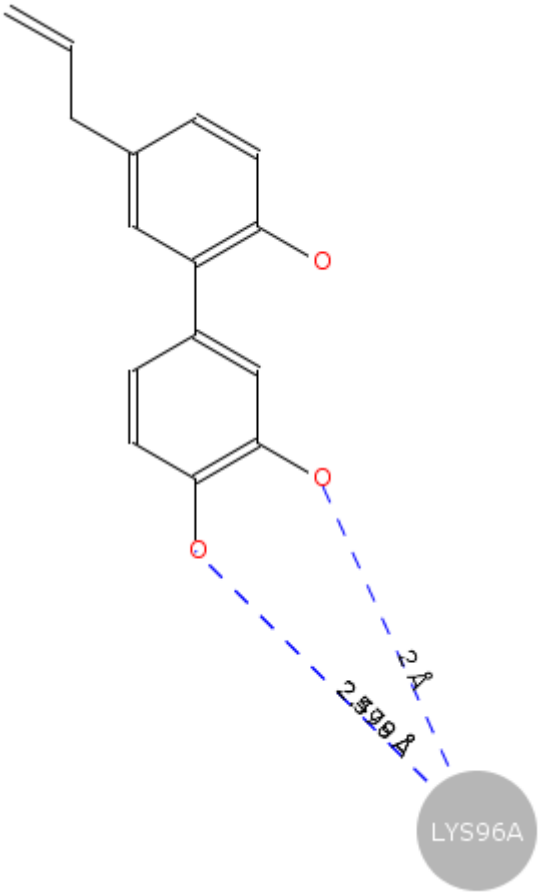


Figure 5. Hydrogen bonding of Streblusol E with Human Hepatitis B Viral Capsid(1QGT); Blue Broken Line- Hydrogen Bonding.

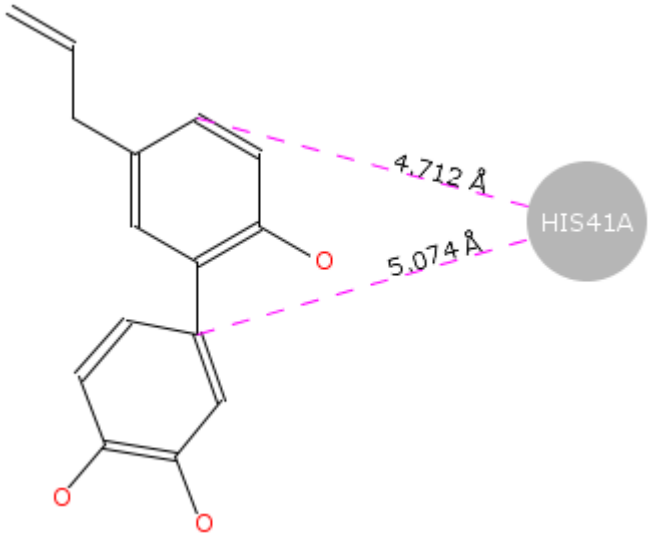


Figure 6. Aromatic/pi-pi staking of Streblusol E with hepatitis B X-interacting protein(3MSH); Pink Broken Line: Aromatic/pi-pi staking.

3. Materials and Methods

Proteins used for GRIP Docking

EF3-CaM complexed with PMEApp (1PK0): Adefovir dipivoxil, a drug approved to treat chronic infection of hepatitis B virus, effectively inhibit EF-induced cAMP accumulation by inhibiting calmodulin(CaM)-activated adenylyl cyclase (Shen et al., 2004).

Deoxycytidine kinase complexed with Lamivudine & ADP (2NOA): L-nucleoside analogs represent an important class of small molecules for treating both viral infections and cancers. These pro-drugs achieve pharmacological activity only after enzyme-catalyzed conversion to their tri-phosphorylated forms. Crystal structure of human deoxycytidine kinase (dCK) in complex with the L-nucleosides (-)-beta-2',3'-dideoxy-3'-thiacytidine (3TC), an approved anti-human immunodeficiency virus (HIV) agent and troxacitabine (TRO), an experimental anti-neoplastic agent was used. The first step in activating these agents is catalyzed by dCK. The capability of dCK to phosphorylate both D- and L-nucleosides and nucleoside analogs derives from structural properties of both the enzyme and the substrates themselves (Sabini et al., 2007).

NDPK H122G and Tenofovir-diphosphate (3FKB): Tenofovir is an acyclic phosphonate analog of deoxyadenylate used in AIDS and hepatitis B therapy. Tenofovir diphosphate, its active form can be produced by human nucleoside diphosphate kinase (NDPK), but with low efficiency, and that creatine kinase is significantly more active (Koch et al., 2009).

Human Hepatitis B Viral Capsid (HBCAG) (1QGT): Hepatitis B is a small enveloped DNA virus that poses a major hazard to human health. The crystal structure of the T = 4 capsid has been used. The monomer fold is stabilized by a hydrophobic core that is highly conserved among human viral variants. Association of two amphipathic alpha-helical hairpins results in formation of a dimer with a four-helix bundle as the major central feature. The capsid is assembled from dimers via interactions involving a highly conserved region near the C terminus of the truncated protein used for crystallization. The major immunodominant region lies at the tips of the alpha-helical hairpins that form spikes on the capsid surface (Wynne et al., 1999).

Hepatitis B X-interacting protein at high resolution (3MSH): Hepatitis B X-interacting protein (HBXIP) is a ubiquitous protein that was originally identified as a binding partner of the hepatitis B viral protein HBx. HBXIP is also thought to serve as an anti-apoptotic cofactor of survivin, promoting the suppression of pro-caspase-9 activation (Garcia-Saez et al., 2011).

Docking studies

Vlife MDS 4.4 is very robust software with inclusion of all the necessary simulation modules. The structure of streblusol E in the study has been drawn in the 2D drawing application (2D Draw app) of MDS 4.3, followed by its conversion into 3D form by using default conversion procedure. Best conformer with the minimum energy was used for the docking analysis (Singla and Bhat, 2010; Singla et al., 2013). Molecular docking energy evaluations are usually carried out with the help of scoring function like dock score, PLP score, potential of mean force (PMF) score, steric and electrostatic score, etc. The PLP function is incorporated by the MDS Vlife Science software in the GRIP docking method which calculates the ligand-receptor binding affinity in terms of the PLP score. The PLP score is designed to enable flexible docking of ligands to perform a full

conformational and positional search within a rigid binding site. Streblusol E was docked into the active site of 1PK0, 1QGT, 2NOA, 3FKB and 3MSH that can be obtained in the co-crystallized with adefovir diphosphate, lamivudine, tenofovir monophosphate & tenofovir diphosphate or by the use of cavities. The parameters fixed for docking simulation was like this- number of placements: 50, rotation angle: 10o, exhaustive method, ligand-wise results: 10, scoring function: PLP score. By rotation angle, ligand would be rotated inside the receptor cavity to generate different ligand poses inside the receptor cavity. By placements, the method will check all the 50 possible placements into the active site pocket and will result out best placements out of 50. After docking simulation, the best docked conformer of streblusol E and reference ligands were then checked for their interactions with targeted proteins like hydrogen bonding, hydrophobic, pi-staking/aromatic, charge and vanderwaal's interactions (Igoli et al., 2014a, 2014b; Malleshappa and Patel, 2013; Singla et al., 2012; Singla, 2014; VLife , 2013) .

Drug Metabolism and Pharmacokinetics

Various parameters like hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), total polar surface area (TPSA), flexibility, rotatable bonds, solubility (LogS), solubility at pH 7.4 (LogS @ pH 7.4), lipophilicity (LogP), lipophilicity at pH 7.4 (LogP @ pH 7.4), affinity towards cytochrome P450 2C9 isoform (2C9 pKi), hERG inhibition (hERG pIC50), blood brain barrier crossing capability (BBB log([brain]:[blood]); BBB category) , human intestinal absorption (HIA category), substrate for P-glycoprotein (P-gp category),), affinity towards cytochrome P450 2D6 isoform(2D6 affinity category), plasma protein binding (PPB90 category) and composite site lability of Streblusol E on three isoforms of cytochrome P450 i.e 3A4, 2D6 and 2C9 were calculated using StarDrop software of Optibrium Ltd (Optibrium Ltd).

In Silico Prediction of Toxicity

Using Derek Nexus module in StarDrop(liaison between Optibrium Ltd. and LHASA ltd), probability of Streblusol E to exert toxicity against various toxicological endpoints like carcinogenicity, mutagenicity, genotoxicity etc were calculated and reporting under four reasoning level like

- No Report – no evidence of toxicity or nothing to report
- Probable- there is atleast on strong argument for the proposition and none against it
- Plausible – the weight of evidence supports the proposition
- Equivocal – there is an equal weight of evidence for and against the proposition (Lhasa Ltd.; Segall and Barber, 2014).

4. Conclusions

Streblusol E, bioactive from Streblus asper has potential to inhibit hepatitis B virus. Its in silico studies with various target proteins further strengthens its efficacy as anti-hepatis B viral agents.

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Author Contributions

RKS arranged the financial grant for this project as well as collected the data. RG and BD had helped in the data analysis and manuscript drafting. VBG lead the study, analyse the data, finalize the manuscript. All authors have read and approved the final version of manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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