

DengueVrsEllagic Acid & Ferric Carboxymaltose: *InSilico*

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Abstract

Backgrounds: Dengue viruses are transmitted to humans via mosquito bites from infected Aedes species (Aedesegypti or Aedesalbopictus). Dengue fever affects over half of the world's population, or about 4 billion people. Dengue fever is a common cause of sickness in high-risk settings. **Methods:** In the current study two serotypes of Dengue viruses namely DENV1 and DENV2 taken for the study. Here two important compounds namely Ellagic acid and Ferric Carboxymaltose chosen for the targets to be inhibited. In silico docking approach performed to dock the two compounds against the DENV1 and DENV2 viruses of Dengue. Autodock 4.2 tool chosen for the docking purpose. **Results:** Dengue i.e., DENV-1 & 2 indicate excellent binding property with Ellagic Acid & Ferric Carboxymaltose of the order -6.02 kcal/mol & -6.9 kcal/mol, respectively. Either are hematinic; pregnancy safe; non-toxic; complete synergy between either vis-à-vis virus targets/binding sites; with supportive therapies; etc. Novel. It was found that, the Ellagic acid is more effective for DENV1 virus and Ferric kcal/mol, respectively. **Conclusions:** It can be stated that, these two drugs can be better approach for future study against the Dengue viruses and expected drug candidates.

Keywords: Dengue; Ellagic Acid; Ferric Carboxymaltose; InSilico; Synergistic.

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INTRODUCTION

Dengue (Spanish phone) nomenclature as the acronym DENV wherein DEN = dengue & V = virus. It has 1-4 serotypes. All are self-limiting typhoid of the *Flaviviridae* family [1]; & yellow. Mutates in nature and hence presents inter-continental or even intra-sub continental genetic variations [2] longitudinal and or latitudinal. Are arbo-virus (Ar = arthropod & Bo = borne) as they are vectored by the arthropods-mosquito (*Aedes* {3 spp}) which are abundant common carriers of poly viruses (tropical-equatorial belts). DENVs are positive, single-strand RNA, enveloped in 3 lipids

coats, limited by 11.5kD (= medium range heavy); icosahedral. Serotype 1 & 2 are pathogenic. Clinically, DENV-1 is marked with red eyes. DENV-2 is marked by lower platelet count. Either with shooting pyrexia; blistering rash (torso either side); arthralgia; myalgia; debilitating headache (difficulty in keeping eyes open); plummeting platelet count (thrombocytopenia); hemorrhage & falling hematocrit; shock (O2 insufficiency in cerebral parenchyma & the coronary) [3]. DENV-3 & 4 are near nonpathogenic and are reported few and far between. Symptoms (DENV-1&2) manifests at about 5th-6th day and wane by the 10th (self-

limiting). There are no therapies save & except supportive (paracetamol) & symptomatic redress of the secondary pathologies (common) and the response pathologies (individual basis). Most cases respond. Grave prognosis is associated with co-morbidities. However, (i) decreasing RBC count & related phenomenon (ii) plummeting platelet count (iii) hemorrhage. In pandemic covid DENV is a sure candidate to because syndemic that complicate normal prognosis towards grave. All this necessitates search for specific, safe, therapeutics, which thus far has been conspicuous by absence. However, drug discovery is fraught with pitfalls & cost overruns. And whereas, computational pre-modeling cuts costs; saves time; averts many a pitfalls and serves society better. In-silico route has therefore been the choice path [4]. And very recently used by Behera *et al.*, to screen-evaluate 56 commercially available drug moieties that have been pan globally re-purposed for Covid combat [5]. In this communication we report (A) Ellagic acid EA (B) Ferriccarboxymaltose FC as insilico study results vis-à-vis DENV-1 & 2, respectively. Either offer excellent binding affinity and other indicators. EA since 2004 has continuously & variedly been reported to be anti-virus [6, 7]. FC not till this communication. Furthermore, these two compounds are physiology\pregnancy safe (jointly with paracetamol) and offer scope for inter-compound (even multi drug) complementarities cum supplementing use with synergistic therapeutic effect. Novel, vis-à-vis DENV.

MATERIAL & METHODS

Target Serotypes

Only 2 serotypes of Dengue virus DENV-1 and DENV-2. Others are less pathogenic and also not prevalent.

Structure Selection

Protein structures of the either serotypes have been selected from the PDB(Protein Data Bank) database [8].

Drug Selection and Structure Finding

(i) Ellagic acid and (ii) Ferric carboxymaltose are the two drug candidate compounds (*note-i*).

The respective structures were downloaded from PubChem Database [9] in SDF file format and converted into .pdb format in Discovery studio software.

Binding Sites Selection

CASTP web server has been used to find the binding sites of the protein structures [10].

Serotypes Structure Selection

Chain A of the PDB structure/s are necessary for in silico investigations. For DENV-1, PDB ID 4FFT [11] and for DENV-2, the PDB ID 1AON [12] have been taken and prepared for docking with chimera program as illustrated in figure 1 and figure 2 respectively.

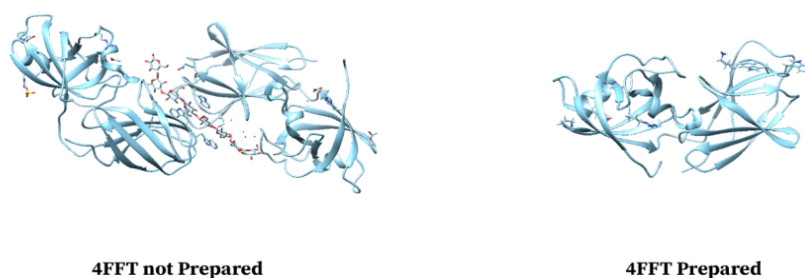


Figure 1: Structure of 4FFT and its prepared form for docking by Chimera program

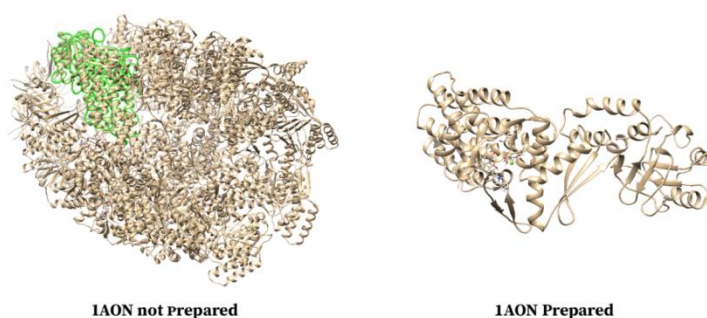


Figure 2: Structure of 1AON and its prepared form for docking by Chimera program

Molecular Docking With Serotypes Structures

Serotypes DENV 1 and 2 were docked at their (predicted) binding sites using Autodock 4.2 tool [13].

RESULTS

BINDING SITES

The binding sites of the proteins were predicted by using the CASTp webserver. For DENV-1 with PDB ID 4FFT, the binding sites predicted are – VAL320, PHE337, SER338, THR339, ARG350, LEU351, ALA369, GLU370, PRO371, PRO372 and ILE378. For DENV-2, with PDB id 1AON, the predicted binding sites are ALA35, ASN37, LYS38, LEU294, MET297, MET301, LYS334, ILE335, PRO336, PHE337, GLU338, ILE339, ARG350, LEU351, VAL354, ASN355, PRO356, ALA369, ILE379, GLY381 and GLN386

MOLECULAR DOCKING

For Molecular Docking on Autodock 4.2 tool the grid box value for DENV-1 protein taken are X-40, Y-60 and Z-56. For DENV-2 the grid box values are X-66, Y-94 and Z- 52. Ellagic acid and Ferric carboxymaltose were docked against the DENV-1 and DENV-2 proteins.

Figure 3 and 4 shows the interaction of Ellagic acid with DENV-1 Protein in 2d and 3d, respectively. Figure 5 and 6 shows the interaction of Ferriccarboxymaltose with DENV-1 Protein in 2d and 3d, respectively. Figure 7 and 8 shows the interaction of Ellagic acid of with DENV-2 Protein in 2d and 3d, respectively. Figure 9 and 10 shows the interaction of Ferric carboxymaltose with DENV-2 Protein in 2d and 3d, respectively.

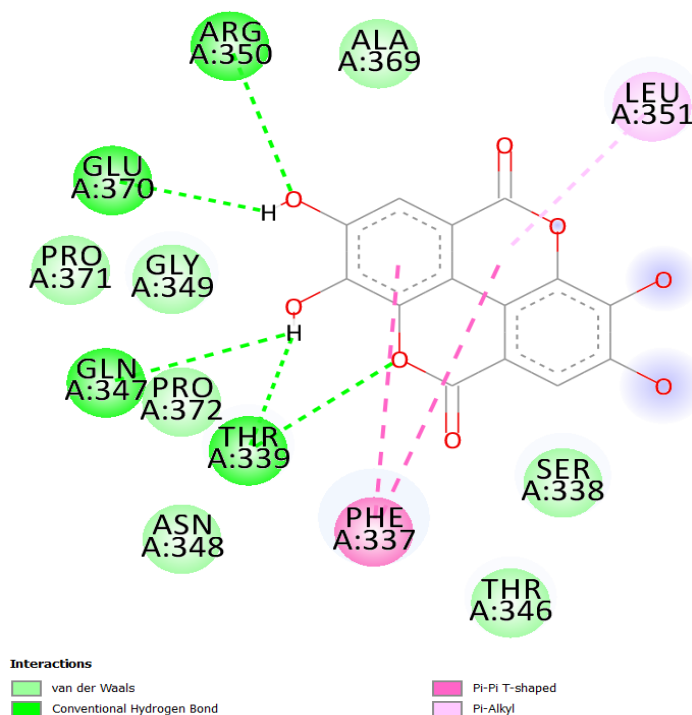


Figure 3: Shows the interaction of Ellagic acid with DENV-1 Protein in 2d

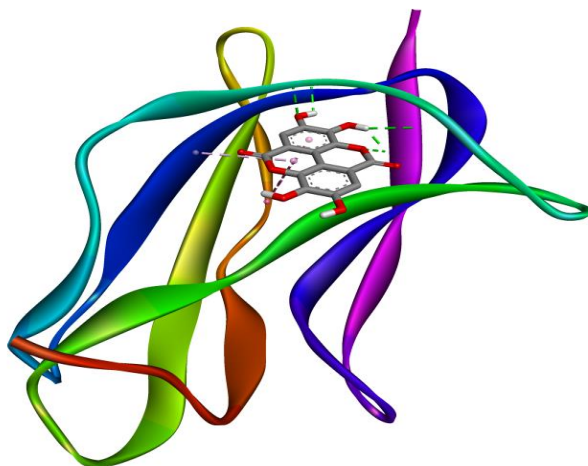


Figure 4: Shows the interaction of Ellagic acid with DENV-1 Protein in 3d

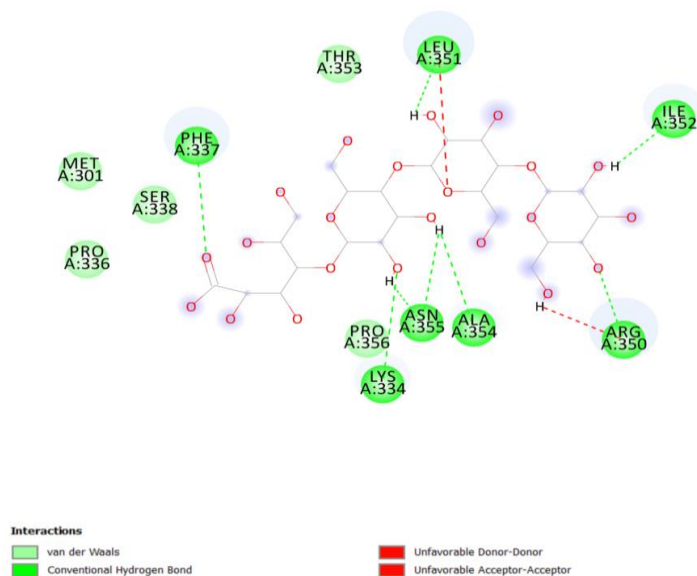


Figure 5: Shows the interaction of Ferriccarboxymaltose with DENV-1 Protein in 2d

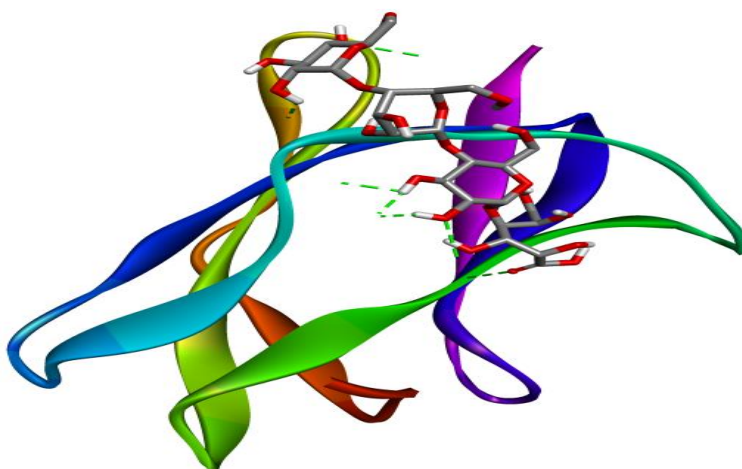


Figure 6: Shows the interaction of Ferriccarboxymaltose with DENV-1 Protein in 3d

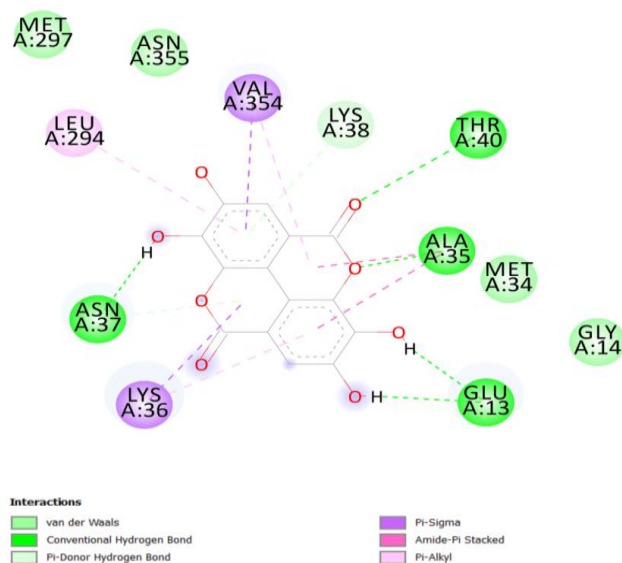


Figure 7: Shows the interaction of Ellagic acid of with DENV-2 Protein in 2d

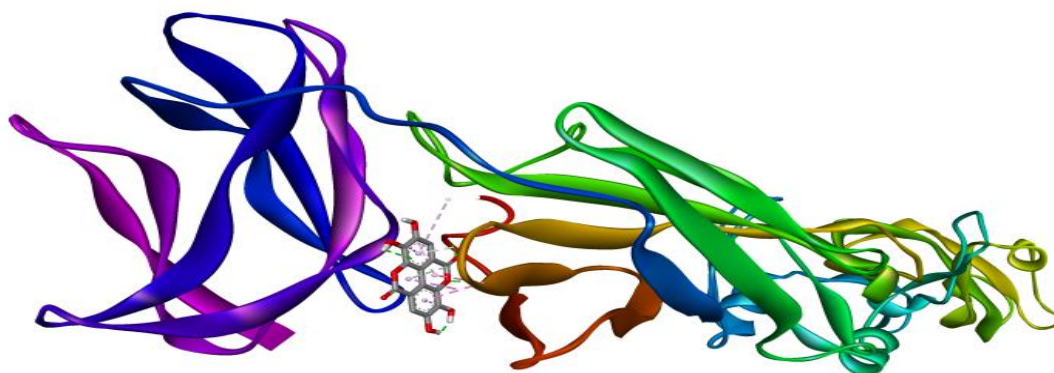


Figure 8: Shows the interaction of Ellagic acid of with DENV-2 Protein in 3d

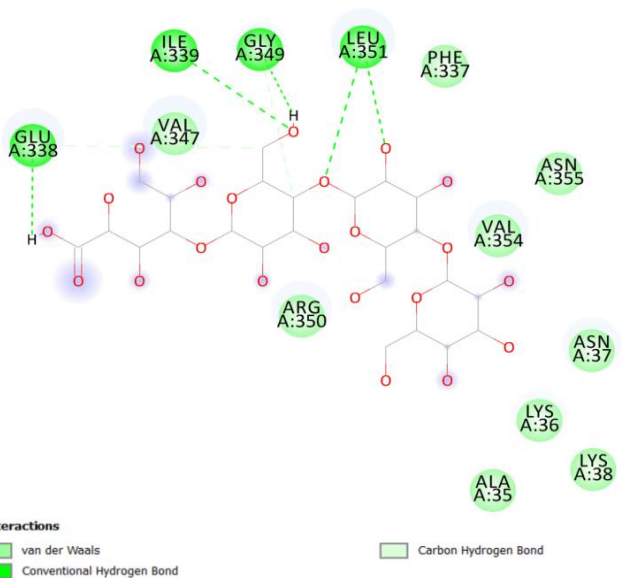


Figure 9: Shows the interaction of Ferric carboxymaltose with DENV-2 Protein in 2d

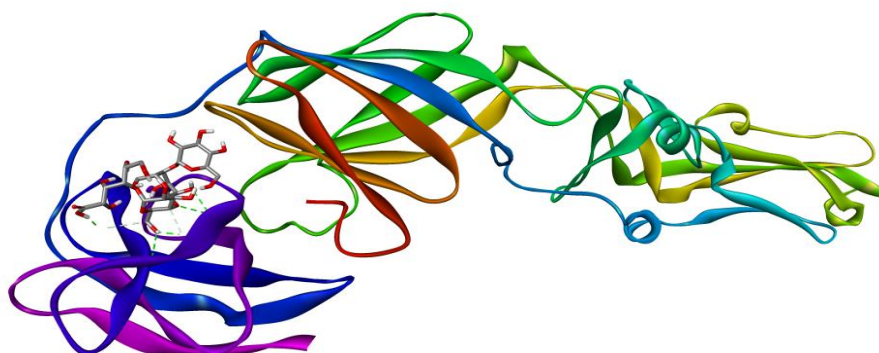


Figure 10: Shows the interaction of Ferric carboxymaltose with DENV-2 Protein in 3d

Table 1 and Table 2 give the docking results.

Table 1 indicates that Ellagic acid has a marginally greater binding affinity than Ferric carboxymaltose against DENV-1 @ -6.02 kcal/mol.

Table 2 indicates that Ferric carboxymaltose has a marginally greater binding affinity than Ellagic acid against DENV-2 @ -6.9 kcal/mol.

Table 1: Docking Study of Ellagic Acid and Ferric Carboxymaltose with DENV 1 Protein (PDB ID- 4FFY)

Sl. No.	PubChem CID	Drug	Binding Energy (Kcal/Mol)	Ligand Efficiency	Internal Energy	No. of H - Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	5281855	Ellagic Acid	-6.02	-0.27	-7.21	5	THR339,ARG350, GLN347,GLU370	2.449968
2.	86278165	Ferric carboxymaltose	-5.9	0.0	-8.47	8	LYS334,PHE337, ARG350,ILE352, LEU351,ALA354, ASN355	2.47008875

Table 2: Docking Study of Ellagic Acid and Ferric Carboxymaltose with DENV 2 Protein (PDB ID-10AN)

Sl. No.	PubChem CID	Drug	Binding Energy (Kcal/Mol)	Ligand Efficiency	Internal Energy	No. of H - Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	5281855	Ellagic Acid	-6.63	-0.3	-7.83	5	ALA35, THR40,GLU13, ASN37	2.597082
2.	86278165	Ferric carboxymaltose	-6.9	0.05	-6.2	5	ILE339,LEU351, GLY349,GLU338	2.694988

DISCUSSION

Dengue fever is a worldwide arboviral virus spread by Aedes mosquitoes that affects an estimated 2.5 billion people and is a fast expanding public health issue. Each year, there are between 50 and 100 million illnesses, with approximately 500,000 patients being admitted to hospitals with serious and life-threatening conditions [14]. The virus causes various symptoms in persons of various ages. It is minor in adults but dangerous in children and teenagers. The virus exists in four different forms in the world (DENV1, DENV2, DENV3, DENV4) [15]. The evaluated genes in this study belong to the first two types of this virus called DENV-1 and DENV-2. PDB ID for DENV-1 is 4FFT and for DENV-2 is 1AON.

Type-A cellulose-binding modules (CBMs), which are components of modular cellulases, bind to crystalline cellulose and improve enzyme performance. EXLX1, a bacterial expansin with the potential to loosen plant cell walls, was studied for cellulose binding. EXLX1 has a considerable affinity for crystalline cellulose through D2, but not for soluble cellooligosaccharides. Calorimetry revealed that cellulose binding was predominantly entropic. The crystal structures of EXLX1 complexed with cellulose-like oligosaccharides were solved, and we discovered that EXLX1 binds the ligands via hydrophobic interactions between three linearly organized aromatic residues in D2. The oligosaccharide was sandwiched between two D2 domains with opposing polarity, revealing a new kind of ligand-mediated dimerization [16].

Chaperonins help with protein folding by consuming ATP. They occur as multi-subunit protein assemblages made up of stacked rings of subunits. GroEL asymmetric intermediates are generated in *Escherichia coli* using the co-chaperonin GroES and nucleotides attached to only one of the seven-subunit rings (the cis ring) rather than the opposite ring (the trans ring). The GroEL-GroES-(ADP)₇ complex structure illustrates how bound GroES can stabilize a folding chamber with ADP confined to the cis ring via substantial en bloc motions of the cis ring's intermediate and apical domains. The apical domains' elevation and twist double the volume of the central cavity and bury hydrophobic peptide-binding residues at the GroES interface and between GroEL subunits, resulting in a hydrophilic cavity lining that promotes protein folding. The inward tilt of the cis equatorial domain generates an outward tilt of the trans ring, which prevents a second GroES from binding. This negative allosteric mechanism, when paired with recent functional discoveries, proposes a model for an ATP-driven folding cycle that requires a double toroid [17]. We identified best pocket of these targets and select best chain for docking. Chain A it's our choice in both of them.

CONCLUSION

Between DENV -1 & DENV-2, serotype-1 is more pathogenic. Against it, either compound involves a very large swath of amino acid residues. Although either compound is very different on all parameters, they score closely, which posits them as complementing and synergistic compounds. A nice pair for therapeutic considerations.

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We stand on the broad shoulders of the vary many workers pre to us who all have done pioneering works.

Declarations of interest: Authors declared that they have no conflict of interest and no financial support.

NOTE – i: Is a veritable & deep domain of supporting historical data; collateral information and references thereof. Visit: SUPPLEMENTARY FILE.

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Supplementary File

India's national school of medicine Ayurveda (plural-life) in compendium text form is noted from c.4-5th A.D., and medicaments as (i) functional food, e.g., EA (ii) processed moieties, e.g., FC. Ayurvedic recessions and recensions are available in Sanskrit (self gelling) and in all major indo vernaculars including indo Islamic school of medicine\\$. Our twin moieties are indicated for 'anemia' (at presentation); mechanics being 'hematinic' (erythropoetic during therapeutic period = novel) and are noted in 'n' number of formulations ranging the entire indo historical period until c.1800 {S-1}. And modern medicine have robust heritage with (i) & (ii). Since >20yrs before present EA has been used by Bhattacharya vis-à-vis malaria & malignancy {S2-5}. AND FC type pre cursers of Fe (& other metals) ashes as powders & liquid in fixed has been used in anemia; geriatric care; solid - liquid cancers; metastasis; bone marrow suppression; all stages of malignancy including prophylaxis; palliative;

end of life stage care; anti-viral and step-by-step drug making process enumerated in public domain {S 6-10}. Such academic treatments are not noted in any other schools of medicine {S 11;12}.

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