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# Molecular docking analysis of *Carica papaya* Linn constituents as antiviral agent

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**Abstract**

*Carica papaya* (papaya) fruits are available throughout the world and it is well accepted as food or as a quasi-drug. Aqueous papaya leaves extract have been used as treatment for dengue fever. This prompted us to carry out the docking study on these nine selected ligands (phyto-constituents of papaya) which are carpaine, dehydrocarpaine I and II, cardenolide, p-coumaric acid, chlorogenic acid, caricaxanthin, violaxanthin and zeaxanthin. These phyto-constituents were evaluated on the docking behaviour of dengue serotype 3 RNA-dependent RNA polymerase (RdRp); influenza A (H1N9) virus neuraminidase (NA); chikungunya virus glycoprotein (E3-E2-E1) and chikungunya virus non-structural protein2 (nsP2) protease using Discovery Studio Version 3.1. In addition, molecular physicochemical, drug-likeness, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) and TOPKAT (Toxicity Prediction by Komputer Assisted Technology) analyses were done. The molecular physicochemical analysis revealed that cardenolide and p-coumaric acid (2 ligands) complied with Lipinski's rule of five. Dehydrocarpaine II, cardenolide, caricaxanthin, violaxanthin and zeaxanthin all the five ligands were predicted to have plasma protein binding (PPB) effect. Docking studies and binding free energy calculations revealed that p-coumaric acid exhibited very least binding energy irrespective of its target protein. Hence, the results of this present study exhibited the potential of these nine ligands as antiviral agent.



## Introduction

*Carica papaya* Linn is commonly known as papaya. It is well known for its food and nutritional values and moreover it is one among the popular fruits of the world. It is also called as "fruit of a common man", owing to its high nutritive value and moreover it's available for reasonable price throughout the world (Krishna *et al*., 2008). The fruit, flower, seed, leaf, bark and root of papaya tree are known to posses many biological active compounds, in which alkaloid is an important group of interest. For example, carpaine (alkaloid) from papaya leaf has been shown to have antiprotozoal, anthelmintic, antiplasmodial (Julianti *et al*., 2014) and antithrombocytopenic activity (Zunjar *et al*., 2016). Similarly, danielone from papaya fruit has been reported to have antifungal activity against *Colletotrichum gloeosporioides* (Yogiraj *et al*., 2014).

Various parts of papaya have been utilized in traditional medicine in different parts of the world. For instance, daily consumption of green papaya leaves and as well as herbal infusion have been reported in some areas of Indonesia as means for preventing malaria disease (Julianti *et al*., 2014). Similarly aqueous papaya leaves extract have been used as treatment for dengue fever, which help the patient to increase platelets, white blood cells and neutrophil counts (Ahmad *et al*., 2011). In other report, flavonoid from papaya has been shown to inhibit viral non structural 2B and 3 (NS2B-NS3) protease complex and thereby prevents dengue 2 viral (DENV-2) assembly using molecular docking study (Senthilvel *et al*., 2013). This prompted us to carry out the docking study on these nine selected ligands (phyto-constituents of papaya) which are carpaine, dehydrocarpaine I and II, cardenolide, p-coumaric acid, chlorogenic acid, caricaxanthin, violaxanthin and zeaxanthin. These phyto-constituents were evaluated on the docking behaviour of dengue serotype 3 RNA-dependent RNA polymerase (RdRp); influenza A (H1N9) virus neuraminidase

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(NA); chikungunya virus glycoprotein (E3-E2-E1) and chikungunya virus non-structural protein2 (nsP2) protease with investigation on the enzymes putative binding sites using Discovery Studio Version 3.1. Therefore, the present study aims to determine the nine *Carica papaya* phyto-constituents as antiviral agent especially against dengue, influenza and chikungunya viruses using molecular docking method.

## Materials and Methods

*Ligand preparation*

Chemical structures of the ligands i) carpaine (CID442630); ii) dehydrocarpaine I (HMDB30271); iii) dehydrocarpaine II (HMDB30273); iv) cardenolide (Chemspider ID19954501); v) p-coumaric acid (CID637542); vi) chlorogenic acid (Chemspider ID1405788); vii) caricaxanthin (Chemspider ID4444647); viii) violaxanthin (Chemspider ID395237) and ix) zeaxanthin (Chemspider ID444421) were retrieved from PubMed (www.pubmed.com) compound, human metabolome (www.hmdb.ca/metabolites) and Chemspider (www.chemspider.com) compound database respectively.

*Target protein identification and preparation*

The three dimensional structures of the dengue RNA-dependent RNA polymerase (RdRp) (PDB ID: 3VWS with resolution of 2.1 Å), influenza neuraminidase (PDB ID: 1L7F with resolution of 1.8 Å), chikungunya glycoprotein (PDB ID: 3N44 with resolution of 2.35 Å) and chikungunya nsP2 protease (PDB ID: 3TRK with resolution of 2.4 Å) were obtained from the Research Collaborator for Structural Bioinformatics (RCSB) Protein Data Bank (Anonymous, www.rcsb.org). A chain of all of the proteins (except for chikungunya glycoprotein, where A, B and F) was pre-processed separately by deleting ligand, as well as the crystallographically observed water molecules (water without hydrogen bonds).

*Molecular descriptors calculation*

Molinspiration online database was used for the nine selected ligands to calculate thirteen descriptors (www.molinspiration.com) which are log P, polar surface area, molecular weight, number of atoms, number of O or N, number of OH or NH, number of rotatable bonds, volume, drug likeness including G protein coupled receptors (GPCR) ligand, ion channel modulator, kinase inhibitor and nuclear receptor ligand, and the number of violations to Lipinski's rule.

*ADMET and TOPKAT analysis*

Both of ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) and TOPKAT (Toxicity Prediction by Komputer Assisted Technology) tests were performed using Discovery Studio® 3.1 (Accelrys, San Diego, USA). ADMET analysis was performed using human intestinal absorption (HIA), aqueous solubility (AS), blood brain barrier (BBB), cytochrome P450 2D6 (CYP2D6), plasma protein binding (PPB) and hepatotoxicity (HT) descriptors. As for the TOPKAT analysis, aerobic biodegradability (AB), Ames mutagenicity (AM), ocular irritancy (OI), skin irritancy (SI) , skin sensitization (SS) and oral toxicity in rat (LD50 in g/Kg of body weight) descriptors were used.

*Docking studies*

Docking studies were carried out on the crystal structures of dengue RNA-dependent RNA polymerase (RdRp), influenza neuraminidase, chikungunya glycoprotein and chikungunya nsP2 protease retrieved from Protein Data Bank using the CDOCKER protocol under the protein-ligand interaction section in Discovery Studio® 3.1 (Accelrys, San Diego, USA). In general, CDOCKER is a grid-based molecular docking method that employs CHARMM force fields. A protein was firstly held rigid while the ligands were allowed to flex during the refinement. Two hundred random ligand conformations were then generated from the initial ligand structure through high temperature molecular dynamics followed by random rotations, refinement by grid-based (GRID I) simulated annealing, and a final grid-based or full force field minimisation (Wu *et al*., 2003). In this experiment, the ligand was heated to a temperature of 700 K in 2000 steps and the cooling steps were set in 5000 steps to 300 K with the grid extension set to 10 Å. Hydrogen atoms were added to the structures and all ionisable residues were set at their default protonation state at a neutral pH. For each ligand, top ten ligand binding poses were ranked according to their CDOCKER energies, and the predicted binding interactions were then analysed from which the best among the ten ligand binding poses was chosen and carried out *in situ* ligand minimization using standard protocol.

## Results

*Molecular descriptors analysis*

Violation of zero will be the main target compound which was observed for cardenolide and p-coumaric acid suggesting that these compounds complied very well with the Lipinski's rule of five. However,

Table 1. Molecular physicochemical descriptors analysis of nine ligands using Molinspiration online software tool

| Ligand | Log A[a] | TPSA[b] | Natoms[c] | MW[d] | noN[e] | nOHNH[f] | Nviolations[g] | Nrotb[h] | Volume[i] |
|---|---|---|---|---|---|---|---|---|---|
| Carpaine | 6.40 | 76.7 | 34 | 478.7 | 6 | 2 | 1 | 0 | 497.4 |
| Dehydrocarpaine-I | 6.60 | 77.0 | 34 | 476.7 | 6 | 1 | 1 | 0 | 491.4 |
| Dehydrocarpaine-II | 6.79 | 77.3 | 34 | 474.7 | 6 | 0 | 1 | 0 | 485.4 |
| Cardenolide | 4.98 | 26.3 | 25 | 342.5 | 2 | 0 | 0 | 1 | 348.9 |
| p-Coumaric acid | 1.43 | 57.5 | 12 | 164.2 | 3 | 2 | 0 | 2 | 146.5 |
| Chlorogenic acid | -0.45 | 164.7 | 25 | 354.3 | 9 | 6 | 1 | 5 | 296.3 |
| Caricaxanthin | 9.64 | 20.2 | 41 | 552.9 | 1 | 1 | 2 | 10 | 600.0 |
| Violaxanthin | 9.00 | 65.5 | 44 | 600.9 | 4 | 2 | 2 | 10 | 615.5 |
| Zeaxanthin | 9.40 | 40.5 | 42 | 568.9 | 2 | 2 | 2 | 10 | 608.0 |

[a] Octanol-Water partition coefficient, [b] Polar surface area, [c] Number of non hydrogen atoms, [d] Molecular weight, [e] Number of hydrogen bond acceptors [ O and N atoms], [f] Number of hydrogen bond donors [ OH and NH groups], [g] Number of Rule of 5 violations, [h] Number of rotatable bonds, [i] Molecular volume.

Table 2. Drug-likeness property analysis of 9 ligands using Molinspiration online software tool

| Ligand | GPCR* ligand | Ion channel modulator | Kinase inhibitor | Nuclear receptor ligand | Protease inhibitor | Enzyme inhibitor |
|---|---|---|---|---|---|---|
| Carpaine | 0.11 | -0.00 | -0.12 | -0.12 | 0.16 | 0.07 |
| Dehydrocarpaine-I | 0.08 | -0.03 | -0.24 | -0.21 | 0.01 | 0.07 |
| Dehydrocarpaine-II | 0.03 | -0.01 | -0.20 | -0.04 | -0.05 | 0.09 |
| Cardenolide | 0.25 | 0.22 | -0.40 | 0.72 | 0.14 | 0.50 |
| p-Coumaric acid | -0.56 | -0.26 | -0.91 | -0.12 | -0.87 | -0.15 |
| Chlorogenic acid | 0.29 | 0.14 | -0.00 | 0.74 | 0.27 | 0.62 |
| Caricaxanthin | -0.03 | -0.25 | -0.20 | 0.49 | 0.02 | 0.24 |
| Violaxanthin | -0.06 | -0.56 | -0.35 | 0.13 | 0.08 | -0.03 |
| Zeaxanthin | -0.08 | -0.36 | -0.24 | 0.35 | 0.01 | 0.13 |

*GPCR- G Protein coupled receptors

carpaine, dehydrocarpaine I and II and chlorogenic acid showed one violation and caricaxanthin, violaxanthin and zeaxanthin showed two violations as shown in Table 1. Similarly in the present study only one ligand (cardenolide) showed active score (>0) towards all the six descriptors (except kinase inhibitor), whereas rest of ligands exhibited active to moderate active scores. Interestingly none of the ligand that shown inactive score (<-5.0), as shown in the Table 2.

*ADMET and TOPKAT analysis*

Table 3 shows the ADMET profile of the nine ligands, wherein cardenolide showed very high blood brain barrier (BBB) penetration effect compared to that of other ligands. Dehydrocarpaine II, cardenolide, caricaxanthin, violaxanthin and zeaxanthin all the five ligands were predicted to have plasma protein binding (PPB) effect. The toxicity profile of nine ligands as depicted in Table 4 all the ligands exhibited degradable nature towards aerobic biodegradability

Table 3. ADMET analysis of nine ligands

| Ligand | HIA | | | AS | | BBB | | PPB | CYP2D6 | HT |
|---|---|---|---|---|---|---|---|---|---|---|
| | PSA | ALog P8 | L* | Log(SW) | L** | Log BB | L*** | Predication | | |
| Carpaine | 78.08 | 6.11 | 2 | -7.57 | 1 | 0 | 4 | F | F | F |
| Dehydrocarpaine -I | 76.60 | 6.08 | 1 | -7.26 | 1 | 0 | 4 | F | F | F |
| Dehydrocarpaine -II | 75.11 | 6.05 | 1 | -6.95 | 1 | 0 | 4 | T | F | F |
| Cardenolide | 26.23 | 4.94 | 0 | -6.83 | 1 | 0.96 | 0 | T | F | F |
| p-Coumaric acid | 58.93 | 1.68 | 0 | -1.38 | 4 | -0.57 | 3 | F | F | F |
| Chlorogenic acid | 168.4 | -0.34 | 3 | -1.26 | 4 | 0 | 4 | F | F | F |
| Caricaxanthin | 20.81 | 10.76 | 3 | -7.96 | 1 | 0 | 4 | T | F | F |
| Violaxanthin | 59.49 | 7.00 | 3 | -4.65 | 2 | 0 | 4 | T | F | F |
| Zeaxanthin | 41.63 | 9.52 | 3 | -6.20 | 1 | 0 | 4 | T | F | F |

HIA-Human intestinal absorption, AS- Aqueous solubility, BBB-Blood brain barrier, PPB-Plasma protein binding, CYP2D6- cytochrome P450 2D6, HT-hepatotoxicity, L-Level, F-False and T-True.] *(0-good; 1-moderate; 2-poor and 3-very poor) ;**(0-extremely low; 1-very low; 2-low; 3-good; 4-optimal; 5-too soluble and 6-warning);***(0-very high penetrate; 1-high; 2-medium; 3-low and 4-undefined)

Table 4. Toxicity prediction analysis of nine ligands

| Ligand | AB* | AM** | OI# | SI## | SS♦ | Oral toxicity ▲ |
|---|---|---|---|---|---|---|
| Carpaine | Degradable | Non-mutagen | Irritant | Irritant | Non-sensitizer | 0.58 |
| Dehydrocarpaine-I | Degradable | Non-mutagen | Irritant | Irritant | Non-sensitizer | 0.23 |
| Dehydrocarpaine-II | Degradable | Non-mutagen | Irritant | Irritant | Non-sensitizer | 0.40 |
| Cardenolide | Degradable | Non-mutagen | Irritant | Irritant | Sensitizer | 2.90 |
| p-Coumaric acid | Degradable | Non-mutagen | Irritant | Non-irritant | Sensitizer | 1.42 |
| Chlorogenic acid | Degradable | Non-mutagen | Irritant | Non-irritant | Non-sensitizer | 1.48 |
| Caricaxanthin | Degradable | Non-mutagen | Irritant | Irritant | Sensitizer | 3.97 |
| Violaxanthin | Degradable | Non-mutagen | Irritant | Irritant | Sensitizer | ND* |
| Zeaxanthin | Degradable | Non-mutagen | Irritant | Irritant | Sensitizer | 4.56 |

AB*- Aerobic biodegradability; AM**- Ames mutagenicity; OI#- Ocular irritancy; SI##- Skin irritancy; SS♦- Skin sensitization and Oral toxicity▲- Oral toxicity in rat ($LD_{50}$ in g/Kg of body weight-rat)

effect. All of the ligands were predicted to have ocular irritancy effect in human.

*Molecular docking study*

The docking studies and binding free energy calculations reported in Table 5A show that violaxanthin had the highest interaction energy (-59.17 kcal/mol) with that of dengue RNA-dependent RNA polymerase (RdRp). In contrast, p-coumaric acid showed the least interaction energy (-22.39 kcal/mol) compared to other ligands. Interestingly four ligands (carpaine, dehydrocarpaine I and II and cardenolide) exhibited interaction with Thr413 amino acid residue of dengue RNA-dependent RNA polymerase (RdRp) as shown in Table 5A. As for the docking studies and binding free energy calculations with influenza neuraminidase, violaxanthin exhibited the highest interaction energy (-53.54 kcal/mol) as shown in Table 5B. However, in the present study four ligands (carpaine, dehydrocarpaine I and II and cardenolide) fail to dock with influenza neuraminidase. Moreover, two ligands (violaxanthin

Table 5 A. The interaction energy analysis of nine ligands with that of dengue serotype 3 RNA-dependent RNA polymerase (RdRp) using Discovery Studio® 3.1

| Ligand name | -cDocker interaction energy (kcal/mol) | Interaction amino acid residue | Bond distance (Å) |
|---|---|---|---|
| Carpaine | 54.83 | Thr413 | 2.3 |
| | | Asn492 | 1.9 |
| Dehydrocarpaine-I | 50.70 | Lys401 | 2.3 |
| | | Thr413 | 1.9 |
| Dehydrocarpaine-II | 50.00 | Thr413 | 2.4 |
| | | Asn492 | 1.1 |
| | | Gly604 | 2.0 |
| Cardenolide | 35.72 | Thr413 | 1.3 |
| p-Coumaric acid | 22.39 | Val603▪ | 2.9 |
| | | Gly604 | 1.9 |
| | | Thr605 | 2.1 |
| | | Tyr606 | 2.2 |
| Chlorogenic acid | 38.09 | Lys401♦ | 5.8 |
| | | Ser600 | 2.0 |
| | | Gly602 | 1.1 |
| | | Thr605 | 2.1 and 2.3 |
| Caricaxanthin | 56.84 | Asp663 | 1.7 |
| Violaxanthin | 59.17 | Arg792 | 2.0 |
| | | Ser796 | 1.8 |
| | | Ile797 | 1.6 |
| | | His801 | 2.3 |
| Zeaxanthin | 57.04 | Ser600 | 1.7 |
| | | Asn609 | 2.2 |

▪ Pi-Sigma interaction, ♦ Pi-+ interaction

Table 5 B. The interaction energy analysis of nine ligands with that of influenza A (H1N9) virus neuraminidase (NA) using Discovery Studio® 3.1

| Ligand name | -cDocker interaction energy (kcal/mol) | Interaction amino acid residue | Bond distance (Å) |
|---|---|---|---|
| Carpaine | F* | - | - |
| Dehydrocarpaine-I | F* | - | - |
| Dehydrocarpaine-II | F* | - | - |
| Cardenolide | F* | - | - |
| p-Coumaric acid | 25.80 | Arg292 | 1.9 |
| | | Arg371 | 1.7 |
| Chlorogenic acid | 43.00 | Arg152 | 2.2 |
| | | Asn221 | 2.0 |
| | | Arg224◊ | 6.2 |
| | | Ser245 | 1.7 |
| | | Thr247 | 2.2 |
| | | Arg292 | 2.1 |
| | | Tyr406 | 2.3 |
| Caricaxanthin | 51.81 | No interaction | - |
| Violaxanthin | 53.54 | Glu227 | 1.9 |
| Zeaxanthin | 51.43 | Glu227 | 1.8 |

*F- Fails to dock, ◊+-Pi interaction

and zeaxanthin) showed interaction with Glu227 amino acid residue of influenza neuraminidase. The docking studies and binding free energy calculations reported in Table 5C show that violaxanthin had the

Table 5 C. The interaction energy analysis of nine ligands with that of chikungunya virus glycoprotein (E3-E2-E1) using Discovery Studio® 3.1

| Ligand name | -cDocker interaction energy (kcal/mol) | Interaction amino acid residue | Bond distance (Å) |
|---|---|---|---|
| Carpaine | F* | - | - |
| Dehydrocarpaine-I | F* | - | - |
| Dehydrocarpaine-II | F* | - | - |
| Cardenolide | F* | - | - |
| p-Coumaric acid | 22.52 | ValB135 | 1.3 and 2.3 |
| | | ProB152 | 2.3 |
| | | LysF181 | 1.7 |
| | | ArgF247◊ | 4.7 |
| Chlorogenic acid | F* | - | - |
| Caricaxanthin | 48.63 | AsnB263 | 2.1 |
| Violaxanthin | 52.82 | AsnB263 | 1.3 |
| Zeaxanthin | 52.03 | AsnB263 | 1.1 |

F*- Fails to dock, ◊- +-Pi interaction

Table 5 D. The interaction energy analysis of nine ligands with that of chikungunya virus non-structural protein2 (nsP2) protease using Discovery Studio® 3.1

| Ligand name | -cDocker interaction energy (kcal/mol) | Interaction amino acid residue | Bond distance (Å) |
|---|---|---|---|
| Carpaine | F* | - | - |
| Dehydrocarpaine-I | F* | - | - |
| Dehydrocarpaine-II | F* | - | - |
| Cardenolide | F* | - | - |
| p-Coumaric acid | 22.31 | Lys1239 | 2.0 |
| Chlorogenic acid | 46.82 | Lys1042 | 2.1 |
| | | Glu1043 | 1.4 |
| | | Lys1045 | 0.64 and 1.0 |
| | | Phe1225 | 1.8 and 2.0 |
| | | Lys1239◊ | 3.8 |
| Caricaxanthin | 50.79 | No interaction | - |
| Violaxanthin | 53.38 | No interaction | - |
| Zeaxanthin | 53.93 | No interaction | - |

F*- Fails to dock, ◊ +-Pi interaction

highest interaction energy (-52.82 kcal/mol) with that of chikungunya glycoprotein. However, in the present study five ligands (carpaine, dehydrocarpaine I and II, cardenolide and chlorogenic acid) fail to dock with chikungunya glycoprotein. Interestingly three ligands (caricaxanthin, violaxanthin and zeaxanthin) exhibited interaction with Asn263 amino acid residue of chikungunya glycoprotein B chain. As for the docking studies and binding free energy calculations

with chikungunya nsP2 protease, p-coumaric acid showed the least interaction energy (-22.31 kcal/mol) as shown in Table 5D. However, in the present study four ligands (carpaine, dehydrocarpaine I and II and cardenolide) fail to dock with chikungunya nsP2 protease. Two ligands (p-coumaric acid and chlorogenic acid) exhibited interaction with Lys1239 amino acid residue of chikungunya nsP2 protease as shown in Table 5D.

## Discussion

Natural products have been serving as a main source of potential drugs. Recently, four natural product derivatives have been approved as an antiviral drug out of 138 drugs approved up to 2014 (Newman and Cragg, 2016) and which actually encourages more studies and research in natural product drug discovery programme. Interestingly, some proteolytic viral enzymes namely viral polymerase, integrase and reverse transcriptase serves as target for developing new antiviral agents. Because these enzymes, plays vital role in viral replication and assembly of the mature viral particle (Mishra *et al*., 2013). Searching for available foods/food products is still another wise strategy to develop specific inhibitors against these viral enzymes. *Carica papaya* fruits are available throughout the world and it is well accepted as food or as a quasi-drug (Kovendan *et al*., 2012). In the present study, we carried out molecular docking analysis on *Carica papaya* constituents as antiviral agent against i) dengue serotype 3 RNA-dependent RNA polymerase (RdRp); ii) influenza A (H1N9) virus neuraminidase (NA); iii) chikungunya virus glycoprotein (E3-E2-E1) and iv) chikungunya virus non-structural protein2 (nsP2) protease. Bhatt and co-workers (2013) reported that over half (50%) of the world's population is at high risk for infection by dengue virus. Reiner and co-workers (2014) reported that force of infection (FoI) in the case of dengue virus (DENV) has been observed high for dengue serotype 3 and 4, when compare to that of dengue serotype 1 and 2. RNA-dependent RNA polymerase (RdRp) is an enzyme which catalyzes the replication of RNA from an RNA template. It is a vital protein encoded in the genomes of all RNA containing viruses including Dengue virus and its activity is essential for maintaining viral cycle and replication (Bhattacharya *et al*., 2008). In general, RdRp enzymes family had three conserved sub-domains such as palm, fingers and thumb. RdRp from dengue virus serotype 3 (DENV-3) has been reported to be new target for developing novel antiviral compounds against dengue fever (Hansen *et al*., 1997 and Ariza *et al*., 2014). In the present study, all nine ligands had docked well with RNA-dependent RNA polymerase (RdRp) of dengue serotype 3 viral enzyme. Yogiraj and co-workers (2014) had summarized four pilot studies on use of *Carica papaya* as therapeutic agent for dengue fever management. Similarly, Senthilvel and co-workers (2013) had reported that both p-coumaric acid and chlorogenic acid inhibits viral non structural 2B and 3 (NS2B-NS3) protease complex. The two above mentioned reports were in good agreement with the present study.

Influenza is commonly called as flu, which is a serious infectious disease caused by influenza virus. At present much attention has been gained among the researchers to develop inhibitors of influenza neuraminidase (NA), because it serves as a main drug target for both prophylaxis and treatment for influenza infection. Shaukat and co-workers (2011) reported that papaya leaves extract at low concentrations (2 to 8 µg/ml) fails to inhibit influenza (H7N3) virus replication. Similarly in the present study three papaya alkaloids (carpaine, dehydrocarpaine I and II) fail to dock with influenza neuraminidase (NA). Chlorogenic acid has been reported to inhibit influenza A (H5N1) virus neuraminidase (Luo *et al*., 2011) and influenza A (H7N9) virus neuraminidase respectively (Liu *et al*., 2015). The p-coumaric acid has been reported to have anti-influenza viral activities in mice model, by prolonging survival rates and reducing virus titers in bronchoalveolar lavage (BAL) fluids (Pie *et al*., 2016). The above mentioned reports were in good agreement with the present study.

Chikungunya is an infectious disease caused by chikungunya virus. *Aedes albopictus* and *Aedes aegypti* are two vectors responsible for chikungunya virus transmission. Kovendan and co-workers (2012) reported that *Carica papaya* methanolic leaf extract has shown good larvicidal and pupicidal activity against the chikungunya vector (*Aedes aegypti*). Chlorogenic acid has been reported to have antiviral activity against chikungunya virus (Buhner, 2013).

## Conclusion

In the present study, it was found that three ligands (caricaxanthin, violaxanthin and zeaxanthin) has the potential to dock with all the four targeted proteins, whereas four ligands (carpaine, dehydrocarpaine I and II and cardenolide) failed to dock and bind with the three targeted proteins. Interestingly all the nine ligands showed the potential to dock with dengue serotype 3 RNA-dependent RNA polymerase (RdRp), which again demonstrate the use of papaya

as therapeutic agent for dengue fever management. Hence, it is strongly suggested that the results of this present study has paved better understanding of these nine ligands of *Carica papaya* Linn as potential antiviral agent.

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