Indian J.Sci.Res. 18(2): 55-61, 2018

ISSN: 0976-2876 (Print)
ISSN: 2250-0138(Online)

# A COMPUTATIONAL ANALYSIS OF THE THERAPEUTIC EFFECT OF CARICA PAPAYA LEAVES AGAINST DENGUE FEVER

**K. ANJU KRISHNAN[a], M.S. LATHA[b1] AND B. SRUTHY[c]**

[ab]Department of Chemistry, Sree Narayana College, Neduvarancode P O, Chengannur, Kerala, India
[c]Department of Chemistry SreeNarayana College, Kollam, Kerala, India

## ABSTRACT

**Dengue is a fast spreading viral disease that poses major threat to human health all over the world. At present there is no specific drug available for this fever. Extract of papaya leaves are found to be very effective against the disease. Here an attempt is made to identify the phytochemical responsible for the therapeutic effect by*insilico* analysis. Dengue fever is caused by four different serotypes of viruses which come under the family of flavivirus. The vectors for the virus are *Aedesalbopictus* and *Aedesaegypti* mosquitoes. The NS3 helicase in complex with ssRNA play a vital role in the replication of flavivirus RNA and is an important target for drug development. Here the therapeutic activity of phytochemicals in Carica papaya leaves against Dengue 4 virus (DEN4) is investigated using Schrodinger software. Among the various compounds present in *Carica papaya*, Myricetin, Riboflavin, Kaempferol, Protocatechuic acid were found to have good docking results, qikprop result and interactions with the protein. This is accompanied by the formation of hydrogen bonds present between the compounds and amino acid residues in the active site of the protein. Our result indicates that these compounds can be further developed as a drug for the treatment of dengue fever.**

**KEYWORDS:** Carica Papaya, Insilico, Docking, Qikprop, Myricetin, Riboflavin, Kaempferol, Protocatechuic Acid.

Dengue fever is a fast spreading viral diseases and has become an increasing treat all over the world. The disease is transmitted through mosquitoes of the type Aedesaegypti and Aedesalbopictus (Tomas Jelinek 2000). While sucking blood by mosquito which is a carrier of dengue virus, the human get affected by dengue fever. The fever is caused by virus of four different serotypes (DEN1, DEN2, DEN3, and DEN4) (Barbara W Johnson 2005) together come under the family flavivirus. The dengue virus is capable of causing three different illnesses they are Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). Dengue fever usually causes fever, skin rash, severe muscle pain. But in some cases there are most severe symptoms and makes complications the condition is termed as DHF ,( Duane J Gubler 1998). Majority of DHF is seen in children under 15. DSS is another severe health problem caused by the virus.In most cases DHF proceeds to DSS with symptoms such as bleeding, abdominal pain, blood pressure drop. This is a severe health problem and if not treated properly will cause death. The recovery from one dengue serotype provides immunity against that particular serotype. The single strand of RNA is the dengue virus genome (Stacia L Phillips et.al 2016 ) which can encode three structural proteins (Capsid, Membrane, Envelope) ( Kuhn RJ et.al 2002) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) (Julianna D Zeidler et.al 2017.). Among these the non-structural proteins has an important role in viral replication and assembly

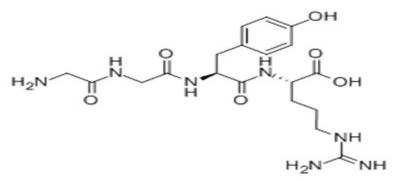
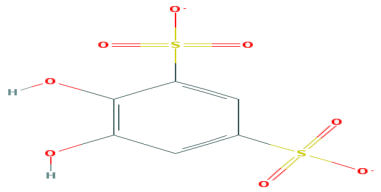
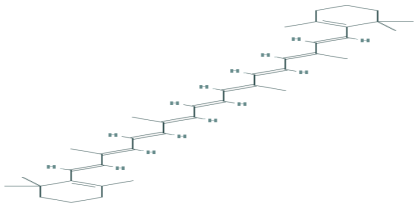
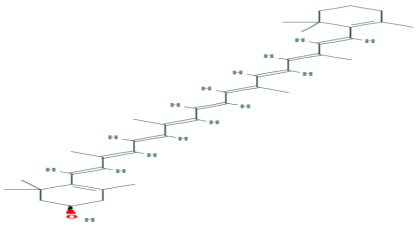
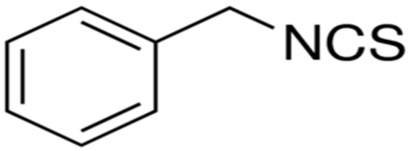
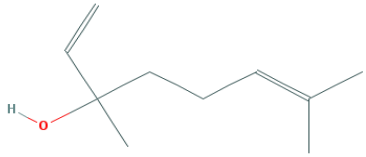
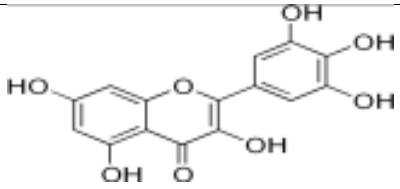
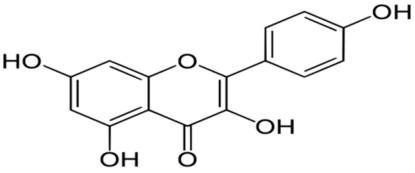
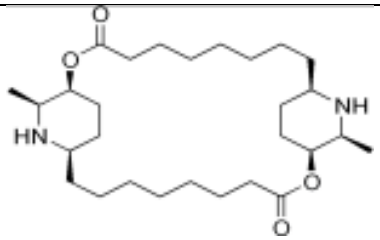
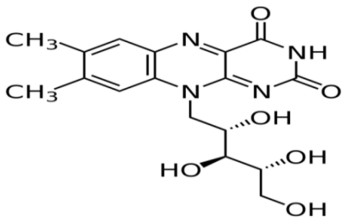
Carica papaya leaves are found to be very effective against dengue fever. Carica papaya Linnaeus is a herbaceous member belongs to the family Caricaceae. It is not a tree but an herb which contains a self-supporting system (Dick Gross 2003). The plant is capable of producing natural compounds in the leaf bark and twig tissues which provide pronounced anti- tumour and pesticidal properties. The root juice is very useful against cough, bronchitis and other respiratory diseases. The fruits are found to be very effective against ulcers and impotence also the plant extract can be used as a blood purifier. All these pharmacological properties of the plants are due to the variety of phytochemicals present in it.

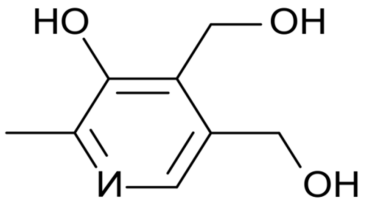
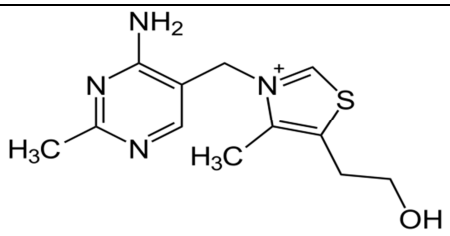
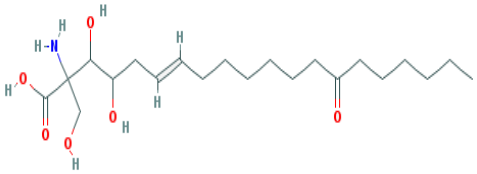
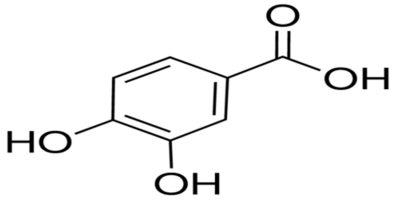
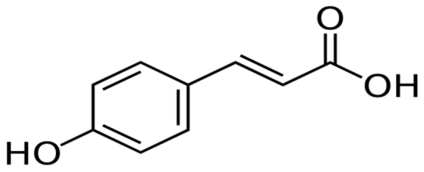
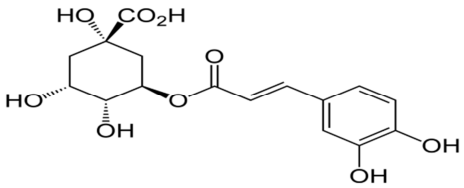
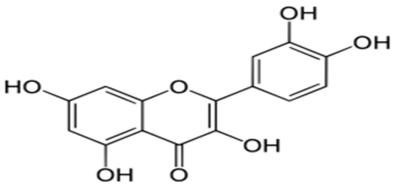
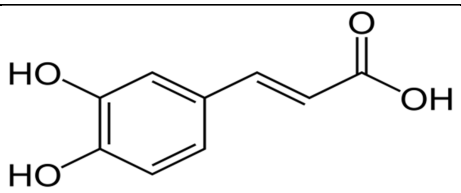
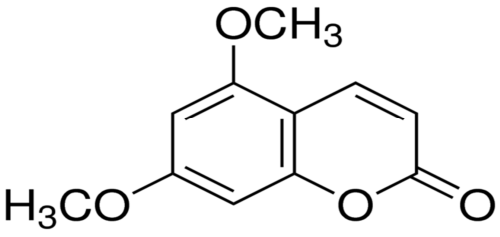
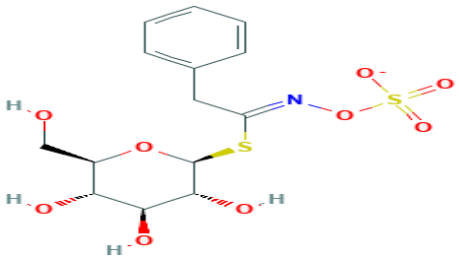
The NS3 helicase in complex with ssRNA (PDB id: 2JLU) comes under the classification Hydrolase has an important function in the flavivirus RNA replication mainly in dengue virus 4 and thereby constitute an important drug target

The present study focussed on identifying the components in Carica papaya which are responsible for the action against dengue virus 4 (DEN4) by using the software Schrodinger by taking 2JLU as the target protein (Table 1).

[1]Corresponding Author

**Table 1: Phytochemicals selected for the study is given below**

| | |
|---|---|
|  Papain |  Chymopapain |
|  Beta- carotene |  Beta- cryptoxanthin |
|  Benzyl isothiocyanate |  Linalool |
|  Myricetin |  Kaempferol |
|  Carpaine |  Riboflavin |

| | |
|---|---|
|  Pyridoxine |  Thiamine |
|  Myrocin |  Protocatechuic acid |
|  P-coumaric acid |  Chlorogenic acid |
|  Quercetin |  Caffeic acid |
|  5,7-Dimethoxy coumarin |  Benzyl glucosinolate |

## MATERIALS AND METHODS

Schrodinger software suite is a drug design software uses both ligand and structure based methods. It provides accurate, reliable and high performance computational technology to solve problems. Schrodinger also provides solutions and services for the design, selection and optimization of Novel drug candidates. This provides various applications in Pharmaceutical, Biotechnology and Material science.

### Docking In Schrodinger

The primary step of docking in Schrödinger is the protein preparation by using the protein preparation wizard, which is designed to ensure structural optimization and making high confident structures that are important in modelling applications. In X-ray crystallographic structures it needs more time and effort to solve problems like missing hydrogen atoms, incomplete side chains and loops, flipped residues. Since the accurate starting structures are important in computational drug design the step is very important. The attached water is removed and the protein is optimized and minimized so that the protein is ready for docking process.

The ligand in pdf format is imported and then it is prepared using Ligprep. One of the main advantages of the software is that more than one ligand can be considered for docking studies with the protein at the same time. By performing Ligprep accurate, energy minimized 3D molecular structures are generated.

The identification of fast, accurate and practical binding site sitemap is used. It is very useful and effective means to find and exploit the characteristic ligand binding sites. Sitemap treat entire protein to identify binding site whose size, functionality and extent of solvent exposure meet the specifications of user. Site score is the scoring function that is used to asses a site's propensity for ligand binding, which helps to eliminate those not likely to be pharmaceutically relevant.

Glide grid uses grid to pre calculate the binding interactions at different positions within the binding site. Glide offers excellent docking accuracy. It also identifies the correct binding modes for large set of test cases. The ligand- receptor docking is done by Glide dock. When docking process is complete the docking score is noted.

### QIK PROP

Qik prop predict the large variety of properties like octanol/water and water/gas logPS, logBB, logS, overall CNS activity, logIC50 for HERG k-channel blockage. It identifies the molecules have computed properties that fallout in the normal range of known drugs, this helps in filtering out candidates with most unsuitable ADME properties. This also helps to select the most suitable lead compound

### Protein Data Bank

The crystallographic database consist of 3D structural data of macromolecules such as proteins and nucleic acids. The structure of the desired protein is searched in PDB and the structure is downloads in pdb text format.

### PUBCHEM

The database of chemical molecules which consist of small molecules and substance descriptors with fewer than 1000 atoms and 1000 bonds. The structure of the molecules are downloaded from pubchem in the sdf format

## RESULTS

The protein 2JLU is docked with twenty phytochemicals in Carica papaya (Nisar Ahmad et.al 2011) (AshaRoshan et.al 2014) ( Ngyozi Awa Imaga et.al 2010) (A U Ogan 1971A) , the four components are seems to poses good docking score as well as Qik prop studies. (Table 2) (Figure 1 to Figure 8).

**Table 2: The results of the protein with the components**

| PROTEIN | PHYTOCHEMICAL | DOCKING SCORE | STARS | LIPINSKI RULE OF FIVE |
|---|---|---|---|---|
| 2JLU | Myricetin (5281672) | -8.433 | 1 | 1 |
| 2JLU | Riboflavin (493570) | -8.059 | 0 | 0 |
| 2JLU | Kaempferol (5280863) | -5.659 | 0 | 0 |
| 2JLU | Protocatechuic acid (72) | -5.651 | 0 | 0 |

**Stars-** the range of values is 0-5

The descriptors and properties included in the determination of #stars are: MW, dipole, PSA, volume, donor HB, accept HB, glob, QPlogPC16, QPlogPoct, QPlogPw, QPlogPo/w, logS, QPlogBB, WP

**Lipinski Rule of Five-** The range of values is 0-4 (Lipinski CA et.al 2001)

- Molecular weight < 500
- QPlogPo/w < 5
- Donor HB < 5
- Accept HB < 10

The compounds that satisfy these rules are considered to be drug like

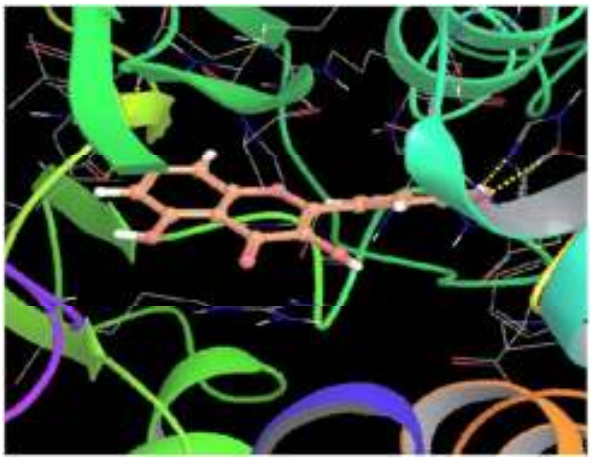


**Figure 1: Docking image of Myricetin with the protein**

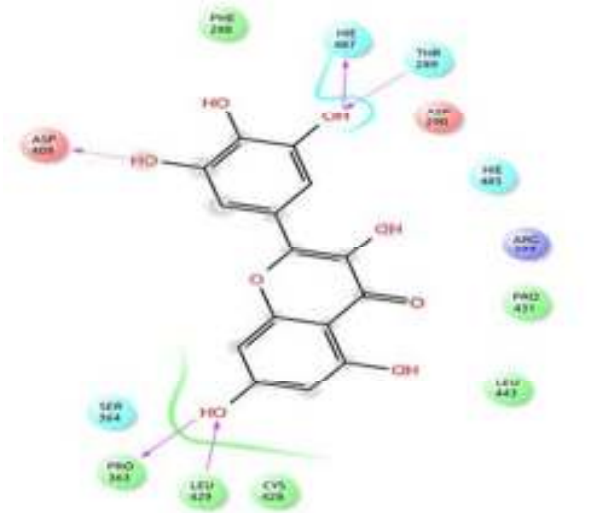


**Figure 2: Interactions of the Myricetin with the protein**

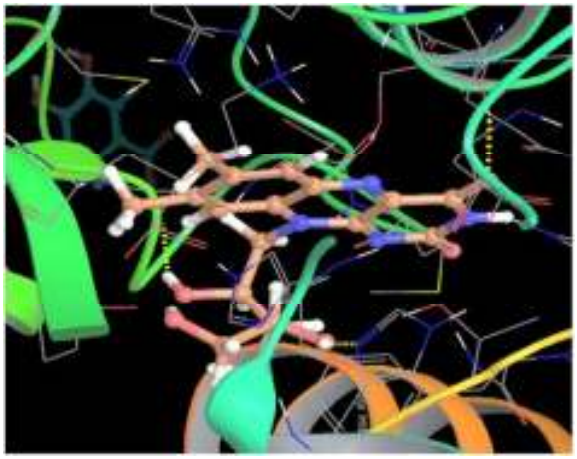


**Figure 3: Docking image of Riboflavin with the protein**

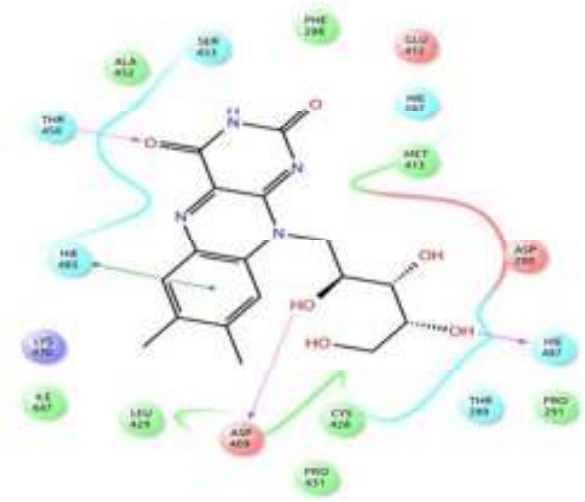


**Figure 4: Interaction of Riboflavin with the protein**

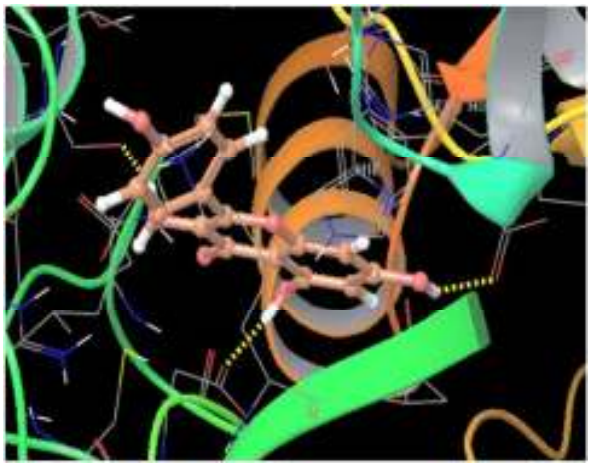


**Figure 5: Docking image of kaempferol with the protein**

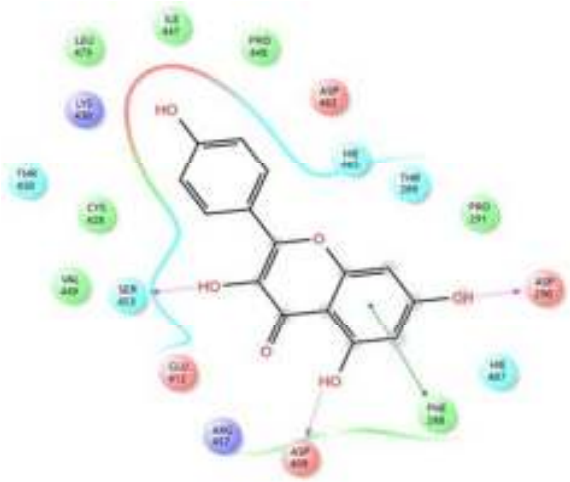


**Figure 6: Interaction of kaempferol with the protein**

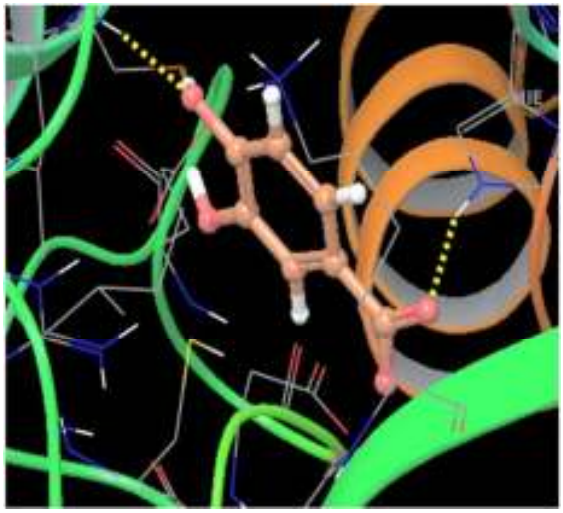


**Figure 7: Docking image of Protocatechuic acid with the protein**

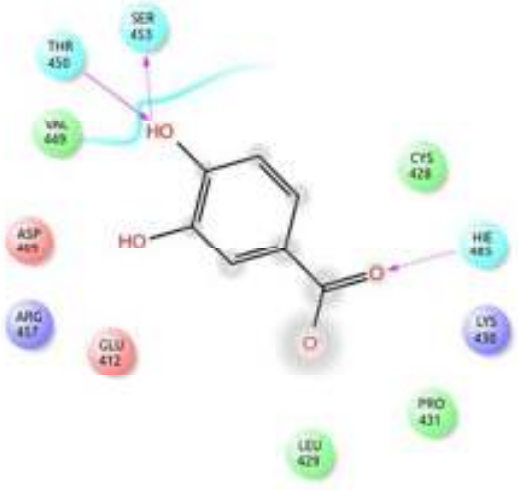



**Figure 8: Interaction of protocatechuic acid with the protein**

From the docking results it is evident that the four phytochemicals/components in Carica papaya shows good docking score, qikprop results and also show good interactions with the target protein.

The component Myricetin shows better docking score and interaction with the protein. The compound shows hydrogen bond interactions of the OH groups with amino acid HIE487 having bond length 1.99159 and dihedral angle 119.701 also with the amino acid THR289 with bond length 1.89852 and dihedral angle 95.5523, with LEU429 having bond length .35109 and dihedral angle 126.629, and with the amino acid GLY196 with bond length 2.16691 and dihedral angle 119.977, and with PRO363 having bond length 1.94379 and angle 125.918 and also with the amino acid ASP409 having bond length 1.72461 and angle 121.683.

The target protein has better interaction with the component Riboflavin. There are two types of hydrogen bond present one type is of the OH groups with amino acid HIE487 with bond length 1.96933 and dihedral angle 119.813 and also with the amino acid ASP 409 having bond length 2.03931 and dihedreal angle 131.588. The other type of hydrogen bond is formed between oxygen and the amino acid THR 450 with bond length 1.85343 and dihedral angle 113.353. The π-π stacking edge to face interaction is also present with HIE 485 with bond length 4.98164 and angle 77.7119

The docking of Kaempferol shows better interaction and docking score with the protein. It shows hydrogen bonds of OH groups with ASP 290 with bond length 2.1649 and angle 120.22 and with ASP 409 with bond length 1.71039 and angle 99.1143 and also with the amino acid SER412 with bond length 1.87523 and dihedral angle 104.84. The compound also shows π-π stacking edge-face interaction with PHF288 with bond length 5.47006 and angle 81.3184.

Protocatechuic acid also shows better interaction with the protein. It shows hydrogen bond between OH groups and the aminoacid THR 450 with bond length 2.04365 and angle 104.504, also with the amino acid SER453 having bond length 1.97351 and dihedral angle 141.919. Hydrogen bond is also present between HIE 485 and the oxygen with the bond length 1.90305 and angle 131.424.

The Qik prop studies of the compounds with the target protein shows that they obey the qik prop properties range so they can have less toxicity.

## CONCLUSION

The ligands are docked against the active site of the protein by using Schrodinger software. Among the twenty phytochemicals Myricetin, Riboflavin, kaempferol and Protocatechuic acid gave good docking score with the target protein. Qik prop analysis of these compounds show they are good and having drug like properties.

From this work it has been concluded that the compounds in Carica papaya shows good docking results, qik prop results and interaction with the target proteins .so they can be good lead compounds against Dengue 4 virus. Hopefully expecting further studies on these compounds may result in novel drug against Dengue fever.

## AKNOWLEDGEMENT

To the authorities of 27th Swadeshi Science Congress for giving the opportunity for publishing the paper

## REFERENCES

Jelinek T., 2000. Dengue Fever In International Trevellers, Clinical Infectious Diseases, **31**:144-147.

Ahmad N., Fazal H and Ayaz M., 2011. Dengue fever treatment with Carica papaya leaves extracts, Asian Pacific Journal of Tropical Biomedicine, pp.330-333.

Hettige S., 2008. Salutary effects of Carica papaya leaf extract in Dengue fever patients- a pilot study, Sri Lankan family physician, pp.17-19.

Barbara W. Johnson, 2005. Serotype-Specific Detection of Dengue Viruses in a Fourplex Real-Time Reserve Transcriptase PCR Assay, Journal of Clinical Microbiology, pp. 4971-4983.

Kuhn R.J., Zhang W., Rossmann M.G., Pletnev S.V., Corver J., Lenches E., Jones C.T., Mukhopadhavay S., Chipman P.R., Strauss E.G., Baker T.S. and Strauss J.H., 2002. Structure of Dengue virus: implications for flavivirus organization, maturation and fusion, Pubmed, pp.717-725.

Roshan A., Verma N.K. and Gupta A., 2014. A Brief Study on Carica Papaya, IJCTPR.

Lipinski C.A., Lombardo F., Domjny B.W. and Feenev P.J., 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Pubmed.

Julianna D. Zeidler, Lorena O., Siqueira F., Glauce M. Barbosa and Andrea T. DaPoian, 2017. Non-Canonical Roles of Dengue Viruses Non-Structural Proteins,Viruses.

Stacia L. Phillips, Erik J. Soderblom, Shelton S. Bradrick and Mariano A. Garicia-Blanco, 2016. Identification of Proteins Bound to Dengue Viral RNA In Vivo Reveals New Host Proteins Important for Virus Replication , American Society For Microbiology.

Ngyozi Awa Imaga, George O., Gbenle, Veronica I., 2010. Phytochemical and antioxidant nutrient constituets of Carica papaya and Parquetinanigrescens extracts, Scientific Research and Essays, pp. 2201-2205.

Ogan A.U., 1971. The basic constituents of the leaves of Carica papaya, Phytochemistry, **10**:2544-2547.

Duane J. Gubler, 1998. Dengue and Dengue Hemorrhagic fever, Clinical Microbiology Reviews, pp.480-496.