



## COMPARATIVE DOCKING STUDY OF DIFFERENT IMMUNOSUPPRESSIVE DRUGS AGAINST CALCINEURIN IN ALZHEIMER'S DISEASE

Vineeta Singh<sup>1</sup>, Vijaya Nath Mishra<sup>2</sup>, Vibha Pandey<sup>3</sup>, Thakur M K<sup>4</sup>,  
Rameshwar Nath Chaurasia<sup>2\*</sup> and Deepika Joshi<sup>2</sup>

<sup>1,3,2</sup>Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, UP (India)

<sup>4</sup>Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi-221005 U.P. (India)

### ARTICLE INFO

#### Article History:

Received 26<sup>th</sup> May, 2017

Received in revised form 5<sup>th</sup>

June, 2017 Accepted 6<sup>th</sup> July, 2017

Published online 28<sup>th</sup> August, 2017

#### Key words:

Insilico, Alzheimer's disease, Calcineurin, Lipinski filter, Patch Dock Score. Discovery Studio 2.0

### ABSTRACT

**Background:** Increasing age is the greater risk factor for Alzheimer's disease. In older organisms, the brain is less plastic, in part due to a dysregulation of Ca<sup>2+</sup> dynamics. The environment of the aged brain, further insulted by the presence of oligomeric amyloid beta, may result in an enhancement of Calcineurin activity sufficient to explicate several negative outcomes observable as decreased neurotransmission, synaptic loss, tau pathology, neuroinflammation, and cell death in Alzheimer's affected brain. Therefore, it is prudent to consider the possibility of Calcineurin inhibition as a pharmacological target in the development of novel Alzheimer's disease therapies.

**Method:** The present *insilico* study makes a comparative analysis of different immunosuppressant against Calcineurin which acts as molecular switch in the AD pathology. This study has been conducted by using different bioinformatics tools and software as Lipinski filter online tool, discovery studio 2.0 and patch dock tool.

**Result:** By docking study it has been observed that among cyclosporine, pimecolimus, tacrolimus and voclosporin; voclosporin shows higher affinity to the target molecule Calcineurin with higher patch dock score.

**Conclusion:** Voclosporin may present as possible ligand for the targeted protein calcineurin, for suppression of neuroinflammation which is the prominent causative agent for progression of Alzheimer's disease.

Copyright©2017 Vineeta Singh et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## INTRODUCTION

About 1% of the total neuronal protein is calcineurin (CN). The designation "CN" reflects the initial belief that it was uniquely expressed in neurons. It is found conserved from yeast to man and present in various group of cell types where it respond to the binding of activated calmodulin (CaM) in several ways, involving modulating immune response, plasticity in neurons, inducing formation of muscles and cell death. CN is recognized as protein phosphatase 2B (PP2B), which is serine and threonine phosphatase sensitive to Ca<sup>2+</sup> highly expressed in central nervous system(CNS) and first discovered from mammalian brain<sup>1</sup>. CN is heteromeric protein having catalytic subunit (CN A) and regulatory subunit (CNB)<sup>2</sup> is similar to the protein phosphatase 1(PP1) and having resemblance with the protein phosphatase-2A, it also shares 30-50% sequence homology with calmodulin (CaM)<sup>3</sup>. Among known phosphatases CN of this family is singular in that it is regulated by the CaM making it more unambiguously and extensively sensitive to the Ca<sup>2+</sup> alteration<sup>4</sup>.

\*Corresponding author: **Rameshwar Nath Chaurasia**  
Department of Neurology, Institute of Medical Sciences,  
Banaras Hindu University, Varanasi-221005, UP (India)

Promiscuous trends of the phosphatase, Ca<sup>2+</sup> entry within the neurons and subsequent CN activation act as signal for powerful cellular processes have impact on the cell survival and growth. CN has diverse substrate as cAMP response element binding (CREB)<sup>5</sup>, phosphorylated forms of nuclear factor of activated T- cells (NFAT)<sup>6</sup> glycogen synthase kinase-3 beta (GSK- 3β), PP1, microtubule-associated protein tau (MAP-tau), and Bcl-2 associated death protein (BAD)<sup>7</sup>. A hyperactivation of CN has several downstream effects which makes evidence for their involvement in AD pathogenesis.

The AD brain is susceptible to hyperactivation of CN and downstream consequences due to its decreased ability to regulate intracellular Ca<sup>2+</sup> levels. The additional insult of amyloid beta oligomers further disrupts synaptic homeostasis, resulting in a subtle, prolonged increase in calcium that facilitates the expression of long term depression. Activation of CN by CaM disrupts the phosphatases interaction with tau, possibly leading to tau hyperphosphorylation. CN also mediates the dephosphorylation of several cellular proteins: pCREB, pNFAT, p-PP1, p-GSK-3, and pBAD. This could putatively explain four observations in AD models and pathogenesis; synaptic protein loss, neuroinflammation

(neuronal and astrocytic), decreased neurotransmission, hyperphosphorylated tau, and cell death. Therefore, inhibition of CN or the promotion of positive plasticity may serve as viable therapeutic strategies for combating early stage AD impairment.

### Calcineurin and AD

In AD brain the expression of CN is found up regulated, which was higher in the prefrontal cortex<sup>8</sup>. However, on the downstream of CN, several isoforms of NFAT get increased such as NFAT1 and NFAT3 with its different isoforms was found increased in the hippocampal region of the brain, this shows a correlation with the MMSE and soluble amyloid beta (A $\beta$ )<sup>9</sup>. It had also found that with decreased MMSE score reduced pCREB<sup>10</sup> was found in the hippocampus region in hippocampal region of the AD Brain.

### Calcineurin and Tau

Tau protein is the component of the microtubule associated protein which is responsible for the assembly and organization of the micro tubule<sup>11</sup>. Microtubule governs the intraneuronal transport<sup>9</sup>. It has been found earlier that phosphorylated tau has reduced affinity to the  $\mu$ -tubule leads to the dissociation of tau from microtubule causes microtubule depolymerisation and hence disruption of intraneuronal transport has been seen<sup>12-14</sup>. Hence aberrant tau phosphorylation leads to the gain of the toxic function causes pathological tau to get assembled into paired-helical filaments (PHFs)<sup>15</sup> and sequester the normal tau. Neurons containing tangles and neuron surrounding the plaques in AD brain shows strong CN immunoreactivity<sup>16,17</sup> validates that CN modulate tau phosphorylation and suggested that decreased CN activity may be in part responsible for hyperphosphorylation of tau. Researchers has been found that CN subunits A and B are directly associated to the tau<sup>18</sup>. CaM impairs the binding between tau and CN. Therefore CN interact with tau in basal level of Ca<sup>2+</sup>, during increased Ca<sup>2+</sup> level activated CaM binds to the CN distrupts its interaction with tau results in the hyperactivation of CN causes reduced dephosphorylation of tau. CN also dephosphorylate GSK-3 $\beta$ <sup>19</sup>; now this activated pGSK-3 $\beta$ , phosphorylates tau at the same epitopic position which is found phosphorylated in AD brain<sup>20</sup>.

### Calcineurin and A $\beta$

In hippocampal neurons<sup>21, 22</sup> the fibrillar oligomeric A $\beta$  get accumulate in the synapse due to metal ion concentration<sup>23</sup>. A $\beta$  disrupts functionality and structure of the synapses causes increase in phosphorylation of the AMPA which causes long term potentiation<sup>24</sup>. A $\beta$  effect CN activity by perturbing intracellular Ca<sup>2+</sup>, as it is acts as Ca<sup>2+</sup> channel<sup>25</sup>. It is also hypothesized that it may interact with NMDA receptor<sup>26</sup>,  $\alpha$ -nicotinic acid receptor<sup>27</sup> or metabotropic glutamate receptors<sup>28</sup>. For this kind of interaction and channel forming property it is hypothesized that oligomeric A $\beta$  binds to and signals through full amyloid precursor protein<sup>29</sup>. A $\beta$  induces higher intracellular Ca<sup>2+</sup> following CN hyperactivity leads to CN dependent cell death in cell culture<sup>30, 31</sup>. A $\beta$  also induces loss of dendritic arborisation and neuritic dystrophies through CN-NFAT dependent mechanism<sup>32</sup>. Increased CN activity leads to the apoptosis, as it dephosphorylates pBAD, now BAD is able to dissociate from the scaffolding proteins and translocate to the mitochondria, where it forms pro-apoptotic

dimer with protein Bcl-X (L)<sup>33</sup> triggers cytochrome-C release from mitochondria and hence initiates apoptosis<sup>34</sup>. CN dephosphorylates pNFAT to NFAT which moves to the nucleus and induces transcription of genes involved in production of cytokines and inflammation. The present *In silico* study, a comparative analysis of different immunosuppressant against target protein-CN has been done, to find out immunosuppressant with higher binding affinity. Structure based drug designing has been done, that solely depend on three dimensional structures of biological targets. Structures are obtained from x-ray crystallography and NMR spectroscopy. Structural based drug designing is followed by drug target identification, preparation of targeted protein, virtual screening of the drug compound which increase sophisticated level of filtration of potential compound, then molecular docking of the drug Candidates and then to find out the best lead like compound with further optimization of the compounds to finalize the lead.

## METHOD

### Retrieval of target proteins and ligands

The present work was focused on molecular docking studies on immunosuppressants such as cyclosporin, voclosporin, tacrolimus and pimecolimus against CN protein 5c1v.pdb responsible for regulation of several proteins involved in Alzheimer's disease progression by means of the causing expression of gene for cytokine modulation and inflammation. The protein sequence was retrieved from NCBI by using URL [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov) and the 2-D structure of protein from PDB (protein data bank)<sup>35</sup> by using URL <http://www.rcsb.org/PDB>. Initially the target proteins were selected which are involved in the pathogenesis. The structural information of the target proteins (CN) was obtained from PDB (Fig.1). Therapeutic molecules which are use as preventive agent such as cyclosporine, and their structure has been obtained by pubchem database.



Figure 1 PDB structure of Calcineurin protein

### Identification of the drug linkage property by Lipinski filter rule

The drug molecules selected were re-evaluated for their drug likeliness by using "Lipinski Rule of Five" to predict which drug molecules would fail because of poor pharmacokinetics employing bioinformatics software.

### Screening of lead molecules

After choosing the target protein and inhibitory drug compounds there visualization was done on discovery studio

2.0 (Fig.4a, Fig.4b, Fig.4c and Fig.4a). It was also used for visualization of target protein and ligand interaction.

**Docking studies**

In docking studies the interaction between target and ligands were studied. The ligand screened was loaded in to patch dock and docking studies were carried out. Patch dock docking is based on the positive scores, which is resultant of interaction of possible ligand and targeted protein molecule. A positive score denotes a higher affinity of ligands and targeted proteins.

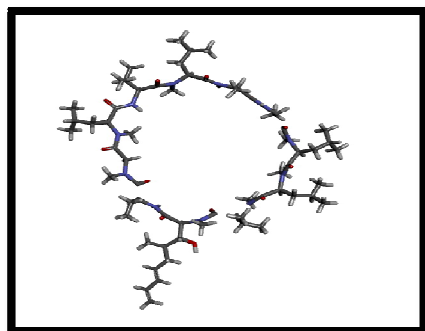


Figure 2a Voclosporin\_CID 6918486

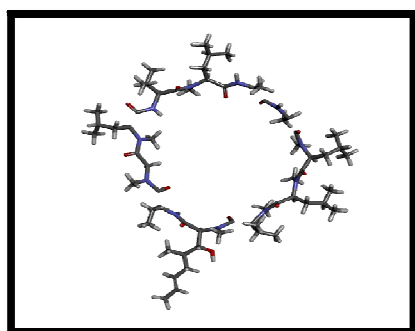


Figure 2b Cyclosporin\_CID 5284373

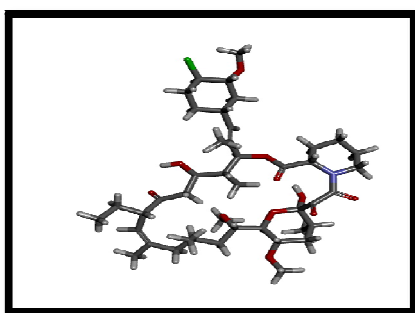


Figure 2c Pimercolimus\_CID 53486290

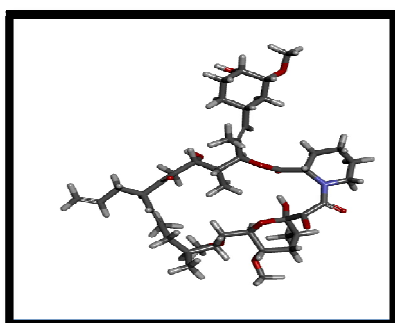


Figure 2d Tacrolimus\_CID 445643

Figure 2 Therapeutic ligand Structure from pubchem

The druglikeness property of Tacrolimus CID 445643 (Fig.2a), Voclosporin CID 6918486 (Fig.2b), Pimercolimus CID 53486290 (Fig.2c), and Cyclosporine CID 5284373 (Fig.2d) was assessed by using online tool of Lipinski filter rule of five<sup>36</sup>, according to which drugs should follow minimum two properties among molecular weight (dalton)/ H-bond acceptor/ H-bond acceptor/ log p/ molar refractivity/ activation energy. Table 1 show that tacrolimus, voclosporin, pimercolimus and cyclosporine fulfil the drug likeness criteria of Lipinski filter rule by having minimum 2 properties of druglikeness.

**Table 1** Identification of the drug linkage property of Cyclosporine, Voclosporin, Pimercolimus and Tacrolimus by Lipinski filter rule

Name of Compound	Molecular Wt. (Dalton)	H-bond Acceptor	H-Bond Donor	Log P	Molar refractivity	Activation Energy
Optimum Drug likeness	<500	<10	<5	<5	40-130	3.5 Å
Cyclosporin	1201.00	20	5	2.267	327.276	3.5Å
Vaclosporin	1213.00	20	5	3.431	332.970	3.4Å
Pimercolimus	789.00	12	2	3.242	211.227	3.5 Å
Tacrolimus	803.00	13	3	4.368	212.592	3.5 Å

Docking study of CN with different ligand has been done by the PatchDock<sup>37</sup> (fig.3a, 3b, 3c and 3d) which showed PatchDock scores, which is based on maximum complementarity between, CN and selected ligands.

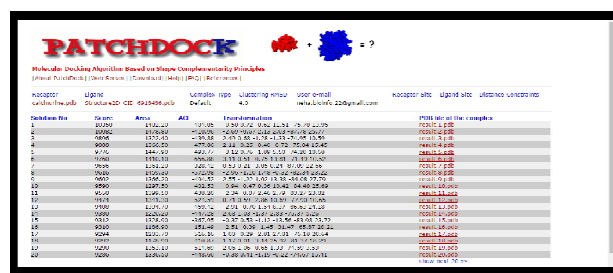


Figure 3a Patch dock score of Voclosporin targeted against CN

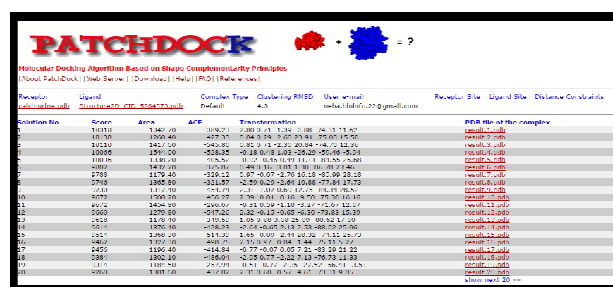


Figure 3b Patch dock score of Cyclosporine targeted against CN

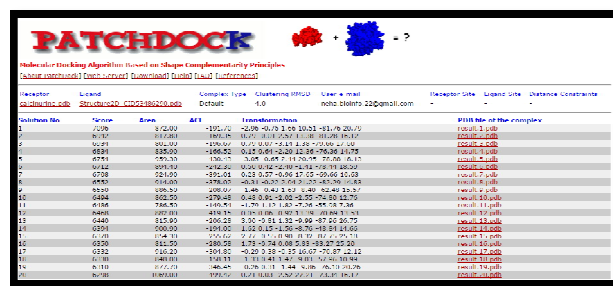


Figure 3c Patch dock score of Pimercolimus targeted against CN

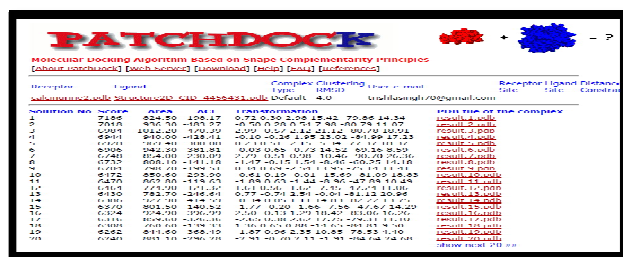


Figure 3d Patch dock score of Cyclosporine targeted against CN

Best docking property is determined by the highest docking score. Among four immunosuppressant drugs, voclosporin shows highest docking scores 10350 (Fig.3a) followed by cyclosporine (10318), tacrolimus (7186) and pimecolimus (7096).

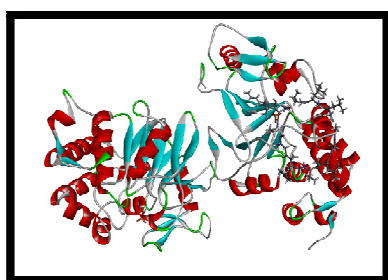


Figure 4 a CaN-Voclosporin interaction and Visualization by Discovery Studio 2.0 and 4

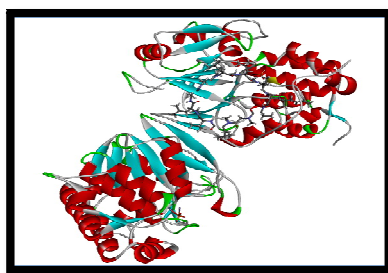


Figure 4 b CaN-Cyclosporine interaction and Visualization by Discovery Studio 2.0

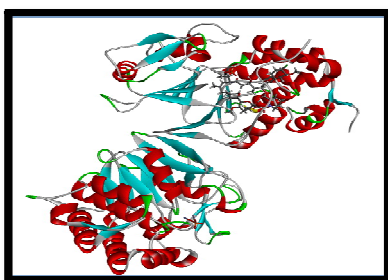


Figure 4 c CaN-Pimecolimus interaction and Visualization by Discovery Studio 2.0

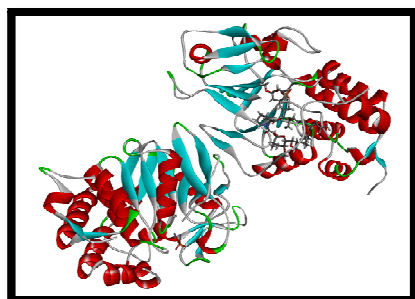


Figure 4 d CaN Tacrolimus interaction and Visualization by Discovery Studio 2.0

Identification of active site of calcineurin with different immunosuppressant drug was done by the discovery studio 2.0 software (Fig.5a, Fig.5b, Fig.5c, and Fig.5d) where voclosporin showed highest affinity with the CN.

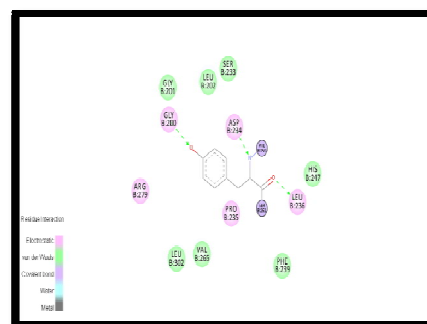


Figure 5 a Possible interaction of amino acids of calcineurin with Voclosporin and its visualization by Discovery Studio 2.0

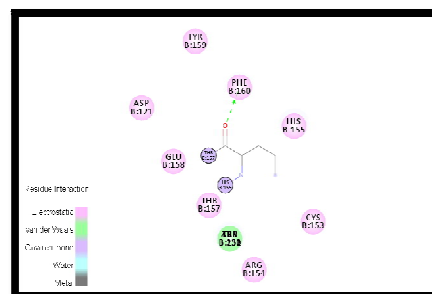


Figure 5 b Possible interaction of amino acids of calcineurin with Cyclosporine and its visualization by Discovery Studio 2.0

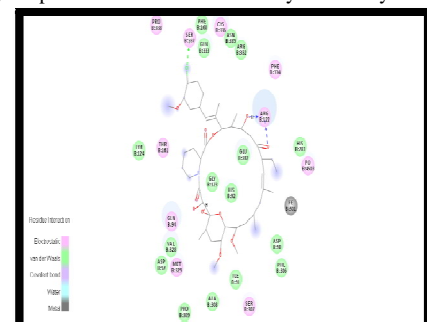


Figure 5 c Possible interaction of amino acids of calcineurin with Pimecolimus and its visualization by Discovery Studio 2.0

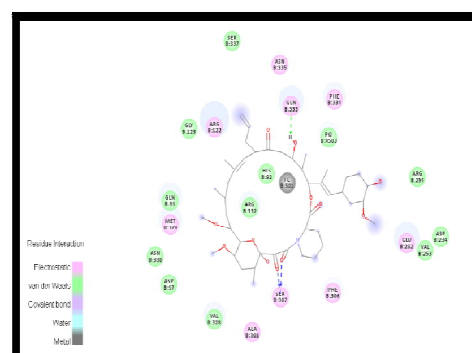


Figure 5 d Possible interaction of amino acids of calcineurin with Tacrolimus and its visualization by Discovery Studio 2.0

## DISCUSSION

Different docking studies have been frequently used for drug development, for study of binding affinity of inhibitor molecules to target proteins. In a similar study done by Harish<sup>38</sup> *et al* mentioned about these different inhibitor

molecules to target proteins and their binding affinity. Known inhibitors, voclosporin, pimercolimus, tacrolimus and cyclosporine are used as drug in the treatment of CN related disorders. It is found difficult to study the binding affinity of protein-ligand complex *invitro* and *invivo*. The crystal structure of CN and inhibitor molecules and docking software enables us to study their affinity for each other. The current study predicts the binding affinity of voclosporin, pimercolimus, tacrolimus and cyclosporine with CN using PatchDock. In the present study, binding affinity by means of patch dock score shows that voclosporin, pimercolimus, tacrolimus and cyclosporine have binding affinity with CN. Interaction with the Calcineurin and selected ligands will be an asset to identify the appropriate drug before moving towards, pharmaceutical interventions and clinical trials for treating AD. As AD is a symptomatic problem so depending on the persistence and prevalence of the symptom it is being diagnosed. The targeted protein acts as CN molecular switch behind pathogenesis of AD. In the past decades drug target discovery by applying various available bioinformatics tool has opened a gateway for prediction of drug targeted pathogenesis against particular disorder or disease. In the present study Lipinski filter rule of five is used to check the eligibility of the candidate drug. Our target drug fulfils the Lipinski filter rule have five properties as molecular weight (dalton)/ H-bond acceptor/ H-bond donor/ log p/ molar refractivity. Of these mentioned five properties, a candidate drugs have to be fulfil the criteria by containing two properties which are also followed by our selected candidate drug. In our study we use PatchDock online tool for docking analysis between CN and our selected drugs such as tacrolimus, voclosporin, pimercolimus and cyclosporine. PatchDock shows docking results by means of PatchDock score. PatchDock score is based on the complementarity pattern between protein and drugs. A higher PatchDock score shows higher complementarity between target protein and ligand. In our study among tacrolimus, voclosporin, pimercolimus and cyclosporine, voclosporin acquires higher PatchDock score signifies highest complementarity between CN and voclosporin (10350).

## CONCLUSION

Drug target discovery is a best tool to formulate any pharmaceutical compound. Here we have proposed significant role of *insilico* analysis to study CN and its target site in the terms of voclosporin concluded that voclosporin is showing higher affinity with CN in treating AD. However, further *in vitro* and *in vivo* studies are required for enhanced knowledge on the mechanism of inhibitory action.

## References

1. Klee, C.B., Krinks, M.H. 1978. Purification of cyclic 3'5'-nucleotide phosphodiesterase inhibitory protein by affinity chromatography on activator protein coupled to sepharose. *Biochemistry*, 17:120-126.
2. Klee, C.B., Crouch, T.H., Krinks, M.H. 1979. Calcineurin – calcium binding and calmodulin-binding protein of the nervous system. *PNAS*, 76: 6270-6273.
3. Yakel, J.L. 1997. Calcineurin regulation of synaptic function: from ion channels to transmitter release and gene transcription. *Trends Pharm. Sci.*, 18:124-134.
4. Rusnak, F., Mertz, P., 2000. Calcineurin: form and function. *Physiol. Rev.*, 80: 1483-1521.
5. Bito, H., Deisseroth, K. 1996. Tsien R.W. CREB phosphorylation and dephosphorylation: a Ca2 (+)- and stimulus duration-dependent switch for hippocampal gene expression. *Cell.*, 87(7): 1203-1214.
6. Rao, A., Luo, C., Hogan, P.G. 1997. Transcription factors of the NFAT family: regulation and function. *Ann. Rev. Immun.*, 15: 707-747.
7. Wang, H.G., Pathan, N., Ethell, I.M., Krajewski, S., Yamaguchi, Y., Shibasaki, F., McKeon, F., Bobo, T., Franke, T.F., Reed, J.C. 1999. Ca2+-induced apoptosis through CN dephosphorylation of BAD. *Science*, 284: 339-343.
8. Lian, Q.Y., Ladner, C.J., Magnuson, D., Lee, J.M. 2001. Selective changes of calcineurin (protein phosphatase 2B) activity in Alzheimer's disease cerebral cortex. *Exp. Neurol.*, 167: 158-165.
9. Grundke-Iqbal, I., Iqbal, K., Tung, Y.C., Quinlan, M., Wisniewski, H.M., Binder, L.I. 1986. Abnormal phosphorylation of the microtubule associated protein-tau in Alzheimer cytoskeletal pathology. *Proc. Natl. Acad. Sci. U. S. A.*, 83: 4913-4917.
10. Yamamoto-Sasaki, M., Ozawa, H., Saito, T. Rosler, M., Riederer, P. 1999. Impaired phosphorylation of cyclic AMP response element binding protein in the hippocampus of dementia of the Alzheimer type. *Brain Res.*, 824: 300-303.
11. Goedert, M., Crowther, R.A., Garner, C.C. 1991. Molecular characterization of microtubule-associated proteins-tau and MAP2. *Trends Neurosci.*, 14: 193-199.
12. Lindwall, G., Cole, R.D. 1984. Phosphorylation affects the ability of tau-protein to promote microtubule assembly. *J. Biol. Chem.*, 259: 5301-5305.
13. Drechsel, D.N., Hyman, A.A., Cobb, M.H., Kirschner, M.W. 1992. Modulation of the dynamic instability of tubulin assembly by the microtubule-associated protein tau. *Mol. Biol. Cell.*, 3: 1141- 1154.
14. Iqbal, K., Alonso, A.D.C., Chen, S., Chohan, M.O., El-Akkad, E., Gong, C.X., Khatoon, S., Li, B., Liu, F., Rahman, A., Tanimukai, H., Grundke-Iqbal, I. 2005. Tau pathology in Alzheimer disease and other tauopathies. *Biochim et Biophys. Acta - Mol. Basis Disease*, 1739: 198-210.
15. Gong, C.X.; Singh, T.J.; Grundkeiqbal, I.; Iqbal, K. 1994. Alzheimers disease abnormally phosphorylated-tau is dephosphorylated by protein phosphatase-2B (calcineurin). *J. Neurochem.*, 62: 803-806.
16. Billingsley, M.L., Ellis, C., Kincaid, R.L., Martin, J., Schmidt, M.L., Lee, V.M.Y. 1994. Trojanowski, J.W. Calcineurin immunoreactivity in Alzheimers-disease. *Exp. Neurol.*, 126: 178-184.
17. Brion, J.P., Couck, A.M., Conreur, J.L. 1995. Calcineurin (phosphatase 2B) is present in neurons containing neurofibrillary tangles and in a subset of senile plaques in Alzheimers-disease. *Neurodegeneration*; 4: 13-21.
18. Yu, D.Y., Tong, L., Song, G.H., Lin, W.L., Zhang, L.Q., Bai, W., Gong, H., Yin, Y.X., Wei, Q. 2008. Tau binds both subunits of calcineurin, and binding is impaired by calmodulin. *Biochim Biophys Acta*; 1783(12): 2255-2261.

19. Kim, Y., Lee, Y.I., Seo, M., Kim, S.Y., Lee, J.E., Youn, H.D., Kim, Y.S., Juhn, Y.S. 2009 Calcineurin dephosphorylates glycogen synthase kinase-3 beta at serine-9 in neuroblast-derived cells. *J. Neurochem.*, 111: 344-354.
20. Hanger, D.P., Hughes, K., Woodgett, J.R., Brion, J.P., Anderton, B.H. 1992. Glycogen-synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau – generation of paired helical filament epitopes and neuronal localization of the kinase. *Neurosci. Lett.*, 147: 58-62.
21. Gong, Y.S., Chang, L., Viola, K.L., Lacor, P.N. 2003. Lambert, M.P.; Finch, C.E.; Krafft, G.A.; Klein, W.L. Alzheimer's disease-affected brain: presence of oligomeric A beta ligands (ADDLs) suggests a molecular basis for reversible memory loss. *Proc. Nat. Acad. Sci. U.S.A.*, 100: 10417-10422.
22. Lacor, P.N., Buniel, M.C., Chang, L., Fernandez, S.J., Gong, Y.S., Viola, K.L., Lambert, M.P., Velasco, P.T., Bigio, E.H., Finch, C.E., Krafft, G.A., Klein, W.L. 2004. Synaptic targeting by Alzheimer's related amyloid beta oligomers. *J. Neurosci.*, 24: 10191-10200.
23. Deshpande, A., Kawai, H., Metherate, R., Glabe, C.G., Busciglio, J. A. 2009. Role for synaptic zinc in activity-dependent A beta oligomer formation and accumulation at excitatory synapses. *J. Neurosci.*, 29: 4004-4015.
24. Zhao, D., Watson, J.B., Xie, C.W. 2004. Amyloid  $\beta$  prevents activation of calcium/calmodulin-dependent protein kinase II and AMPA receptor phosphorylation during hippocampal long-term potentiation. *J. Neurophysiol.*, 92: 2853-2858.
25. Arispe, N., Rojas, R., Pollard, H.B. 1993. Alzheimer-disease amyloid beta-protein forms calcium channels in bilayer membranes blockade by tromethamine and aluminum. *PNAS*, 90: 567-571.
26. De Felice, F.G., Velasco, P.T., Lambert, M.P., Viola, K., Fernandez, S.J., Ferreira, S.T., Klein, W.L. 2007. Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor dependent mechanism that is blocked by the Alzheimer drug memantine. *JBC*, 282: 11590-11601.
27. Hernandez, C.M., Kaye, R., Zheng, H., Sweatt, J.D., Dineley, K.T. 2010. Loss of alpha 7 nicotinic receptors enhances beta-amyloid oligomer accumulation, exacerbating early-stage cognitive decline and septohippocampal pathology in a mouse model of Alzheimer's disease. *J. Neurosci.*, 30: 2442-2453.
28. Renner, M., Lacor, P.N., Velasco, P.T., Xu, J.A., Contractor, A., Klein, W.L., Triller, A. 2010. Deleterious effects of amyloid beta oligomers acting as an extracellular scaffold for mGluR5. *Neuron*, 66: 739-754.
29. Lorenzo, A., Yuan, M.L., Zhang, Z.H., Paganetti, P.A., Sturchler-Pierrat, C., Staufenbiel, M., Mautino, J., Sol Vigo, F., Sommer, B., Yankner, B.A. 2000. Amyloid beta interacts with the amyloid precursor protein: a potential toxic mechanism in Alzheimer's disease. *Nat. Neurosci.*, 3: 460-464.
30. Agostinho, P. and Oliveira, C. 2003. Involvement of calcineurin in the neurotoxic effects induced by amyloid-beta and prion peptides. *Eur. J. Neurosci.*, 17: 1189-1196.
31. Reese, L.C., Zhang, W., Dineley, K.T., Kaye, R., Taghialatela G. 2008. Selective induction of calcineurin activity and signaling by oligomeric amyloid beta. *Aging Cell*, 7: 824-835.
32. Wu, H.Y., Hudry, E., Hashimoto, T., Kuchibhotla, K., Rozkaine, A. Fan, Z., Spires-Jones, T., Xie, H., Arbel-Ornath, M., Grosskreutz, C.L., Bacskai, B.J., Hyman, B.T. 2010. Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. *J. Neurosci.*, 30: 2636-2649.
33. Loo, D.T., Copani, A., Pike, C.J., Whittemore, E.R., Walencewicz, A.J., Cotman, C.W. 1993. Apoptosis is induced by beta-amyloid in cultured central nervous system neurons. *PNAS*. 90:7951-7955.
34. Agostinho, P., Lopes, J.P., Velez, Z., Oliveira, C.R. 2008. Overactivation of calcineurin induced by amyloid-beta and prion proteins. *Neurochem. Intl.*, 52: 1226-1233.
35. Berman, H. M. 2008. "The Protein Data Bank: A historical perspective", *Acta Cryst.*, A64: 88-95.
36. Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J. 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev.*, 23:3-25.
37. Schneidman-Duhovny, D., Inbar, Y., Nussinov, R., Wolfson, H.J. 2005. PatchDock and SymmDock: servers for rigid and symmetric docking. *Nucleic Acids Res.*, 33: W363-367.
38. Harish, B., M., Devraju, K., S., Gopi, A., Saraswathi, R., Anushree, Babu, R., L., Chidanada, S., S. 2013. *In silico* binding affinity study of calcineurin study to calcineurin and its close associates. *Indian J Biotechnol.*, 12:213-217

**How to cite this article:**

Vineeta Singh *et al* (2017) 'Comparative Docking Study of Different Immunosuppressive Drugs against Calcineurin in Alzheimer's Disease', *International Journal of Current Advanced Research*, 06(08), pp. 5571-5576.  
DOI: <http://dx.doi.org/10.24327/ijcar.2017.5576.0753>

\*\*\*\*\*