American Journal of Pharmacological Sciences, 2016, Vol. 4, No. 2, 28-30
Available online at http://pubs.sciepub.com/ajps/4/2/3

DOI:10.12691/ajps-4-2-3

In silico Analysis and Molecular Docking Comparison of Curcumin and Bisdemethoxycurcumin on Transthyretin

Dong-Chan Kim[1,2,*], Jae-Ki Ryu[1]

[1]Department Biomedical Laboratory Science, Gimcheon University, Gimcheon City, 39528, South Korea
[2]Institute of Health Science Research, Gimcheon University, Gimcheon City, 39528, South Korea
*Corresponding author: channok@naver.com

Abstract In this study, we investigated and compared the binding affinity of curcumin and its derivative, bisdemethoxycurcumin (BDMC), on the chain A domain of the transthyretin (TTR) protein by computational docking studies. The three dimensional crystallographic structure of TTR was obtained from PDB database (PDB ID: 4PMF). Computational docking analysis was performed using PyRx, Autodock Vina, and Discovery Studio Version 4.5 option based on scoring functions. The curcumin showed optimum binding affinity (docking energy) with TTR with the binding energy of -5.08 kcal/mol as compared to the BDMC (-4.76 kcal/mol). These results indicated that curcumin could be more potent ligands to the TTR than BDMC. Therefore, curcumin can be applied to the fields of the TTR-induced alzheimer's disease regulation.

Keywords: *Alzheimer's disease, bisdemethoxycurcumin, curcumin, in silico molecular docking, transthyretin*

Cite This Article: Dong-Chan Kim, and Jae-Ki Ryu, "*In silico* Analysis and Molecular Docking Comparison of Curcumin and Bisdemethoxycurcumin on Transthyretin." *American Journal of Pharmacological Sciences*, vol. 4, no. 2 (2016): 28-30. doi: 10.12691/ajps-4-2-3.

1. Introduction

Curcumin (chemical structure shown in Figure 2) is the major phenolic yellow pigment in turmeric (C*urcuma longa*) and its derivatives existing minor in the herb are demethoxycurcumin and bis-demethoxycurcumin (BDMC; chemical structure shown in Figure 2). There are extensive evidences indicating that curcumin and turmeric extract can be useful for the treatment of several types of neurodegenerative illnesses, for example, alzheimer's and parkinson's diseases [1,2,3].

Transthyretin (TTR) is a 55 kDa-homotetrameric protein (Figure 1) which is tightly related with the alzheimer's disease progression [4]. Misfolding and aggregation of TTR protein structure significantly induce the neurodegeneration [5]. Previous report suggested that the dissociation of TTR tetramer to monomer precedes amyloid fibril formation [6]. Therefore, the stability of TTR oligomeric state is the determining factor for alzheimer's disease. In addition, blocking of TTR amyloidosis with the effective ligands that bind to TTR active site is also known as good approach to stabilize the oligomeric structure of TTR, thus reducing the progression of the neurodegeneration [7]. Pullakhandam et al, reported that curcumin effectively stabilized the TTR [8] and Li et al, showed that curcumin reduced the monomer of TTR with Tyr114Cys mutation via autophagy in cell model of familial amyloid polyneuropathy [9].

In present study, we compared curcumin with BDMC for binding ability to TTR. The original chemical form of curcumin contains two methoxy groups at two aromatic rings, but BDMC contains none. Thus, it would be valuable to investigate the relevence of the methoxy group of the aromatic ring in the curcumin structure and binding affinity feature on the TTR with BDMC.

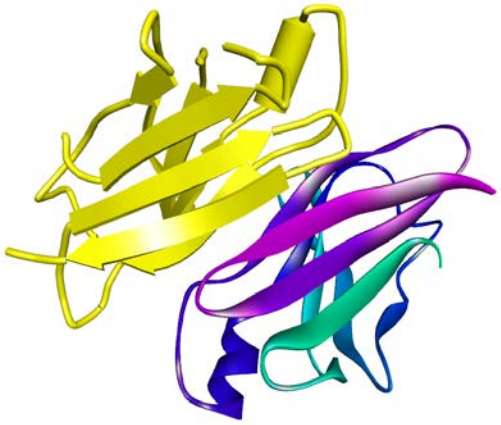

Figure 1. Three dimensional protein structure of TTR. Yellow colored domain is the TTR chain A.

2. Materials and Methods

Models of the curcumin and BDMC in complex with TTR chain A were generated through molecular docking analysis. In order to predict and compare the binding positions of curcumin and BDMC on TTR, we implemented a docking program, PyRx software using Autodock 4 (http://pyrx.sourceforge.net, Scripps Institute) [10]. The three dimensional (3D) crystal structure of TTR (PDB ID = 4PMF) was downloaded from PDB (http://www.rcsb.org/pdb/) and TTR chain A was selected.

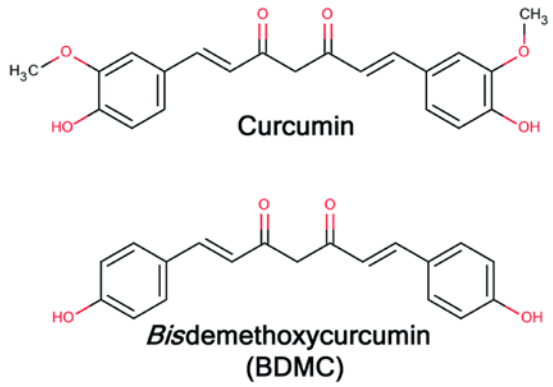

Figure 2. Chemical structure of curcumin and BDMC

The 3D structure of all single compounds were downloaded from The PubChem Project (http://pubchem.ncbi.nlm.nih.gov/, pubchem CID: curcumin = 969516, BDMC = 5315472). Before docking, all water molecules and the cofactors were removed. The 3D structures were optimized by energy minimization using Discovery Studio 4.5 version (DS, Accelrys Software Inc., USA)[11]. The X, Y, Z grid of the curcumin binding site on the TTR chain A was indentified and calculated with the "centroid program" in the DS 4.5 (X= 19.337, Y=42.037, Z=35.848) [12]. PyRx was used to dock curcumin and BDMC into the X/Y/Z grid of the TTR with the flexible docking option turned on. To examine the docking conformational space comprehensively, the search efficiency was set at 100%. The highest binding affinity (the lowest docking energy) score was chosen to explore the binding mode of docked compound in the TTR protein using PyRx program. For the analysis of the docking calculations, 9 conformers were considered for each ligand-macromolecule complex, and the resulting docking clusters were calculated with a 2.0 Å root mean squared deviation (RMSD) tolerance on the heavy atoms [13]. The two-dimensional (2D) and 3D molecular interaction models of the docked compound on the TTR protein and receptor surface shape modeling (involving hydrogen bonding) were displayed using the DS v. 4.5 [14]. The significance level of the curcumin binding affinity on the TTR was set at $*p \leq 0.05$ versus BDMC. All data were represented as the means ±SEM (Standard Error of the Means).

3. Results

PyRx Autodock 4 docking analysis was applied to investigate the molecular binding interactions of curcumin and BDMC molecules, respectively with TTR chain A (Figure 3) and to elucidate the possible molecular mechanism. As shown in Table 1, curcumin interacted with 6 amino acid residues (Conventional hydrogen bond: ASN98, ASP99, SER100, Pi-Alkyl interactions: ALA120, VAL122, Pi-Sigma interaction: THR96) (Figure 4A and Figure 4C, Table 1) and BDMC interacted with 4 amino acid residues (Conventional hydrogen bond: VAL94, ALA120, Pi-Alkyl interactions: ALA120, Pi-Pi Stacked interaction: PHE95, Carbon hydrogen bond: VAL93, Pi Donor hydrogen bond: ALA120) (Figure 4B and 4D, Table 1). The shortest bond length between the curcumin and the TTR was 2.09Å and the partner amino acid was ASP99 (Figure 4C). The longest bond length between the curcumin and the TTR was 4.92Å and the interacting amino acid residue was VAL122 (Figure 4C).

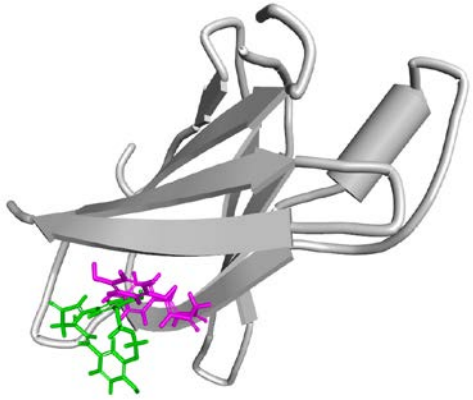

Figure 3. Three dimensional molecular docking pattern and binding position of the curcumin (green color) and the BDMC (purple color) on the TTR chain A active site

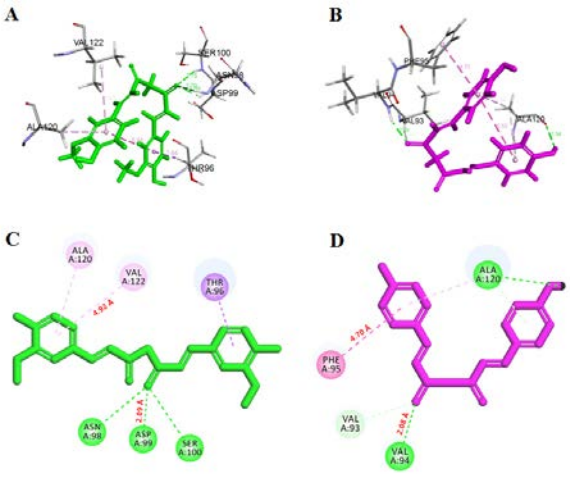

Figure 4. In silico molecular docking pattern of the curcumin (green color) and BDMC (purple color) with the TTR active site. Three dimensional (A and B) and two dimensinal (C and D) patterns

Table 1. Molecular interactions and interacting residues of the TTR protein with curcumin and BDMC

Interaction / Ligands	Conventianal hydrogen	Pi -Sigma	Pi -Alkyl	Pi-Pi	Carbon hydrogen	Pi-Donor hydrogen
Curcumin	ASN98 ASN99 SER100	THR96	ALA120 VAL122	-	-	-
BDMC	VAL94, ALA120	-	ALA120	PHE95	VAL93	ALA120

The shortest bond length between the BDMC and the TTR was 2.08Å and the residue was VLA94 (Figure 4D). The longest bond length between the BDMC and the transthyretin was 4.70Å and the partner was PHE95 (Figure 4D). The average molecular binding affinity (docking energy) scores of the curcumin and BDMC on the transthyretin were -5.08 kcal/mol (curcumin, SEM ±0.15) and -4.76 kcal/mol (BDMC, ±0.32) (Table 2). The

numbers of the binding modes were nine (n=9). Based on the present molecular docking study, curcumin appeared as a strong binder to the TTR active site than the BDMC and the interacting numbers of amino acids and conventional hydrogen bonds might be critical factors for regulating target protein activity. These data also suggest that computer aided drug design process using PyRx and Discovery Studio tools is highly reliable and can be a good example for indentifying the action mechanism between the TTR and its interacting ligands.

Table 2. Biding affinity to the TTR protein

Docking Energy (kcd/mol)		SEM
CURCUMIN	-5.08	±0.15 (N=9)
BDMC	-4.76*	±0.32 (N=9)

N=numbers of binding modes
*p<0.01.

4. Discussion

Traditionally, the turmeric has been commonly used as a spice in curries and flavoring agents, and coloring agents. BDMC is a natural curcumin chemical analogue and had been regarded as a strong antioxidant [15]. In spite of the variety of pharmacological activities of curcumin and BDMC reported earlier, this study was undertaken to evaluate the comparative effect of curcumin and BDMC for binding ability to the TTR protein chain A.

TTR binds Aβ peptide, preventing its deposition and toxicity. TTR is decreased in Alzheimer's disease patients. Recently, many evidence suggests a wider role for TTR in CNS neuroprotection, including in ischemia, regeneration and memory.

Through this experiment, we could find that curcumin has strong binding affinity to the TTR and interacts with more amino acid residues than the BDMC does. In a previous report, curcumin and BDMC had different redox properties due to the ortho-methoxy group in position 3 of the phenyl moiety of the curcumin [16]. As we already mentioned above, curcumin has two symmetric ortho-methoxy phenols linked through the α,β-unsaturated β-diketone moiety, BDMC, which is also symmetric, is deficient in the two ortho-methoxy substitutions (Figure 2). Thus, curcumin and BDMC exhibit significantly different binding affinity on the TTR (Table 2). Docking studies usually need a minimum of 10 analogues to get a proper SAR. In this study, we compared only 2 analogues. This might be too premature to comment on SAR. In further study, over 10 chemical analogues of the curcumin to the TTR active site ought to be done to clarify SAR relevence.

Curcumin and BDMC could be useful as sources of potential therapeutics or lead molecules for prevention or treatment of Alheimer's disease. For practical use of curcumin as novel anti-Alzheimer's disease products to proceed, further toxicity and clinical research is needed to establish their human safety and whether this activity could be exerted in vivo after consumption of the product by humans. Thus, we can conclude that not only the decrease of one methoxy group of curcumin but also the central methylenic hydrogen in the central seven carbon chain and β-diketone moiety may affect the difference in TTR binding activities. The interesting point of the our study is that this research is the first approach about curcumin and BDMC on TTR binding. In addition, many previous reports exhibited that long term treatment of curcumin can induce toxicity. Thus, our results suggesting that BDMC can be prescribed as safe alternative for TTR regulation and Alzheimer's diasese than curcumin.

Acknowledgement

This work is supported by the Gimcheon University Research Grant (Project Code # = gc15007).

References

[1] Goozee KG, Shah TM, Sohrabi HR, Rainey-Smith SR, Brown B, Verdile G, et al. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. The British journal of nutrition 2016;115:449-65.

[2] Jayaraj RL, Elangovan N, Manigandan K, Singh S, Shukla S. CNB-001 a novel curcumin derivative, guards dopamine neurons in MPTP model of Parkinson's disease. BioMed research international 2014;2014:236182.

[3] Ji HF, Shen L. The multiple pharmaceutical potential of curcumin in Parkinson's disease. CNS & neurological disorders drug targets 2014;13:369-73.

[4] Shwartsman AL, Sarantseva SV. [Compensatory function of transthyretin in Alzheimer's disease]. Tsitologiia 2011;53:772-7.

[5] Vieira M, Saraiva MJ. Transthyretin: a multifaceted protein. Biomolecular concepts 2014;5:45-54.

[6] Saelices L, Johnson LM, Liang WY, Sawaya MR, Cascio D, Ruchala P, et al. Uncovering the Mechanism of Aggregation of Human Transthyretin. J Biol Chem 2015;290:28932-43.

[7] Yokoyama T, Takaki S, Chosa K, Sato T, Suico MA, Teranishi Y, et al. Structural stabilization of transthyretin by a new compound, 6-benzoyl-2-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione. Journal of pharmacological sciences 2015;129:240-3.

[8] Pullakhandam R, Srinivas PN, Nair MK, Reddy GB. Binding and stabilization of transthyretin by curcumin. Archives of biochemistry and biophysics 2009;485:115-9.

[9] Li H, Zhang Y, Cao L, Xiong R, Zhang B, Wu L, et al. Curcumin could reduce the monomer of TTR with Tyr114Cys mutation via autophagy in cell model of familial amyloid polyneuropathy. Drug design, development and therapy 2014;8:2121-8.

[10] Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry 2010;31:455-61.

[11] Lei Q, Liu H, Peng Y, Xiao P. In silico target fishing and pharmacological profiling for the isoquinoline alkaloids of Macleaya cordata (Bo Luo Hui). Chinese medicine 2015;10:37.

[12] Rohmah RN, Hardiyanti F, Fatchiyah F. Inhibition on JAK-STAT3 Signaling Transduction Cascade Is Taken by Bioactive Peptide Alpha-S2 Casein Protein from Goat Ethawah Breed Milk. Acta informatica medica : AIM : journal of the Society for Medical Informatics of Bosnia & Herzegovina : casopis Drustva za medicinsku informatiku BiH 2015;23:233-8.

[13] Sambasivarao SV, Roberts J, Bharadwaj VS, Slingsby JG, Rohleder C, Mallory C, et al. Acetylcholine promotes binding of alpha-conotoxin MII at alpha3 beta2 nicotinic acetylcholine receptors. Chembiochem : a European journal of chemical biology 2014;15:413-24.

[14] Usha T, Middha SK, Goyal AK, Karthik M, Manoj D, Faizan S, et al. Molecular docking studies of anti-cancerous candidates in Hippophae rhamnoides and Hippophae salicifolia. Journal of biomedical research 2014;28:406-15.

[15] Li YB, Gao JL, Zhong ZF, Hoi PM, Lee SM, Wang YT. Bisdemethoxycurcumin suppresses MCF-7 cells proliferation by inducing ROS accumulation and modulating senescence-related pathways. Pharmacological reports : PR 2013;65:700-9.

[16] Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, et al. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochem Pharmacol 2008;76:1590-611.