JPR INFO .com
Journal of Pharma Research

Journal of Pharma Research
Available online through
www.jprinfo.com

Research Article
ISSN: 2319-5622

Insilico analysis of curcumin and its analogues as potential inhibitors of Indoleamine 2, 3-dioxygenase

C. Varshini, P. Vinitha, R. Priyanka, Ramaraj. K and Ronaldo Anuf. A*
Department of Biotechnology, Kamaraj college of Engineering and Technology, Virudhunagar, Tamilnadu, INDIA.

Received on: 16-10-2015; Revised and Accepted on: 30-10-2015

ABSTRACT

Curcumin is an active phytoconstituent derived from Curcuma longa commonly known as turmeric. Curcumin is extensively used in Indian traditional medicine for the treatment of various disorders like rheumatism, diabetic wounds, hepatic disorders, and skin diseases. Various studies suggest the potential use of curcumin for the treatment and prevention of cancer which is mediated through multiple mechanisms. However the poor bioavailability and low solubility limits its therapeutic use. Hence the present study aims at exploring the interaction of curcumin and its analogues against indoleamine 2, 3-dioxygenase 1 protein, a promising target for anticancer immunotherapy. Our study demonstrated that among the derivatives, curcumin diglucoside showed more potent activity with maximum hydrogen bond interaction and a Mol Dock score of -205.20 as compared with curcumin with a Mol Dock score of -158.025. However further experimental studies has to be performed to establish these analogues as potential candidates for cancer therapy.

Keywords: *Indoleamine 2, 3-dioxygenase, IDO, Curcumin.*

INTRODUCTION

Curcumin is a polyphenolic, non-flavonoid compound and it is one of the major ingredients of turmeric (*Curcuma longa*) and responsible for the therapeutic properties of turmeric in traditional medicine. Curcumin showed various biological and medicinal activities. (Gescher AJ et. al)., Therefore it is important to know about the relationship between structure and biological activities of curcumin.

Curcumin consists of a phenolic ring, alternating double bond and β-dicarbonyl group. It can exist in several tautomeric forms such as 1, 3 diketo form, 2 equiv enolate form and etc. The water stability of the curcumin is very poor because of its rigid and planarity structure. So, the absorption from digestive system into blood circulation is very low. β-dicarbonyl group, which is present in curcumin is unstable and easily decomposed, which causes low blood concentration and further reduces pharmacological potency of curcumin (Anand P et. al., 2007). Phase I clinical trials suggested that it is safe to consume orally 12 g/day of curcumin for human beings (Strimpakos AS et. al., 2008). Curcumin is a pleotropic compound, whose unique mechanisms of action are directed towards several targets such as cell proteins including transcription factors, protein kinases, enzymes, inflammatory mediators and anti-apoptotic proteins (Goel A et. al. 2008). And it also shown that it have effective growth inhibitory activity for various tumors (Sharma RA et. al., 2004).

Tumors have developed various strategies to escape immune attack (Zou et al., 2005). Recently, indoleamine 2,3-dioxygenase (IDO) a molecule capable of preventing T cell-driven rejection of allogeneic fetuses during pregnancies (Munn DH et al., 1998) has attracted the attention of scientists. Indoleamine 2,3-dioxygenase (IDO) is an intracellular heme enzyme that catalyses the initial and rate-limiting step in the metabolism of the essential amino acid tryptophan along the kynurenine pathway. (Soliman H et al.,2010). First, tryptophan depletion can directly lead to T-cell growth arrest in the G1 phase of the cell cycle. Second, alternative degradation of tryptophan produces metabolites shown to be toxic for CD8+ T cells and natural killer cells. Furthermore, IDO has the ability to convert naive T cells to immunosuppressive regulatory T cells (Fallarino F et al., 2006). High levels of IDO expression are found in patients with ovarian carcinoma, hepatocellular carcinoma, invasive cervical carcinoma, non-small cell lung carcinoma, colon carcinoma and endometrial carcinoma and are associated with poor prognosis (De Jong RA et al., 2012).Elevated tryptophan catabolism in the urine and blood of tumor-bearing patients has been recognized for many decades, perhaps explained by the discovery of common IDO1 overexpression in tumors. Immuno-histochemical analysis of colon tumors indicated that IDO1 overexpression is associated with a significant reduction of CD3+ infiltrating T cells and higher occurrence of liver metastases in colorectal cancer patients. In case of ovarian cancer IDO1 was found to be overexpressed in serous-type ovarian cancer where it was associated with decreased patient survival. IDO1 overexpression was also associated with resistance to paclitaxel. In the present study, we investigated the effect of curcumin and its analogues in suppressing the activity of the Indoleamine 2,3-dioxygenase protein. Further the binding interaction of curcumin analogues such as Curcumin bis-acetate, Curcumin diglucoside, Demethyl Curcumin and Curcumin pyrazole were explored using ligand based approach to propose the inhibitory activity of curcumin against IDO1 receptor.

***Corresponding author:**
Ronaldo Anuf. A
Department of Biotechnology,
Kamaraj college of Engineering and Technology,
Virudhunagar, Tamilnadu, INDIA.
**E-Mail: ronaldoanuf@gmail.com*

MATERIALS AND METHOD

1. Ligand Preparation:

The structure of flavonoid compounds were retreived from Pubchem (https://pubchem.ncbi.nlm.nih.gov/) and Chemspider database (http://www.chemspider.com/). The compounds were converted into comfortable format (sdf) using Open Babel tool. The energy minimized structure were used for docking studies.

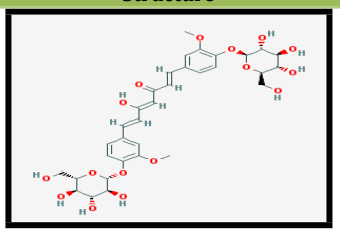
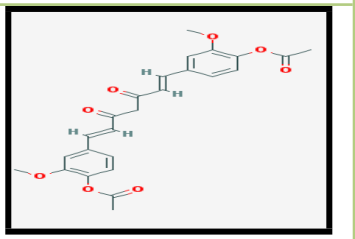
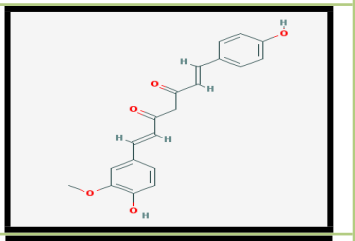
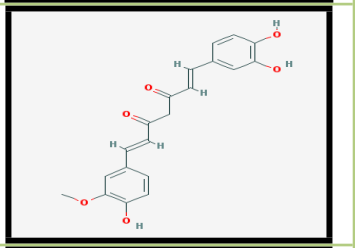
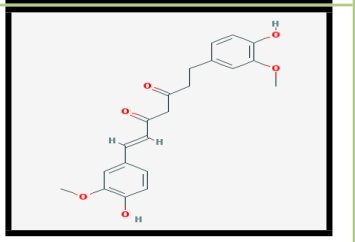
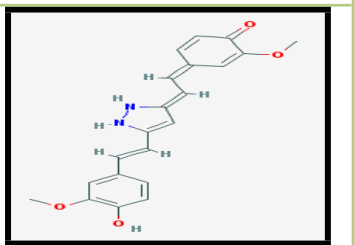
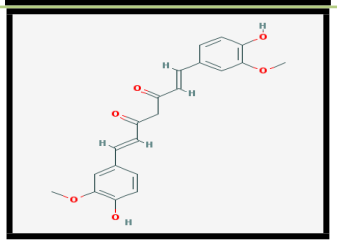
2. Protein Preparation:

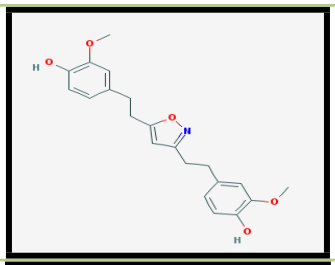
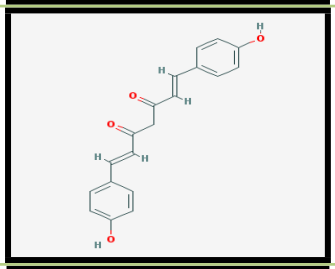
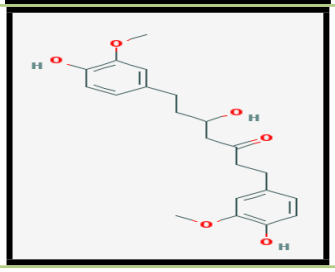
The three dimensional crystal structure of the target protein indoleamine 2,3 dioxygenase 1 (IDO1) was retreived from Protein Data Bank (http://www.pdb.org/). The PDB ID for the selected target protein was 2D0T. The bonds, bond orders, explicit hydrogen, charges (calculated by MVD), flexible torsion and Tripos atom types for the protein were selected if any found omitted by using Protein Preparation, module of Molegro Virtual Docker for the protein Indoleamine 2,3 dioxygenase 1 (IDO1). The side chain flexibility analysis were performed which provides valuable insights to increase docking algorithms and grants an index of amino acid side chain flexibility, which potentiality aids in molecular docking. The atoms away from the binding site are neglected using ignored distant atom option. The active sites on the Indoleamine 2,3 dioxygenase 1 were analysed using Molegro Virtual Docker.

3. Molecular docking:

Molegro virtual docker works on the basis of Moldock SE search algorithm. The docking algorithm was set at a maximum iteration of 1500 with a simple evolution size of 50 and minimum of 5 runs. The population size was set at 50 with energy threshold of 100 at each step. The least minute was set as 10 minutes, the torsions/translations/rotations of the ligand protein interaction were tested and the one giving lower energies is chosen for further studies. The bonds flexibility of the ligands were fixed and the side chain flexibility of the amino acids in the binding cavity was set with a tolerance of 1.10 and strength of 0.90 for docking simulations. RMSD threshold for multiple cluster poses was set at <2.00.

The reranking score function is estimated more expensive than the scoring function used during the docking simulation but it is commonly better than the docking score function at analyzing the best pose among several poses originating from the same ligand (Ramaraj K et al., 2014). Binding affinities were estimated using Molegro data modeler The scoring function used by MolDock is derived from the piecewise linear potential (PLP) scoring functions which further improves these score with a new hydrogen bonding term and new charge schemes (Thomson et. al., 2006).

S.No	Compound name	Structure
1	Curcumin diglucoside	
2	Curcumin bis-acetate	
3	Monodemethoxycurcumin	
4	Demethyl Curcumin	
5	Dihydrocurcumin	
6	Curcumin pyrazole	
7	Curcumin	

8	Tetrahydrocurcumin	
9	Bisdemethoxycurcumin	
10	Hexahydrocurcumin	

RESULTS AND DISCUSSION

Natural products derived from medicinal plants and their synthetic derivatives have been used as a good lead molecule in case of cancer treatment (Anuf.AR et al., 2014). Docking analysis was carried out for the curcumin and its analoges against the target protein Indoleamine 2,3-dioxygenase (IDO 1) using Molgro docking software so as to evaluate the efficacy of these compounds in suppressing the activity of target protein. The Moldock score, docking score and rerank score of the curcumin analogues were displayed in table.1.

Table No. 1: Moldock score for curcumin and its analogues against target protein

S.NO	LIGAND	MOLDOCK SCORE	RERANK SCORE	HBOND	DOCKING SCORE
1	Curcumin diglucoside	-205.707	-182.161	-13.5369	-216.495
2	Curcumin bis-acetate	-172.712	-134.11	-5.67842	-170.739
3	Monodemethoxycurcumin	-167.561	-142.96	-8.27061	-173.517
4	Demethyl Curcumin	-167.063	-115.582	-12.4088	-172.792
5	Dihydrocurcumin	-165.886	-138.099	-7.85996	-176.787
6	Curcumin pyrazole	-163.99	-136.373	-4.94124	-167.417
7	Curcumin	-158.025	-77.0222	-5.7118	-167.586
8	Tetrahydrocurcumin	-152.226	-110.937	-0.84518	-155.814
9	Bisdemethoxycurcumin	-148.171	-126.011	-6.02105	-156.445
10	Hexahydrocurcumin	-135.793	-96.3895	-6.56724	-138.373

The Curcumin analogue, Curcumin diglucoside showed more potent inhibitory activity against IDO 1 protein. Curcumin diglucoside is a naturally occurring plant bioflavonoid present in curcumin and possesses a wide range of biological application including anticancer. The interaction of the compound with the target protein was analysed using Molegro viewer module.

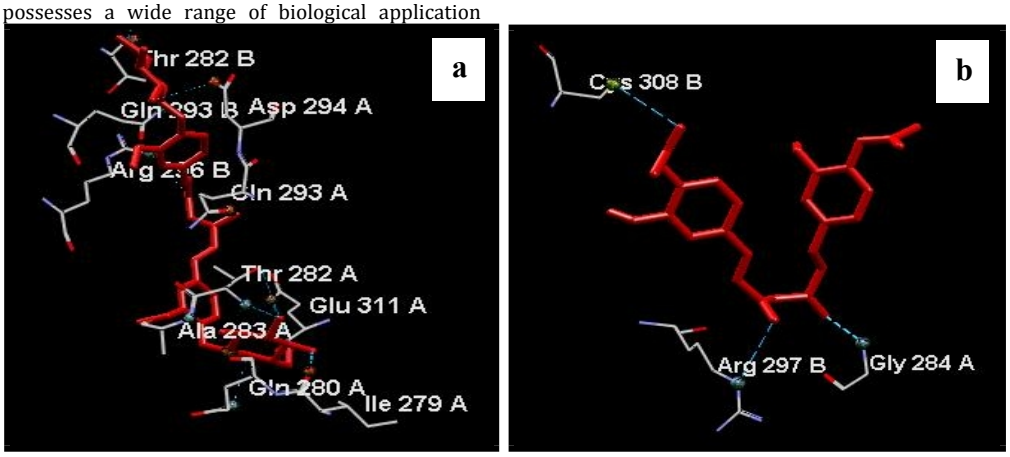


Fig. 1 a) Interaction of Curcumin diglucoside with IDO-1 protein, b) Interaction of Curcumin bis-acetate with IDO-1 protein visualized using Molegro viewer.

The receptor bound ligand Curcumin diglucoside bound deeply in binding pocket region. The active compound Curcumin diglucoside bound with receptor with a moldock score of –205.107. The compound displayed interaction with seven different aminoacids with a total of 13 hydrogen bond interactions. Amino acid residue of IDO-1 involved in binding with Curcumin and its analogues were displayed in Table 2.

Table No. 2: Amino acid residue of IDO-1 involved in binding with Curcumin analogues

S.No	Compound name	Hydrogen bond interaction with Amino acid	No. of Hydrogen bond
1	**Curcumin diglucoside**	Ile 279 A, Gln 280 A, Thr 282 A, Ala 283 A, Gln 293 A, Asp 294 A, Thr 282 B, Gln 293 B, Arg 296 B	13
2	**Curcumin bis-acetate**	Gly 284 A, Arg 297 B, Cys 308 B	3
3	**Monodemethoxycurcumin**	Asp 274 A, Ile 279 A, Gln 281 A, Gln 293 A, Leu 120 B, Pro 121 B, Arg 297 B	7
4	**Demethyl Curcumin**	Asp 274 A, Ile 279 A, Gln 281 A, Gln 293 A. Leu 120 B. Pro 121 B	8
5	**Dihydrocurcumin**	Ile 279 A, Thr 282 A, Gln 293 A, Arg 296 A, Pro 121 B, Arg 304 B	6
6	**Curcumin pyrazole**	Glu 311 A, Arg 297 B	5
7	**Curcumin**	Ile 279 A, Gln 293 A, Pro 121 B, Arg 297 B, Arg 304 B	6
8	**Tetrahydrocurcumin**	Gln 293 A, Pro 121 B, Arg 304 B	3
9	**Bisdemethoxycurcumin**	Arg 193 A, Asp 274 B, Ile 279 A, Gln 293 A, Pro 121 B	5
10	**Hexahydrocurcumin**	Gly 284 A, Gln 290 A, Arg 297 B	3

CONCLUSION

The present molecular docking studies provide insights into inhibition of IDO-1 by curcumin analogues. Docking study propose that Curcumin diglucoside has a high binding affinity for IDO-1 protein. This study has led to the development of novel lead molecules which would help to develop enzymatic mechanisms allowing tumors to resist or escape immune rejection.

REFERENCE:

1. Gescher AJ, Sharma RA, and Steward WP. Cancer chemoprevention by dietary constituents: a tale of failure and promise. Lancet Oncol., **2001**; 2: 371–379.
2. Strimpakos AS and Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. Antioxid Redox Signal, **2008**; 10: 511–545.
3. Goel A, Kunnumakkara AB, and Aggarwal BB. Curcumin as "curecumin": from kitchen to clinic. Biochem. Pharmacol., **2007**; 19, 19.
4. Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, Marczylo TH, Morgan B, Hemingway D, Plummer SM, et al., Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin. Cancer Res., **2004**; 10(20): 6847–6854.
5. Zou W, Immunosuppressive networks in the tumour environment and their therapeutic relevance. Nat. Rev. Cancer, **2005**; 5(4): 263-274.
6. Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, Brown C, Mellor Al. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science, **1998**; 281(5380): 1191-1193.
7. Soliman H, Mediavilla-Varela M, Antonia S. Indoleamine 2,3-dioxygenase: is it an immune suppressor? Cancer J., **2010**; 16: 354-9.
8. Fallarino F, Grohmann U, You S, McGrath BC, Cavener DR, Vacca C, Orabona C, Bianchi R, Belladonna ML, Volpi C, Santamaria P, Fioretti MC, Puccetti P. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naïve T cells. J. Immunol., **2006**; 176: 6753-61.
9. De Jong RA, Kema IP, Boerma A, Boezen HM, van der Want JJ, Gooden MJ, Hollema H, Nijman HW. Prognostic role of indoleamine 2,3-dioxygenase in endometrial carcinoma. Gynecol. Oncol., **2012**; 126(3): 474-80.
10. Kannan Ramaraj, Alexander Ronaldo Anuf. Inhibition of FGFR2 signal transduction in Acne Vulgaris using Bioactive Flavonoids: An Insilico approach, A. J. Med. Pharm. Sci., **2014**; 2(2): 136-142.
11. Thomsen R, Christensen MH. MolDock: A New Technique for High-Accuracy Molecular Docking. *J. Med. Chem.,* **2006**; 49(11): 3315.
12. Anuf AR, Breethi Natarajan, Shahila Stephen and Kannan Ramaraj. Insilico Analysis of Plumbagin and its synthetic analogues as potential Bcl-2 Inhibitors, A. J. Med. Pharm. Sci., **2014**; 2(2): 108-114.

How to cite this article:

Ronaldo Anuf. A *et al.,: Insilico* analysis of curcumin and its analogues as potential inhibitors of Indoleamine 2, 3-dioxygenase, J. Pharm. Res., 2015; 4(10): 335-339.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil