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Targeting study of plant alkaloid Bereberine act as a natural drug inhibitor of Hsp90(Heat shock proteins)

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Abstract: Berberine a plant alkaloid is investigated as inhibitor of Hsp90(heat shock protein)by computer modelling and docking studies. Hsp90 is chaperon protein which stabilises proteins for tumour growth. The ATP regions in Hsp90 such as Asn37. Leuc34, Asp79, Asn92, Gly121 were selected as targeted amino acids. Here we report anti cancer effects of berberine which inhibited Hsp90 proteins activity, it also suppressed independent growth of tumour cells by disrupting the ATP site regions in Hsp90. In molecular docking and simulation studies inhibition was due to direct binding of berberine with ATP regions. This report suggests that berbeine is a natural and clear molecular target for anti cancer activity of Hsp90, which might contribute to chemo preventive potential of certain natural drugs.

Keywords: Alkaloid Bereberine,natural drug inhibitor of Hsp90,Heat shock proteins.

1. Introduction

Berberine is an isoquinoline alkaloid from nature plants like *Berbera Species* has demonstrated multiple pharmalogical and biological activities[1] against many cancer cells, it is a traditional anticancer drug which have been applied in Chinese medicine[2] from many decades. Berberine plays key role in inhibition[3] 0f Hsp90 active sites by using Molecular Docking studies

Hsp90 protein[4] is a chaperon protein which regulates the temperature of proteins in the other hand it stabilises the tumour growth proteins, which is responsible for many type of cancers. Here we report the Hsp90 inhibition study to control the Hsp90 stabilisation against tumour growth, so we target the ATP sites (Asn37, Leuc34, asp79, Asn92, Gly121) of Hsp90 proteins for inhibitions. Inhibition of this sites are essential to control the activity cancer cells[5-7]

2. Experimental

2.1 Receptor Preparation

The 3D structure of Hsp90 was retrieved from the Hsp90 from PDB databank[8] (PDB id:1US7) The Hsp90 is designed such as it has a binding receptors were carried out for molecular docking. The structure which is imported into Schrodinger docking tools (Maestro9.0) subjected to delete waters and add Hydrogen to

the molecule. Then the resultant molecule should undergo pre process, optimization and minimisation simulations for ligand binding interactions

2.2 Ligand preparation

The Berberine structure which is retrieved from ZINC Data base(code: Zinc03779067)[9].The resultant molecule were carried out for minimization under 5000 cycles in conjugate gradient method for preparing to dock the binding receptor of Hsp90 Proteins

2.3 Software

The software which is used for docking is Schrodinger suite Docking[10] platform Maestro9.0, which has a special package features of all components and flexible adjusting of parameters and docking, molecular studies and drug design methods[11].

2.4 Docking studies

The resultant protein preparation wizard structure[12][import to Maestro platform, then we pick the ligand receptors by using grid box contains the x, y, z constraints. Adjust x=2.96 ,y=3;47, z=5.46 at the receptor sites. Then the prepared ligand is imported and run the Induced fit docking. The docking score and gliding scores were obtained from 17 hits then choose the best score and gliding energy from 17 out fits.

3. Results

The 3D structure[13] was generated after 17 outfits of Induced docking and the residues at ATP sites were bind by ligand and form a clear representation of inhibition. The sites which were docked had highest docking score is -6.035 and lowest is -4.3 and the gliding energy is -39.92 and lowest is -33.04.these are the effective and efficient report of any natural drug inhibition for Hsp90 proteins[14]. The resultant values of 17 docking induced outfit were represented in Fig1.The important ATP sites which ligand docking interacted sites are (Asn37, Leuc34, asp79, Asn92, Gly121)block the energy supply to Hsp90 proteins so, the HSp90 proteins gradually inhibited in cells body represented in Fig2.so,by these studies we can evaluate that berberine is natural and effective inhibitor of Hsp90 proteins[15].

Row	In	Title	Aux	docking score	glide energy
[17]	–	InducedFit-out			
1	■	ZINC03779067		-5.776783	-36.387885
2	□	ZINC03779067		-5.886533	-39.926783
3	□	ZINC03779067		-6.035291	-39.597947
4	□	ZINC03779067		-5.378039	-37.373232
5	□	ZINC03779067		-5.428500	-33.972591
6	□	ZINC03779067		-5.293889	-33.126501
7	□	ZINC03779067		-4.989704	-33.617614
8	□	ZINC03779067		-4.920866	-36.950297
9	□	ZINC03779067		-5.520087	-37.315902
10	□	ZINC03779067		-5.265301	-33.042899
11	□	ZINC03779067		-4.876623	-36.114464
12	□	ZINC03779067		-4.606404	-29.609585
13	□	ZINC03779067		-4.874092	-34.787120
14	□	ZINC03779067		-5.646674	-36.727465
15	□	ZINC03779067		-4.863854	-37.981551
16	□	ZINC03779067		-4.305628	-34.520908
17	□	ZINC03779067		-4.571404	-35.667232

Fig1. The Induced fit docking results of 17 cycles

Fig1.The induced docking hits of ligand protein interactions

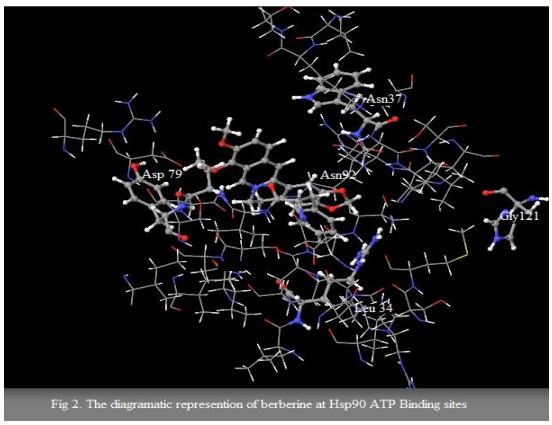
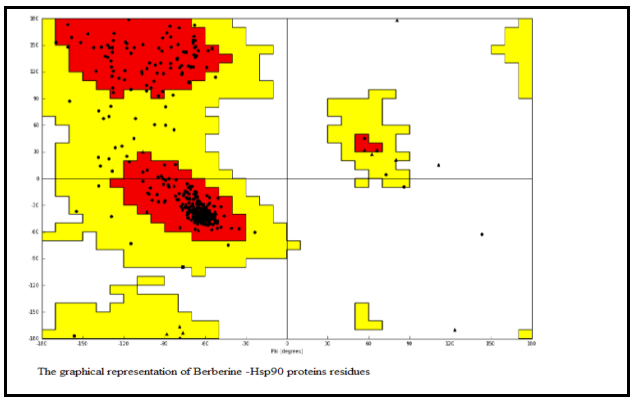


Fig 2. The diagramatic represention of berberine at Hsp90 ATP Binding sites



The graphical representation of Berberine -Hsp90 proteins residues

4. Discussion

The docking results are evaluated from the Maestro platform, The relative accuracy and site of interactions at protein ligand complex is satisfactory. Negative binding energy is an evidence for the formation of positive results. The ATP sites which were bind at docking site residues which blocks the energy supply to Hsp90 proteins. This study provide an opportunity to explore the emergence of natural drugs. Our analysis here is Natural drug Berberine can induce the Hsp90 proteins in widely acceptable docking studies.

5. References

1. Yang Liu, Li Zhang, Haiyan Song, and Guang J, Update on Berberine in Nonalcoholic Fatty Liver Disease 2013, http://dx.doi.org/10.1155/2013/308134
2. Dechwisissakul P, Bavovada R, Thonghoo P, Maison T: Pharmacognostic identification of Hamm. Thai J Pharm Sci 2000; 24(suppl):31.
3. Wagner, H., :Multitarget therapy-The future of treatment of more than just functional dyspepsia. Phytomedicine., 2006 13:122-129.
4. Siligardi G, Hu B, Panaretou B, Piper PW, Pearl LH, Prodromou C. Cochaperon regulation of conformational switching in the Hsp90 ATPase cycle. J Biol Chem 2004;279:51989–98.
5. Neckers L. Hsp90 inhibitors as novel cancer chemotherapeutic agents. Trends Mol Med 2002;8:55–61.
6. Ramanathan RK, Trump DL, Eiseman JL, et al. Phase I pharmacokinetic- pharmaco dynamic study of 17-(allylamino)-17-demethoxyGA (17AAG, NSC 330507), a novel inhibitor of heat shock protein 90, in patients with refractory advanced cancers. Clin Cancer Res 2005;11: 3385–91.
7. Westerheide SD, Bosman JD, Mbadugha BN, et al. Celastrols as inducers of the heat shock response and cytoprotection. J Biol Chem 2004;279:56053–60.
8. H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, P. E. Bourne The Protein Data Bank, Nucleic Acids Res2000. 28, 235–242.
9. D. M. Smith, K. G. Daniel, Z. Wang, W. C. Guida, T.-H. Chan, Q. P. Dou Docking studies and model development of tea polyphenol proteasome inhibitors: Applications to rational drug design, Proteins Struct. Funct. Bioinform2004. 54, 58–70.
10. Reardon DA, Wen PY. Therapeutic Advances in the Treatment of Glioblastoma: Rationale and Potential Role of Targeted Agents. Oncologist. 2006;11:152–64.
11. Frieboes HB, Lowengrub JS, Wise S, et al. Computer simulation of glioma growth and morphology. NeuroImage. 2007;37:S59–70.
12. Q. Zhang, Y. Peng, X.I. Wang, S.M. Keenan, S. Arora, W.J. Welsh, Highly potent triazole-based tubulin polymerization inhibitors, J. Med. Chem. 50 2007 749–754.
13. Y. Qian, H.J. Zhang, P.C. Lv, H.L. Zhu, Synthesis, molecular modeling an biological evaluation of guanidine derivatives as novel antitubulin agents, Bioorg. Med. Chem. 18 , 2010 8218–8225.
14. M. Theuerkorn, G. Fischer, C. Schiene-Fischer, Prolyl cis/trans isomerase signalling pathways in cancer, Curr. Opin. Pharmacol. 11,2011, 281–287.
15. H.A. Velazquez, D. Hamelberg, Conformational selection in the recognition of phosphorylated substrates by the catalytic domain of human Pin1, Biochemistry 50 2011, 9605–9615.

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