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Volume 11(10)

Insights from the molecular docking of curcumin to the virulent factors of *Helicobacter pylori*

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Received September 23, 2015; Accepted October 01, 2015; Published October 31, 2015

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Abstract:
The domains of virulent (Ureα/β, VacA-p55, and CagA) factors of Helicobacter pylori play a pivotal role in developmental processes of numerous diseases including gastric cancer. The pharmacological role of curcumin indicates that it could regulate the signaling of virulent factors by interacting with active domains. However, the controlling mechanism of the curcumin interactions and the binding diversity on structural basis of virulent (Ureα/β, VacA-p55, and CagA) factors are unknown. Curcumin as therapeutic agent was filtered by using Lipinski rule's five and the druglikeness property for assessment of pharmacological properties. Here outcome of molecular docking presented the 3-D structure of curcumin complex, that interacted with especially conserved residues of target domains. The structure revealed that the curcumin complexation with domains of these proteins provided structural insight into the diverse nature of proteins (Ureα/β, VacA-p55, and CagA) recognition. In silico study elucidated that the broad specificity of curcumin was achieved by multiple binding mode mechanisms such as distinct hydrogen and hydrophobic interactions with involvement of binding energy. The higher score of curcumin in complexation with both subunits Ureα/β showed the stable binding, and less stability with VacA-p55 complexation with lower score. Curcumin exhibited good interaction with these targeted virulent factors, although extensive interactions of curcumin with Ureα/β subunits could have an important implication to prevent survival and colonisation of H. pylori in stomach.

Keywords: Curcumin, Docking, *Helicobacter pylori*, Residues.

Background:
H. pylori is a gram negative bacteria infecting about 50% of the world population and recognised as an etiologic agents in different types of gastrointestinal diseases [1]. It is only bacteria known to inhabit the human stomach. *H. pylori* secretes virulent factors like urease, vacuolating associated gene A (VacA), and cytotoxic associated gene A (CagA) for pathogenesis in human stomach **[2]**.

The enzyme urease hydrolyses the urea into ammonia for neutralization of acidic environment in human lumen and establishing the neutral microenvironment surrounding the bacteria. The cytoplasmic urease protects the bacteria in acidic environment by increasing periplasmic pH and membrane potential in combination with UreI, a proton-gated urea channel **[3]**. The urease of *H. pylori* consists of two different subunits of α (61.7 kDa) and β (26.5 kDa) **[4]** and synthesises a huge complexes, whose molecular mass has been estimated about 600 kDa **[5]**. The VacA of *H. pylori* secretes toxin, that induces for extensive vacuolation in the cytoplasm of mammalian cells **[6]**. VacA is translated into protoxin (140 kDa), that undergoes N- and C-terminal cleavage at the time of secretion process to yield a mature 88-kDa toxin, p88 **[7]**. VacA intoxicates multiple types of human cells causing a several types of cellular effects **[6]**. Two domains of VacA (p33 and p55) have been identified after partial proteolysis of p88 into fragments of 33 and 55 kDa, respectively **[8]**. The residues (6-27) of N-terminal p33 domain (1-311) have a hydrophobic region, that involves in pore formation (18,28), whereas p55 domain (residues 312-821) contains one or more cell-binding domains **[9]**. When it expresses intracellularly, the minimum portion of VacA requires for cell-vacuolating activity comprising the entire p33 domain and about 110 aa from the N terminus of p55 **[10].**

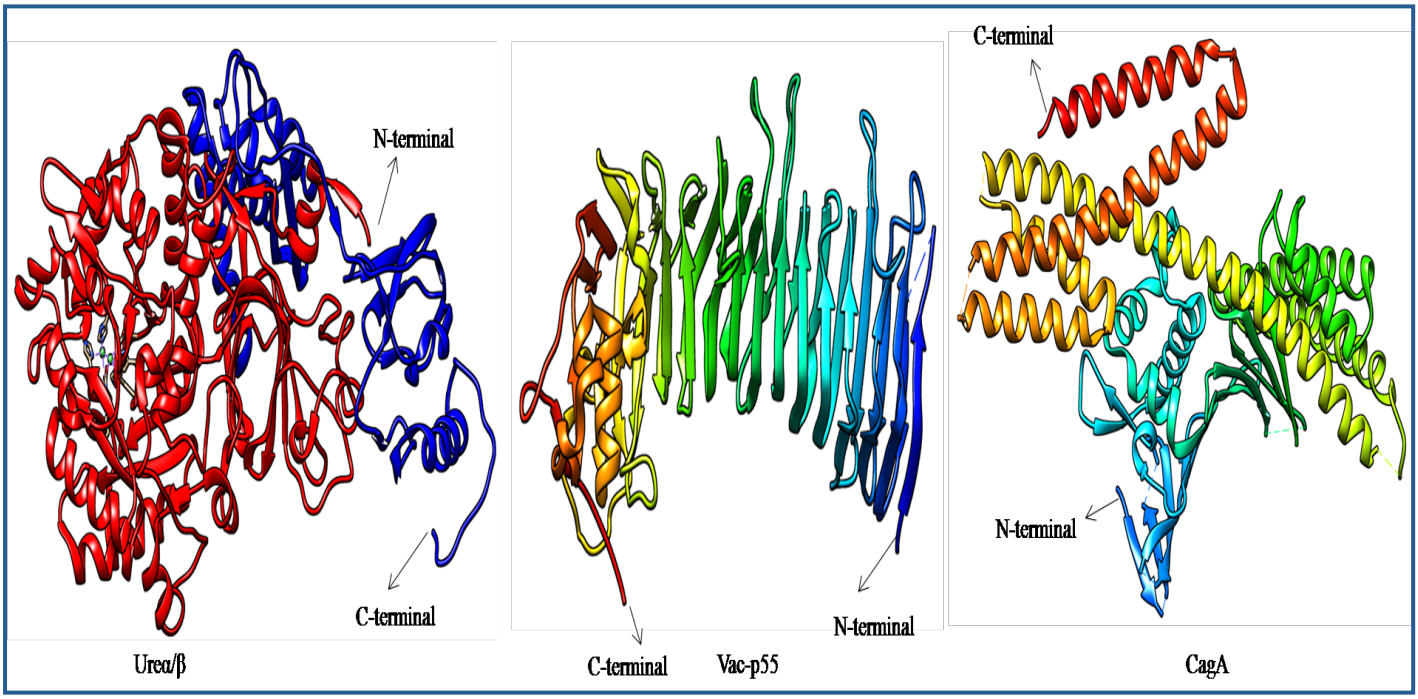

Figure 1: 3D-structure of virulent proteins showing N/C-terminal.

The most extensive virulent factors harbour the cag pathogenicity island (cag-PAI), and its 40-kb DNA fragment encodes the cytotoxin CagA and a type IV secretion system (cag-T4SS) **[11]**. The unique protein CagA is found in *H. pylori* and has been established at time of cytotoxin expression, developing to gastric polyps and adenocarcinoma in transgenic mice **[12]**. After screening of soluble fragment throughout **[13]** and analysis on vivo proteolysis data, CagA has been described as a protein consisting of two functional domain **[14]**. Much attention has been paid to the role of the C-terminal domain (residues 885-1,186). The Pro-Ile-Tyr-Ala (EPIYA) motifs become tyrosine phosphorylated by Src and Abl kinases in eukaryotic cells **[15]**. Further, phosphorylated CagA binds and activates Src homology 2 domain phosphatase (SHP2) via its SH2 domains, leading to dephosphorylation and inactivation of Src family kinases for cytoskeleton rearrangement **[16]**. Other effects of Cage is independent of phosphorylation. Such as, specific sequences named as MKI located in the CagA C terminus stop Par1b/MARK2 kinase activity to mimic the enzyme's natural substrate **[17]**. The inhibition of the PAR1b/MARK2 perturbs atypical PKC signaling, that disrupts the tight junction as well as loss the cell polarity **[18]**. It has been indicated that the N-terminal portion of CagA (CagA1-884) interacts with intracellular partners, such as ASPP2 **[19]**, RUNX3 **[20]**, TAK1, and TRAF6 **[21]** in gastric cancer development.

Curcumin is a main component of turmeric (*Curcuma longa*) and generally used as a natural medicine. Curcumin is a non-toxic polyphenolic compound **[22]** and have several important medicinal properties such as antioxidant, anti-inflammatory, antimicrobial, and anticancerous **[23]**. Study based on computation approaches suggested that curcumin may play an inhibitory role against CagA+ *H. pylori* **[24]**. Such properties of curcumin immensely supports to develop of modern medicines for the treatment of various diseases **[25]**. Thus, curcumin may be a potential therapeutic agent for *H. pylori* infection. Still the preferential action of curcumin for virulent (Ureα/β, VacA-p55, and CagA) factors of *H. pylori* are remained to be elucidated. Therefore, we have strived by *in silico* approaches to address an insight from the structural interactions of curcumin with virulent factors of *H. pylori*.

Methodology:

The traditional Indian medicine curcumin (PubChem ID: CID_969516) structure published in literature was downloaded in SDF (standard data file) file from the database PubChem for computational study **[26]**. For molecular docking analysis, the SDF file of curcumin was converted into PDB (protein data bank) by using the software UCSF Chimera **[27]**. The crystal structures of virulent proteins were retrieved from data base PDB (protein data bank) as shown in **Figure 1.** The urease crystal structure has been published in an article which possesses two subunit α and β **[28]**. The structural file of urease (PDB ID: 1E9Z) with resolution 3.00 A was retrieved from PDB. The size of α subunit (61.7 kDa) was 238, whereas β subunit (26.5 kDa) had 569 sequences. The crystal structure of other virulent factor VacA has been explained by Gangwer et al. (2007) **[29]**. The PDB ID: 2QV3 of VacA was retrieved from PDB possesses resolution 2.40 A^0. The amino acid length of VacA was 457 with mass 55 KDa. The crystal structure of CagA protein has been reported in the literature which possess different confirmations **[15]**. The protein structures file of CagA (PDB ID: 4VDZ) containing resolution 3.19 A^0 was retrieved from PDB **[30]**. Amino acids length was 1,186 (CagA1-884 N-terminal, CagA885-1,186 C-terminal) with mass of 120 kDa.

ADME and Druglikeness Analysis

Molecular properties such as membrane permeability and bioavailability of leading compounds are always associated with some basic molecular descriptors such as logP (partition coefficient), molecular weight (MW), or number of hydrogen bond acceptors and donors in a molecules **[31]**. These molecular properties were used in formulating "rule of five" **[32]**. Lipinski's rule states, that molecules with good membrane permeability has MW ≤ 500, hydrogen bond donors ≤ 5 and

acceptors ≤ 10. Therefore, Lipinski's Rule of Five was used to test the bioavailability characteristics such as absorption, distribution, metabolism, and elimination (ADME) of lead molecule curcumin. In the present study, these molecular properties and Druglikeness score of curcumin were estimated by using Molinspiration tool **[33]**.

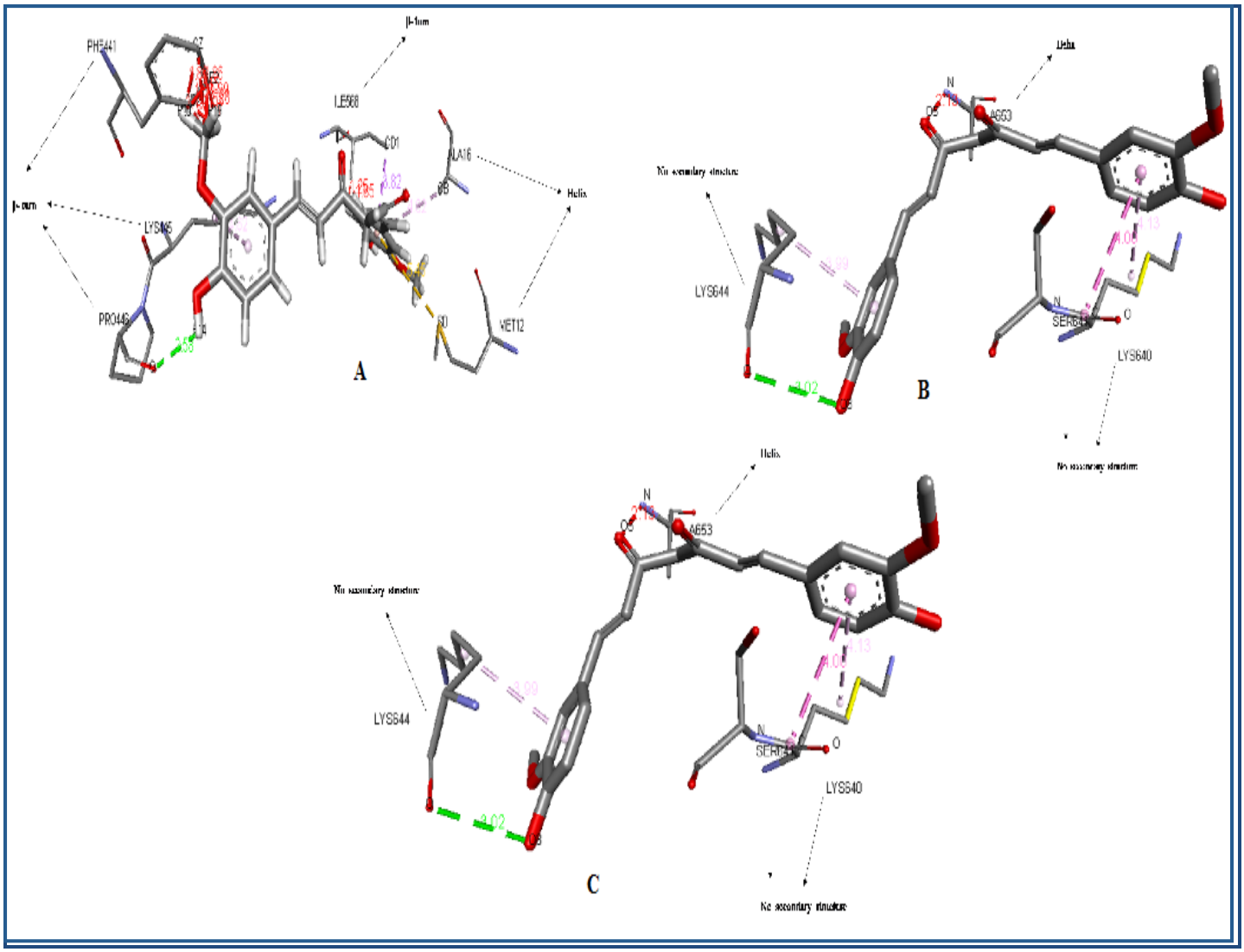

Figure 2: Visualisation of curcumin complexed with virulent proteins of *H. pylori* showed in stick and line representation : **A)** Ureα/β; B) Vac-p55 **; C)** CagA

Molecular Docking of compounds

The molecular docking was accomplished to investigate the binding mode of curcumin with virulent (Ureα/β, VacAp55 and CagA) proteins, especially the binding sites of the receptor. The conservative residues and active sites in these virulent proteins were calculated and identified by Bayesian method using ConSurf web server **[34]**.

Docking study of curcumin was performed using PatchDock online server **[35]**. The clustering RMSD was 4.0 A⁰ and the complex type was set to default. The number of solutions with their score, area, and desolvation energy were obtained. PatchDock provided results, that were ranked according to geometric shape complementarily score after molecular shape representation and surface patch matching. Further, the Discovery Studio 4.0 Client was used for visualisation and determining the mode of interaction between the receptor and ligands **[36]**.

Results & Discussion:

Analysis of ADME property and Druglikeness Score

Nonbactericidal concentrations of curcumin showed downregulation of *H. pylori* induced AID expression in gastric epithelial cells via inhibition of NFkappaB pathway **[37]**. Increasing complications due to rapid use of conventional therapy stimulate to develop new non-antibiotic antibacterial agents against *H. pylori* infection that are safe, highly effective and have specific cellular targets **[38]**. Curcumin have often failed to rich at clinic level, even though have potential in vitro inhibitors of desired targets due to insufficient cautions to these issues. Therefore, initially a wide spread agreement related to ADME and drug-like properties should be employed as soon as possible in the discovery of drug rather optimization of molecule properties **[39]**. The molecular properties and bioactivity of curcumin were determined by using online data server Molinspiration and elucidated logP values along with

other physiochemical properties like molecular mass, the number of hydrogen bond acceptors and the number of hydrogen bond donors. Molecule violating more than one of the Lipinski's rule may have problems in bioavailability. The results associated with Lipinski rule reveals that the curcumin has zero violations of Rule of 5 **Table 1 (see supplementary material).**

Hence, subsequently druglikeness scores were determined for analysing the drug-like bioactivity of curcumin. More than half of clinical trials have failed to demonstrate the pharmacokinetic properties of curcumin. Therefore, the evaluation of curcumin is essential to understand its pharmacokinetic properties and to find out interactive potency against desired targets. Hence, in the present study, we have strived to explore the overall druglikeness score for curcumin supported. Khan *et al.* (2013) have mentioned on a research article that the larger bioactivity score of compounds indicates probability for higher activity of the particular molecule **[40]**. It has been explained that the bioactivity score of molecule (>-0.50) possesses considerable biological activities and if score is less than -0.50, presumed to be inactive **[41]**. The combination of GPCR, ion channel modulator, kinase inhibitor, nuclear receptor ligands, protease inhibitor, and enzyme inhibitor are assigned to predict the druglikeness score that predict the curcumin properties in formulation as drug. The obtained values of druglikeness score show that the curcumin can have potency to follow the druglikeness score (>-0.50) **Table 2 (see supplementary material).**

Docking results of curcumin with virulent proteins

The biological activities of curcumin in vivo condition is still enigma due to its instability at different physiological condition **[42]**. Although, curcumin is considered as a potential therapeutic agent against pathogenic activities of *H. pylori* infection due to inhibition of NF-jB activation and cell scattering **[43]**. The present study based on molecular docking hypothesised that the binding affinity or interactive properties of curcumin with target virulent (Ureα/β, VacAp55 and CagA) proteins are comparable to understand the binding affinity of complexed structure. The therapeutic effect of curcumin against *H. pylori* infection has suggested its potential as an alternative therapy, and opens the way for further studies on identification of novel antimicrobial targets of curcumin **[44]**. Curcumin treatment exerted a significant anti-inflammatory effect in *H. pylori*-infected mucosa and indicating the promising role of a nutritional approach in the prevention of *H. pylori* infection, while the eradication or prevention of colonization by conventional drugs is not available **[45]**. *H. pylori*-induced gastric inflammation in rats with increased NF-κB activation and macromolecular leakage could be reduced by curcumin application **[46]**. The results obtained from PatchDock data server show that the interactive features of curcumin may have an adversary effect on Ureα/β, VacAp55 and CagA of *H. pylori*. Therefore, docking analysis was accomplished and results were assigned as score, area and atomic contact energy (ACE). In all cases score of docking results showed extensive interactions of curcumin with the residues of virulent proteins. Moreover, the conservative residue of virulent (Ureα/β, VacAp55, and CagA) protein indicates strong binding sites. The molecules interaction with conservative residues of protein disrupts the structural integrity of protein, so that it could not maintain the global scaffold. Kumar *et al*. (2011) suggested that the involvement of conservative residues in interactions of molecules with receptors play important role in development of therapeutic approaches **[47]**. In the present study, we undertook molecular docking of curcumin against an ensemble of virulent factors: acid neutralising urease (Ureα/β), vacuole forming (VacAp55) and tumor inducing protein (CagA) to discover preferential binding affinity of curcumin as anti-cancerous molecule. Our docking results reveal that the curcumin have potential to interact with residues of each virulent factors.

The crystal structure of urease subunits (Ureα/β) in complexation with curcumin has been determined at 4.0 A^0 by molecular docking. The structure reveals that the overall interactions of urease subunits made complex with curcumin by molecular interactions **(Figure 2a).** The molecular interactions of urease involves residues from both subunits, the residues (MET12 and ALA16) from α-subunit and other residues (PHE441, PRO446, LYS445, and ILE568) from β-subunit for stable binding with curcumin atoms. The structural contacting of urease contributes conserved residues (ALA16) from α-subunit and residues (PHE441, LYS445, PRO446, and ILE568) of β-subunits in complexation with curcumin molecule. The residues (MET12 and ALA16) from helix and other residues (LYS445 and ILE568) from β-turn make hydrophobic interactions with curcumin. Curcumin had extensive interaction with residue PHE441 of β-turn through hydrogen bonds. The atom H20 of curcumin interacted with PHE441 atoms (CE2, CD2, and CZ), whereas the atoms H18 and C21 of curcumin involved in interactions with atoms (CD2 and CE2) of PHE441. Whereas, atom H19 of curcumin interacted with single atom (CE2) of PHE441. The CG2 of ILE568 made atomic interaction with H19 and C16 of curcumin through hydrogen bond. The atom O of PRO446 involved to be stable binding with H14 of curcumin through hydrogen bond. Curcumin made effective interaction with both subunits α/β of urease and indicated the disruption of global scaffold of structural urease for inactivation of biological activities. Though, it has been reported that the curcumin has highly anti-urease activities in case of *H. pylori* infection **[48]**. **Figure 2b** displayed the stable complexation of curcumin with VacAp55 protein. The interactions were made by contacting residues from helix ASN810 and β-turn (GLU724, ASN666, and SER714) with curcumin atoms. The atom (OE2) of conservative residue GLU724 made stable interaction with H20 of curcumin through hydrogen bond. The atom CA (ASN810) made stable binding with atom O5 of curcumin by hydrogen bond, whereas ASN666 involved in hydrophobic interactions with curcumin. Curcumin atom O4 interacted with CB and CG of SER714 through hydrogen bond, though CB of SER714 made H-bond interaction with atom H14 of curcumin. These effective interactions indicated that the curcumin could stop oligomerization of p55 domain of VacA that is essential for the cytotoxic activities at time of vacuole formation. Torres *et al.* (2004) have reported that p-33/p-55 interactions are essential for VacA assembly into oligomeric structures that leads to vacuolating cytotoxic activity in epithelium tissues **[49]**.

The high levels of MMP-3 and -9 in gastric tissues of mice or cultured cells due to infection by Hp strains (either cag+ve or cag-ve) are reduced by curcumin treatment. This curcumin mediated downregulation of MMP-3 and -9 levels in Hp-infected mice and cultured cells exhibited its immense therapeutic potential against Hp associated gastrointestinal diseases **[50]**. Earlier, Mahady et al. (2002) have reported that the curcumin exerts its chemopreventive effects against CagA+

H. pylori **[51]**. Curcumin made stable binding with CagA protein as shown in **Figure 2c.** The main interactive residues (LYS640, SER641 and LYS644) with no secondary structure and ALA653 from helix were involved in contacting with curcumin atoms. The residues LYS640 and conservative residues LYS644 made hydrophobic interactions with curcumin molecule. The atoms C of LYS640 and O of SER641 made extensive intramolecular interactions with curcumin structure through hydrogen bond, then complex of both LYS640 and SER644 interacted with curcumin atom (O5) through hydrogen bonds. These interaction of CagA with curcumin indicated that the secondary structure of CagA for oncogenic activities could be disturbed by molecular interactions of curcumin.

Binding scores analysis of complexes

Table 3 (see supplementary material) represented the solutions of each complexes after molecular docking of curcumin with Ureα/β, VacAp55, and CagA virulent proteins of *H. pylori* and assigned as geometric score, interface area size, and desolvation energy. The highest geometric score (5382) in curcumin interaction with urease subunits was conferred better interaction and complexation, that was supported by interface area size (683.10) and desolvation energy ACE (-111.67). The lowest geometrical score (4974) along with interface area size (633.90) and desolvation energy ACE (-83.09) appeared in complexation of VacAp55 with curcumin. Whereas, in contacting of curcumin with CagA oncoprotein, there were geometrical score (5060), interface area size (581.20), and desolvation energy ACE (-114.13).

Conclusions:

Our study concluded that the curcumin has high potential to perturb the global scaffolds of structural virulent proteins (urease subunits, VacAp55, and CagA) of *H. pylori*. Though, the highest geometrical score of curcumin-urease complex showed the most extensive interactive potential of curcumin with urease, indicated the inhibitory potential by inhibiting of colonisation and survival of *H. pylori* in stomach for diseases development. These structural interactions of curcumin with urease indicated that further activities of *H. pylori* could be perturbed such as no secretion of other virulent factors like VacA and CagA prompting for diseases development. A major drawback of this study was to associate with built structures of ligands and receptor, that may have not be reliable. However, it is suggested that the curcumin could play major inhibitory role against pathogenic activities of *H. pylori* by interacting with either of virulent factors

Acknowledgment:

The authors are grateful to the Department of Botany, Banaras Hindu University, India for providing computational facilities. This study is financially supported by University Grant Commission project A/C-01 for Junior and Senior Research Fellowship.

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Edited by P Kangueane
Citation: **Srivastava *et al.*** Bioinformation 11(10): 447-453 (2015)

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Supplementary material:

Table 1: *In silico* determination of physicochemical pharmacokinetics for curcumin by using online server Molinspiration

Details	**Curcumin**
Octanol-water coefficient partition	2.303
Polar surface area	93.066
Number of nonhydrogen atoms	27
Molecular weight	368.385
Number of hydrogen-bond acceptors (O and N atoms)	6
Number of hydrogen-bond donor (OH and NH atoms)	2
Number of Rule of 5 violations	0
Number of rotatable bonds	8
Molecular volume	332.182

Table 2: Estimation of Druglikeness scores of curcumin by using online server Molinspiratio

Properties	GPCR	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Curcumin	-0.06	-0.2	-0.26	0.12	-0.14	0.08

Table 3: Binding score of curcumin complexation with virulent factors of *Helicobacter pylori* 26695

Receptors	Score	Area	ACE
Urease	5382	683.10	-111.67
VacA p55	4974	633.90	-83.09
CagA	5060	581.20	-114.13