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Impact of the Anti-Inflammatory Medication Tramadol Hydrochloride on *Staphylococcus aureus* Multidrug Export Protein, MepA, using *In Silico* Chemical Repurposing Methods

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Abstract: *Staphylococcus aureus* (*S. aureus*), is a common human pathogenic bacteria that can cause a number of infectious disorders. Infectious diseases are the second leading cause of mortality for people globally. MepA belongs to the MepRAB cluster and is an efflux protein that is controlled by MepR. It has been previously proved that MepA acts as a potential multidrug resistant gene in *Staphylococcus aureus*. This study involves the use of chemical repurposing techniques, where the non-steroidal anti-inflammatory drug, Tramadol hydrochloride, is introduced into MepA protein in order to find out the efficiency of inhibition of the drug. Our results clearly shows that the drug has interacted with the various transmembrane regions present in MepA protein. Our docking scores along with H-bond interactions have proved that the bacterial protein has been down-regulated by Tramadol hydrochloride. In conclusion, the 3D molecular interactions between MepA and Tramadol hydrochloride has revealed that the anti-inflammatory drug also shows the presence of anti-bacterial activity against the multidrug resistant protein, MepA of *Staphylococcus aureus*.

Keywords: MepA, *Staphylococcus aureus*, Tramadol hydrochloride, Drug docking

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Introduction

One of the key mechanisms of bacterial resistance is considered to be the efflux of antimicrobial drugs and biocides (Li *et al.*, 2009). A multidrug resistance (MDR) phenotype is the consequence of the problem being worsened by the ability of certain efflux proteins to transport several substrates with well-defined structural characteristics. Due to their secondary structure and the energy source they make use of, to move substrates, MDR-conferring efflux proteins based on membrane are identified in all bacteria and are a member of one of five protein families (Borges-Walmsley *et al.*, 2003). These families consist of the significant facilitator superfamily (MFS), ATP-binding cassette (ABC), resistance-nodulation-division (RND), multidrug and toxin extrusion (MATE) and small multidrug resistance (SMR) proteins. All proteins make use of ion gradients, excluding ABC proteins, the functions of which are enabled by ATP cleavage. While the Na^+ gradient may be used by MATE family proteins, the H^+ gradient is frequently utilized (Morita *et al.*, 2000). Only one MATE transporter (MepA) is encoded in the genome of *Staphylococcus aureus* N315; these are the fewest and least comprehended of the MDR efflux proteins.

The MepR, a repressor of the MarR family that is encoded immediately upstream of mepA, regulates the expression of MepA (Kaatz *et al.*, 2000). Structural and functional research works on MepR have demonstrated that it is responsive to substrate and binds to the promoter regions of both MepR and MepA. The characteristics of MepR differ to a great extent based on the manner in which it interacts with each of the operator site. MepR binds to the MepR operator as a single dimer, but to the MepA operator as a dimer of dimers. A second dimer is recruited, possibly cooperatively, after the first dimer binds to a main, high-affinity location (Kumaraswami *et al.*, 2005).

In the absence of substrates, the expression of mepAis successfully terminated. Nonetheless, the presence of MepA greatly reduced the affinity of MepR for the MepA operator site as opposed to a considerably more diminished effect at the MepR operator (Kaatz *et al*., 2006).

Drug repurposing, also known as repositioning, redirection, or reprofiling, is increasingly becoming a desirable and financially feasible method for finding new indications for licensed or investigational medications due to the high risk, significant expense, and sluggish pace of new drug discovery and development. In recent years, there have been notable achievements (Zhan *et al*., 2022). The major purpose of the present investigation is to find out the efficiency of the Non-steroidal Anti-inflammatory drug (NSAID), Tramadol hydrochloride against the multidrug resistant bacterial protein, MepA of *Staphylococcus aureus* using advanced *in silico* protocols.

Materials and Methods

Drug Repurposing Technique:

Tramadol hydrochloride with anti-inflammatory properties was focused for molecular docking studies. The 2D and 3D structures of the anti-inflammatory drug was selected from PubChem (Kim *et al*., 2016)(https://pubchem.ncbi.nlm.nih.gov/) in order to carry out molecular docking studies. Using UnitProt database (https://www.uniprot.org/uniprotkb/P03372/entry#sequences), the protein sequence of MepA was retrieved. The MepA protein was modelled into 3D structure using SwissModelserver (Waterhouse *et al*., 2018) (https://swissmodel.expasy.org/).

3D Drug Docking:

One of the most popular *in silico* drug discovery techniques is molecular docking, which looks at the ideal conformations of tiny molecules when they come into contact with MepA. Docking tests were performed on MepA, Tramadol hydrochloride, and the antibiotic.

To anticipate the 3D interaction between the receptor and ligand molecules, the 3D docked file format of the ligand and the receptor sequence (MepA) was uploaded to CB Dock server (Yang Liu

et al., 2022) (http://hdock.phys.hust.edu.cn/). Information regarding H-bond interaction was also provided by CB Dock study.

3D Drug –Receptor interactions:

A molecular visualization tool named Discovery Studio Software was used to show the 3D structure following molecular drug docking studies of Tramadol hydrochloride with MepA.

Results

The major reason for choosing the MDR protein is that it plays a major role in microbial research. The MATE family multidrug efflux pump (MepA), a protein of unknown function (MepB), and a MarR family repressor (MepR; known to suppress MepA production) are all encoded by the MepRAB gene cluster of *Staphylococcus aureus*. Previous studies have demonstrated that MepR is autoregulatory as well, suppressing the expression of its own gene. Variably elevated expression of MepA was the major effect of exposing strains with a MepR::lacZ fusion with MepR supplied in trans under the control of an inducible promoter, or a MepA::lacZ fusion alone, to subinhibitory doses of MepA substrates. MepR binds upstream of MepR and MepA, with a seemingly stronger affinity for the mepA binding site, according to mobility shift experiments. Differentially, MepA substrates prevented MepR from binding to each site; the MepR-MepA operator interaction was most affected (Kaatz *et al.*, 2006, Schindler *et al.*, 2015).

The amino acid sequence of MepA protein (*Staphylococcus aureus*) was retrieved from UniProt database (Table 1). The total length of amino acid sequence is 450aa. Its molecular weight was 48758.96. Its theoretical pI was 6.96. The amino acid composition was as follows: Ala (A) 42 9.3% Arg (R) 8 1.8% Asn (N) 15 3.3% Asp (D) 11 2.4% Cys (C) 3 0.7% Gln (Q) 8 1.8% Glu (E) 13 2.9% Gly (G) 40 8.9% His (H) 5 1.1% Ile (I) 56 12.4% Leu (L) 63 14.0% Lys (K) 16 3.6% Met (M) 27 6.0% Phe (F) 36 8.0% Pro (P) 12 2.7% Ser (S) 29 6.4% Thr (T) 19 4.2% Trp (W) 1 0.2% Tyr (Y) 13 2.9% Val (V) 33 7.3% Pyl (O) 0 0.0% Sec (U) 0 0.0% (B) 0 0.0% (Z) 0 0.0% (X) 0 0.0%. The highest amino acid component is Leucine.

3D visualization was done using Discovery Studio Software. The red coloured structures represent Alpha Helix, green coloured structures represent Turns and white coloured regions represent Random Coils (Fig. 1). The method of determining a protein's three-dimensional structure from its amino acid sequence, known as protein structure prediction, has important uses in a number of industries, including biotechnology, bioinformatics, and medicine. These uses include understanding protein function and disease causes, as well as designing and developing new drugs. Our predicted model only shows alpha helix (red), turns (green) and random coiled regions (white). There is no beta sheet present in the model.

3D visualization of MepA protein of *Staphylococcus aureus* was done using Discovery Studio Software. The yellow coloured spacefill model structures represent the hydrophobic regions present in the modelled protein (Fig. 2). Protein folding, stability, and function depend heavily on hydrophobic areas. While polar and charged amino acid residues often live on the protein's surface and interact with water, they mainly help the protein's three-dimensional structure by pushing non-polar amino acid residues to group together and form a hydrophobic core. This hydrophobic impact stabilizes the protein's original shape and is a key factor in protein folding. Our research works infers that there are more hydrophobic regions when compared to hydrophilic regions.

3D visualization of MepA protein of *Staphylococcus aureus* was done using Discovery Studio Software. The yellow coloured spacefill model structures represent the hydrophilic regions in the modelled protein (Fig. 3). In many applications, hydrophilic regions-- which draw in water and other polar molecules-- are essential. They are used in medication delivery for higher oral bioavailability and drug solubility, in coatings for greater spreading and adherence, and in

Table 1: Amino acid sequence of MepA protein (*Staphylococcus aureus*) retrieved from UniProt database

MKDEQLYYFEKSPVFKAMMHFSLPMMIGTLLSVIYGILNIYFIGFLEDSHMISAISLTLPVFAILMGLGNLFGVGAGTYISRLLGA
KDYSKSKFVSSFSIYGGIALGLIVILVTLPFSDQIAAILGARGETLALTSNYLKVMFLSAPFVILFFILEQFARAIGAPMISMIGMLAS
VGLNIILDPILIFGFDLNVVGAALGTAISNVAAALFFIIYFMKNSDVVSVNIKLAKPNKEMLSEIFKIGIPAFLMSILMGFTGLVLNL
FLAHYGNFAIASYGISFRLVQFPELIIMGLCEGVVPLIAYNFMANKGRMKDVIKAVIMSIGVIFVVCMIAVFTIGHHMVGLFTTD
QAIVEMATFILKVTMASLLLNGIGFLFTGMLQATGQGRGATIMAILQGAIIIPVLFIMNALFGLTGVIWSLLIAESLCALAAMLIV
YLLRDRLTVDTSELIEG

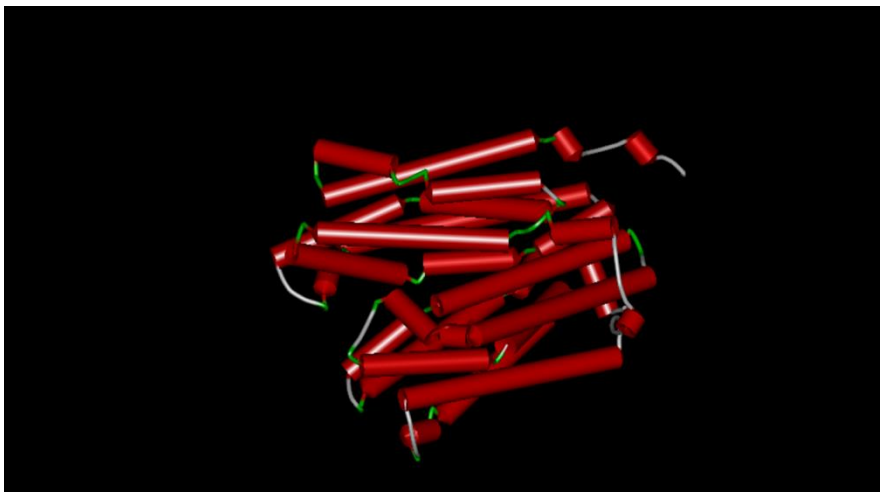

Fig. 1: 3D structure of MepA protein of *Staphylococcus aureus*.

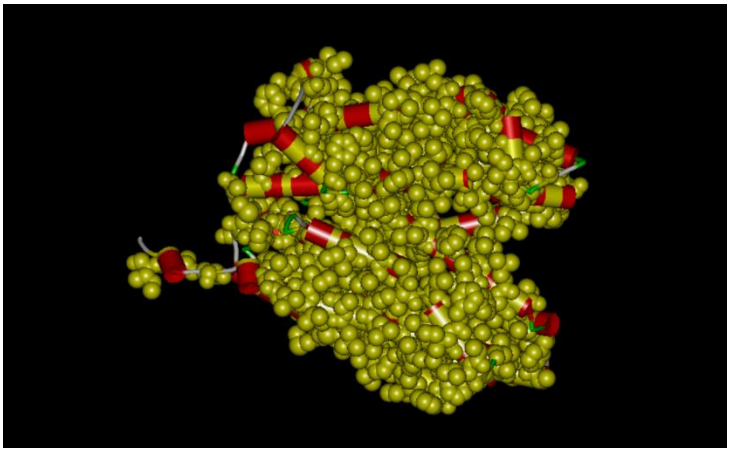

Fig. 2: 3D structure of MepA protein of *Staphylococcus aureus*.

biomedical applications for improved lubricity and anti-fouling qualities. Our research works infers that there are fewer hydrophilic regions when compared to hydrophobic regions.

3D visualization of Tramadol hydrochloride was done using Discovery Studio Software. The red coloured structures represent Oxygen, blue coloured structures represent Nitrogen, grey coloured structures represent Carbon, green coloured structure represents Chlorine and white coloured structures represent Hydrogen (Fig. 4). Severe pain can be temporarily relieved with Tramadol. It should only be used when non-opioid painkillers have failed to control pain or are not

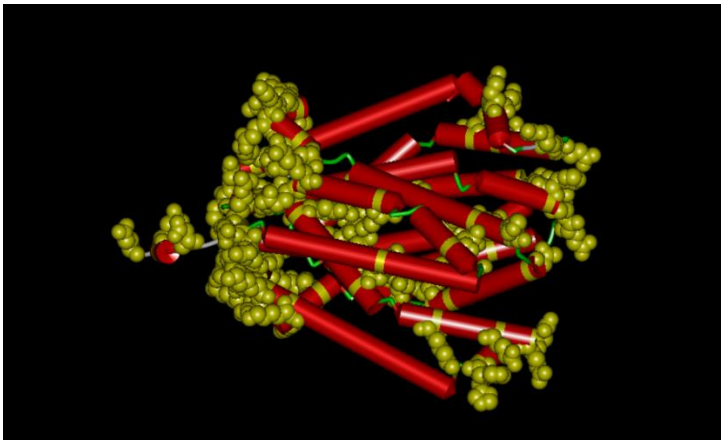

Fig. 3: 3D structure of MepA protein of *Staphylococcus aureus*.

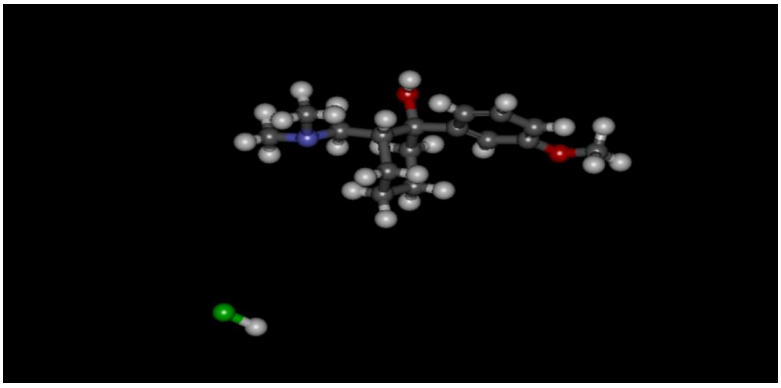

Fig. 4: 3D structure of Tramadol hydrochloride.

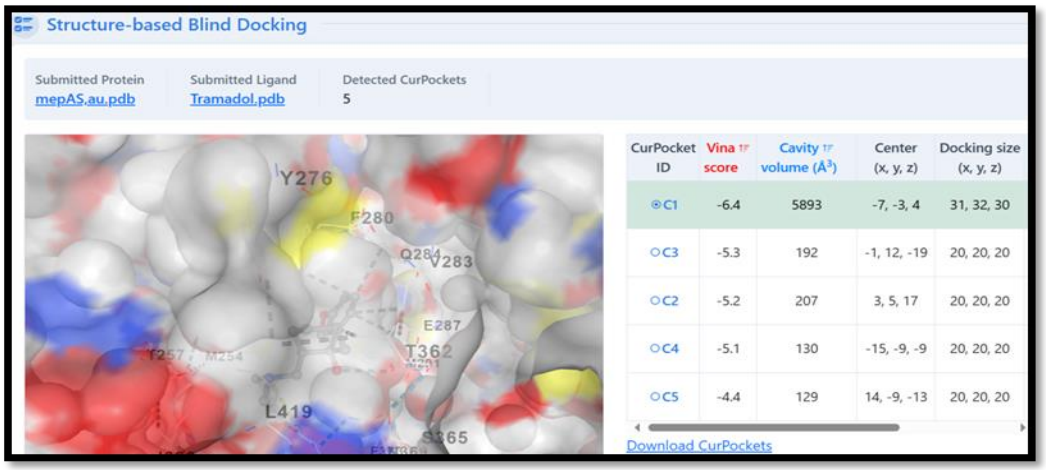

Fig. 5: CB Dock server showing the binding score between MepA protein of *Staphylococcus aureus* and Tramadol hydrochloride.

well tolerated. It is generally not advised to use Tramadol to treat chronic (long-term) pain.

The highest negative score of -6.4 kcal/mol indicates a good binding efficiency between MepA and the drug (Fig. 5). In drug development, drug binding scores-- which are determined by molecular docking and scoring are essential for locating prospective drug candidates. They aid in- (i) determining the best ligand binding positions inside a protein's binding site; (ii) Sorting ligands

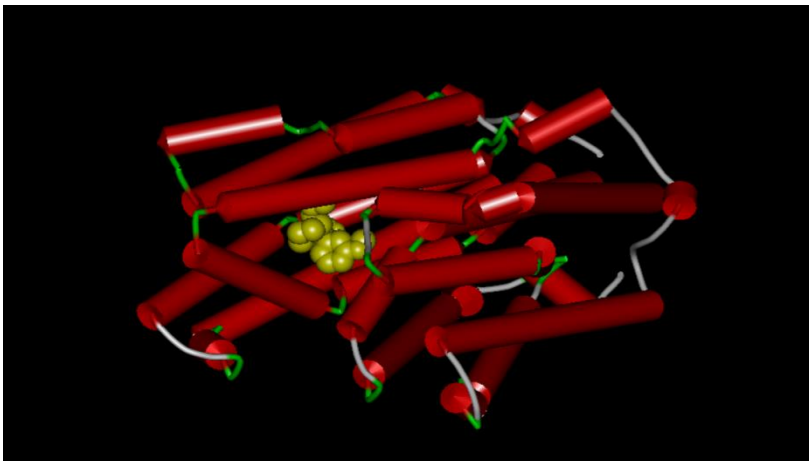

Fig. 6: 3D complex structure of MepA with Tramadol hydrochloride.

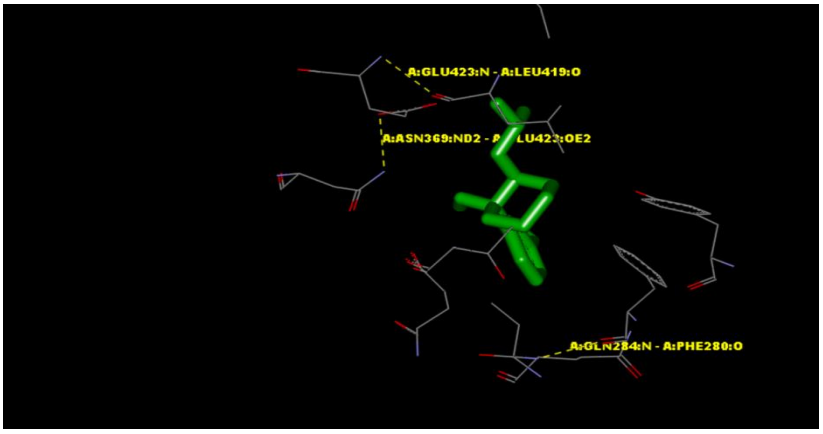

Fig. 7: 3D H-bond interaction between MepA and Tramdol Hydrochloride with respective amino acid interacting at H-bonds, with position number.

according to their expected binding affinities; and (iii) differentiating between compounds that are active and those that are not. Here, we use AutoDockVina for drug binding score prediction between Tramadol hydrochloride and MepA of *Staphylococcus aureus*.

3D complex structure of MepA with Tramadol hydrochloride was done. Yellow coloured structure represents Tramadol hydrochloride in spacefill model view (Fig. 6). All biological processes in living things are based on molecular recognition, which is the process by which biological macromolecules connect with one another or with different small molecules with a high specificity and affinity to produce a particular complex. Proteins, a significant class of biological macromolecules, bind to other molecules or to themselves to carry out their tasks. Therefore, a thorough comprehension of protein–ligand interactions is essential to comprehending biology at the molecular level. Furthermore, understanding the processes behind protein-ligand recognition and binding can help with medication development, design, and discovery. In our study, we have used Discovery Studio Software in order to view the complex form of MepA and Tramadol hydrochloride.

Protein-ligand binding is widely thought to be facilitated by H-bonds. However, there is frequently no net increase in binding affinity when H-bond donors or acceptors are added to create stronger protein-ligand interactions (Fig. 7). By

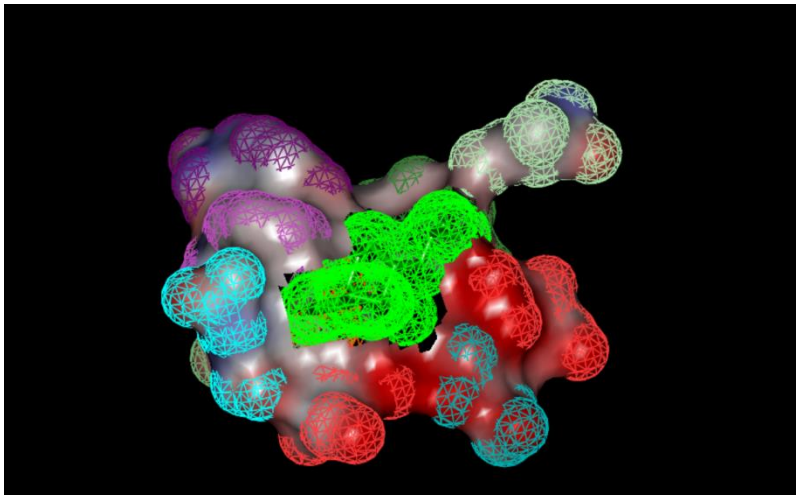

Fig. 8: 3D Electrostatic interaction between MepA and Tramdol hydrochloride.

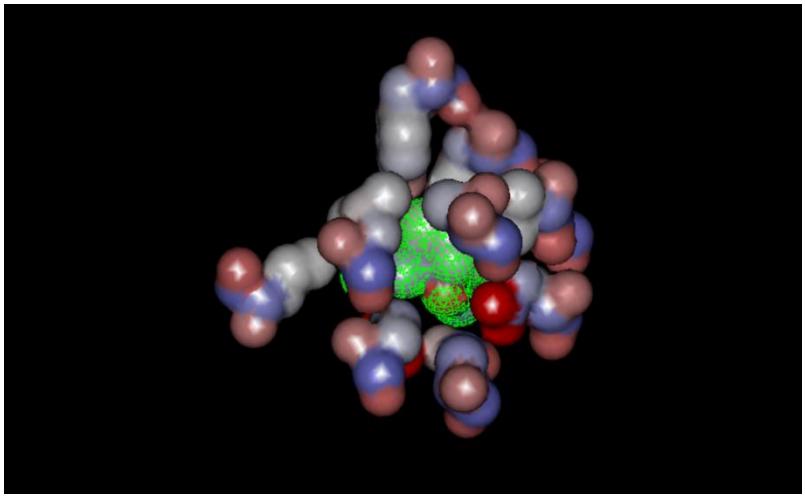

Fig. 9: 3D Van der Waals interaction between MepA and Tramadol Hydrochloride.

pushing protein-bound water molecules into the bulk solvent, H-bonds have also been shown to increase ligand binding affinity rather than specifically target protein-ligand interactions. In our study, the amino acids present at the H-bond regions between MepA and Tramadol hydrochloride is shown using Discovery studio software in 3D view.

Green coloured structure indicates Tramadol hydrochloride which binds with MepA with electrostatic force (Fig. 8). Drug design heavily relies on the computational investigation of protein-ligand interactions. We can gain an idea of a small organic molecule's potential as a ligand to the binding site of a protein target by measuring its ligand binding energy. We may claim that all docking systems, including AutoDock4, AutoDockVina, and Molegro Virtual Docker, use scoring algorithms that simulate the binding affinity by adding up all of the different kinds of protein-ligand interactions. Electrostatic interactions between the ligand and the protein are taken into account by the majority of scoring systems.Our study clearly revealed that electrostatic interactions occur between Tramadol hydrochloride and the functional domains of the MepA protein.

Figure 9 illustrates 3D Van der Waals interaction between MepA and Tramadol hydrochloride. Green coloured structure indicates

Table 2: Binding score obtained from the docking of Tramadol hydrochrloride with MepA of *Staphylococcus aureus* using CB-Dock server

Name of the bacteria	Tramadol hydrochloride
MepA (*Staphylococcus aureus*)	-128.61 kcal/mol

Tramadol hydrochloride which binds with MepA with Van der Waals force. When two atoms are so close to one another that their outer electron clouds barely touch, van der Waals interactions take place. A nonspecific, nondirectional attraction is produced as a result of the charge variations this action causes. With a decrease proportional to the sixth power of the separation, these interactions are highly distance dependent. In this study, we have clearly explained the *Van der Waals* interaction between Tramadol hydrochloride and MepA using Discovery Studio software.

Table 2 illustrates Binding score obtained from the docking of Tramadol hydrochrloride with MepA of *Staphylococcus aureus* using CB-Dock server.

Discussion

The length of the amino acids of MepA is 451 aa (Table 1). It was discovered that strains of *Staphylococcus aureus* with elevated resistance to several antibiotic compounds overexpress MepA, a member of the MATE family (Huet *et al.*, 2008). It has been demonstrated that MepA overexpression in *Staphylococcus aureus*results in MDR (Kaatz *et al.*, 2005). Like the other MATE transporters, MepA exports a wide range of molecules with different structures but similar properties. MepA substrates are usually aromatic, hydrophobic, and have a delocalized positive charge. The 3D structure of MepA was modelled using Swiss Model Server in order to perform drug docking studies (Fig. 1). Assuming that proteins with similar sequences and known structures are evolutionarily related, homology modeling techniques are used to match the target to a group of these proteins (Martí-Renom *et al.*, 2000; Johnston and Denis, 2005).

According to Adam *et al.* (2008), these techniques usually need to predict the three-dimensional form of a query protein with greater than 30% consistency with the known protein sequence or sequences. Figure 2 shows that the hydrophobic regions and Figure 3 shows the hydrophilic regions. The 3D structure of the above-mentioned protein functional domains were predicted in order to identify how the selected drug inhibits the corresponding regions.

Tramadol hydrochloride was chosen from NCBI PubChem compound database. When (R,R)-tramadol hydrochloride reacts with one molar equivalent of hydrogen chloride, it forms (R,R)-tramadol hydrochloride, the (R,R)-enantiomer of the racemic opioid analgesic, which has ten times the analgesic power of the (S,S)-enantiomer. Adrenergic uptake inhibitor, antitussive, capsaicin receptor antagonist, muscarinic antagonist, nicotinic antagonist, NMDA receptor antagonist, opioid analgesic, serotonergic antagonist, mu-opioid receptor agonist, kappa-opioid receptor agonist, mu-opioid receptor agonist, adrenergic uptake inhibitor, and opioid analgesic are some of its functions. There is a (R,R)-tramadol(1+) in it. It is the enantiomer of the hydrochloride of (S,S)-tramadol (Fig. 4).

Table 1 represents the CB-Dock binding scores. Higher negative value indicates greater binding affinity between MepA and Tramadol hydrochloride. CB Dock server was used in order to perform docking in an accurate manner (Fig. 5). A common technique for predicting binding processes and ligand affinities is protein–ligand docking. Computer-aided drug discovery (CADD) can be effectively accomplished through the use of protein-ligand docking. Many research and

commercial technologies currently enable protein–ligand docking (Meiler *et al.*, 2006; Marialke *et al*., 2008; Morris *et al.*, 2009; Yuriev *et al.*, 2013; Pagadala *et al.*, 2017).In order to find the most energy-efficient binding mode, most docking technologies require knowledge of the ligand binding region, including the rotation and translation of a ligand in this region.

Various researchers have also proved the efficiency of CB Dock server in quality docking of proteins and ligands (Liu *et al.*, 2017, Zashumo *et al.*, 2023, Grace *et al.*, 2024). Figures 6-9 show the various types of binding interactions between MepA and Tramadol hydrochloride. Molecular dynamic studies have clearly revealed that the Transmembrane regions directly interact with the following domain regions: GLN:284, PHE:280, ASN:369, GLU:423, LEU:419.

Conclusion

The entire *in silico* study clearly shows that based on chemical repurposing techniques, the drug, Tramadol hydrochloride directly binds with the potential multidrug resistant protein of *Staphylococcus aureus*, MepA at the functional Transmembrane Domain regions. It was proved that the Non-Steroidal Anti-Inflammatory Drug (NSAID), Tramadol hydrochloride has anti-bacterial activity exclusively against the MepA of *Staphylococcus aureus.* This drug is efficient in downregulating the bacterial protein. Hence, we finally conclude that the existing anti-inflammatory drug can also be used against anti-bacterial infections associated with *Staphylococcus aureus* in humans.

Ethical Statement

In this context, an ethical statement does not apply, as no formal ethical requirements or guidelines are imposed or expected.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. They collaborated in designing the research, conducting thorough analysis, drafting the manuscript, and refining its content. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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