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Research Article

A Molecular Docking Approach For The Identification Of Catechol Potentiality Inhibition Against Staphylococcus Aureus Enterotoxin

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ABSTRACT

Staphylococcus aureus enterotoxin (SE) is one of the potent toxins that is responsible for causing food poisoning, toxic shock syndrome (TSS), and affects the central nervous system. Antibiotics are predominantly used to curb the infections. However, in the recent times, antibiotic resistance has development as one of the major problems in treating infections. In this context, we thought that naturally occurring compounds can be efficacious. Thus, we intended to analyse catechol against SE, with gentamicin as control, using in silico tools. The docking studies revealed a binding energy of -86.84 kcal/mol and -37.14 kcal/mol for catechol and gentamicin, respectively. Besides, the hydrogen bonding was found to be shorter which elucidates the bonding is much stronger than expected. In concurrence with the previous studies using *Harpullia arborea* (Blanco) Radlk, bark extract, we elucidated the antimicrobial effect against *S. aureus*. The present study appraises our previous studies of *Harpullia arborea* (Blanco) Radlk, which is used in traditional medicine for curing digestive issues. Further studies will be conducted to deep dive and understand the interaction of catechol with SEs and to develop catechol as a potent inhibitor against SEs.

Keywords: *Staphylococcus aureus*, Enterotoxin, Catechol, In silico analysis, docking, binding capacity.

INTRODUCTION

Staphylococcus aureus is a common gram-positive opportunistic pathogen that can be attributed to several human infections. *S. aureus* evades the opsonophagocytosis mechanism attaching the host cell (1). Upon attachment, *S. aureus* secretes toxins that can easily penetrate the blood stream disrupting the cellular lipid bilayer, infecting the host organ system, especially, cardiac and bone tissues (2). Besides, enterotoxins also damage the leucocytes, sebaceous glands and propagate the infection, paralysing the smooth muscles causing extensive tissue lesions and toxic effects on the

central nervous system. Additionally, *S. aureus* can also cause wide range of infections including toxic shock syndrome (TSS) and food poisoning [1, 3].

The *S. aureus* enterotoxins are a part of toxin superfamily that comprises of 23 types of *Staphylococcus* enterotoxins (SEs) and *Staphylococcus* enterotoxins-like toxins (SEls). The SEs are superantigenic toxins share a common structural and biochemical properties, sequence homology, function and phylogenetic relationship with the SEls [3-5]. The SEs constitutes amino acids tyrosine, aspartic acid and glutamic acid. Besides, presence of Staphylococcus antigen core and cysteine loops enables the elicitation of emetic activity [1]. This antigen core bypasses the common antigen recognition mechanism leading to enormous release of proinflammatory cytokines and chemokines. Further, SEs is thermostable; resist proteolytic enzymes in the digestive tract and the intestinal flora, affecting the humans. The SE and SEls are unique, distinctly adaptive, virulent and redundant enough to cause a wide range of infections [1, 6]. However, how these toxins exhibit an emetic response in both humans and animals, and which receptor does it bind to elicit an antigenic response is yet to be understood completely.

Harpullia arborea (Blanco) Radlk., known as tulip-wood tree, commonly used in Kerala as a leech repellent, for curing digestive problems in Tamil Nadu, etc [7]. In the previous study, we investigated the anti-cancer activity of *Harpullia arborea* (Blanco) Radlk. bark extract. Further, the presence of several phytoactive constituents were analysed using GC-MS. There were around 20 compounds identified; of which catechol was identified as the major phytoactive constituent (Unpublished Data). Catechol, a benzenediol compound consists of benzene core, also called as pyrocatechol is a naturally-occurring metabolite in vegetables and fruits. It is widely reported to be compound eliciting antimicrobial, anticancer effects, etc. In this present study, we intended to understand analyse the interaction between catechol and enterotoxin from *Staphylococcus aureus* using *in silico* approach.

MATERIALS AND METHODS

SE gene (GenBank Code: *OZY71337.1*) was converted into amino acid sequence using CPH 3.0 model serve and confirmed using Discovery Studio 3.5. Structure of Catechol (CID: 289) 2D *de novo* structure from PubChem was converted to 3D structure using Online Smiles Translator (https://cactus.nci.nih.gov/index.html). The molecular docking was performed using PatchDock server. The binding affinities and ligand protein interaction of Catechol was studied in comparison with the control compound, gentamicin. Besides, calculated partition coefficient (clogP), drug likeness and polar surface area (PSA) and total surface area (TSA), topological polar surface area (TPSA), etc., was determined using Osiris Datawarrior 5.5.0.

RESULTS AND DISCUSSION

In the current study, binding activity of one of the major active phytoconstituent catechol identified in *Harpullia arborea* (Blanco) *Radlk*. bark was determined involving molecular docking studies. The results were compared with the control antibiotic, gentamicin. Figure 1A & 1B provides the surface topology of the *Staphylococcus* enterotoxin, while the Figure 1C & 1D provides the 2D & 3D structures of catechol, respectively. A comparison of the ligand molecules was also carried out using Osiris Datawarrior 5.5.0 (Table No 1).

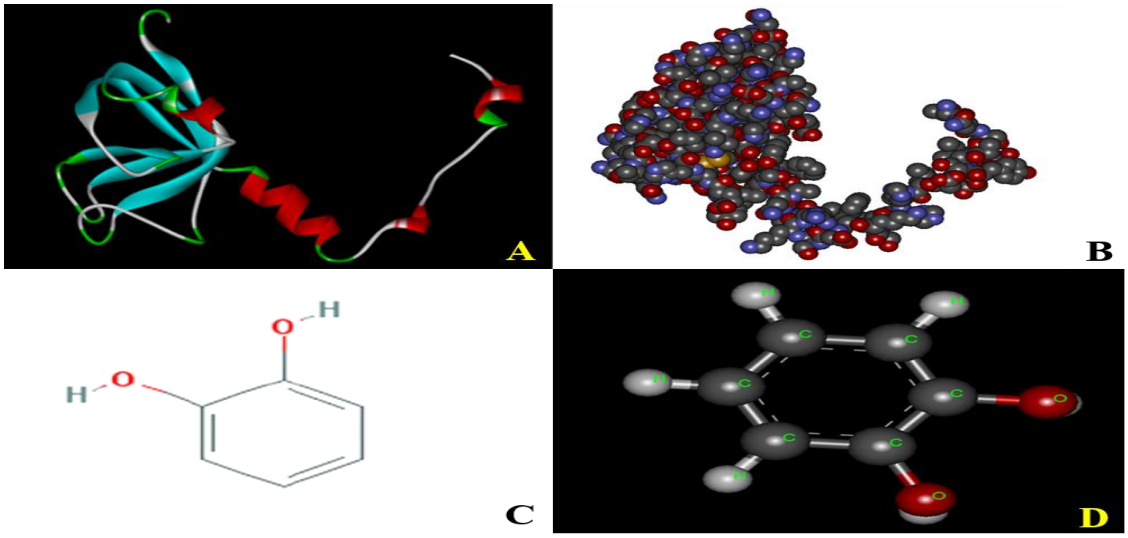

Figure No 1A & B - 2D and 3D Staphylococcus enterotoxin; C & D - 2D and 3D structure of catechol (Discovery studio software – Ball and Stick model).

Upon analysing the 3D structure of catechol, it was deduced that SE has 4-α-helices and 11-β-sheets. The binding of SE and catechol revealed that there are 70 conserved binding regions in the SE with amino acids, including, TYR64, TRP63, TYR94, GLY93, GLU34, ASN33, MET96, SER206, ILE29, GLN28, ASN25, TYR205, LEU23, AL100, HIS54 and SER102 (Figure 2B). Wherein, hydrogen (H) bonds formation was observed between catechol and Nitrogen of VAL98 and Oxygen of MET96 in SE (Figure 2C). Likewise, docking of gentamicin with SE, exposed the conserved binding sites with amino acids LEU87, LYS98, ARG85, ASP84, LYS111, PHE93, ASN8, MET96, GLU49, TYR50, SER51, GLN144, PRO74, ILE72 (Figure 2D). Hydrogen bond formed between gentamicin and the active sites of amino acids at nitrogen of PHE97 and oxygen of VAL98 (Figure 2E). The binding energy of catechol with SE was found to be -86.84 kcal/mol and that of gentamicin was about -37.14 kcal/mol (Table 1). Thus, the binding energy of catechol when compared with gentamicin was found to be better. This clearly demonstrated that catechol may be a potential inhibitor of *Staphylococcus aureus* enterotoxin.

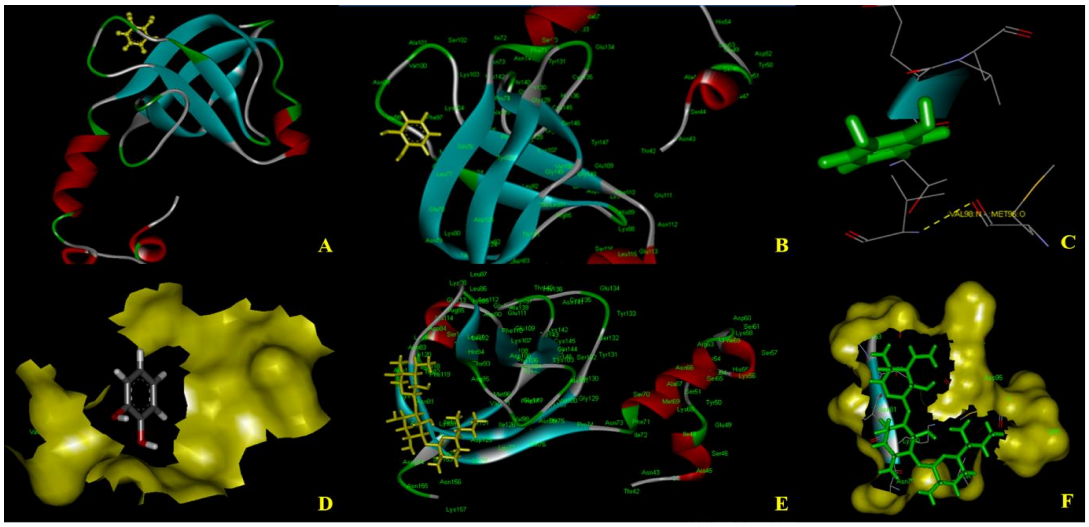

Figure No 2A – 3D image of SE with catechol; B - Interaction of SE receptor with catechol; C – Binding of catechol to SE active zone; D - 3D image of SE with gentamicin; E - Interaction of SE receptor with gentamicin; F - Binding of gentamicin to SE active zone.

Table No 1

Molecular drug docking (Patch dock server-high binding values)

Molecule Name	**Catechol**	**Gentamicin**
Molecular Weight	110.1	477.6
No. of Atoms	8	33
SlogP	1.1	-2.2
TPSA	40.5	199.7
Flexibility	1	15.9
No. of Rotatable bonds	2	13
cLogS	-1.024	-1.181
H-Acceptors	2	12
H-Donors	2	8
Total Surface Area	85.96	345.02
Relative PSA	0.30479	0.42905
Polar Surface Area	40.46	199.73
Drug likeness	-2.2721	4.8824
LE from SlogP	1.5363	--
LLE from SlogP	7.9904	--
LELP from SlogP	0.63023	--

Catechol consisting three isomeric benzenediols is a potent anticancer compound predominantly found in plants [8]. Our previous studies on *Harpullia arborea* (Blanco) *Radlk.* Bark extract was revealed that >80% of the bark comprises catechol as one of the phyto active components. Also, catechol is known to exhibit antimicrobial properties [9]. In the present study, catechol was compared with the aminoglycoside antibiotic, gentamicin for its binding capacity with SE. Generally, interaction and hydrogen bond formation of the protein with catechol and gentamicin occurs at PHE30, LYS32 and HIS165. However, in the present study, the interaction and hydrogen bonds formed with VAL, MET and PHE. Besides, the lengths of the hydrogen bonds formed are shorter in length [10, 11]. This elucidates that the bonding between the ligand and the receptor is strong. This can be confirmed with the binding scores of catechol and gentamicin with a negative binding energy of -86.64Kcal/mol and -37.14 Kcal/mol, respectively. Additionally, the molecule also follows the Lipinski's rule of 5 for new molecular entity (NME) [12]. Previously, studies conducted on catechol embedded hydrogels, catechol-conjugated chitosan, and catechol-functionalised chitosan with hydrocaffeic acid revealed a significant antimicrobial against Methicillin Resistant *Staphylococcus aureus* [13-15]. With patients becoming resistant to carbapenems [16], and there is a constant search for effective and alternative antimicrobial agents that are naturally available.

Harpullia arborea (Blanco) Radlk. Bark extract has been previously studied by us for its antibacterial effect. Also, in traditional medicine, it is known to be used for digestive problems. Besides, our GSMS analysis confirmed that catechol is one of the major phytoactive constituents in *Harpullia arborea* (Blanco) Radlk. bark. Catechol from transformed into several forms has proved to be a potent antimicrobial agent not only against S. aureus, *Pseudomonas putida, Pseudomonas pyocyanea, Corynebacterium xerosis* and fungi such as *Fusarium oxysporum, Penicillium italicum,* with all being pathogenic species [17]. This affirms that catechol can be a potent inhibitor against *Staphylococcus enterotoxin* preventing several disorders in humans.

CONCLUSION

In the current era, infections are often treated with antibiotics. Avid use of antibiotics may result in antibiotic resistance and may result in the mortality of the individual. S. aureus enterotoxin is a toxin known to cause food poisoning and toxic shock. Owing to the current scenario, there is a need for identifying alternative molecule which can be efficiently be used to treat SE infection. In this context, catechol, through in silico analysis has displayed better binding capacity with stronger hydrogen bonds with SEs. This will enable us to use catechol as a potent inhibitor for SE related toxicity. Further study on catechol and SE *in vitro* and *in vivo* against SE will elucidate its efficacy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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