

## ***IN-SILICO* CHARACTERIZATION OF *STAPHYLOCOCCUS AUREUS* VIRULENCE FACTOR TSST-1 ASSOCIATED WITH CARDIAC ARREST**

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### Abstract

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Super-antigen of *Staphylococcus aureus*, Toxic shock syndrome toxin-1 (TSST-1) is associated with cardiac failure. Its virulence should be controlled in sustainable ways. Current study was designed to explore the characteristics of virulence factor TSST-1. For this purpose, its sequence was retrieved from UNIPROT database and subjected to assessment through SOPMA and PROTPARAM tools, SWISS-MODEL server and MEME suite. PROTPARAM tool

analysis demonstrated extinction coefficient ( $24410 \text{ M}^{-1}\text{cm}^{-1}$ ), instability index (34.12) and GRAVY (-0.529) values of TSST-1. Highest number of amino acids (120) made up random coil followed by extended strand (61 amino acids) and alpha helix (53 amino acids). MEME suite analysis revealed conserved domains in TSST-1. i. e., FENREQLDNIHGLMR, DWQISG, KYGPKF, WKISMND, MNFFJL, NTEKPP, RLKKKQH,

GEKVDL, LAISALD and DEIKKFEA with p-value of 4.39e-47. Designing the drugs that could bind the 2D structural components of TSST-1, to cause misfolding of proteins, could be the best route for pathogenicity reduction. Developing the vaccines targeting the conserved motifs might also be a sustainable approach for decreasing the TSST-1 associated virulence.

**Keywords:** Toxic shock syndrome toxin-1, *Staphylococcus aureus*, configuration, Ramachandran, MEME tool

### 1. Introduction

Toxic shock syndrome toxin-1 (TSST-1) is encoded by *tst* gene. This gene is localized in pathogenicity islands of *Staphylococcus*. i. e., SaPI1 and SaPI2. The encoded protein has molecular weight of 21.9kDa (Koosha et al. 2016). Ninety percent menstrual toxic shock syndrome (TSS) causing *Staphylococcus aureus* strains produce this protein. Once in the blood stream, it activates the immune system. It interacts with antigen presenting cells (APCs) and T-cells via MHC-II molecules and V $\beta$  region of TCR, respectively. It results in excessive production of cytokines including IL-1, IFN- $\gamma$  and TNF- $\alpha$  causing toxic shock syndrome (TSS) (Guo et al. 2023; Oliveira et al. 2022). Different symptoms of syndrome include, hypotension, sudden high fever of 38.9°C, skin lesions desquamation on hand palms and feet soles, dysfunctions in organs, nausea, muscle ache, mental confusion and increase in blood flow to eyes, throat and mouth (Touaitia et al. 2025).

In addition to *S. aureus*, several other bacteria that produce this toxin are; *Yersinia pseudotuberculosis*, *Streptococcus pyogenes*, *Mycoplasma arthritidis* and *Pseudomonas fluorescens* (Igwe et al. 2003; Wei et al. 2002). *S. aureus* regulates TSST-1 secretion genetically via proper system which includes accessory gene regulator (*agr*) system, SaeRS two component system, *sarA*, Rot and SigB systems. In additions, the secretion is also controlled by availability of iron and glucose, pH level, oxygen tension, mucosal surfaces, abscesses, chronic infections and biofilms (Chen et al. 2021; Dufresne et al. 2024; Huber et al. 2020; Maduta et al. 2024; Neumann et al. 2020; Sapugahawatte et al. 2020).

TSS could be treated with antibiotics like linezolid and clindamycin, immunoglobulins (IVIG), monoclonal antibodies (mABs), cytokine inhibitors like anti-IL-6 and anti-TNF- $\alpha$ , anti-virulence strategies and vaccine development. But these

techniques did not prove effective due to multidrug resistance (MDR) development, high cost and persistent nature of TSST-1 virulence factor (Cheung et al. 2021; Lacey et al. 2022; Touati et al. 2025; Courçon et al. 2022). So, there is need to explore cost effective approaches for inhibition of this protein.

Core of this protein comprises of beta sheets with alpha helices flanking at ends of molecule (Noli et al. 2022). This structural organization confers persistence to overall molecule even in the presence of high temperature and acidic conditions and proteases. This stability contributes to its long term persistence in clinical environments. Keeping in view, this persistent nature of TSST-1 we initiated current project aiming at exploration of physicochemical characteristics, secondary (2D) and tertiary (3D) configurations and conserved domains of enzyme. These characteristics might help in engineering of this enzyme via genetic manipulations leading to reduction in its persistence.

## 2. Methodology

### 2.1 UNIPROT database

To retrieve the sequence of amino acids of TSST-1 of *S. aureus*, UNIPROT database (<https://www.uniprot.org>, accessed on June 2025) was accessed. The protein sequence comprised of 234 amino acids with 26306 Da molecular weight (Figure 1). The accession number of TSST-1 is P06886.

MNKKLLMNFIVSPLLLATTATDFTPVPLSSNQIIKTAKASTNDNIKDLLDWYSSGSDTFTNSEVLD  
NSLGSMRIKNTDGSISLIIFSPYYSPAFTKGEKVDLNTKRTKKSQHTSEGTYIHFQISGVTNTEKLPT  
PIELPLKVKVHKGDSPLKYGPKFDKKQLAISTLDFEIRHQLTQIHGLYRSSDKTGGYWKITMNDGST  
YQSDLSKKFEYNTEKPPINIDEIKTIEAEIN

*Figure 1: Sequence of toxic shock syndrome toxin-1 (TSST-1) protein retrieved from UNIPROT database, documented in current study*

### 2.2 PROTPARAM Tool

To predict the physical and chemical attributes of virulence factor, ExPaSy PROTPARAM tool (<https://web.expasy.org/protparam/>, accessed on June 2025). Properties analyzed were molecular weight, number of amino acids, chemical formula, number of Aspartate and Glutamate residues, proportion of arginine and lysine residues, theoretical isoelectric point (pI), extinction coefficient, estimated half-life, aliphatic index, instability index and Grand Average of Hydropathicity (GRAVY).

### 2.3 SOPMA Tool

To predict the secondary (2D) configuration of TSST-1, Self-Optimized Prediction Method with Alignment (SOPMA) tool ([https://npsa.lyon.inserm.fr/cgi-bin/npsa\\_automat.pl?page=NPSA/npsa\\_sopma.html](https://npsa.lyon.inserm.fr/cgi-bin/npsa_automat.pl?page=NPSA/npsa_sopma.html), accessed on June 2025) was employed. Aspects of 2D structure computed included alpha helix, extended sheet and random coil. Parameters of tool considered for analysis were output width (70), window width (17) and similarity threshold (8).

### 2.4 SWISS-MODEL Server

For protein modelling, SWISS-MODEL (<https://swissmodel.expasy.org>, accessed on June 2025) was consulted through ExPaSy web server. The server predicted 3D configuration through protein homology modelling in which target amino acid sequence was compared with templates. i. e., protein structures determined experimentally.

### 2.5 MEME Tool

Multiple Em for Motif Elicitation (MEME) tool (<https://meme-suite.org/meme/tools/meme>, accessed on June 2025) was consulted to predict the conserved motifs of TSST-1 virulence factor. Classic motif discovery mode, three motif number and any number of repetitions (anr) for site distribution was selected. Input was provided as type in sequence. This analysis determined the repeating sequence patterns of protein.

## 3. Results

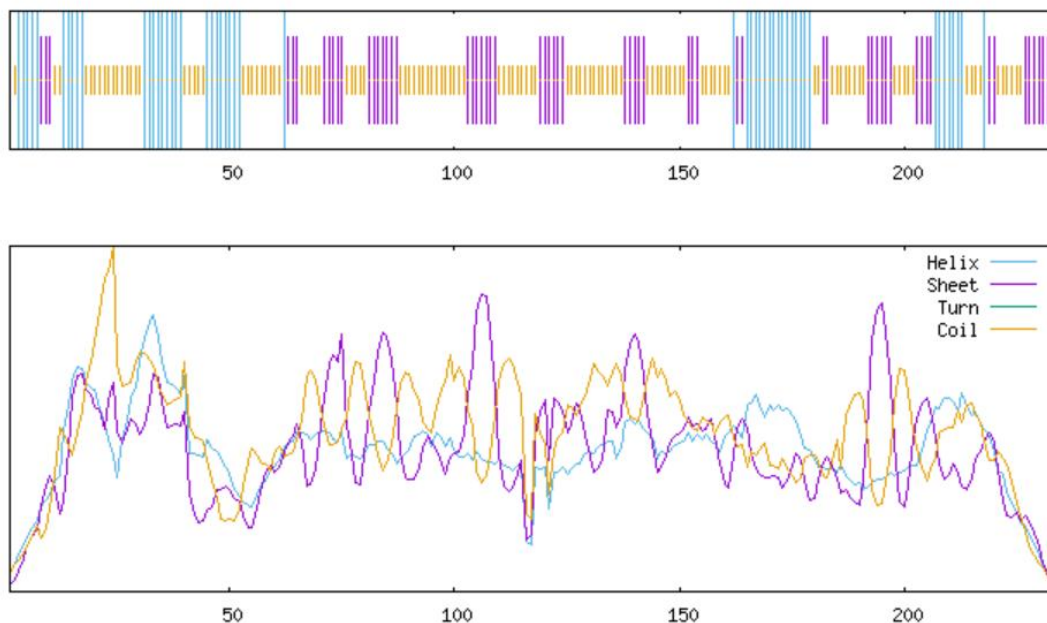
### 3.1 Prediction of Physicochemical Properties

TSST-1 was found to comprise of 234 amino acids and 26305.89 Da molecular weight. Theoretical pI was 8.80. Twenty-six Asp and Glu residues while twenty-nine arginine and lysine residues were found. TSST-1 exhibited the formula  $C_{1182}H_{1868}N_{304}O_{365}S_4$ . Values of extinction coefficient, instability and aliphatic index, GRAVY and half-life observed were  $24410 \text{ M}^{-1}\text{cm}^{-1}$ , 34.12, 80.00, -0.529 and > 10 hour, respectively (Table 1).

### 3.2 Prediction of Secondary (2D) Configuration

Among the 234 amino acids, fifty-three took part in formation of alpha helix, sixty-one in extended strand formation and one hundred and twenty in random coil formation (Table 1). This indicated alpha helix comprising of 22.65% amino acids. The extended

strand and random coil were found to comprise of 26.07 and 51.28% amino acids (Figure 2).



Parameters :  
 Window width : 17  
 Similarity threshold : 8  
 Number of states : 3

Figure 2: Prediction of secondary (2D) configuration of *S. aureus* associated TSST-1 protein based on SOPMA tool

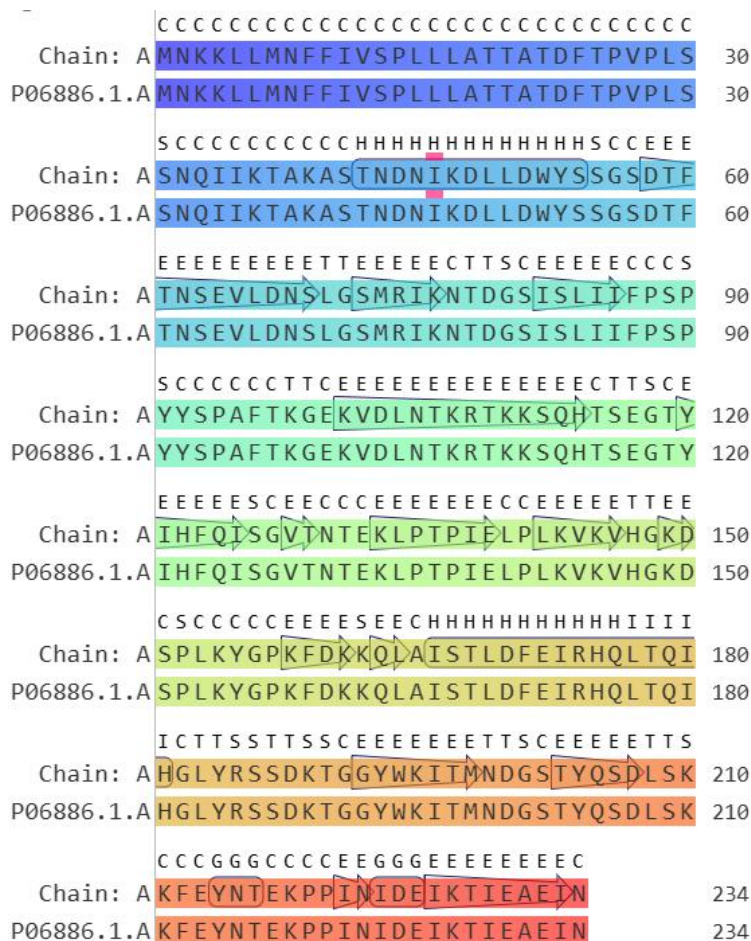
Table 1: Assessment of physicochemical properties, 2D and 3D configuration of TSST-1 protein based on PROTPARAM and SOPMA tool and SWISS-MODEL server

#	Properties of TSST-1 assessed in current study	
1	Physicochemical properties	No. of amino acids: 234 Theoretical pI: 8.80 Molecular weight: 26305.89 Total number of Asp and Glu: 26 Total number of Arg and Lys: 29 Formula: C <sub>1182</sub> H <sub>1868</sub> N <sub>304</sub> O <sub>365</sub> S <sub>4</sub> Extinction coefficient: 24410 M <sup>-1</sup> cm <sup>-1</sup> Estimated half-life: > 10 hour

	Instability index: 34.12
	Aliphatic index: 80.00
	GRAVY: -0.529
2	Secondary configuration
	Alpha helix: 53 (22.65%)
	Extended strand: 61 (26.07%)
	Random coil: 120 (51.28%)
3	Three dimensional configuration
	MolProbity score: 1.41
	Clash score: 0.54
	Ramachandran favoured: 93.10%
	Ramachandran outliers: 1.29%
	Rotamer outliers: 2.33%
	C-beta deviations: 4
	Bad bonds: 0/1895
	Bad angles: 18/2566
	Twisted non-proline: 1/220

### 3.3 Prediction of three-dimensional (3D) configuration

This analysis showed 100 % sequence identity with toxic shock syndrome toxin-1 protein (P06886.1.A) with GMQE score of 0.86 (Figure 3). Major proportion of structure was comprised of extended sheets as compared to alpha helix (Figure 4A). Ramachandran plot based quality assessment of predicted configuration is shown in Figure 4B. The plot indicated MolProbity and Clash scores of 1.41 and 0.54, respectively. The 93.10% proportion of plot was lying in favoured region with 1.29% Ramachandran outliers and 2.33% Rotamer outliers.



**Figure 3: Alignment of TSST-1 sequence documented in current study with P06886.1.A**  
 The C-beta deviations, bad bonds, bad angles and twisted non-proline content was found as 4, 0/1895, 18/2566 and 1/220.

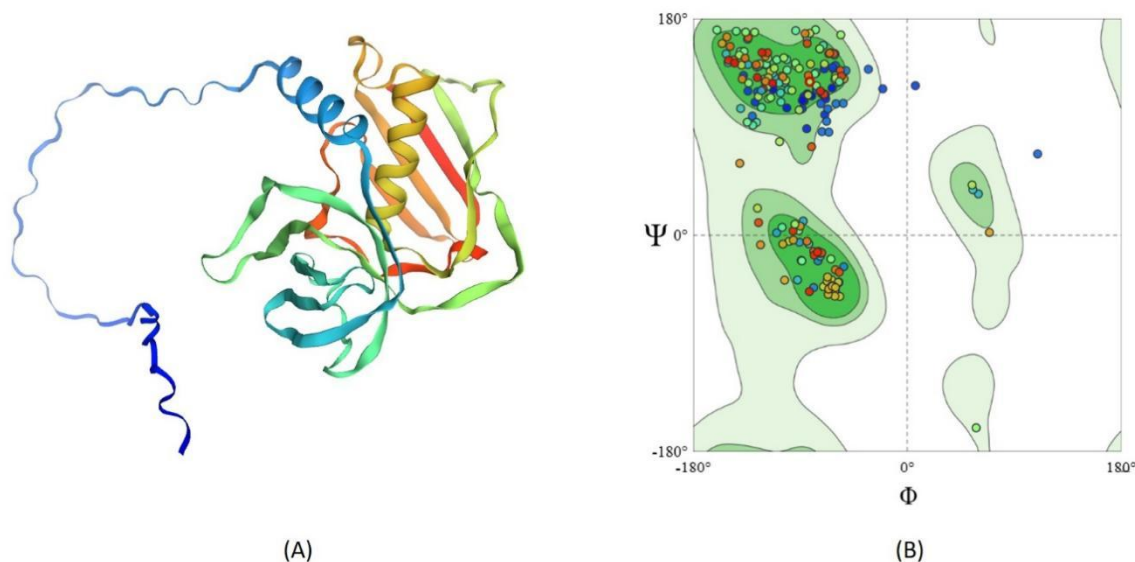


Figure 4: Prediction of three dimensional (3D) configuration of *S. aureus* associated TSST-1, documented in current study, based on SWISS-MODEL

(A) 3D configuration (B) Quality assessment of 3D structure via Ramachandran plot

### 3.4 Prediction of conserved motifs

Ten conserved motifs were predicted using MEME suite with p-value of 4.39e-47. The ten major motifs identified were FENREQLDNIHGLMR, DWQISG, KYGPKF, WKISMND, MNFFJL, NTEKPP, RLKKKQH, GEKVDL, LAISALD and DEIKKFEA (Figure 5).

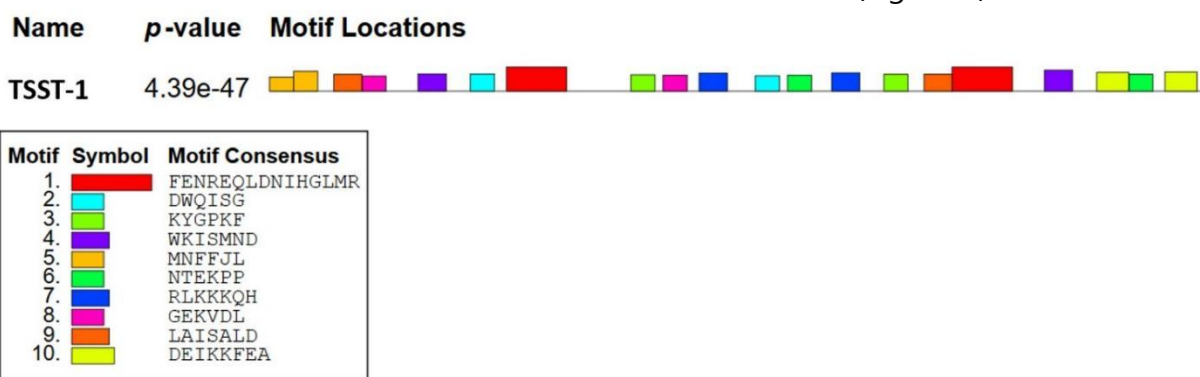


Figure 5: MEME tool based prediction of conserved motifs of *S. aureus* associated TSST-1 virulence factor

The Table 2 shows the detailed characteristics like E-value, p-value, log-likelihood ratios, relative entropy and bayes threshold. Motifs FEIRHQLTQIHGLYR and

FTNSEVLDNSLGSMR were found with E-value of 1.7e+001 and p-values of 3.32e-17 and 4.14e-15, respectively.

Table 2: *Assessment of conserved motifs of S. aureus associated TSST-1 assessed via MEME tool*

#	E-value	p-value	LLR	RE	BT	Motif sequence
1	1.7e+001	3.32e-17	75	54.2	6.76818	KQLAISTLD FEIRHQLTQIHGLYR SSDKTGGYW K
2		4.14e-15				LDWYSSGSD FTNSEVLDNSLGSM IKNTDGSISL T R
3	2.1e+002	7.70e-8	31	22.3	6.82655	STNDNIKDLL DWYSS SDTFTNSEVL G
4		4.24e-7				SQHTSEGTYI HFQISG VTNTEKLPTP
5	2.2e+002	1.04e-7	31	22.3	6.82655	VKVH GKDSP KYGPKF DKKQLAISTL L
6		1.63e-7				SISLIIFPSP YYS PAF TKGEKVDLN T
7	4.2e+002	2.09e-9	35	25.4	6.82018	YRSSDKTGG WKITMN GSTYQSDLS Y D K
8		7.60e-8				PLSSNQIIKT AKASTN NIKDLLDWY D S
9	4.5e+002	6.20e-9	30	21.5	6.82655	MNKKL MNFFI SPLLLATTAT L V
10		1.59e-6				MNKKL MNFFIVSPLL L
11	6.2e+002	9.73e-8	30	22	6.82655	QSDLSKKFEY NTEKP INIDEIKTIE P
12		2.54e-7				YIHFQISGVT NTEKLP TPIELPLKVK
13	4.1e+002	2.47e-8	34	24.6	6.82018	TEKLPTPIEL PLKVKV GKDSPLKYG H P
14		3.26e-8				KGEKVDLNT RTKKSQ TSEGTYIHFQ

15	2.1e+003	2.45e-7	29	20.6	5.67371	K	H				
						SPYYSPAFTK	GEKVD	NTKRTKKSQ			
							L	H			
16		5.34e-7				PLLATTATD	FTPVPL	SSNQIIKTAK			
17	3.1e+003	9.64e-8	322	22.8	6.82018	KYGPKFDKK	LAISTLD	FEIRHQLTQI			
						Q					
18		1.06e-7				MNFFIVSPLL	LATTAT	FTPVPLSSN			
							D	Q			
19	4.2e+003	1.09e-8	36	26.1	6,81378	YNTEKPPINI	DEIKTIEA	EIN			
20		1.62e-8				TMNDGSTY	DLSKKFEY	NTEKPPINID			
						QS					

LLR: log likelihood ratio, RE: relative entropy, BT: bayes threshold

Motifs DWYSSG and HFQISG were identified with E- and p-values of 2.1e+002, 7.70e-8 and 4.24e-7, respectively. Domains KYGPKF (p-value = 1.04e-7) and YYSPAF (p-value = 1.63e-7) were predicted with E-value of 2.2e+002. Motifs WKITMND and AKASTND predicted with E-value (4.2e+002) and p-values (2.09e-9 and 7.60e-8, respectively). E-value of 4.5e+002 was predicted for domains MNFFIV (6.20e-9) and MNKKLL (1.59e-6). The E-value found for NTEKPP (p-value of 9.73e-8) and NTEKLP (p-value of 2.54e-7) was 6.2e+002. E-value of 4.1e+002 was observed for PLKVKVH (p-value 2.47e-8) and RTKKSQH (p-value 3.26e-8). Motifs GEKVDL (p-value = 2.45e-7) and FTPVPL (p-value = 5.34e-7) were predicted with E-value of 2.1e+003. Domains LAISTLD (p-value = 9.64e-8) and LATTATD (p-value = 1.06e-7) were identified with E-value of 3.1e+003. The domains DEIKTIEA (p-value of 1.09e-8) and DLSKKFEY (p-value of 1.62e-8) were predicted with E-value of 4.2e+003.

#### 4. Discussion

TSST-1 is *S. aureus* associated super-antigen. Current study analysis of TSST-1 via SWISS-MODLE predicted monomeric configuration of protein which is in accordance with literature (McCormick et al. 2003; Zhu et al. 2023).

An emerging anti-virulence therapy is to target the conserved motifs and domains of virulent proteins. In current study, we identified twenty motifs. i. e., FEIRHQLTQIHGLYR, FTNSEVLDNSLGSMT, DWYSSG, HFQISG, KYGPKF, YYSPAF,

WKITMND, AKASTND, MNFFIV, MNKLL, NTEKPP, NTEKLP, PLKVKVH, RTKKSQH, GEKVDL, FTPVPL, LAISTLD, LATTATD, DEIKTIEA and DLSKKFEY, in TSST-1. The active sites in these motifs can be identified to prepare the drugs which may bind and block these active sites (Khatun et al. 2023). Conserved domains linked with toxin production via enzymes signaling and quorum sensing (QS) might be inhibited. These motifs are the best targets for vaccines (Gudepu et al. 2026). All these methods disarm bacteria rather than killing or forcing them to mutate leading to reduction of infection.

Exploring the 2D and 3D configurations of TSST-1 form basis of another significant anti-virulence approach. It unravels the structural vulnerability of pathogens (Dehbanipour and Ghalavand 2022). Drugs capable of binding the alpha helices or beta sheets may be designed that will tend to lock the protein in misfolded configuration causing their inactivation (Kane et al. 2018).

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**Informed Consent:** N/A

**Ethical Approval:** N/A

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**Submission Declaration and Verification:** The manuscript has not been submitted anywhere else and is not under consideration by any other journal.

**Data Availability Statement:** The amino acid sequence of TSST-1 virulence factor documented in current study are available on UNIPROT database (). The accession ID of protein is P06886.1.A.

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