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Research Article

DOCKING BASED INSIGHTS INTO LUTEOLIN AND POLYPHENOLS TARGETING SORTASE A IN *STAPHYLOCOCCUS AUREUS* ASSOCIATED WITH DENTAL CARIES

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ABSTRACT

Dental caries is a biofilm-mediated disease and recent evidence has highlighted Staphylococcus aureus as a contributing pathogen. Sortase A (SrtA), a membrane bound transpeptidase responsible for anchoring surface proteins to the bacterial cell wall, plays a key role in virulence. SrtA is a desirable target for antivirulence as it supports colonisation. To evaluate the efficacy of luteolin, a dietary flavonoid, in inhibiting the function of Staphylococcus aureus SrtA through molecular docking, and to compare its effectiveness with that of curcumin, epigallocatechin gallate (EGCG), and quercetin. Docking simulations were conducted using the SrtA crystal structure (PDB ID: 1T2W). An analysis was conducted to compare and contrast the binding affinity and interaction patterns of luteolin from our study to the docking data that had previously been documented in literature for curcumin, EGCG, and quercetin. Luteolin bound to the catalytic site of SrtA with an energy of –8.29 kcal/mol, forming stable hydrogen bonds and hydrophobic interactions. Its affinity was stronger than curcumin, comparable to quercetin, and slightly lower than EGCG. While EGCG's hydroxyl-rich structure enhanced binding, luteolin displayed a balanced interaction profile and superior pharmacokinetic traits, including oral bioavailability and metabolic stability. Luteolin demonstrates strong binding affinity to SrtA and possesses favourable pharmacological properties, positioning it as a promising candidate for a natural antivirulence agent. Future biochemical and in vivo investigations could explore strategies and confirm its role in targeting biofilms associated dental caries.

Keywords: Dental caries, Flavonoids, Sortase A, Staphylococcus aureus, Luteolin, Natural products.

INTRODUCTION

Dental caries, which is more commonly known as tooth decay, is a persistent condition that continues to be a significant public health concern on a global scale. (Heng C, 2016). This condition can develop as a result of a variety of factors, such as host variables, saliva composition, nutritional intake, and dental hygiene practices. The degradation of tooth enamel by acids produced by the metabolism of bacteria is the cause of the condition (Rajasekaran JJ, Krishnamurthy HK *et al*., 2024). The dental biofilm, a structured community of microorganisms residing on tooth surfaces, is fundamental to this process (Karygianni L Ren Z *et al*., 2020; Marsh PD, 2006). Streptococcus mutans was presumed to be the primary agent responsible for dental caries for a long period of time (Forssten SD, Björklund M *et al*., 2010). Recent findings indicate a polymicrobial origin, emphasising the role of multiple species in the progression of the disease (Zhu Y, Wang Y *et al*., 2023). Among these, Staphylococcus aureus has received the greatest amount of attention. Despite S. aureus's long history as a systemic and cutaneous pathogen, new evidence has connected it to oral biofilms and early childhood caries (Donkor ES, Kotey FC, 2020). Its persistence in biofilm environments is dependent on

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Sortase A (SrtA) and other virulence factors. SrtA is a membrane-bound transpeptidase that effectively attaches proteins containing the LPXTG motif to the bacterial cell wall, thereby promoting biofilm adhesion to surfaces and increasing their stability (Jonsson IM, Mazmanian SK *et al*., 2003; Schneewind O, Missiakas D, 2019). Inhibition of SrtA promotes colonisation, though it is not critical for bacterial survival, making it a potential strategy to reduce bacterial pathogenicity (Alharthi S, Alavi SE *et al*., 2021; Schneewind O, Missiakas D, 2019). The pathogenicity of bacteria can be reduced by inhibiting SrtA, which in turn reduces the pressure that bacteria are under to develop resistance to antibiotics (Wang J, Li H, *et al*., 2018).

Natural products are good choices for antivirulence because they have a lot of different structures and are usually safe. Polyphenols are of particular interest in this category. Flavonoids such as luteolin, quercetin, and epigallocatechin gallate (EGCG) have been shown to interfere with the formation of bacterial biofilms and, in some cases, directly inhibit SrtA. (Hasibuan PAZ, Simanjuntak Y *et al*., 2024; Nitulescu G, Margina D *et al*., 2021; Tang SN, Singh C *et al*., 2010). Researchers have also found that curcumin, a diarylheptanoid from turmeric that is not a flavonoid, binds to SrtA and stops it. This illustrates the potential efficacy of plant-derived pharmaceuticals in this medical sector (Luo H, Liang DF *et al*., 2017; Park BS, Kim JG *et al*., 2005). Fruits, vegetables, and medicinal plants serve as sources of the flavonoid luteolin, which has been extensively researched for its anti-inflammatory, antioxidant, and antibiofilm properties (Caporali S, De Stefano A *et al*., 2022; Liu X, Zuo J *et al*., 2023; Taheri Y, Sharifi-Rad J *et al*., 2021). The potential of this compound as a SrtA inhibitor has not been thoroughly assessed. Luteolin's pharmacological characteristics and simple structure render it an optimal subject for investigation. This investigation utilised molecular docking to evaluate the interaction between luteolin and S. aureus SrtA, while also comparing its binding affinity to that of three previously studied naturally occurring compounds namely, curcumin, EGCG, and quercetin. Utilising these standards to examine luteolin gives us information about its part in natural antivirulence strategies that can target progression of dental caries.

MATERIALS AND METHODS

Protein preparation

The crystal structure of *S. aureus* Srt A (PDB, ID: 1T2W; resolution 1.08 Å) was obtained from Protein Data Bank. Crystallographic water molecules and heteroatoms were eliminated using PyMOL (Figure 1). AutoDock Tools (ADT, version 1.5.7) was used to assign Kollman charges and add polar hydrogens (Figure 2). Following that, the receptor was saved in PDBQT format.

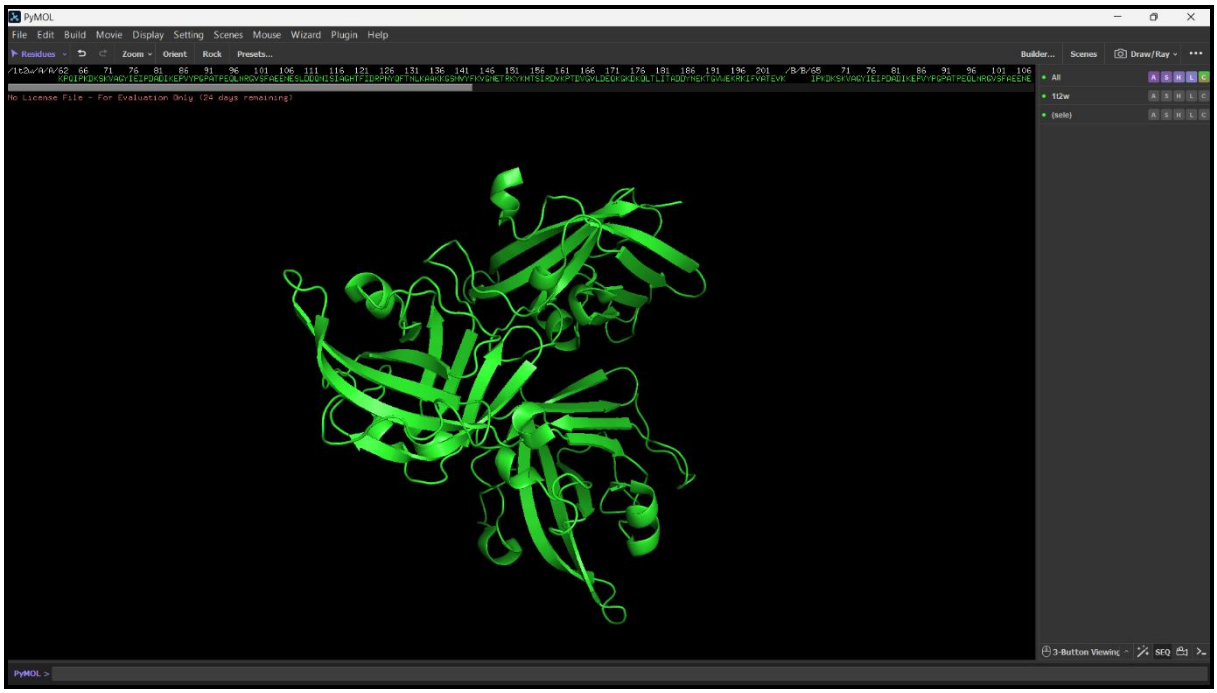

Figure 1. Three-dimensional structure of *Staphylococcus aureus* Sortase A (PDB ID: 1T2W) after refinement, visualized in PyMOL.

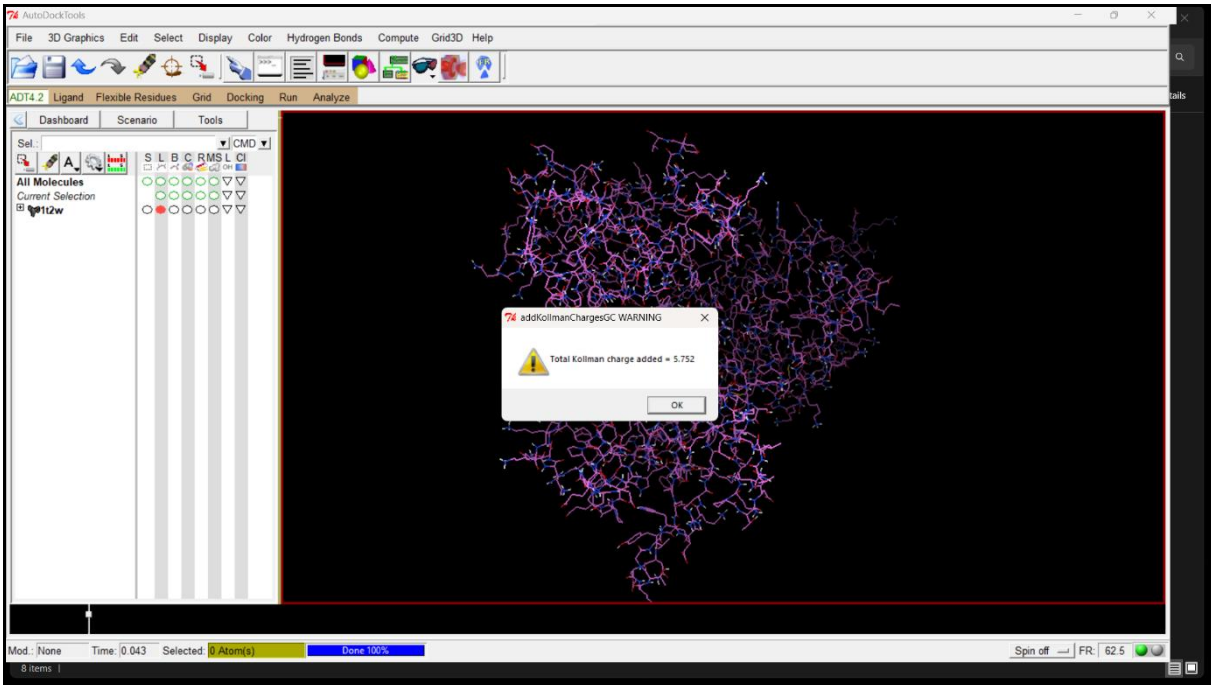

Figure 2. Refined structure of Sortase A after removal of crystallographic water molecules, addition of polar hydrogen atoms, and assignment of Kollman charges in AutoDock Tools.

Ligand preparation

The luteolin structure (PubChem CID: 5280445) was obtained from PubChem in SDF format. The molecule was converted to PDB format using Open Babel following energy minimisation performed in Avogadro with the MMFF94 force field. Charges were added using ADT, and rotatable bonds were identified prior to exporting the ligand in PDBQT format (Figure 3).

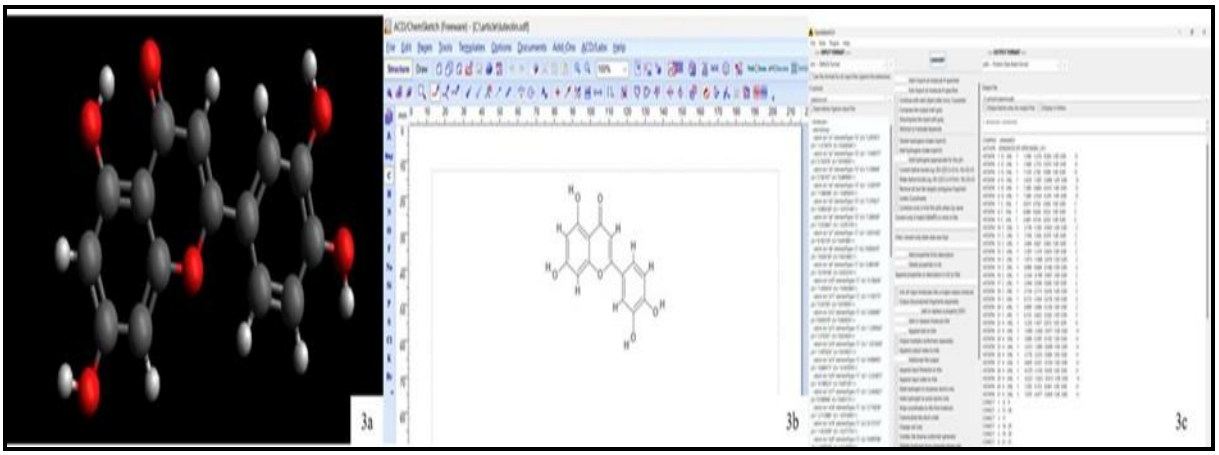

Figure 3. Preparation of luteolin ligand structure: (a) chemical structure retrieved from PubChem, (b) optimization in Avogadro, and (c) conversion to PDB format using Open Babel.

Docking protocol for luteolin

Docking simulations were conducted using AutoDock 4.2, which utilised the Lamarckian Genetic Algorithm (LGA). The SrtA catalytic site located at coordinates X = -18.011, Y = -28.184, and Z = -14.814 functioned as the center of the grid box, which measured 60 × 60 × 60 points with a spacing of 0.375 Å (Figure 4).

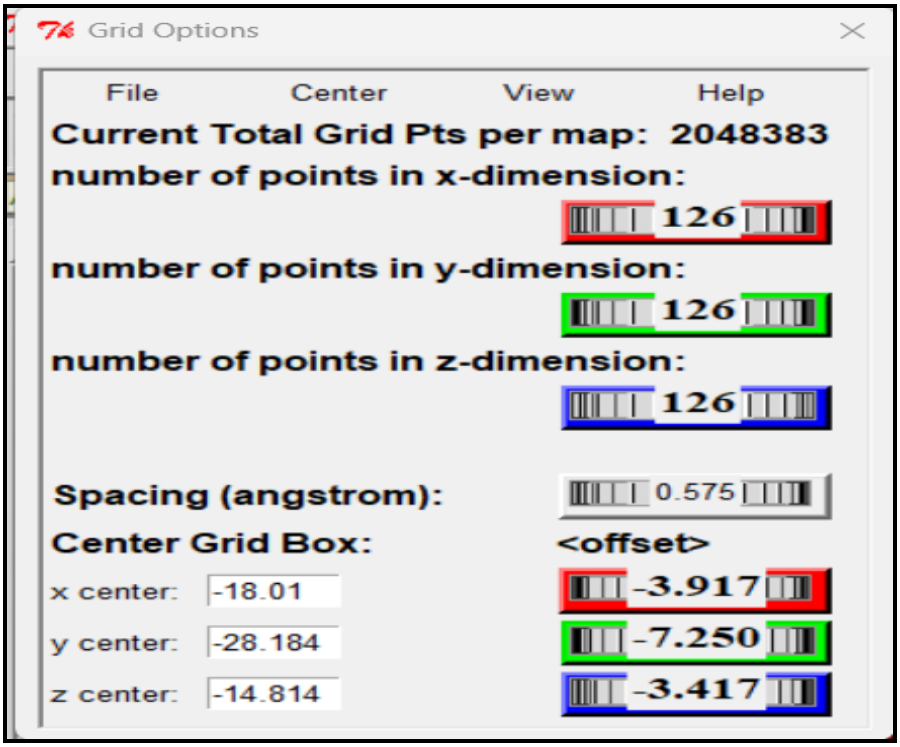

Figure 4. Grid box configuration centered on the Sortase A catalytic site for docking simulations, shown with coordinates X = –18.011, Y = –28.184, Z = –14.814.

Ten independent trials were conducted, each involving a population size of 150, a total of 2,500,000 energy evaluations, and 27,000 generations. Clustering was performed at a root mean square deviation (RMSD) of 2.0 Å, and the pose with the lowest energy from the most populated cluster was selected for analysis.

Interaction analysis

With an emphasis on hydrogen bonding, hydrophobic interactions, and general ligand orientation within the catalytic groove, luteolin binding poses were investigated using PyMOL and Discovery Studio Visualizer. The binding energies and interactions for quercetin, curcumin, and EGCG were taken from published research.

RESULTS AND DISCUSSION

Molecular docking demonstrated that luteolin might bind to SrtA's catalytic groove in a number of ways. With a binding value of –8.29 kcal/mol, the most stable form was maintained by hydrophobic contacts and hydrogen bonds with significant catalytic residues (Figure 5).

Table 1. Comparative binding energies and key interactions of luteolin and reference polyphenols with *Staphylococcus aureus* Sortase A (SrtA).

Compound	Binding Energy (kcal/mol)	Key Interactions	Source
Luteolin	–8.29	Catalytic groove; Hydrogen bonds and hydrophobic contacts	Current study
Curcumin	–7.2 to –7.8	Cys184, His120	(Hu P, Huang P *et al*., 2013)
EGCG	–8.5 to –9.2	Multiple hydrogen bonds with conserved residues	(Song M, Teng Z *et al*., 2017)
Quercetin	~–8.0	Active site groove residues	(Wang J, Song M *et al*., 2018)

Footnotes -EGCG denotes epigallocatechin gallate; kcal/mol signifies kilocalories per mole.

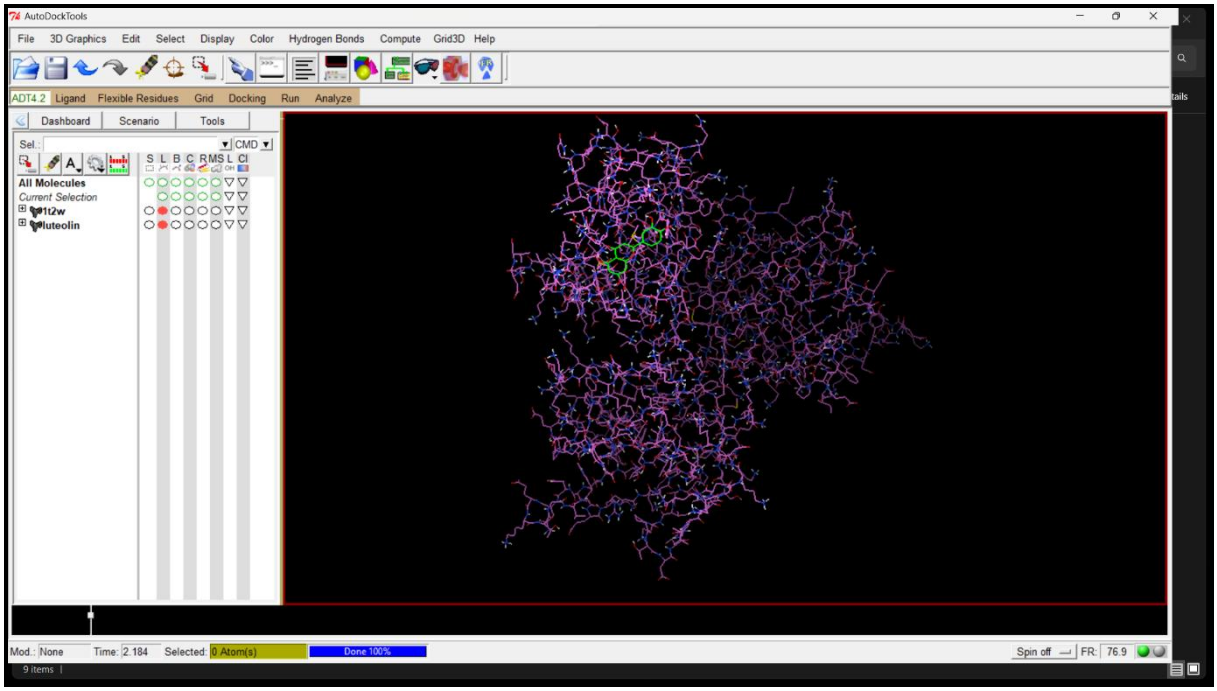

Figure 5. Predicted docking pose of luteolin within the Sortase A active site, highlighting hydrogen bonding and hydrophobic interactions.

A stable protein-ligand complex was established as a result of these interactions. The predicted binding mode was further strengthened by the identification of three binding clusters, with the lowest-energy conformation belonging to the most populated group, as determined by cluster analysis. Docking results from published studies were reviewed for curcumin, EGCG, and quercetin. Their reported binding affinities and key interactions are summarized in Table 1. In comparison to these substances, luteolin showed similar affinity to quercetin, stronger binding than curcumin, and only marginally weaker interactions than EGCG [Figure 6]. The conserved catalytic residues of all four compounds were capable of forming hydrogen bonds, suggesting a shared inhibitory mechanism against SrtA.

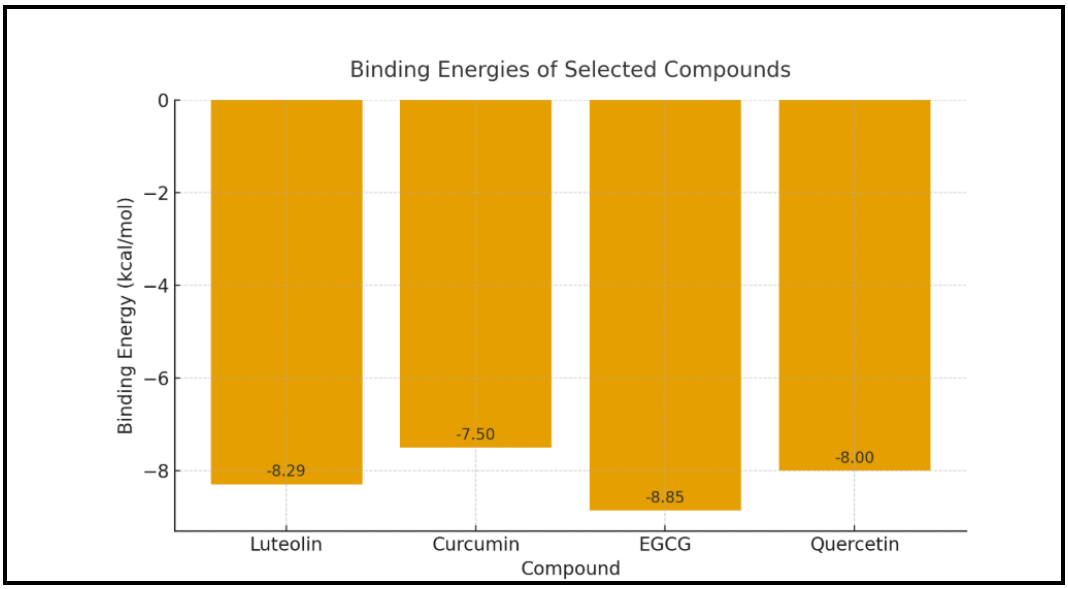

Figure 6. Comparative binding energies of luteolin and reference polyphenols with Sortase A of *Staphylococcus aureus*.

The bar diagram compares the binding affinities (kcal/mol) of luteolin, curcumin, EGCG and quercetin with Staphylococcus aureus Sortase A. The graphical representation clearly indicates that luteolin's affinity is close to that of quercetin and only slightly lower than EGCG, suggesting a stable and favorable interaction within the catalytic site. These findings reinforce the potential of luteolin as a promising natural inhibitor of Sortase A.

Molecular docking studies show that luteolin is a promising option for blocking Staphylococcus aureus Sortase A. The catalytic pocket has a stable association, as evidenced by the expected binding energy of –8.29 kcal/mol, which is sustained by hydrogen bonding and hydrophobic interactions. Luteolin had a stronger affinity than curcumin, a binding strength similar to quercetin, and an activity that was only slightly weaker than that of EGCG when compared to other natural compounds that have been investigated. This relative ranking aligns with the differences in their structural scaffolds and interaction patterns. The superior binding affinity of EGCG can be attributed to its highly hydroxylated structure, facilitating multiple hydrogen bonds with conserved residues (Liu J, Ghanizadeh H *et al*., 2021; Zhong Y, Ma CM *et al*., 2012). Luteolin, despite having fewer hydroxyl groups, achieves a favourable balance between polar and hydrophobic interactions, which enhances both stability and selectivity. Luteolin presents several practical advantages from a pharmacological standpoint. Luteolin is better at being absorbed and metabolised in the body than curcumin, which doesn't work well in the body, and EGCG, which is unstable in vivo (Anand P, Kunnumakkara AB *et al*., 2007; Furniturewalla A, Barve K, 2022; Geng YF, Yang C *et al*., 2021; Krupkova O, Ferguson SJ *et al*., 2016; Sarawek S, Derendorf H *et al*., 2008; Yasuda MT, Fujita K *et al*., 2015). These features enhance the probability of sustaining therapeutic levels within biological systems.

Beyond SrtA inhibition, luteolin has been shown to disrupt biofilm formation and quorum sensing, extending its applicability beyond single-target interactions. In the context of dental caries, a polymicrobial and biofilm-driven condition, this dual activity is valuable because it has the potential to act synergistically by suppressing adhesion and microbial communication, (Geng YF, Yang C *et al*., 2021; Rudin L, Roth N *et al*., 2023). Broader protection against biofilm-associated virulence in the oral cavity may be achieved by an agent that possesses both mechanisms. A comparative framework was implemented in this investigation to substantiate the conclusions. The docking data acquire translational relevance when luteolin is compared with pharmacologically validated agents such as curcumin, EGCG, and quercetin. In practical applications, luteolin's superior pharmacokinetic profile may offset its slightly lower affinity compared to EGCG. Curcumin, however, exhibits limited efficacy in directly inhibiting SrtA due to its instability and suboptimal binding affinity. However, it is important to recognise certain limitations. The protein–ligand system is fundamentally simplified by docking techniques, which are unable to adequately take conformational flexibility, solvent dynamics, or cellular context into account. The comparative results were derived from studies utilizing various docking protocols, leading to methodological variability. Conclusions are further limited to the predictive level by the lack of experimental validation, such as enzymatic assays or biofilm inhibition models. Despite these constraints, the study provides a rational basis for subsequent research. Molecular dynamics simulations and in vitro assays could validate the stability and biological relevance of luteolin SrtA interactions. Longer-term, in vivo models of dental biofilm development would clarify whether luteolin's dual actions SrtA inhibition and quorum-sensing modulation translate into measurable reductions in caries progression. The results indicate that luteolin is a potent natural product candidate for antivirulence treatment when combined. Due to its balanced interaction profile, positive pharmacological characteristics, and multifunctional antibiofilm potential, luteolin is distinguished from other phytochemicals that have been tested against SrtA. However, further validation is necessary.

CONCLUSION

The binding of luteolin to S. aureus SrtA was significant (-8.29 kcal/mol), surpassing curcumin, equalling quercetin, and approaching EGCG levels. As a result of its excellent bioavailability, stability, and docking affinity, lutein possesses a significant amount of potential as a natural antivirulence agent. This data indicates that luteolin may be a promising candidate for therapeutics that target dental caries biofilms; however, additional experimental validation is required to draw definitive conclusions.

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CONFLICT OF INTERESTS

The authors declares no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

All the data generated or analyzed in this current study are presented in the manuscript.

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