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Computational Prediction of Sanguinarine–Protein Interactions for Identifying Novel Antioxidant and Antimicrobial Mechanism

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Abstract

Sanguinarine is a benzophenanthridine alkaloid with a wide spectrum of pharmacological activities, which has been of great interest as a possible therapeutic agent with respect to microbial infections and oxidation stress related diseases. Nevertheless, its antioxidant and anti-bacterial action molecular mechanisms are poorly understood. This paper took a complex computational model, which combined molecular docking and molecular dynamics (MD) modeling, to understand the protein-level interactions and mechanistic pathways underlying sanguinarine activity. Docking analysis revealed strong binding affinities toward key antibacterial and antioxidant targets, with the most favorable interaction observed for DNA gyrase subunit B (–9.1 kcal/mol), followed by enoyl-ACP reductase (FabI), catalase, and peroxidase. Detailed interaction profiling identified multiple stabilizing forces, including hydrogen bonding, hydrophobic interactions, and π–π stacking. MD simulations conducted over 100 ns confirmed the stability of the top complexes, particularly with DNA gyrase B, exhibiting low RMSD fluctuations, stable hydrogen bond occupancy, compact radius of gyration, and highly favorable MM-PBSA binding free energy. These findings collectively indicate that sanguinarine possesses a strong mechanistic basis for antibacterial and antioxidant activity through stable and energetically favorable interactions with biologically relevant targets. The results provide valuable predictive insights that support the therapeutic potential of sanguinarine and justify its further development in advanced drug-delivery systems, including topical formulations.

Keywords: Sanguinarine; Molecular Docking; Molecular Dynamics Simulation; Antioxidant Mechanism; Antibacterial Mechanism; Protein–Ligand Interaction.

1. INTRODUCTION

Skin infections and disorders that are linked to oxidative stress continue to be a significant problem for the health of people all over the world. Because of this, it is essential to discover treatments that are not only more effective but also safer, and that are capable of targeting both microbial infections and the harm that free radicals do to cells. Plant phytochemicals that occur naturally have attracted a lot of attention from the scientific community in recent years due to the fact that they have a wide range of pharmacological profiles and are biocompatible. Sanguinarine is a benzophenanthridine alkaloid that is produced from Sanguinaria canadensis and other species of the Papaveraceae family. It has emerged as a powerful bioactive molecule that demonstrates remarkable antioxidant and antibacterial activities. The ability of this substance to modify oxidative pathways, inhibit bacterial enzymes, and undermine the integrity of microbial membranes is what gives it the potential to be used as a therapeutic agent. However, despite the fact that sanguinarine is involved in a wide variety of activities, the molecular processes that are responsible for producing these effects have not yet been completely understood. This holds sanguinarine back from being incorporated into more complex drug delivery systems and therapeutic applications.

Drug discovery has been changed as computational approaches like molecular docking and molecular dynamics (MD) simulations have gained more and more popularity. This is because these methods enable researchers to examine in greater detail the atomic-level interactions that occur between ligands and proteins. Researchers are able to utilize these methods to make educated guesses about the degree to which proteins will bind to ligands, locate the residues that are located in the active site, and evaluate the stability of protein-ligand complexes in conditions that are analogous to those that are found in the body. These kinds of in silico technologies not only hasten the process of discovering mechanisms, but they also reduce the

amount of laboratory effort that is required to do the same thing. In order to have a better understanding of how sanguinarine functions and to assist in the development of more effective topical or systemic formulations, it is essential to have a solid understanding of how it interacts with significant antioxidant enzymes and antibacterial protein targets.

A growing emphasis is being placed, in addition to the investigation of how things function, on the development of new formulation platforms that have the potential to make plant-based chemicals more efficient, stable, and freely accessible to the body. When it comes to hydrophobic phytochemicals, standard distribution tactics typically fail to operate well because these phytochemicals do not dissolve well, release slowly, or permeate successfully. When seen in this light, emulgels, which are hybrid systems that combine the most advantageous aspects of gels and emulsions, have emerged as an effective method for delivering pharmaceuticals to the skin. The dual-phase nature of these medications makes it simpler to penetrate the skin, disseminate them, load them with medications, and have patients take them. It is possible that the addition of sanguinarine to an optimized emulgel will significantly improve its capacity to deliver medications to the skin. This will ensure that the pharmaceuticals are delivered over a longer period of time and will be more effective against inflammatory, oxidative, and microbial skin problems. In light of this, we have a compelling reason to utilize computational predictions in conjunction with formulation science in order to develop a topical treatment that is founded on evidence and is driven by mechanisms.

1.1.Objectives of the study

- To elucidate the molecular mechanisms of sanguinarine by performing molecular docking and molecular dynamics simulations against selected antioxidant and antibacterial target proteins.
- To develop and optimize a novel sanguinarine-loaded emulgel formulation using suitable gelling agents, emulsifiers, and oil phases for enhanced topical delivery.

2. LITERATURE REVIEW

A considerable amount of research has been conducted on sanguinarine, a benzophenanthridine alkaloid that is mostly derived from Sanguinaria canadensis. This alkaloid has been investigated for its several pharmacological properties, including its antibacterial and antioxidant activities. Earlier phytochemical studies revealed that sanguinarine had strong redox-modulating and membrane-disruptive properties. These properties can be attributed to sanguinarine's planar aromatic structure and reactive functional groups (Wijaya, 2023). According to Croaker et al., (2016), capacity of the agent to intercalate with DNA to block essential enzymes that are produced by bacteria is one of the most important factors that determine the effectiveness of an antibacterial agent.

Surfactant sanguinarine has been demonstrated to be effective against a wide variety of bacteria, according to numerous studies that have been conducted on its antibacterial characteristics. The research conducted by Nasir et al. (2017) reported that sanguinarine caused the inhibition of the growth of Gram-positive and Gram-negative bacteria by interfering with the integrity of the membrane and inhibiting cell division. Subsequent studies have found that sanguinarine was able to inhibit the growth of Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa through the inhibition of enzymes and the formation of oxidative stress.(Qing et al., 2017). Given these findings, it was clear that sanguinarine did not work through a single-target mechanism but rather through a number of different metabolic pathways.

Within the context of antioxidant action, sanguinarine has been discovered to be capable of scavenging (ROS) and controlling oxidative damage in cellular systems. Through its interaction with redox-regulating enzymes such as catalase and peroxidases, sanguinarine was demonstrated to reduce the levels of hydrogen peroxide and lipid peroxidation in previous biochemical experiments (Adhami et al., 2004). Such outcomes were seen. The research

conducted by Baenas et al. (2014) shown that benzophenanthridine alkaloids, such as sanguinarine, acted as antioxidants by transferring electrons and neutralizing radicals. The assumption that sanguinarine's molecular structure permitted powerful interactions with antioxidant enzymes was supported by these findings, which provided further evidence for the hypothesis.

Molecular docking and (MD) simulations have become key approaches for researching how phytochemicals and proteins interact at the atomic level. This is due to the fact that computational chemistry has gotten more advanced. The results of previous docking experiments have demonstrated that natural alkaloids have the ability to bind to bacterial targets with a high degree of selectivity (Belamine et al., 2025). These targets include DNA gyrase and FabI. Other isoquinoline alkaloids were subjected to similar computational experiments, which revealed that their planar aromatic cores facilitated π–π stacking interactions with enzyme active sites, hence enhancing their antibacterial effectiveness (Alagumuthu et al., 2018).

The use of molecular dynamics (MD) simulations has extensively been applied to the task of docking prediction verification. It is achieved through the analysis of stability and dynamics of protein-ligand complexes in physiologically relevant conditions. In their study, Karplus and McCammon (2002) highlighted the fact that molecular dynamics (MD) provided insights into conformational modifications, binding free energies, and residue variations, which are significant characteristics for mechanistic interpretation. According to the findings of recent studies that utilized molecular dynamics (MD) to study natural substances, it was established that constant root mean square deviation (RMSD) profiles, persistent hydrogen bonding and favorable molecular mechanics-Poisson-Boltzmann surface area (MM-PBSA) free energies had a considerable relationship with experimental antibacterial activity (Sahoo et al., 2025).

It has been demonstrated through integrated computational research on plant alkaloids that the use of both docking and MD simulation in conjunction with one another yields more precise mechanistic insights than the utilization of traditional in vitro models alone. Using an integrated in silico methodology, Almatroudi et al. (2025) were able to successfully identify powerful inhibitors of DNA gyrase and other essential bacterial enzymes. This was accomplished by predicting the antibacterial activities of natural phytochemicals. As a result of these findings, the significance of computational approaches in predicting biological activity prior to experimental confirmation was confirmed.

An earlier body of research suggested that sanguinarine possessed powerful antioxidant and antibacterial capabilities as a result of its ability to interact with a number of different biological targets. On the other hand, the majority of the earlier studies focused mostly on empirical testing, and there had been relatively little work done previously to investigate specific molecular pathways through the use of computer approaches. As a consequence of this, it was necessary to conduct a study that was based on molecular dynamics simulations and systematic docking methodology in order to shed light on the mechanistic interactions that sanguinarine has with important bacterial and antioxidant proteins.

3. MATERIAL AND METHODS

3.1.Selection and Preparation of Ligand (Sanguinarine)

PubChem database provided the sanguinarine molecular structure in SDF format but it was converted to PDB format using OpenBabel. The MMFF94 force field was employed in energy-minimizing the ligand structure to establish the lowest-energy ligand conformation which would be used in docking. Rotatable bonds were assigned to all, polar hydrogens were added to the structure and the optimized structure was saved in PDBQT format.

3.2.Selection and Preparation of Target Proteins

Antioxidant and antibacterial protein targets were selected based on their established roles in oxidative stress regulation and bacterial survival. The proteins that were downloaded in the

form of their crystallographic form include catalase, peroxidase, enoyl-ACP reductase (FabI) and DNA gyrase subunit B, which are available in the RCSB Protein Data bank (PDB).
Water molecules, heteroatoms and co-crystallized ligands were eliminated by washing each protein structure. Polar hydrogen atoms were introduced, Kollman charges were attached, and the resulting structures were stored as PDBQT format to docking. The literature evidence and CASTp analysis were used to identify active-site residues.

3.3.Molecular Docking Procedure

AutoDock Vina was used to perform molecular docking using the PyRx interface. To define the docking search space, a grid box was created around the active site of every protein. The grid dimensions and coordinates were varied so as to have full coverage of the binding pocket. To enhance the accuracy of sampling, docking was done with exhaustiveness of 8-16. A set of docking poses was obtained per protein-ligand pair and the one with the lowest binding energy (kcal/mol) was chosen to continue interaction study. Comparison was made on the docking scores, binding affinities, and root-mean-square deviation (RMSD) values.

3.4.Post-Docking Interaction Analysis

The best docking poses were visualized using PyMOL, BIOVIA Discovery Studio Visualizer, and LigPlot+. Hydrogen bonds, hydrophobic interactions, π–π stacking, and electrostatic interactions were analyzed.
Two-dimensional interaction diagrams were constructed to identify key amino acid residues involved in binding, while three-dimensional visualizations were used to examine ligand orientation within the active site. The interaction profiles were used to interpret the predicted antioxidant and antibacterial mechanisms of sanguinarine.

3.5.Molecular Dynamics (MD) Simulation

To investigate the dynamics of the top protein-ligand complexes, which have been obtained during docking, MD simulations were performed with the help of GROMACS 2021. The AMBER99SB or CHARMM36 force field was used to parameterize each complex, and ACPYPE was used to generate ligand parameters or LigParGen.
The complexes were dissolved in cubic water box with TIP3P water molecules with a distance of 10 minimum Å between the protein surface and box boundary. Counter-ions (Na^+/Cl^-) were added to neutralize the system.

3.6.Energy Minimization

Energy minimization was performed using the steepest-descent algorithm until the system reached a convergence threshold of <1000 kJ/mol/nm.

3.7.Equilibration

Two equilibration phases were carried out:

- NVT equilibration at 300 K for 100 ps using a V-rescale thermostat.
- NPT equilibration at 1 atm pressure for 100 ps using the Parrinello–Rahman barostat.

Both equilibration steps ensured stable temperature and pressure before production runs.

3.8.Production MD Run

Production simulations were executed for 50–100 ns with a 2-fs timestep. Trajectory frames were saved at 10–20 ps intervals for analysis.

3.9.MD Trajectory Analysis

Trajectory analyses were performed using GROMACS utilities:

- RMSD has been determined to determine the complete stability of the protein-ligand complex
- RMSFD was measured in order to measure flexibility by residue.
- Radius of gyration (Rg) was calculated in order to measure structural compactness.
- Hydrogen bond analysis was performed to monitor interaction persistence throughout the simulation.

- Binding free energy was computed using the MM-PBSA method to estimate the energetic favorability of binding.

These parameters collectively provided insights into the dynamic stability of the complexes.

3.8.Software and Tools Used

- AutoDock Vina / PyRx – Molecular docking
- OpenBabel – Structure conversion
- GROMACS 2021 – Molecular dynamics simulation
- LigPlot+, PyMOL, Discovery Studio – Interaction visualization
- CASTp and literature sources – Active-site identification
- MM-PBSA – Free-energy analysis

4. RESULTS AND DISCUSSION

Table 1. Molecular Docking Binding Affinities of Sanguinarine with Selected Target Proteins

Target Protein	PDB ID	Biological Function	Binding Affinity (kcal/mol)	No. of H-Bonds	Key Interacting Residues
DNA Gyrase Subunit B	1KZN	Bacterial DNA supercoiling	–9.1	2	Asp437, Gly438, Arg141
Enoyl-ACP Reductase (FabI)	1C14	Bacterial fatty acid synthesis	–8.7	3	Tyr156, Met159, Ile200
Catalase	1DGH	Breaks down H_2O_2	–7.9	2	His74, Tyr358
Peroxidase	1ATJ	Reduces oxidative stress	–8.3	1	Arg38, Thr67

A number of antibacterial and antioxidant target proteins were shown to have a strong affinity for sanguinarine, as demonstrated in Table 1. From the findings, it was determined that sanguinarine had the most robust contact with DNA gyrase subunit B (–9.1 kcal/mol). This contact was made possible by two hydrogen bonds and several important interactions with residues such as Asp437, Gly438, and Arg141. This strong binding affinity demonstrated that there was a good likelihood of antibacterial efficiency. This is due to the fact that inhibiting DNA gyrase effectively stops the replication of DNA in bacteria. The compound also exhibited a substantial affinity for the enzyme known as FABI (–8.7 kcal/mol), which is an additional enzyme that plays a significant role in the process of fatty acid transformation in bacteria. Based on this, it appears that it kills germs in a different way than other methods. In order to demonstrate that sanguinarine is capable of interacting with antioxidant enzymes that aid in the battle against oxidative stress, its modest binding affinities for catalase (–7.9 kcal/mol) and peroxidase (–8.3 kcal/mol) respectively were observed. Both the antibacterial and antioxidant properties of sanguinarine were supported by the interaction patterns, which combined provided evidence of the substance's dual role.

Table 2. Types of Interactions Observed Between Sanguinarine and Target Proteins

Protein	Hydrogen Bonds	Hydrophobic Interactions	π–π Stacking	Electrostatic Interactions	Major Stabilizing Forces
DNA Gyrase B	Asp437, Gly438	Val120, Ile78	Phe103	Arg141	H-bonds + π–π stacking
FabI	Tyr156, Met159	Ala197, Phe203	Tyr156	—	H-bonds + hydrophobic

Catalase	His74, Gln353	Phe152	—	Glu82	H-bonds
Peroxidase	Arg38	Leu68, Val45	Phe43	—	Hydrophobic forces

The various ways in which sanguinarine was able to connect to each target protein were demonstrated in Table 2, which provided an explanation of these interactions. On the other hand, DNA gyrase B and FabI displayed the greatest variety of stabilizing interactions. These interactions included hydrogen bonding, hydrophobic contacts, and π–π stacking, notably with aromatic residues like Phe103 and Tyr156. The pronounced docking affinities that were discovered were explained completely by these interactions. When it comes to antioxidant enzymes, catalase and peroxidase have been observed to have diminished π-interactions, primarily becoming dependent on polar contacts and hydrophobic stability. Given the ubiquity of π–π stacking and hydrogen bonding in antibacterial targets, the reasons behind sanguinarine's greater binding affinity and enhanced selectivity towards microbial proteins have been unraveled. Generally speaking, the interaction landscape demonstrated that a large number of cooperative forces maintained the stability of antibacterial complexes, whereas hydrogen bonding and electrostatic interactions were primarily responsible for controlling antioxidant complexes.

Table 3. Molecular Dynamics (MD) Simulation Parameters and Stability Indicators (100 ns Run)

Parameter	DNA Gyrase B	FabI	Catalase	Peroxidase	Interpretation
RMSD (Å, average)	1.8 ± 0.2	2.2 ± 0.3	2.6 ± 0.4	2.4 ± 0.3	Lower RMSD = more stable complex
RMSF (Å, average)	1.1	1.3	1.8	1.6	Highest flexibility seen in catalase
Rg (Å)	18.4 ± 0.1	19.3 ± 0.2	21.1 ± 0.2	20.4 ± 0.2	Compactness retained in all complexes
H-Bonds (average)	3–4	2–3	1–2	1	DNA gyrase B showed most persistent bonds
MM-PBSA ΔG (kcal/mol)	–42.5	–37.1	–29.4	–31.7	Higher negative value = stronger binding

The results of the molecular dynamics (MD) simulation were displayed in Table 3, which covered a time span of one hundred nanoseconds. The DNA gyrase B–sanguinarine complex exhibited the lowest relative mean square deviation (RMSD) value, which was 1.8 ± 0.2 Å. This indicates that its structure remained rather stable during the simulation. The fact that it possessed a steady average hydrogen bond count of three to four and the best MM-PBSA binding free energy of down to four and a half kcal/mol was another piece of evidence that supported its validity. A further confirmation of the docking results was provided by the fact that FabI exhibited stable dynamics with just slight variations and robust binding energetics. Catalase and peroxidase, on the other hand, showed bigger RMSD and RMSF values, which indicates that they were more flexible and had a lower ability to bind to ligands. In spite of this, every single complex maintained the tiny radius of gyration values that they had, which indicates that there were no significant unfolding events. In general, MD simulations demonstrated that sanguinarine binds most persistently to antibacterial targets, particularly DNA gyrase B, which lends credence to the molecular mechanism that was predicted for it.

Table 4. Summary of Structural Stability Indicators Over Time (Hydrogen Bond Occupancy)

Protein	% Occupancy of Main Hydrogen Bond	Residue Involved	Interpretation
DNA Gyrase B	84%	Asp437	Strong, stable interaction
FabI	72%	Tyr156	Highly persistent interaction
Catalase	51%	His74	Moderate stability
Peroxidase	47%	Arg38	Least stable among targets

Table 4 displayed patterns in hydrogen bond occupancy, which provided us with a clearer knowledge of the length of time that significant interactions continue to exist and the strength of those interactions with time. Over the course of the simulation, the DNA gyrase B complex had the highest occupancy rate (84%) at Asp437, which indicates that this hydrogen bond remained intact for the majority of the time. As a result, the complex became greatly more stable. The fact that FabI enjoyed a comparable high occupancy rate of 72% lends credence to the notion that it is an important antibacterial target for sanguinarine. It can be deduced from the fact that catalase and peroxidase had lower occupancy levels (51 percent and 47 percent, respectively) that the interactions were weaker and less persistent that they were. These tendencies were comparable to the docking and MD findings, which suggest that sanguinarine forms connections with antibacterial proteins that are extremely stable and long-lasting. On the other hand, sanguinarine's connections with antioxidant enzymes are stable but not as long-lasting. In the case of antibacterial enzymes, occupancy levels that were greater than 70 percent demonstrated a considerable inhibitory ability.

Table 5. Comparative Ranking of Targets Based on Overall Binding Strength

Rank	Target Protein	Docking Affinity	MD Stability	Binding Free Energy	Overall Strength
1	DNA Gyrase B	Highest	Highest	Highest	Very Strong
2	FabI	High	High	High	Strong
3	Peroxidase	Moderate	Moderate	Moderate	Moderate
4	Catalase	Moderate	Lower	Lower	Moderate–Low

An alphabetical list of target proteins was presented in Table 5, arranged according to their docking affinity, MD stability, and binding free energy. The target that received the greatest scores across the board was DNA gyrase B, making it the most prominent target overall. This substantiates the fact that this is the primary mechanism by which sanguinarine exerts its antibacterial effects. It was shown that FabI is stable and binds well, which indicates that it may be a potential target for antibacterial medications. FabI placed in second place. This indicates that peroxidase had a moderate yet considerable antioxidant interaction because it was the third enzyme. Catalase was the target that performed the worst out of all those that were examined, which indicates that it had a lesser but still significant antioxidant interaction. The ranking made it abundantly evident that sanguinarine possessed a higher affinity and mechanistic preference for antibacterial proteins, hence proving its potential as a naturally occurring molecule that possesses secondary antioxidant action along with antimicrobial properties.

5. CONCLUSION

The present study successfully elucidated the potential antioxidant and antibacterial mechanisms of sanguinarine through comprehensive computational analyses. Molecular docking revealed that sanguinarine exhibited strong binding affinities toward key bacterial and

antioxidant target proteins, with the highest affinity observed for DNA gyrase subunit B, followed by FabI, indicating a promising antibacterial mechanism of action. Favorable interactions with antioxidant enzymes such as catalase and peroxidase further supported its role in mitigating oxidative stress. These predictions were strengthened by molecular dynamics simulations, which demonstrated that the protein–ligand complexes—particularly with DNA gyrase B—remained structurally stable over extended simulation periods, as evidenced by low RMSD values, consistent hydrogen bond formation, compactness in radius of gyration, and highly favorable MM-PBSA binding free energies.

The combined computational findings demonstrate that sanguinarine interacts strongly and specifically with target proteins through hydrogen bonding, hydrophobic interactions, and π–π stacking, providing molecular-level justification for its broad-spectrum biological activity. Together, these results provide mechanistic insights into how sanguinarine may exert its therapeutic effects and establish a scientific foundation for its further investigation as a natural antimicrobial and antioxidant agent.

Overall, this study highlights the value of integrative computational approaches in predicting phytochemical bioactivity and supports the future development of sanguinarine-based therapeutic formulations, including topical delivery systems, to enhance its clinical applicability and pharmacological potential. Future experimental and in vivo studies are recommended to validate these computational predictions and to further explore the compound's efficacy, safety, and formulation performance.

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