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MINI-REVIEW ARTICLE

Unravelling Proteomic Pathways: Mechanistic Insights into Schiff Base-Mediated Disruption of Microbial Protein Integrity and Antimicrobial Potential

Jatin Kishore Sharma[1,*] and Sushil Kumar[1]

[1]*School of Pharmaceutical Sciences, Faculty of Pharmacy, IFTM University, Lodhipur Rajput Moradabad-244102 (U.P.), India*

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Abstract: Proteins are essential to the survival and pathogenicity of microorganisms, serving as structural components, enzymes, and regulatory elements. Schiff bases, organic compounds formed by the condensation of primary amines with carbonyl compounds, have emerged as promising antimicrobial agents due to their ability to disrupt microbial protein integrity. This study investigates the multifaceted interactions between Schiff bases and microbial proteins, revealing key mechanistic insights such as membrane disruption, enzyme inhibition, metal chelation, and Reactive Oxygen Species (ROS) generation. Notably, Schiff bases demonstrate potent activity against multidrug-resistant strains, including *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, and exhibit synergistic effects when combined with conventional antibiotics. Proteomic analysis highlights their impact on survival-associated and pathogenicity-related proteins, including chaperones, efflux pumps, and virulence factors. These findings underscore the novelty of targeting microbial proteomes and stress-response pathways, positioning Schiff bases as versatile candidates for next-generation antimicrobial therapies.

Keywords: Protein, Schiff base, microbes, enzymatic activities, bacteria, fungi.

1. INTRODUCTION

Proteins, often regarded as the workhorses of the cell, are essential for the biochemical processes that sustain life. These complex molecules, composed of amino acids, perform a multitude of functions critical to an organism's survival and adaptability [1-2]. In the microscopic worlds of bacteria and fungi, the proteome, the complete set of proteins expressed by an organism, reflects an astonishing diversity, shaped by their unique ecological niches and survival strategies [3-4]. The bacterial and fungal proteomes are a testament to nature's versatility and ingenuity. These microorganisms inhabit environments ranging from the human gut and deep-sea hydrothermal vents to arid deserts. The adaptability of their proteomes is key to their evolutionary success [5-6]. Proteins in these microorganisms not only catalyse a myriad of metabolic reactions but also contribute to structural integrity, signal transduction, and regulatory mechanisms. This multiplicity of roles underscores the complexity and sophistication of microbial life [7].

Schiff bases, a class of organic compounds formed by the condensation of primary amines with carbonyl compounds, have emerged as potent disruptors of microbial protein integrity. Their ability to bind to proteins and alter their structures makes them promising candidates for antimicrobial therapy [8-10]. Schiff bases exhibit a wide range of biological activities, including antibacterial, antifungal, antiviral, and anticancer properties (Fig. **1**) [11-14].

Understanding the interactions between Schiff bases and microbial proteins can provide valuable insights into their mechanisms of action and potential therapeutic applications [15-16]. The study of Schiff bases and their impact on microbial proteomes has profound implications for various fields, including medicine, agriculture, and biotechnology [17]. In medicine, the escalating threat of antimicrobial resistance has rendered many conventional antibiotics increasingly ineffective, prompting the urgent need for novel therapeutic agents. Current antimicrobial strategies often rely on single-target mechanisms, which pathogens can quickly circumvent through genetic mutations, efflux pumps, or enzymatic degradation. In this context, Schiff bases have emerged as promising candidates due to their versatile chemical structures and ability to coordinate with metal ions, enhancing their biological activity. However, despite their potential, most Schiff base derivatives still exhibit limited modes of action, lacking the multi-target capabilities necessary to comprehensively combat resistant strains. Addressing this gap by designing Schiff bases with broad-

*Address correspondence to this author at the School of Pharmaceutical Sciences, Faculty of Pharmacy, IFTM University, Lodhipur Rajput Moradabad-244102 (U.P.) India;
E-mail: jatinkishoresharma7536@gmail.com

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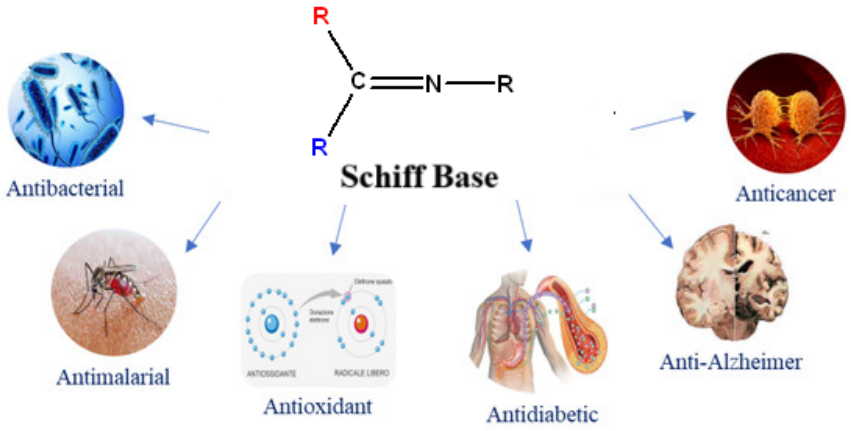


Fig. (1). Biological activities of Schiff bases, highlighting their antimicrobial, antioxidant, anti-inflammatory, anticancer, and enzyme-inhibitory potentials. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

spectrum, multi-target profiles could revolutionize antimicrobial therapy and help outpace the rapid evolution of microbial resistance [18]. In agriculture, Schiff bases can be used to protect crops from microbial infections by targeting proteins essential for the survival and pathogenicity of soil-dwelling bacteria and fungi [19]. In biotechnology, the unique properties of Schiff bases can be leveraged to design novel enzyme inhibitors and protein-modifying agents [20].Furthermore, advancements in proteomics technologies, such as mass spectrometry and bioinformatics, have revolutionized our ability to analyse and understand microbial proteins [21]. High-resolution mass spectrometry enables precise protein identification and quantification, while bioinformatics tools facilitate the interpretation of complex proteomic data. These methodologies have expanded our understanding of the functional diversity and regulatory mechanisms underlying microbial physiology, as well as the effects of Schiff bases on these processes [22]. Environmental factors also play a significant role in shaping the proteomes of bacteria and fungi. Changes in temperature, pH, nutrient availability, and the presence of antimicrobial agents can induce proteomic adaptations that enhance survival and functionality [23]. For instance, the presence of Schiff bases can trigger stress responses in microorganisms, leading to the upregulation or downregulation of specific proteins involved in stress tolerance and resistance mechanisms [24].

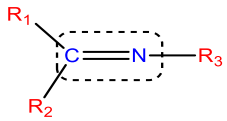
This article aims to provide a comprehensive overview of the impact of Schiff bases on microbial protein integrity. By delving into the mechanisms of action, interactions, and implications of Schiff bases on bacterial and fungal proteomes, we seek to illuminate the intricate molecular pathways that govern microbial life. Through this exploration, we hope to contribute to a deeper understanding of microbial proteomics and foster innovations in antimicrobial therapy and biotechnology.

2. METHODOLOGY

This review was conducted following a narrative review approach. Relevant literature was retrieved from scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Keywords such as *"Schiff bases," "antimicrobial activity," "protein disruption,"* and *"proteomics"* were used in various combinations. Only peer-reviewed articles published in English were included. Studies focusing on synthetic methods, biological evaluations, and mechanistic insights were prioritized, while non-research articles, conference abstracts, and papers lacking sufficient experimental detail were excluded. The reference lists of included articles were also screened to identify additional relevant studies. The gathered information was organized thematically into sections on [chemistry, mechanism of action, proteomic studies, therapeutic implications, *etc.*

3. CHEMISTRY AND STRUCTURAL PROPERTIES OF SCHIFF BASES

Schiff bases are a versatile class of organic compounds characterized by the presence of an imine or azomethine group (>C=N-) (Fig. **2**) [25]. They are formed through the condensation reaction between a primary amine and a carbonyl compound, typically an aldehyde or a ketone. Named after the German chemist Hugo Schiff, who first reported their synthesis in 1864, these compounds have since become integral to the fabric of organic chemistry [26].



R_1,R_2,R_3= Alkyl/Aryl group

Fig. (2). General structure of a Schiff base illustrating the characteristic imine (C=N) functional group formed by the condensation of a primary amine with a carbonyl compound.

3.1. Synthesis of Schiff Bases

The synthesis of Schiff bases is a straightforward, widely used organic reaction that involves the condensation of a primary amine with a carbonyl compound, typically an aldehyde or ketone. This process forms an imine or azomethine group (>C=N-), which is the defining feature of Schiff bases. The reaction is generally carried out under mild conditions, making it a versatile and efficient method for the

preparation of these compounds, as shown in (Fig. **3**) [27-29].

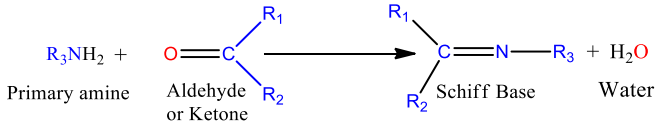


Fig. (3). General procedure for the synthesis of Schiff bases involving the condensation of primary amines with aldehydes or ketones to form the characteristic imine (C=N) linkage.

3.2. General Procedure

To synthesize a Schiff base, begin by selecting a primary amine and a carbonyl compound suitable for the desired product, and dissolve them in a solvent like ethanol or methanol. The reaction is typically carried out under conditions that promote condensation, often using acid or base catalysts. The mechanism involves the nucleophilic attack of the amine on the carbonyl carbon, forming a tetrahedral intermediate, which subsequently loses water to form the Schiff base (imine). The product is isolated and purified using appropriate methods such as filtration or recrystallization. [30-31].

Schiff bases are renowned for their capability to form stable complexes with metal ions, a property that significantly enhances their applications in catalysis, medicine, and materials science. Schiff bases form complexes with metal ions through specific coordination sites. The imine nitrogen atom is the primary donor site, while other atoms, such as oxygen or sulphur, may also participate in binding. These coordination interactions provide stability to the formed complexes. Schiff bases coordinate with metal ions through imine nitrogen atoms and other donor atoms, such as oxygen or sulphur, as shown in Table **1** [32].

3.3. Mechanisms of Antimicrobial Action Schiff Bases Exhibit Antimicrobial Activity through Multiple Mechanisms

3.3.1. Membrane Disruption

The lipophilic nature of some Schiff bases enables them to insert into microbial membranes, disturbing lipid bilayer stability. This leads to increased permeability and leakage of essential cellular contents, such as ions and metabolites. The disruption impairs membrane potential and energy production, often resulting in cell death. Structural features such as hydrophobic groups and aromatic rings enhance this effect [36-37].

3.3.2. Enzyme Inhibition

The reactive C=N (imine) group in Schiff bases can bind to active sites of microbial enzymes, forming covalent or non-covalent interactions. This binding disrupts enzymatic function, halting key processes like DNA replication, transcription, and protein synthesis. Inhibition of these pathways cripples microbial growth and survival. Schiff base targets enzymes selectively, enhancing antimicrobial specificity. Their structural adaptability allows tuning for broad or narrow-spectrum activity [38-39].

3.3.3. Metal Chelation

Schiff base-metal complexes act as potent chelators, binding to microbial DNA or proteins and disrupting their function. The coordinated metal ion enhances reactivity, enabling interactions with sulphur- and nitrogen-rich biomolecules. This interference impairs replication, transcription, and enzyme activity. Chelation can also destabilize metalloproteins essential for microbial survival. Such complexes offer targeted antimicrobial action with improved potency [40].

3.3.4. Reactive Oxygen Species (ROS) Generation

Some Schiff bases, particularly metal complexes, catalyse the production of reactive oxygen species within microbial cells. ROS, such as superoxide and hydroxyl radicals, cause oxidative damage to lipids, proteins, and nucleic acids. The resulting stress overwhelms microbial defense systems, leading to cell dysfunction and death. ROS generation varies with microbial type and Schiff base structure. This mechanism enhances antimicrobial efficacy, especially against resistant strains [41].

4. APPLICATIONS AGAINST RESISTANT MICROBIAL STRAINS

Schiff bases are promising against multidrug-resistant strains due to their diverse modes of action, which reduce the likelihood of cross-resistance. There are various applications, including:

4.1. Antibacterial Activity

Schiff bases, particularly those derived from heterocyclic aldehydes (thiophene, pyridine), show efficacy against resistant bacteria like *Staphylococcus aureus* and *Escherichia coli*. Metal complexes (Cu^{2+}, Zn^{2+}) enhance activity by improving penetration and binding affinity [42-43].

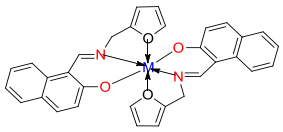
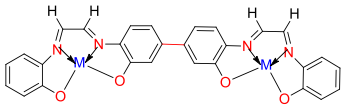
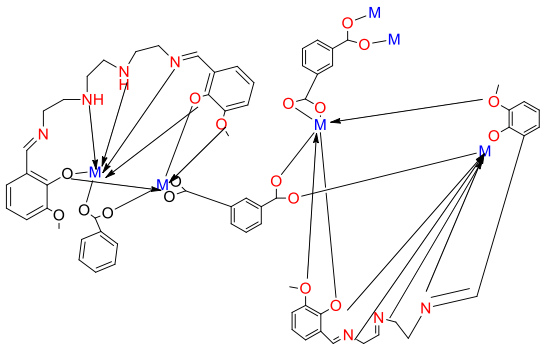
4.2. Antifungal Potential

Schiff bases have emerged as promising antifungal agents, particularly against resistant strains like *Candida albicans*. Their mechanism often involves interference with ergosterol biosynthesis, a critical component of fungal cell membranes, or direct disruption of membrane integrity leading to cell lysis and death. What makes these compounds especially intriguing is the influence of their substituents: electron-donating groups (such as -OH, $-OCH_3$ or $–NH_2$) on the aromatic ring tend to enhance lipophilicity and electron density, which can improve membrane penetration and binding affinity to fungal targets. This structural tuning not only boosts potency but also opens the door to designing selective, less toxic antifungal therapies. In essence, Schiff bases serve as a modular scaffold, with small chemical tweaks yielding significant biological impact [44-45].

4.3. Synergistic Effects

Schiff bases, when combined with antibiotics like ciprofloxacin, show promising potential in combating multidrug-resistant (MDR) strains by enhancing antibiotic efficacy through multiple mechanisms. They can inhibit

Table 1. Types of Schiff base-metal complexes.

Types of Complexes	Structural Presentation	Examples	References
Mononuclear Complexes	Single metal ion coordinated by the Schiff base ligand		[33]
Binuclear Complexes:	Two metal ions bound together by one or more Schiff base ligands		[34]
Polynuclear Complexes	Schiff bases often serve as bridging ligands, connecting multiple metal centres.		[35]

bacterial efflux pumps, raise intracellular antibiotic concentrations, and target alternative cellular pathways that bypass traditional resistance mechanisms. Additionally, Schiff bases may increase membrane permeability and modulate resistance-related gene expression, effectively restoring the potency of antibiotics that have become ineffective. Their structural versatility, especially with electron-donating groups, further amplifies their synergistic impact, making them valuable candidates for the development of next-generation combination therapies [46].

4.4. Biofilm Inhibition

Some Schiff bases prevent or disrupt biofilm formation, a key resistance mechanism, by interfering with quorum sensing or extracellular matrix synthesis. Their customizable structures allow optimization for specific resistant strains, and ongoing research focuses on developing Schiff base-based drugs to combat global antimicrobial resistance [47].

5. OVERVIEW OF MICROBIAL PROTEOMES

Microbial proteomes encompass the entire set of proteins expressed by a microorganism under specific conditions, reflecting its functional and structural capabilities. These proteomes are dynamic, varying with environmental factors, growth phases, and stress responses. They are critical for understanding microbial physiology, survival mechanisms, pathogenicity, and potential therapeutic targets. Proteomics, the large-scale study of these proteins, employs techniques like mass spectrometry, gel electrophoresis, and bioinformatics to map protein expression, interactions, and modifications [48].

Microbial proteomes are diverse across bacteria, fungi, archaea, and viruses, with each organism expressing thousands of proteins tailored to its ecological niche. For example, pathogenic bacteria express virulence factors to evade host defenses, while environmental microbes produce enzymes for nutrient acquisition. Proteomic studies reveal key insights across various sectors, as shown in (Fig. **4**) [49]. Microbial proteomes, representing the complete set of proteins expressed by microorganisms, provide critical insights into cellular machinery, adaptive mechanisms, and responses to environmental cues. Proteomics thus plays a crucial role in mapping microbial stress responses by identifying proteins and their expression dynamics. However, it is limited by incomplete coverage, difficulties in detecting low-abundance or membrane proteins, and the inability to directly correlate protein abundance with functional activity [50-53]. To overcome these gaps, transcriptomics provides complementary insights into gene expression changes and post-transcriptional regulation, while metabolomics captures downstream metabolic alterations that represent real-time functional outcomes of stress. Integrating these omics approaches offers a more holistic view, linking transcriptional regulation, protein abundance, and metabolic flux, and can be further strengthened by alternatives such as phosphoproteomics for post-translational modifications, lipidomics for membrane-associated stress, fluxomics for dynamic pathway analysis, and interactomics for stress-induced protein-protein network change [112-113].

5.1. Proteins Involved in Microbial Survival

There are various proteins that help microbes adapt to environmental changes and establish infections with virulence and pathogenicity in host organisms, as shown in Tables **2** and **3**.

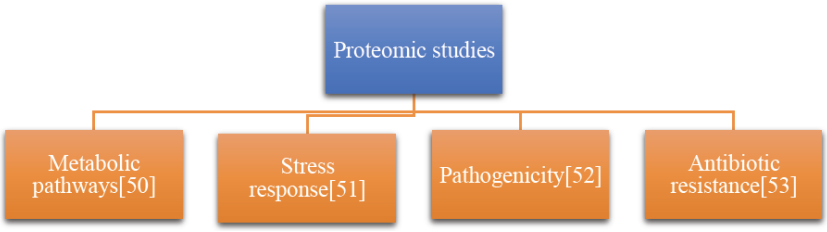


Fig. (4). Proteomic studies reveal key insights into various sectors. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 2. Survival-associated and pathogenicity-associated protein.

Category	Protein	Function/Role	References
Survival-Associated Proteins			
Chaperones & Heat Shock Proteins	DnaK, GroEL	Maintain protein folding under stress (heat, oxidative stress, pH changes).	[54]
Oxidative Stress Response Proteins	Catalase, Superoxide Dismutase	Neutralize reactive oxygen species (ROS) produced by immune cells or environmental factors.	[55]
Nutrient Acquisition Proteins	Siderophores, ABC Transporters	Facilitate the uptake of essential nutrients, such as iron, in nutrient-scarce environments.	[56]
DNA Repair Proteins	RecA, MutS	Repair DNA damage induced by environmental or host stress, maintaining genomic stability.	[57]
Efflux Pumps	AcrAB-TolC (in *E. coli*)	Expel toxic compounds, including antibiotics, contributing to multidrug resistance.	[58]
Pathogenicity-Associated Proteins			
Adhesins	FimH (*E. coli*), InlA (*Listeria*)	Mediate attachment to host cells, critical for initiating infection.	[59]
Toxins	Botulinum Toxin, Cholera Toxin	Disrupt host cell functions, causing tissue damage or immune evasion.	[60]
Type III/IV Secretion Systems	T3SS (*Salmonella*), T4SS (*Legionella*)	Inject effector proteins into host cells to manipulate signaling, the cytoskeleton, or the immune response.	[61]
Biofilm-Forming Proteins	CsgA (*E. coli*)	Promote biofilm formation, increasing resistance to antibiotics and host defences.	[62]
Immune Evasion Proteins	Protein A (*Staphylococcus aureus*)	Bind host antibodies or complement proteins, preventing immune clearance.	[63]

Table 3. Targets and vulnerabilities in microbial pathogens.

Category	Target/Vulnerability	Description/Significance	References
Therapeutic Targets	Essential Proteins	Targeting proteins crucial for survival (ribosomal proteins, MurA) for broad-spectrum antimicrobials.	[64]
	Virulence Factors	Inhibiting adhesins, toxins, or secretion systems to attenuate pathogenicity without inducing resistance.	[65]
	Efflux Pumps	Blocking efflux systems to restore antibiotic sensitivity.	[66]
	Metabolic Enzymes	Disrupting unique microbial pathways (*e.g.,* folate synthesis *via* SulA) for selective targeting.	[67]
Vulnerabilities	Stress Response Dependency	Inhibiting stress proteins (DnaK inhibitors) can sensitize microbes to existing treatments.	[68]
	Biofilm Disruption	Targeting biofilm matrix proteins or quorum sensing to improve antibiotic penetration.	[69]
	Host-Microbe Interface	Blocking adhesins or interaction proteins to prevent infection establishment.	[70]

6. MECHANISMS OF PROTEIN DISRUPTION BY SCHIFF BASES

Schiff bases, formed by the condensation of an amine with a carbonyl compound (typically an aldehyde or ketone), are versatile molecules with significant potential to disrupt microbial proteins. Their ability to interact with proteins stems from their reactive imine (C=N) group and associated chemical properties, making them promising candidates for antimicrobial development. Mechanisms of protein disruption by Schiff bases, focusing on covalent and non-covalent interactions, protein denaturation and aggregation, and inhibition of protein synthesis and function [71,72].

6.1. Covalent and Non-Covalent Interactions

Schiff bases disrupt proteins through both covalent and non-covalent interactions, targeting amino acid residues and altering protein structure or function.

6.1.1. Covalent Interactions

6.1.1.1. Nucleophilic Addition

The electrophilic carbon of the Schiff base imine group reacts with nucleophilic groups on proteins, particularly the primary amines of lysine residues or the thiol groups of cysteine. This forms stable covalent adducts that modify key functional sites. For example, Schiff bases can target lysine residues in enzyme active sites, impairing catalytic activity [73-74].

6.1.1.2. Cross-Linking

Schiff bases with multiple reactive groups can form intra- or intermolecular cross-links between protein chains. This alters protein conformation, disrupts quaternary structure, and inhibits multimeric protein functions (In bacterial secretion systems) [71].

6.1.1.3. Metal Coordination

Many Schiff bases act as ligands, chelating metal ions (Zn^{2+}, Cu^{2+}) essential for metalloproteins. By sequestering or misplacing these ions, Schiff bases disrupt metal-dependent enzymes (In bacterial superoxide dismutase) [75].

6.1.2. Non-Covalent Interactions

Schiff base binds non covalently to target amino acid residues and alters protein structure or function, as shown in Table **4**.

6.2. Protein Denaturation and Aggregation

Schiff bases can induce protein denaturation (loss of native structure) and aggregation (formation of insoluble protein clusters), compromising microbial survival and pathogenicity.

6.2.1. Denaturation

6.2.1.1. Disruption of Secondary/Tertiary Structure

Covalent modification of critical residues (lysine, cysteine) by Schiff bases disrupts hydrogen bonds and electrostatic interactions, stabilizing α-helices or β-sheets. For instance, modification of lysine in chaperone proteins (DnaK) impairs their folding activity [79-80].

6.2.1.2. Hydrophobic Exposure

Schiff base interactions with surface residues can expose hydrophobic core regions, destabilizing the protein's folded state. This is particularly damaging to membrane proteins such as porins and efflux pumps [81].

6.2.1.3. pH Sensitivity

Proteins are highly sensitive to pH changes, which can disrupt their native conformation by altering the ionization states of amino acid side chains, leading to loss of electrostatic interactions, hydrogen bonds, and hydrophobic packing. This destabilization causes denaturation, exposing hydrophobic regions that promote aggregation through non-specific interactions. At extreme pH values, proteins may unfold, lose solubility, and form amorphous aggregates or structured fibrils, depending on the sequence and environment. Such pH-induced denaturation and aggregation are critical considerations in biopharmaceutical formulation, protein storage, and understanding disease-related misfolding [82].

6.2.2. Aggregation

6.2.2.1. Cross-Linking-Induced Aggregation

Covalent cross-links formed by Schiff bases between protein molecules create aggregates, reducing functional protein availability. This is critical for proteins like adhesins, where aggregation disrupts host cell attachment [83].

6.2.2.2. Hydrophobic-Driven Aggregation

Denatured proteins with exposed hydrophobic regions cluster *via* non-covalent hydrophobic interactions, forming

Table 4. Non-covalent interactions of Schiff base.

Interaction Type	Structural Feature of Schiff Base	Protein Target Site	Effect on Binding	References
Hydrophobic Interactions	Aromatic rings or hydrophobic substituents	Hydrophobic pockets in active/allosteric regions	Stabilizes ligand binding *via* van der Waals forces	[76]
Hydrogen Bonding	Imine nitrogen, oxygen, or sulphur atoms	Polar residues (*e.g.,* serine, threonine)	Enhances affinity through directional hydrogen bonding	[77]
π-π Stacking	Aromatic rings	Aromatic amino acids (*e.g.,* phenylalanine, tyrosine)	Facilitates surface/pocket binding *via* π-π interactions	[78]

insoluble aggregates. This can clog cellular processes, such as bacterial biofilm formation [84].

6.2.2.3. Impact on Pathogenicity

Aggregation of virulence factors (toxins, secretion system components) reduces their delivery or activity, attenuating infection [85].

6.3. Inhibition of Protein Synthesis and Function

Schiff bases target various stages of protein synthesis and function, disrupting microbial physiology and survival.

6.3.1. Inhibition of Protein Synthesis

6.3.1.1. Ribosomal Targeting

Some Schiff bases bind to ribosomal proteins or rRNA, interfering with translation. For example, they may mimic natural ligands, competing for binding sites on the 30S or 50S ribosomal subunits, as do antibiotics such as tetracyclines [86-87].

6.3.1.2. tRNA Synthetase Inhibition

Schiff bases covalently modify aminoacyl-tRNA synthetases by targeting nucleophilic residues like lysine in their active sites. This modification disrupts the enzyme's ability to activate amino acids or to charge tRNAs, effectively halting translation and protein synthesis. Such inhibition has promising therapeutic implications, especially in antimicrobial and anticancer strategies, where selective targeting of synthetases can cripple essential cellular functions in pathogens or tumour cells without affecting healthy human tissues [88].

6.3.1.3. Chaperone Disruption

Schiff bases can disrupt protein homeostasis by covalently modifying molecular chaperones like GroEL, which are essential for proper folding of nascent polypeptides. This interference compromises the chaperone's ability to guide and stabilize unfolded or partially folded proteins, resulting in the accumulation of misfolded, non-functional proteins within the cell. Such disruption not only impairs cellular function but can also trigger stress responses or proteotoxicity, making chaperone-targeting Schiff bases a potential strategy in antimicrobial therapies where protein misfolding can be leveraged to selectively damage pathogenic or malignant cells [89].

6.3.2. Inhibition of Protein Function

6.3.2.1. Enzyme Inactivation

Schiff bases inhibit enzymes by covalently modifying active site residues or chelating essential cofactors. For instance, they can target cysteine residues in bacterial β-lactamases, restoring antibiotic susceptibility [90].

6.3.2.2. Membrane Protein Disruption

Schiff bases disrupt membrane-bound proteins (efflux pumps, porins) by altering lipid-protein interactions or forming adducts with extracellular loops, compromising nutrient uptake or drug resistance [91].

6.3.2.3. Virulence Factor Neutralization

Schiff bases can neutralize bacterial virulence by binding to key surface proteins like toxins or adhesins, thereby obstructing their interaction with host cells. A notable example involves Schiff base adducts targeting *Listeria monocytogenes* internalin A (InlA), a surface adhesin crucial for host invasion. By covalently modifying InlA, these adducts prevent its binding to E-cadherin on host epithelial cells, effectively blocking bacterial entry and pathogenesis [92].

6.3.2.4. Signaling Pathway Interference

Schiff bases exert profound effects on bacterial adaptability by targeting two-component regulatory systems, particularly histidine kinases, which serve as environmental sensors and signal transducers. These systems are central to bacterial survival, mediating responses to stress, nutrient availability, host interactions, and antimicrobial threats. Schiff bases can covalently modify nucleophilic residues within the sensor domains of histidine kinases, disrupting their ability to undergo autophosphorylation—a critical step in signal initiation. This interference blocks the transfer of phosphate groups to response regulators, effectively silencing downstream gene expression involved in virulence, motility, quorum sensing, and biofilm formation [93].

6.3.3. Therapeutic Implications and Vulnerabilities

Schiff bases offer strong antimicrobial potential and synergy with antibiotics, but face challenges of selectivity and resistance development, as shown in Table **5**.

7. PROTEOMIC TECHNIQUES FOR ASSESSING PROTEIN INTEGRITY

Proteomic techniques such as 2D gel electrophoresis, Mass Spectrometry (MS), label-free quantification, and bioinformatics approaches are essential for assessing protein integrity, enabling researchers to analyse protein expression, structure, modifications, and interactions. An overview of these methods is presented in Table **6** [98].

8. CASE STUDIES AND EXPERIMENTAL EVIDENCE

8.1. Schiff Bases Against Bacterial Proteomes

Schiff bases exhibit antibacterial activity by interacting with key bacterial enzymes, membranes, or metabolic pathways. Experimental studies highlight their efficacy against both Gram-positive and Gram-negative bacteria, often through mechanisms like enzyme inhibition, membrane disruption, or oxidative stress induction [103].

8.1.1. Thiazolyl-Triazole Schiff Base (2019 Study)

Case Study: A novel thiazolyl-triazole Schiff base (Fig. **5**) was synthesized and tested against Gram-positive (Listeria monocytogenes, Staphylococcus aureus) and Gram-negative (Pseudomonas aeruginosa, Escherichia coli) bacteria.

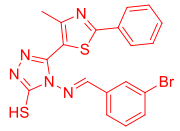


Fig. (5). Thiazolyl-triazole Schiff base [104].

Experimental Evidence: The Schiff base showed superior activity against L. monocytogenes and P. aeruginosa, with antibacterial activity twice that of ciprofloxacin. The minimum inhibitory concentration (MIC) was significantly lower than that of standard drugs, indicating high potency. The study suggested that the Schiff base reduces bacterial nitric oxide synthase (NOS) levels, protecting bacteria from oxidative stress, and may form complexes with metals in bacterial enzyme active sites.

Mechanism: The antibacterial effect likely involves decreasing bacterial NOS activity and disrupting enzyme function *via* metal coordination, thereby enhancing susceptibility to oxidative stress [104].

8.1.2. 4-Aminoantipyrine-Derived Schiff Bases (2025 Study)

Case Study: Schiff bases derived from 4-aminoantipyrine (Fig. **6**) and substituted cinnamaldehydes were evaluated against Multidrug-Resistant (MDR) Gram-positive and Gram-negative bacteria.

Experimental Evidence: Compounds **3f** and **3h** showed strong antibacterial activity, with 3f being the most effective against MDR strains. The MIC ranged from 1-4 µg/mL for **3f** against Enterococcus faecalis, surpassing norfloxacin (MIC 4-8 µg/mL). Molecular docking revealed strong binding affinity for bacterial DNA gyrase, suggesting that inhibition of DNA replication is the mechanism. The bromine atom in **3f** enhanced stability and reactivity, contributing to its bactericidal effect.

Mechanism: These Schiff bases likely disrupt bacterial DNA replication and membrane integrity, as confirmed by docking studies that show interactions with DNA gyrase and other protein targets [105].

8.1.3. Isatin-Derived Schiff Bases (2021 Study)

Case Study: Isatin-based Schiff bases (Fig. **7**) were tested against Bacillus cereus, B. subtilis, S. aureus, E. coli, and MDR E. coli.

Experimental Evidence: MICs ranged from 1.56-50 µg/mL, with synergistic effects when combined with chloramphenicol or kanamycin (4-128-fold potency increase).

Target: Peptide Deformylase (PDF), a bacterial enzyme critical for protein synthesis, was inhibited and validated in S. pneumoniae and E. coli.

Method: Broth microdilution and synergy testing *via* fractional inhibitory concentration (FIC) index.

Significance: Demonstrates Schiff bases as potential components in combination therapies targeting protein synthesis [106].

8.2. Schiff Bases and Fungal Protein Targets

Schiff bases are also effective against fungal pathogens, particularly by targeting proteins involved in fungal cell wall synthesis, biofilm formation, or metabolic processes. Their antifungal activity is often linked to Reactive Oxygen Species (ROS) production or enzyme inhibition [107].

8.2.1. Chitosan-Derived Schiff Bases Against Fusarium (2017-2021 Studies)

Case Study: Chitosan Schiff (Fig. **8**) bases were tested against *Fusarium graminearum and Fusarium oxysporum f.sp. albedinis.*

Experimental Evidence: While less effective than unmodified chitosan against *F. graminearum* (MIC 50 µg/mL vs. 30 µg/mL), specific derivatives (compounds 45 and 46) showed >90% inhibition against *F. oxysporum* at 1 mg/mL. Homology modeling and docking studies targeted Fusarium guanine nucleotide-binding protein (Fgb1) and phytase domain (Fophy), revealing strong binding interactions that correlated with experimental antifungal activity.

Mechanism: The Schiff bases disrupt fungal pathogenicity by binding to Fgb1, reducing germination and heat resistance, and inhibiting Fophy, thereby affecting nutrient acquisition [108]**.**

8.2.2. 4,5-Disubstituted Thiazole Schiff Bases (2024 Study)

Case Study: Novel Schiff bases with 4,5-disubstituted thiazole were synthesized *via* microwave-assisted green chemistry and tested against C. albicans.

Experimental Evidence: The Cu(II) and Zn(II) complexes showed potent antifungal activity, with MIC values of 190-375 µg/mL. Molecular docking against sterol 14-α demethylase (CYP51, PDB: 5TZ1) confirmed strong binding, supporting their antibiofilm activity. The compounds inhibited biofilm formation, a critical factor in fungal resistance.

Mechanism: These Schiff bases target CYP51, disrupting ergosterol biosynthesis in fungal cell membranes, and inhibit biofilm formation through interactions with extracellular matrix components [109].

8.2.3. Quinazoline Schiff Base Complexes (2024 Study)

Case Study: Mixed ligand complexes with a quinazoline Schiff base (Fig. **9**) and glycine were tested against Candida albicans and Aspergillus niger.

Experimental Evidence: Cadmium (II) complex showed superior antifungal activity, with MICs lower than nystatin for C. albicans. Molecular docking targeted fungal N-myristoyltransferase (PDB ID: 3AHU), revealing strong binding affinities.

Method: Agar well diffusion on Sabouraud dextrose agar with a 15 mg/mL concentration of the compound.

Significance: Metal-complexed Schiff bases enhance antifungal efficacy by targeting lipid biosynthesis enzymes [110].

Electron-donating groups stabilize imine bonds and enhance metal coordination, while electron-withdrawing and steric groups modulate lipophilicity, selectivity, and enzyme binding. Imine (C=N) linkages generally confer stronger antimicrobial activity than carbonyl (C=O) linkages due to their superior reactivity and chelation ability (Fig. **10**) [111].

Table 5. Therapeutic implications of Schiff bases, highlighting their antimicrobial potential, synergistic effects with existing antibiotics, challenges of selectivity, risks of microbial resistance, and associated vulnerabilities.

Aspect	Details	Vulnerability	References
Antimicrobial Potential	Schiff bases target essential bacterial proteins (*e.g.,* ribosomal proteins and efflux pumps) and virulence factors, demonstrating promise against multidrug-resistant pathogens.	May affect host proteins if not selective, leading to off-target effects.	[94]
Synergistic Effects	When combined with existing antibiotics, Schiff bases can inhibit resistance mechanisms such as efflux pumps and β-lactamases, thereby enhancing drug efficacy.	Potential for increased toxicity or drug interactions if not carefully optimized.	[95]
Selectivity Challenges	Covalent binding to bacterial targets is effective, but non-specific interactions with host proteins may cause cytotoxicity.	Requires targeted delivery systems or structural refinement to improve specificity.	[96]
Resistance Concerns	Bacteria may adapt by upregulating efflux pumps or mutating target proteins, reducing Schiff base efficacy over time.	Continuous development of new derivatives is essential to stay ahead of the evolution of microbial resistance.	[97]

Table 6. A summary of key analytical methods used to evaluate protein modifications, expression changes, and functional disruptions induced by Schiff base treatments.

Technique	Principle/Description	Application in Schiff Base Studies	References
2D Gel Electrophoresis (2D-GE)	Separates proteins based on isoelectric point (pI) and molecular weight. Visualizes protein expression shifts.	Detects differentially expressed, upregulated, downregulated, or degraded proteins after treatment.	[99]
Mass Spectrometry (MS)	Identifies and characterizes proteins *via* mass-to-charge ratios of ionized peptides (MALDI-TOF, LC-MS/MS).	Determines protein mass, peptide sequences, and post-translational modifications induced by Schiff bases.	[100]
Label-Free Quantification (LFQ)	Quantifies proteins without labelling, using MS signal intensities or spectral counting.	Measures changes in protein abundance across control and Schiff base-treated microbial samples.	[101]
Bioinformatics Tools	Analyses proteomic data for protein identification, quantification, and functional annotation.	Interprets MS data, predicts disrupted pathways, and identifies affected proteins and networks.	[102]

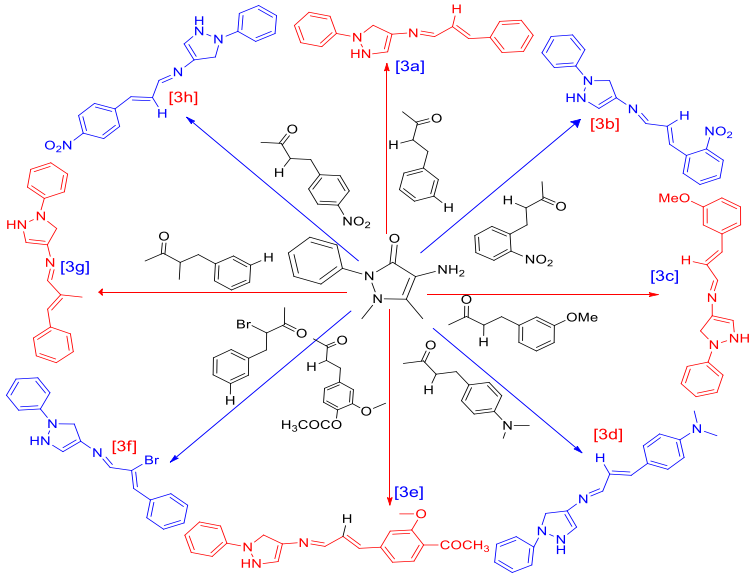


Fig. (6). 4-Aminoantipyrine-derived Schiff bases [105].

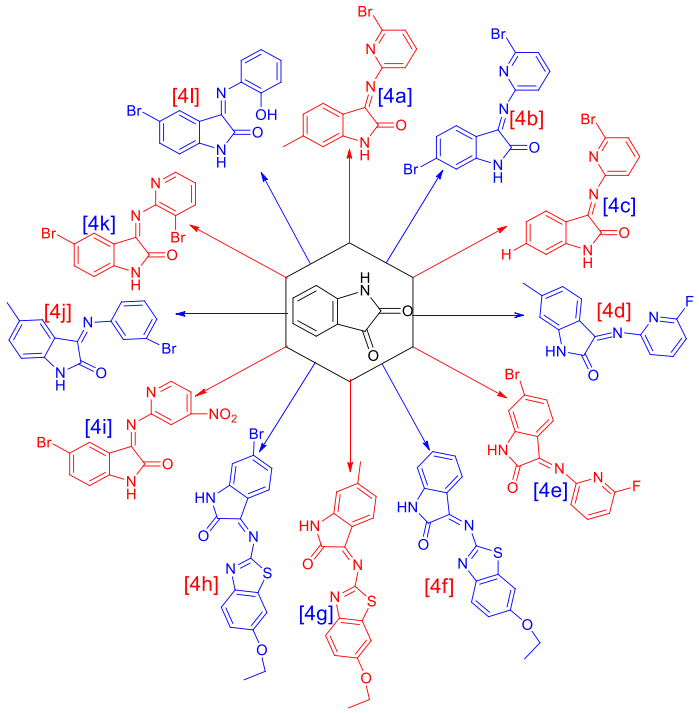


Fig. (7). Isatin-derived Schiff bases [106].

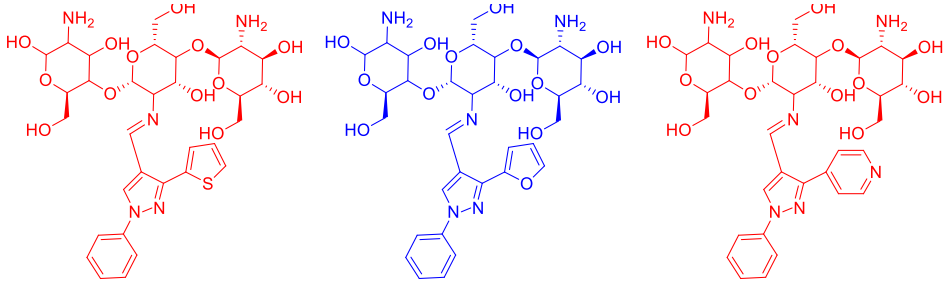


Fig. (8). Chitosan-derived Schiff bases [108].

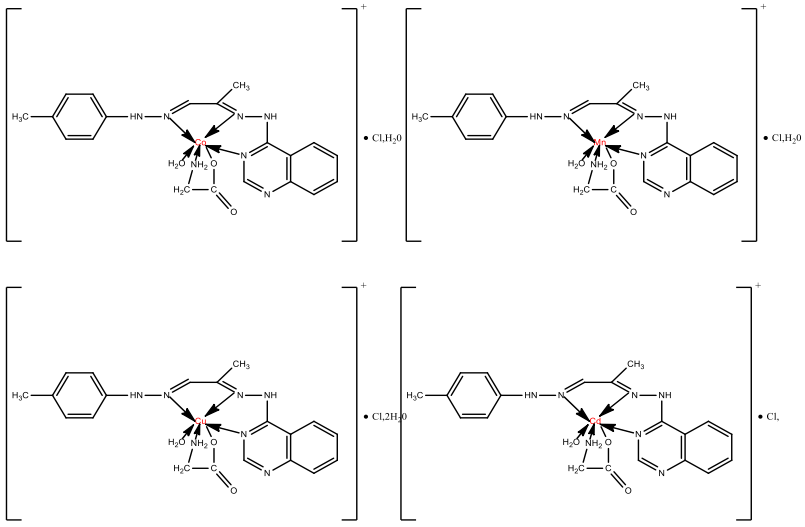


Fig. (9). Quinazoline Schiff base complexes [110].

Based on the above case studies, Schiff base complexes show potent behaviour. Table **7** summarizes the potency of Schiff bases and their complexes against various bacteria.

9. CHALLENGES AND FUTURE PERSPECTIVES

Schiff bases, known for their characteristic carbon-nitrogen double bond, exhibit significant antimicrobial

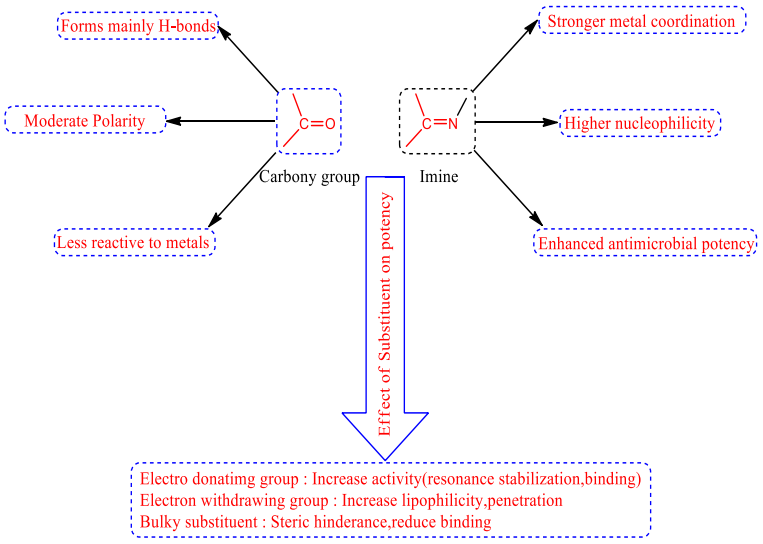


Fig. (10). Effect of substituents on antimicrobial potency: Carbonyl (C=O) vs. Imine (C=N).

Table 7. Effectiveness of Schiff base complexes against microbial strains.

Microbial Strain	Effectiveness	Key Mechanisms of Action	Targeted Microbial Proteins	References
Gram-positive Bacteria				
Staphylococcus aureus (*e.g.,* MRSA)	Highly Effective	Improved penetration and binding affinity; disruption of protein/DNA function.	Penicillin-Binding Proteins (PBPs), DNA gyrase, Topoisomerase IV	[42, 43]
Listeria monocytogenes	Highly Effective	Disruption of virulence factors.	Internalin A, Nitric oxide synthase (NOS)	[92, 104]
Enterococcus faecalis (MDR)	Highly Effective	Inhibition of DNA gyrase, disrupting DNA replication.	DNA gyrase (GyrA/B subunits)	[105]
Bacillus spp. (*B. cereus, B. subtilis*)	Effective	Inhibition of protein synthesis.	Peptide deformylase, Ribosomal proteins	[106]
Gram-negative Bacteria				
Escherichia coli (MDR)	Highly Effective	Enhanced penetration; inhibition of efflux pumps.	AcrA/B-TolC efflux pump, DNA gyrase	[42, 43, 58, 66, 106]
Pseudomonas aeruginosa	Highly Effective	Metal chelation disrupting enzyme function; reduction of bacterial NOS.	Nitric oxide synthase (NOS), β-lactamases	[104]
Fungi				
Candida albicans	Highly Effective	Targeting ergosterol biosynthesis (CYP51 inhibition); biofilm disruption.	Lanosterol 14α-demethylase (CYP51), ALS3 (adhesion protein), HWP1 (hyphal protein)	[44, 45, 109]
Aspergillus niger	Effective	Targeting lipid biosynthesis enzymes.	N-myristoyltransferase (NMT), Chitin synthase	[110]
Fusarium spp. (*F. oxysporum, F. graminearum*)	Effective	Binding to pathogenicity proteins (Fgb1, Fophy) affecting nutrient acquisition.	Fgb1 (G-protein β subunit), Fophy proteins	[108]

properties by disrupting microbial cytoplasmic membranes and inhibiting fungal proteases, ultimately affecting microbial protein integrity. However, elucidating their proteomic pathways remains challenging due to the complexity of microbial proteomes, the need for advanced analytical techniques, the potential development of microbial resistance mechanisms, and the structural diversity of Schiff bases that influences their interactions with different species. Future research should focus on targeted drug development to enhance antimicrobial efficacy, advanced proteomic analyses using techniques such as Mass Spectrometry (MS) for deeper mechanistic insights, and biotechnological

applications-including pharmaceuticals and antimicrobial coatings-which present promising avenues for scientific and medical advancement.

10. FUTURE PERSPECTIVES

To enhance the therapeutic potential of Schiff bases, improving selectivity for microbial proteins over host proteins is crucial. Structural modifications, such as PEGylation, prodrug approaches, and the incorporation of bacterial-targeting ligands, may increase microbial specificity while reducing host toxicity. Delivery systems such as liposomes, chitosan nanoparticles, and hydrogels can further enhance targeted release and bioavailability. Beyond *in vitro* assays, *in vivo* validation using models such as *Galleria mellonella*, *C. elegans*, and murine infection models (sepsis, pneumonia, biofilm-associated infections) will be essential to evaluate efficacy, pharmacokinetics, and safety, ultimately guiding clinical translation [111-115].

CONCLUSION

The exploration of Schiff bases in microbial proteomics offers promising insights into their potential as antimicrobial agents. By disrupting enzymatic functions, structural integrity, and regulatory pathways in bacterial and fungal cells, Schiff bases demonstrate a capacity to compromise microbial survival. Their ability to interfere with key proteins suggests a viable avenue for developing novel therapeutic strategies against resistant pathogens. However, challenges such as microbial adaptation and the structural diversity of Schiff bases necessitate further research to optimize their efficacy and minimize unintended effects. To fully harness their therapeutic potential, future efforts should focus on integrating advanced proteomic techniques with rational drug design, alongside the establishment of standardized protocols for screening, validation, and clinical translation. This approach will be critical for transforming Schiff bases from experimental compounds into reliable candidates for antimicrobial drug development.

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AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Study conception and design: SK; Data collection: JKS; Analysis and interpretation: JKS; Draft manuscript: JKS.

LIST OF ABBREVIATIONS

GE = Gel Electrophoresis

MS = Mass Spectrometry

LFQ = Label-free Quantification

NOS = Nitric Oxide Synthase

MIC = Minimum Inhibitory Concentration

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are basis of this research.

CONSENT FOR PUBLICATION

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The authors declare no conflict of interest, financial or otherwise.

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AI DISCLOSURE STATEMENT

During the preparation of this manuscript, the authors used QuillBot (a language paraphrasing and editing tool) exclusively for language refinement and grammatical improvement. The tool was not used for content generation, data analysis, or interpretation of results. All AI-assisted text was carefully reviewed, verified, and revised by the authors, who take full responsibility for the accuracy, originality, and integrity of the final manuscript.

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