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# Bioinformatics-Driven Molecular Docking and Molecular Dynamics Simulation of Gold Nanoparticle Ligand Complexes for Targeted Antimicrobial Applications

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## ABSTRACT

Inorganic nanoparticles (NPs), such as gold nanoparticles (AuNPs), are one such candidate nanoplatform that has been investigated extensively for its potential to combat multidrug-resistant (MDR) pathogens, due to their tunable size, shape-dependent surface chemistry, and their ability to multivalently conjugate with ligands. Simultaneously, the development of structural bioinformatics, such as molecular docking, molecular dynamics (MD) simulation, quantitative structure activity relationship (QSAR) modelling and machine-learning (ML) toxicity prediction, has revolutionised the rationalization of interactions of nanoparticles with biomolecules before the experiments in wet laboratories. The present review critically synthesises the literature available from 2021 to 2026 dealing with the docking and MD based characterisation of the AuNP–ligand system for targeted antimicrobial therapy. The physicochemical basis of AuNP bioactivity is examined, as well as the computational tool chain developed to model AuNP protein and AuNP membrane interactions, and the translational evidence showing the correlation between in silico predictions of protein binding and in vivo antibacterial, antifungal and antibiofilm activity. Special attention is given to the diversity in the use of different methods and different force fields in docking studies, to the lack of an AuNP-specific force field to guide MD, and thus the uncertainty of transferring docking methods derived from small molecules to a polydisperse AuNP system of many valence states. Based on this, we believe the field has yielded promising binding-affinity and mechanistic information, but there is still a significant disconnect between computational prediction and reproducible clinical translation, and we highlight the areas that need to be addressed to bridge this gap, such as standardisation of the representation of the nanoparticles, treatment of the gold core by hybrid quantum mechanics/molecular mechanics (QM/MM), and integrated ML-driven toxicity screening.

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|---|---|
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## 1. INTRODUCTION

Antimicrobial resistance (AMR) is now recognised as one of the defining public health threats of the twenty-first century, with an estimated 4.95 million deaths associated with bacterial AMR in 2019 alone, of which 1.27 million were directly attributable to resistant infections [1,2]. Projections indicate that, without effective intervention, annual AMR-attributable mortality could rise substantially by 2050, with the heaviest burden falling on south Asia and sub-Saharan Africa [3]. The World Health Organization has repeatedly flagged the shrinking antimicrobial development pipeline as a structural crisis compounding this epidemiological trend [1]. These converging pressures have catalysed interest in nanotechnology-enabled antimicrobial strategies that operate through mechanisms largely orthogonal to conventional antibiotic targets, thereby reducing the likelihood of cross-resistance [4,5]. Metallic nanoparticles, and gold nanoparticles in particular, are attractive candidates because their antimicrobial activity is not confined to a single molecular target; instead, AuNPs and AuNP–ligand conjugates can simultaneously disrupt membrane integrity, generate reactive oxygen species, interfere with ATP synthase and ribosomal function, and act as carriers that concentrate co-administered antibiotics at the site of infection [6-11].

A defining feature of contemporary AuNP antimicrobial research is its deep entanglement with computational biology. Rather than proceeding purely by empirical synthesis-and-test cycles, most recent studies pair wet-laboratory characterisation with in silico target identification, molecular docking of capping ligands or conjugated drugs against candidate bacterial or fungal proteins, and increasingly atomistic or coarse-grained MD simulation of the nanoparticle–membrane or nanoparticle–protein interface [7,19]. This bioinformatics layer is intended to rationalise mechanism of action, prioritise synthetic targets, and provide mechanistic plausibility for observed minimum inhibitory concentrations (MICs). We ask not only what docking and MD studies of AuNP–ligand systems have reported, but how methodologically sound those studies are, whether the computational claims are proportionate to the underlying evidence, and where the field's inferential leaps outrun what current force fields and scoring functions can reliably support [16,18]. This distinguishes the review from prior summaries that catalogue AuNP applications without interrogating the computational pipeline itself.

## 2. REVIEW METHODOLOGY

### 2.1. Review Design and Scope

This study was conducted as a critical narrative review to synthesize and critically evaluate recent evidence on bioinformatics-driven molecular docking, molecular dynamics (MD) simulation, nanoinformatics, and machine-learning approaches applied to gold nanoparticle (AuNP)–ligand systems for antimicrobial applications. The review focused primarily on literature published from January 2021 through July 2026, with particular emphasis on studies investigating AuNP interactions with microbial proteins, membranes, antimicrobial ligands, drug-delivery systems, and computational approaches to nanoparticle toxicity and biological activity.

### 2.2. Literature Search Strategy

A thorough review of literature was done to find and critically analyse published work on computational research for antimicrobial work on AuNP–ligand. The relevant articles were searched in the electronic databases PubMed/MEDLINE, Scopus, Web of Science Core Collection, Google Scholar from January 2021 to July 2026. The keywords were gold nanoparticles, computational modelling, antimicrobial activity, and bioinformatics, and a combination of these keywords were used with boolean operators. Common search terms used were "gold nanoparticles" OR "AuNPs" OR "gold nanoclusters" AND "molecular docking" OR "molecular dynamics" OR "MD simulation" OR "bioinformatics" OR "nanoinformatics" OR "QSAR" OR "machine learning" AND "antimicrobial" OR "antibacterial" OR "antifungal" OR "antibiofilm" OR "antimicrobial resistance" OR "multidrug resistance"). Other keywords included in the additional search included "nanoparticle–protein interaction," "nanoparticle–membrane interaction," "drug conjugation," "force field," "computational toxicology," and "targeted drug delivery. Also, reference lists of relevant research articles and review papers were manually checked for further inclusion of relevant papers.

### 2.3. Eligibility Criteria

Peer-reviewed original research articles and relevant review or methodological papers published in English between 2021 and 2026 were considered. Priority was given to studies involving gold nanoparticles or gold nanoclusters and incorporating molecular docking, molecular dynamics simulation, computational target identification, QSAR, nanoinformatics, machine-learning prediction, or computational toxicity assessment. Studies linking computational findings with in vitro or in vivo antimicrobial, antifungal, or antibiofilm outcomes were considered particularly relevant. Studies involving other nanomaterials were included only when they provided directly transferable methodological insights relevant to AuNP computational modelling and were clearly distinguished from AuNP-specific evidence. Duplicate publications, conference abstracts without sufficient methodological information, editorials, commentaries, non-English publications, and studies without meaningful relevance to nanoparticle bioinformatics or antimicrobial applications were excluded. Purely experimental nanoparticle studies lacking computational or mechanistic relevance were not used as primary evidence for computational conclusions.

### 2.4. Study Selection and Data Extraction

The literature search resulted in the identification of publications that were reviewed with regard to the goal of this review. Recent, peer-reviewed studies reporting the use of computational methods with gold nanoparticles (AuNPs) such as molecular docking,

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molecular dynamics (MD) simulation, nanoinformatics, QSAR, ADMET prediction, and machine learning approaches in antimicrobial research were preferred. Other studies that offered useful insights into methodology or fundamental information related to AuNP–ligand interactions were also included. Data from the selected publications covered data such as publication year, composition/functionalization of nanoparticles, size (when available), ligand/therapeutic payload, the biological targets, computational tools and software used, docking protocols, MD simulation parameters, predicted binding interactions, antimicrobial outcomes, toxicity assessment, and main conclusions from each study. The information retrieved was critically synthesized, highlighting the advances in the field, trends in methodology, limitations, and areas for future research in antimicrobial application of computational nanobiotechnology.

### 2.5. Critical Appraisal and Evidence Synthesis

Because the included literature encompassed heterogeneous computational, experimental, and review designs, statistical pooling or meta-analysis was not considered appropriate. Findings were therefore synthesized qualitatively and critically. Particular attention was given to the validity of nanoparticle representation in docking models, suitability of scoring functions and force fields, treatment of the gold core, simulation conditions, correspondence between computational and experimentally characterized nanoparticles, biological relevance of selected molecular targets, and the extent to which computational predictions were experimentally validated. Docking scores and stable MD trajectories were interpreted as evidence supporting the plausibility of proposed interactions rather than definitive proof of antimicrobial mechanisms. The review also examined reproducibility concerns arising from nanoparticle polydispersity, differences in surface functionalization, force-field selection, simulation protocols, and experimental conditions. Evidence from machine-learning and nanotoxicology studies was assessed with consideration of dataset size, descriptor selection, model validation, and applicability to AuNP systems. The resulting evidence was organized thematically to identify established findings, methodological limitations, translational gaps, and priorities for future research.

## 3. GOLD NANOPARTICLES: PHYSICOCHEMICAL BASIS AND SYNTHESIS

### 3.1. Structural and Optical Properties Relevant to Bioactivity

AuNPs exhibit size- and shape-dependent surface plasmon resonance, a high surface-area-to-volume ratio, and a chemically versatile surface that supports thiol-, amine-, and carboxyl-mediated ligand attachment [9]. These properties underlie two distinct but complementary antimicrobial paradigms: intrinsic nanoparticle bioactivity, in which the bare or lightly capped gold core disrupts bacterial physiology directly, and carrier-mediated bioactivity, in which the AuNP core serves as a scaffold that concentrates and delivers a conjugated antimicrobial ligand (peptide, antibiotic, or phytochemical) to its target [11,29]. Because the two paradigms imply different rate-limiting steps — membrane translocation versus target-protein binding — the appropriate computational strategy differs accordingly: intrinsic bioactivity is best probed by MD simulation of nanoparticle–membrane interaction, whereas carrier-mediated bioactivity is more amenable to conventional ligand–protein docking of the conjugated payload [23,26]. A recurring weakness across the reviewed literature is the conflation of these two paradigms, with docking scores for a capping ligand sometimes presented as if they explained whole-nanoparticle antibacterial activity [13].

### 3.2. Green and Biogenic Synthesis Routes

Green synthesis — using plant extracts, fungal or bacterial metabolites, and other biogenic reducing/capping agents — has become the dominant synthetic route reported in the antimicrobial AuNP literature over the past five years, motivated by reduced toxicity, lower cost, and the intrinsic bioactivity of many phytochemical capping agents [8,10]. Representative examples include bakuchiol-mediated AuNPs evaluated against bacterial and cancer targets with paired network-pharmacology and docking analysis [19], and resveratrol-coated gold nanorods synthesised for anti-Candida activity [32]. A methodological consequence of green synthesis is polydispersity: biogenic reducing agents typically yield a distribution of particle sizes and, in many cases, a mixture of morphologies (spheres, rods, triangles) within a single batch [10,18]. This polydispersity is rarely represented in the accompanying computational work, where docking is almost invariably performed on a single idealised ligand or, at best, a small gold cluster rather than the polydisperse nanoparticle population actually characterised experimentally [18].

## 4. THE BIOINFORMATICS AND COMPUTATIONAL TOOLKIT

### 4.1. Molecular Docking Engines

AutoDock Vina remains the most frequently used docking engine in the AuNP-antimicrobial literature, prized for its speed, open-source availability, and an empirically parameterised scoring function balancing hydrophobic, hydrogen-bonding, and electrostatic terms [16,17]. Recent algorithmic refinements — including improved local-search optimisation and expanded force-field terms in Vina 1.2.x — have modestly improved pose accuracy without fundamentally altering the scoring paradigm [17]. Web-accessible platforms such as the redesigned SwissDock, which now wraps both AutoDock Vina and the physics-based Attracting Cavities algorithm behind a unified interface, have lowered the technical barrier for wet-laboratory groups without dedicated computational infrastructure [15]. These tools were developed and validated on small-molecule ligands binding to well-defined protein pockets; none was purpose-built to represent a several-nanometre gold core coordinated by dozens to hundreds of surface ligands [16]. When applied to AuNP systems, the common workaround is to dock only the capping or conjugated ligand — effectively treating the gold core as an inert delivery vehicle — a simplification that is defensible for carrier-mediated systems but conceptually inadequate when the gold surface itself participates in target binding [18].

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### 4.2. Molecular Dynamics Simulation

Where docking provides a static binding-pose snapshot, MD simulation captures the temporal evolution of AuNP–biomolecule interactions, including ligand reorientation, membrane insertion depth, and nanoparticle-induced lipid demixing [23,25]. All-atom MD studies using CHARMM- or AMBER-derived force fields have characterised how thiolate-protected gold nanoclusters of varying size and surface-ligand charge density partition into phospholipid bilayers, with cationic clusters exhibiting markedly higher membrane affinity than neutral or anionic analogues [23]. Coarse-grained approaches, most commonly MARTINI-based, trade atomistic resolution for access to the microsecond-to-millisecond timescales relevant to full membrane translocation, though different MARTINI parameterisations (POL- versus BMW-MARTINI) can yield qualitatively different binding outcomes for the same functionalised nanoparticle, underscoring a persistent force-field-selection sensitivity in the field [23]. More recent ionic-strength-resolved MD studies have shown that divalent cations such as $Ca^{2+}$ and $Mg^{2+}$ interact more strongly with anionic AuNP surfaces than monovalent $Na^{+}$ or $K^{+}$, with direct implications for how AuNP aggregation behaves in physiological versus in vitro assay buffers [25]. MD has also been used to model AuNPs as drug carriers, for example simulating the co-transport of a hydrophobic and a hydrophilic drug across a DPPC bilayer in the presence of a neutral gold nanoparticle, revealing that the carrier accelerates hydrophobic drug translocation while leaving hydrophilic drug kinetics comparatively unaffected [26]. Replica-exchange MD has additionally been applied to characterise AuNP interactions with amyloidogenic peptides, identifying persistent electrostatic contact sites that are structurally analogous to those proposed for AuNP interactions with cationic antimicrobial peptide sequences [24].

### 4.3. Nanoinformatics, QSAR, and Machine Learning

A distinct but converging computational stream nanoinformatics applies data-driven and machine-learning methods to predict nanoparticle physicochemical behaviour, biodistribution, and toxicity directly from compositional and structural descriptors, without requiring an explicit atomistic simulation [34,36]. Ensemble regression approaches (random forest, XGBoost, LightGBM, CatBoost, and voting regressors) have been applied specifically to predict AuNP antibacterial zone-of-inhibition outcomes from a curated multi-study dataset, achieving prediction accuracies that begin to rival direct experimental screening for lead prioritisation [37]. Parallel ML efforts target nanoparticle cytotoxicity rather than antibacterial efficacy, using descriptors such as size, surface charge, dose, and exposure duration to classify or regress cytotoxic outcomes across heterogeneous nanomaterial datasets [30,38]. A comprehensive review of artificial intelligence applications in nanotoxicology has argued that combining QSAR-style descriptor modelling with ADMET-profiling tools (such as ADMETlab 2.0) and physiologically based pharmacokinetic modelling offers the most defensible near-term path toward predictive nanosafety assessment [39,40].

**Table 1. Principal computational approaches used in gold nanoparticle–ligand antimicrobial research**

| Computational approach | Primary purpose | Typical outputs | Main strength | Major limitation in AuNP research | Representative references |
|---|---|---|---|---|---|
| Molecular docking | Prediction of ligand–protein or nanoparticle-associated ligand–target interactions | Binding pose, binding affinity/score, interacting residues | Rapid screening and prioritization of potential molecular targets | Conventional docking programs were designed primarily for small molecules and may not adequately represent the gold core or multivalent nanoparticle surface | [15–20] |
| Atomistic molecular dynamics | Evaluation of AuNP interactions with proteins, peptides and lipid membranes at atomic resolution | RMSD/RMSF, interaction energies, hydrogen bonding, membrane insertion, structural stability | Provides dynamic information not available from static docking | Gold-specific force-field parameters remain incompletely standardized and simulations are computationally demanding | [23–26] |
| Coarse-grained molecular dynamics | Simulation of larger nanoparticle–membrane systems over longer timescales | Membrane penetration, aggregation, lipid redistribution and nanoparticle orientation | Enables longer simulations and larger biological systems | Results may vary substantially according to coarse-grained parameterization and reduced structural resolution | [23,25] |
| Nanoinformatics | Prediction of nanoparticle | Activity–property relationships, predicted | Allows rapid screening of | Limited by heterogeneous | [30,34–39] |

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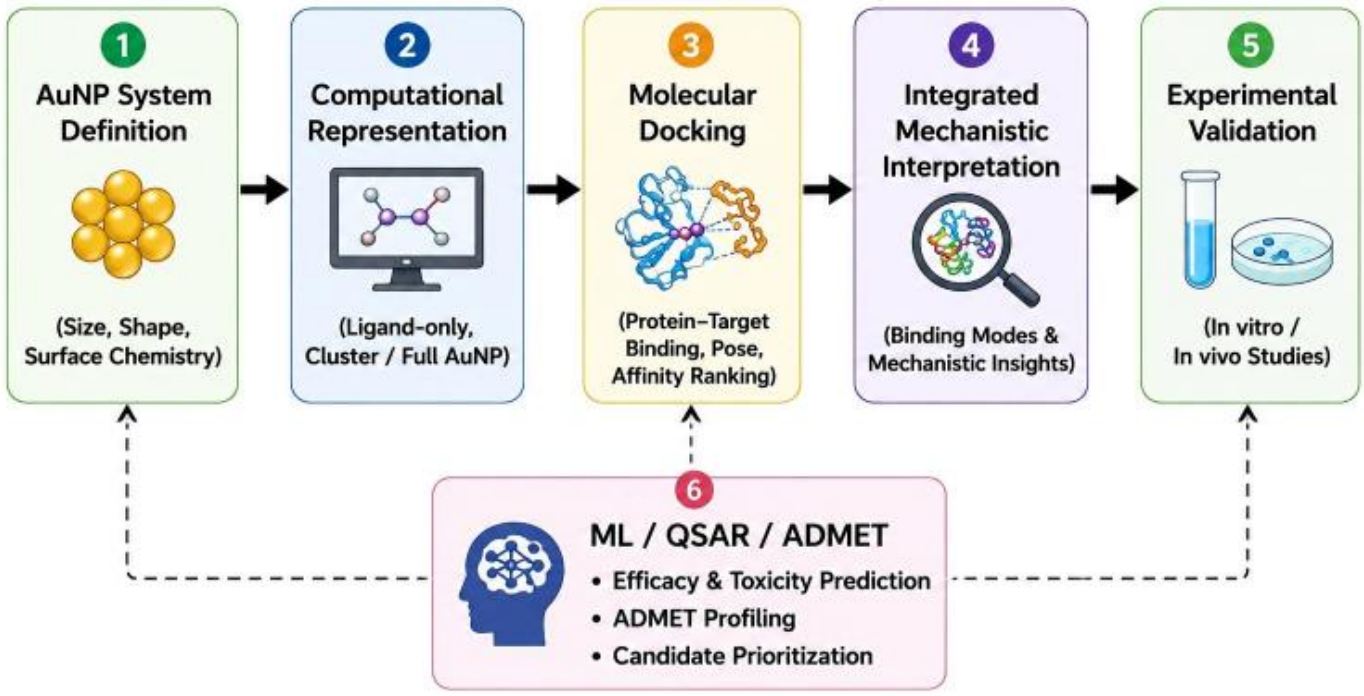
| and QSAR | properties and biological responses from physicochemical descriptors | efficacy and toxicity | many nanoparticle formulations without explicit molecular simulation | datasets, inconsistent nanoparticle characterization and poor external validation | |
| Machine learning | Prediction and prioritization of antibacterial efficacy, toxicity and other biological outcomes | Classification/regression models, feature importance and predicted activity | Can identify complex nonlinear relationships between nanoparticle properties and biological effects | Model performance depends strongly on dataset size, quality and standardization | [34,37–39] |
| ADMET and computational toxicology | Early prediction of safety, exposure and pharmacological suitability | Toxicity risk, absorption, distribution, metabolism and related predictions | Helps integrate safety assessment into early nanoparticle development | Conventional ADMET models are generally optimized for small molecules rather than complex nanomaterials | [30,38–40] |

*Abbreviations: ADMET, absorption, distribution, metabolism, excretion and toxicity; AuNP, gold nanoparticle; MD, molecular dynamics; QSAR, quantitative structure–activity relationship; RMSD, root-mean-square deviation; RMSF, root-mean-square fluctuation.*

**Figure 1. Integrated computational workflow for AuNP-ligand antimicrobial research**




## 5. DOCKING STUDIES OF AUNP–LIGAND SYSTEMS AGAINST ANTIMICROBIAL TARGETS

The dominant experimental design pattern in the reviewed literature couples green or biogenic AuNP synthesis with protein–protein interaction network analysis to nominate candidate bacterial or fungal targets, followed by docking of the capping phytochemical against the shortlisted protein [19]. In the bakuchiol-AuNP study, network pharmacology analysis nominated GNAI3 as the top-

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ranked target with a docking binding energy of −7.5 kcal/mol, compared with −6.9 kcal/mol for the alternative candidate PTGER3, and this ranking was used to prioritise subsequent antibacterial and anticancer bioassays [19]. A comparable workflow has been applied to SARS-CoV-2-relevant targets, where AuNPs and AgNPs were docked onto spike-protein receptor-binding-domain/ACE2 complexes across five viral variants, alongside the natural compound beta-escin, to rank nanoparticle–target binding stability [20]. Although this study addresses an antiviral rather than antibacterial endpoint, its docking methodology treating the nanoparticle surface as a rigid or semi-rigid docking partner against a pre-formed protein–protein complex illustrates a technique now being adapted across the wider AuNP-antimicrobial literature [20].

For antibiofilm applications, docking has been used to screen candidate biofilm-associated proteins (adhesins, quorum-sensing regulators, and extracellular polymeric substance synthases) against nanoparticle-associated ligands, with binding scores used post hoc to rationalise observed reductions in biofilm biomass [21]. A related in silico/in vitro study of green-synthesised zinc oxide nanoparticles against oral biofilm bacteria similarly paired docking against candidate targets with experimental viability assays, a design template increasingly mirrored in AuNP-specific antibiofilm work even though the metal cores differ mechanistically [22]. A systematic survey of docking approaches applied to green-synthesised metal nanoparticles more broadly reported representative binding energies in the range of approximately −7 to −12.5 kcal/mol for metal-oxide nanoparticle-associated ligands docked against bacterial DNA gyrase B, dihydropteroate synthase, thymidylate kinase, and FtsZ, targets chosen because they are validated antibiotic mechanisms of action rather than nanoparticle-specific discoveries [18]. This pattern docking a natural-product capping ligand against a conventional, already-druggable bacterial target is pervasive, and it raises an important interpretive caveat: a favourable docking score against DNA gyrase or FtsZ demonstrates that the capping ligand could plausibly act like a small-molecule inhibitor, but it does not, by itself, establish that this mechanism explains the antibacterial activity of the intact, ligand-decorated nanoparticle as tested experimentally [13,18].

A recent critical review of AuNP antibacterial efficacy has made a related point at the mechanistic level, noting that mass-spectrometry-based metabolomic profiling of AuNP-treated bacteria implicates simultaneous perturbation of protein synthesis, energy metabolism, and quorum-sensing pathways, a multi-target signature that is difficult to reconcile with the single-target framing implicit in most docking-based mechanistic claims [12,13]. The authors argue that docking studies are best interpreted as generating testable, target-specific hypotheses within a broader multi-mechanistic picture, rather than as definitive mechanistic proof [13].

## 6. MOLECULAR DYNAMICS INSIGHTS INTO AUNP–BIOMOLECULE INTERACTIONS

MD simulation contributes a complementary, dynamic perspective that static docking cannot capture, particularly for the membrane-disruption mechanisms believed to underlie much of AuNPs' intrinsic (ligand-independent) antibacterial activity [23,25]. Atomistic MD of thiolate-protected gold nanoclusters interacting with phospholipid bilayers has shown that cluster size, surface-ligand charge density, and aggregation state jointly determine membrane affinity, with the mid-sized Au25(SR)18 cluster in one comparative study exhibiting the strongest membrane affinity among six cluster sizes tested [23]. These findings carry a direct design implication for antibacterial AuNP engineering: surface charge density, not gold-core size alone, appears to be the primary tunable parameter governing membrane engagement, a conclusion that is difficult to reach from docking data alone and illustrates the distinct explanatory value MD adds to the bioinformatics pipeline [23,25]. Ionic-strength-resolved MD work extends this picture by showing that the physiological ionic milieu rather than the nanoparticle alone substantially modulates AuNP aggregation and hence the effective size and surface charge presented to a bacterial membrane in situ [25].

MD-based carrier studies, such as the simulation of flutamide and glutathione co-transport across a DPPC bilayer with a neutral AuNP carrier, demonstrate that nanoparticle conjugation can differentially accelerate transport of hydrophobic over hydrophilic payloads, a mechanistic nuance directly relevant to antimicrobial drug-delivery design where the conjugated antibiotic's polarity will determine whether AuNP carriage meaningfully improves membrane penetration [26]. This class of study also illustrates a broader limitation: most published AuNP-membrane MD work uses idealised, single-lipid-species bilayers (commonly DPPC or POPC), which do not capture the compositional complexity of Gram-negative outer membranes, including lipopolysaccharide, or of fungal ergosterol-rich membranes relevant to antifungal AuNP applications [23,26]. Replica-exchange MD studies of AuNP interactions with the amyloid-beta peptide, while originally motivated by neurodegeneration research, are methodologically instructive for the antimicrobial peptide (AMP)–AuNP field because they demonstrate reproducible identification of persistent, charge-driven binding sites between a capped gold surface and a flexible peptide chain an approach directly transferable to characterising how cationic AMPs orient upon AuNP conjugation [24,27]. To date, however, comparably rigorous replica-exchange or enhanced-sampling MD studies of AMP–AuNP conjugates specifically designed for antibacterial application remain scarce, with most AMP-AuNP papers relying on docking alone to describe the conjugation interface [27].

## 7. TARGETED DELIVERY AND CONJUGATION STRATEGIES

Beyond intrinsic bioactivity, AuNPs are widely engineered as targeted carriers that combine a recognition ligand (peptide, aptamer, or antibody fragment) with a conventional antimicrobial payload, aiming to concentrate drug delivery at the infection site and reduce off-target toxicity [11,30]. Size-controlled AuNPs tethering antimicrobial peptides have demonstrated potent, broad-spectrum activity (0.13–1.25 μM) against clinical isolates including methicillin-resistant Staphylococcus aureus, CTX-M-14-producing Escherichia coli, and multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii, with computational modelling of peptide surface density used to rationalise the observed potency gains over free peptide [27]. Lipopolysaccharide-targeting-peptide-capped chitosan-gold nanoparticles represent a related design strategy, in which the targeting peptide is selected computationally for

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LPS affinity before conjugation, and the resulting nanoparticle is activated by laser irradiation for combined photothermal and chemical antibacterial action [28]. Gentamicin- and vancomycin-conjugated gold nanostructures illustrate the antibiotic-recycling rationale underlying much of this literature: aminoglycoside- or glycopeptide-gold conjugates have been reported to restore or markedly enhance activity against resistant strains relative to the free antibiotic, with proposed mechanisms including enhanced local drug concentration and altered target engagement at the modified cell-wall interface [29].

A recent review explicitly framing gold nanoparticles as multidrug-resistance-countering agents catalogues bacterial growth inhibition, biofilm disruption, reactive-oxygen-species generation, and antibiotic-efficacy enhancement as the principal mechanistic categories through which AuNP-based conjugates act, while cautioning that synergy with conventional antibiotics is not universal and depends strongly on conjugation chemistry and bacterial species [11]. Computational efforts to systematise this conjugation design space integrating docking of the targeting ligand, MD assessment of conjugate stability, and downstream ADMET prediction have recently been proposed as an 'integrated computational insights' framework intended to accelerate rational AuNP drug-delivery design rather than relying on iterative empirical optimisation [30]. Antifungal applications of AuNP conjugation follow an analogous logic. Resveratrol-coated gold nanorods have shown fungicidal activity against Candida albicans at low microgram-per-millilitre concentrations, with reduced biofilm viability, decreased reactive-oxygen-species production, and lowered ergosterol content, alongside favourable in vivo tolerability in a Galleria mellonella model [32]. Separately, incorporating AuNPs into itraconazole-loaded hydrogels has been shown to approximately double the diffusion coefficient of the antifungal through the gel matrix while enhancing anti-Candida activity relative to itraconazole alone, illustrating a formulation-level rather than target-binding rationale for AuNP inclusion [33].

## 8. MACHINE LEARNING AND PREDICTIVE TOXICOLOGY INTEGRATION

As the volume of published AuNP bioactivity data has grown, several groups have applied supervised machine learning directly to structured nanoparticle datasets rather than to individual docking or MD trajectories. An ensemble-regression study using random forest, gradient-boosted, and voting-regressor architectures trained on 322 curated AuNP antibacterial records achieved predictive performance for zone-of-inhibition outcomes that the authors argue could meaningfully triage synthetic candidates ahead of wet-laboratory testing [37]. Complementary nanotoxicology-focused ML work has modelled cytotoxic outcomes as a function of nanoparticle concentration, size, and exposure duration, consistently identifying concentration as the single most influential predictor across multiple algorithms, a finding with direct relevance for AuNP antimicrobial dosing where the therapeutic window between antibacterial and cytotoxic concentrations can be narrow [30,38]. A broader review of artificial-intelligence applications in nanotoxicology has proposed integrating QSAR-style nanodescriptor models with ADMET-profiling suites such as ADMETlab 2.0, arguing that this combination rather than either approach alone offers the most tractable near-term route to predictive, regulator-relevant nanosafety assessment [39,40].

Nanoinformatics reviews more broadly describe machine learning contributions across the nanomedicine pipeline, spanning nanoparticle property prediction, ab initio nanoparticle design in place of trial-and-error synthesis, biodistribution modelling, and biocompatibility assessment, while cautioning that the fragmented, non-standardised state of nanomaterial data repositories currently limits cross-study model transferability [34,35,36]. This data-standardisation gap is, in our assessment, the single greatest structural obstacle to realising the predictive potential these ML approaches otherwise demonstrate on a per-study basis [34].

## 9. CRITICAL ANALYSIS: METHODOLOGICAL LIMITATIONS AND TRANSLATIONAL GAPS

### 9.1. Nanoparticle Representation in Docking Workflows

The single most consequential methodological limitation across the reviewed literature is the representation gap between the nanoparticle actually synthesised and characterised experimentally, and the ligand or small gold cluster actually docked computationally [16,18]. Docking software validated on drug-like small molecules binding rigid or semi-flexible protein pockets is being applied, almost without exception, to the capping or conjugated ligand alone, implicitly treating the gold core as inert [16,18]. This is a reasonable approximation only when the antimicrobial mechanism is genuinely carrier-mediated; where the gold surface itself is proposed to participate in target engagement, as in several intrinsic-bioactivity mechanistic claims, the same simplification becomes a source of unquantified error [13,23].

### 9.2. Force-Field and Scoring-Function Suitability

MD force fields for lipids, proteins, and water are extensively validated, but force-field parameters for gold–ligand and gold–water interactions remain comparatively underdeveloped, and different studies employ different, not always mutually consistent, parameterisations for the gold core [23,25]. The demonstrated sensitivity of nanoparticle–membrane binding outcomes to the choice of coarse-grained model (POL- versus BMW-MARTINI) for chemically identical functionalised nanoparticles is a direct illustration of this problem, and it means that quantitative binding-affinity comparisons across studies using different force fields should be treated with considerable caution [23].

### 9.3. From Binding Energy to Biological Outcome

A favourable docking binding energy or a stable MD trajectory demonstrates thermodynamic or kinetic plausibility of a proposed interaction; it does not, on its own, establish that the interaction is rate-limiting for the observed antimicrobial phenotype [12,13]. Metabolomic evidence that AuNPs simultaneously perturb multiple bacterial pathways underscores that single-target docking

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narratives, however internally consistent, likely capture only part of a broader multi-mechanistic reality [12]. We consider it a persistent weakness of the reviewed literature that docking results are frequently presented as mechanistic conclusions rather than as one hypothesis-generating strand of evidence among several.

### 9.4. Polydispersity, Batch Variability, and Reproducibility

Green-synthesis-derived AuNPs are characteristically polydisperse in both size and morphology, yet computational modelling almost universally uses a single idealised particle or cluster [10,18]. This mismatch is rarely acknowledged as a limitation in the primary literature, and it likely contributes to the batch-to-batch variability in antimicrobial potency documented across independent replications of ostensibly similar green-synthesis protocols [8,10]. Standardised reporting of size-distribution data alongside any accompanying docking or MD analysis would materially improve the interpretability of future studies.

### 9.5. Translational and Regulatory Considerations

Despite two decades of preclinical AuNP-antimicrobial research, clinical translation remains limited, and regulatory pathways for nanoparticle-based antimicrobials are still comparatively immature relative to conventional small-molecule antibiotics [5,6]. Predictive nanotoxicology, if adequately validated, could shorten this translational pathway by front-loading safety assessment before costly in vivo and clinical studies, but current ML toxicity models are trained on heterogeneous, non-harmonised datasets that constrain their regulatory utility at present [38,39].

**Table 2. Major applications, methodological challenges and research priorities in computational AuNP antimicrobial research**

| Research domain | Computational contribution | Major current limitation | Recommended future direction |
|---|---|---|---|
| Antimicrobial target identification | Docking can prioritize bacterial or fungal proteins potentially interacting with AuNP-associated ligands | Favorable docking scores are sometimes interpreted as proof of antimicrobial mechanism | Validate predicted targets experimentally using biochemical, genetic or functional assays |
| Nanoparticle–membrane interaction | MD can characterize membrane adsorption, penetration, lipid disturbance and effects of nanoparticle surface charge | Many simulations use simplified single-component lipid bilayers that do not accurately represent bacterial or fungal membranes | Use biologically realistic Gram-positive, Gram-negative and fungal membrane models |
| AuNP–ligand representation | Computational models simplify complex nanoparticle systems sufficiently for simulation | Docking frequently represents only the ligand or a small gold cluster rather than the experimentally synthesized nanoparticle | Develop validated multiscale and AuNP-specific computational representations |
| Force-field selection | Force fields allow simulation of AuNP interactions with water, proteins and membranes | Gold–ligand and gold–water parameters are not standardized across studies | Develop and benchmark AuNP-specific force fields across independent research groups |
| Targeted antimicrobial delivery | Docking and MD can help optimize peptides, antibiotics and other AuNP-conjugated payloads | Predicted binding or transport improvements may not translate directly to antimicrobial efficacy | Integrate computational predictions with MIC, biofilm and in vivo validation |
| Nanoparticle toxicity | QSAR, ML and ADMET approaches enable preliminary safety prediction | Existing models rely on heterogeneous datasets and conventional molecular descriptors that may inadequately represent nanoparticles | Develop standardized nanotoxicology datasets incorporating particle size, morphology, charge, coating and exposure conditions |
| Reproducibility | Computational modelling enables controlled mechanistic investigations | Experimental AuNPs are commonly polydisperse, whereas computational models usually represent a single idealized structure | Report size distributions and surface characteristics and model representative nanoparticle populations |
| Clinical translation | Integrated modelling may help prioritize candidates before costly experimental testing | Computational predictions remain poorly linked to reproducible clinical outcomes | Combine docking, MD, ML/toxicity modelling and experimental validation within unified development pipelines |

*Abbreviations: ADMET, absorption, distribution, metabolism, excretion and toxicity; AuNP, gold nanoparticle; MD, molecular dynamics; MIC, minimum inhibitory concentration; ML, machine learning; QSAR, quantitative structure–activity relationship.*

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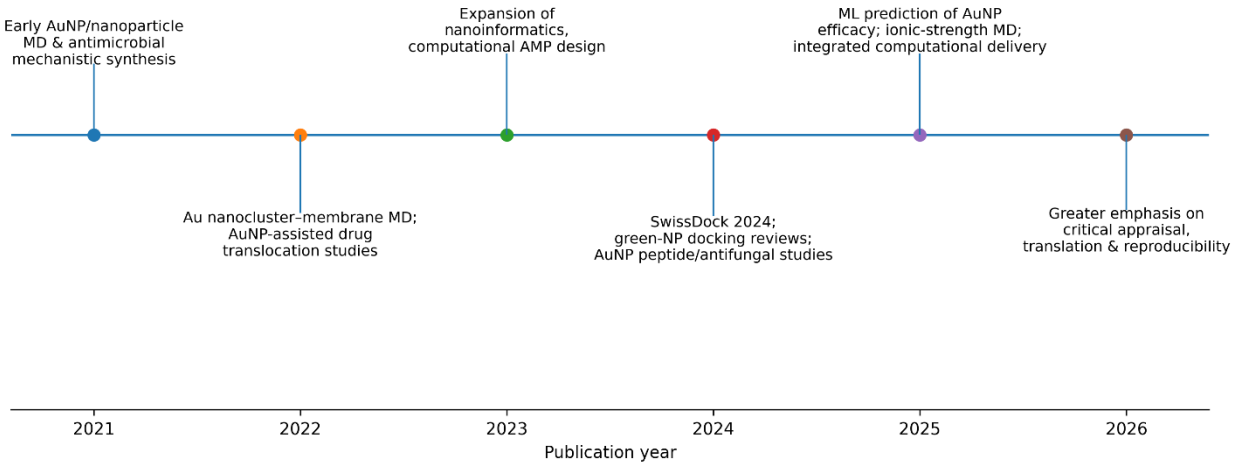
**Figure 2. Evolution of computational themes in the literature cited by this review**




## 10. FUTURE DIRECTIONS

We identify four priorities for the field. First, hybrid quantum mechanics/molecular mechanics (QM/MM) or coarse-grained-with-atomistic-core approaches should be more systematically applied to represent the gold core explicitly in docking and MD workflows, rather than reducing the analysis to the capping ligand alone, particularly for mechanistic claims involving direct gold–biomolecule contact [16,23]. Second, force-field development specific to functionalised gold nanoclusters should be prioritised and benchmarked across research groups to reduce the current sensitivity of MD outcomes to arbitrary parameterisation choices [23,25].

Third, the field would benefit from standardised, shared nanoparticle bioactivity datasets analogous to ChEMBL or PDBbind for small-molecule drug discovery that document particle size distribution, morphology, surface chemistry, and assay conditions alongside antimicrobial outcome, enabling more robust machine-learning model training and cross-study validation [34,37]. Fourth, closer integration of docking, MD, and ADMET/toxicity prediction within a single reported workflow rather than as disconnected analyses within a single paper would allow binding plausibility, dynamic stability, and safety margin to be assessed jointly rather than sequentially [30,40].

Realising these priorities will require closer collaboration between computational and synthetic groups than is typical in the current literature, where the bioinformatics component is often appended to an experimentally driven study rather than co-designed with it from the outset [19,30]. Journals and funders could accelerate this shift by requiring explicit reporting of nanoparticle size distribution and force-field provenance alongside any docking or MD claim submitted for publication.

## 11. CONCLUSION

Gold nanoparticles occupy a genuinely promising position in the search for antimicrobial strategies orthogonal to conventional antibiotic resistance mechanisms, and the bioinformatics toolkit docking, molecular dynamics, and machine-learning-based prediction has meaningfully accelerated hypothesis generation and target prioritisation across this literature. At the same time, a critical reading of the 2021–2026 literature reveals a persistent gap between the sophistication with which nanoparticle antimicrobial phenotypes are characterised experimentally and the comparatively coarse approximations still used to represent those same nanoparticles computationally. Closing this gap through better nanoparticle-specific force fields, standardised shared datasets, and integrated docking–MD–ADMET workflows is, in our assessment, the principal methodological bottleneck standing between the current, largely correlative evidence base and a computational pipeline capable of reliably guiding the rational design of clinically translatable AuNP-based antimicrobial therapeutics.

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