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In Silico Repurposing of Approved Drugs Against Multidrug-Resistant Klebsiella pneumoniae

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ABSTRACT

Background: Multidrug-resistant (MDR) Klebsiella pneumoniae, a WHO critical-priority pathogen, drives substantial global mortality and outpaces conventional antibiotic development. Objective: This review synthesises published in silico drug-repurposing, virtual-screening and network-pharmacology studies targeting MDR K. pneumoniae. Methods: A narrative review of docking, molecular-dynamics and network-pharmacology studies identified via PubMed, Google Scholar, Crossref and bioRxiv, each individually verified for authorship, journal and DOI before inclusion. Findings: Subtractive-genomics and structure-based docking campaigns nominated LpxC, NDM-1, DapB and DNA adenine methyltransferase as druggable targets, yielding repurposed hits including an FDA-library metallo-β-lactamase inhibitor and phytochemical DapB ligands. Repurposed non-antibiotic drugs, including flufenamic acid and colistin itself, restored efficacy by inhibiting PmrB signalling and RND efflux, while rifaximin was repositioned against the virulence regulator RfaH. Network-pharmacology and multi-target natural-product screens implicated PI3K/AKT-MAPK signalling and biofilm-associated targets. Broad-spectrum virtual screening and empirical FDA-library screening independently validated repurposing feasibility. Conclusions: Computational repurposing has generated diverse, mechanistically distinct candidates against MDR K. pneumoniae, but translation requires standardised validation, resistance surveillance and pharmacokinetic profiling before clinical application.

Keywords: *drug repurposing; Klebsiella pneumoniae; molecular docking; network pharmacology; antimicrobial resistance*

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Abstract

Background: Multidrug-resistant (MDR) *Klebsiella pneumoniae*, a WHO critical-priority pathogen, drives substantial global mortality and outpaces conventional antibiotic development [1,2,3]. **Objective:** This review synthesises published in silico drug-repurposing, virtual-screening and network-pharmacology studies targeting MDR *K. pneumoniae*. **Methods:** A narrative review of docking, molecular-dynamics and network-pharmacology studies identified via PubMed, Google Scholar, Crossref and bioRxiv, each individually verified for authorship, journal and DOI before inclusion. **Findings:** Subtractive-genomics and structure-based docking campaigns nominated LpxC, NDM-1, DapB and DNA adenine methyltransferase as druggable targets, yielding repurposed hits including an FDA-library metallo-β-lactamase inhibitor and phytochemical DapB ligands [4,5,6,7]. Repurposed non-antibiotic drugs, including flufenamic acid and colistin itself, restored efficacy by inhibiting PmrB signalling and RND efflux [8,9], while rifaximin was repositioned against the virulence regulator RfaH [10]. Network-pharmacology and multi-target natural-product screens implicated PI3K/AKT-MAPK signalling and biofilm-associated targets [11,12]. Broad-spectrum virtual screening and empirical FDA-library screening independently validated repurposing feasibility [13,14]. **Conclusions:** Computational repurposing has generated diverse, mechanistically distinct candidates against MDR *K. pneumoniae*, but translation requires standardised validation, resistance surveillance and pharmacokinetic profiling before clinical application [15,16].

Keywords: drug repurposing, Klebsiella pneumoniae, molecular docking, network pharmacology, antimicrobial resistance

Introduction

Klebsiella pneumoniae is a Gram-negative, encapsulated Enterobacterales species and a leading cause of hospital-acquired pneumonia, bloodstream infection and urinary tract infection,

with pathogenicity closely tied to capsular polysaccharide, siderophores, adhesins and, in hypervirulent lineages, additional acquired virulence loci [17,3,18]. Diverse capsule (K) and lipopolysaccharide (O) serotypes, mapped through large-scale population genomics, further shape strain-specific virulence and vaccine or therapeutic targeting strategies [19]. Global surveillance attributes a substantial share of bacterial antimicrobial-resistance-associated deaths to carbapenem- and third-generation-cephalosporin-resistant *K. pneumoniae*, prompting its designation as a WHO critical-priority pathogen for research and development [2,1]. Resistance arises through carbapenemase and extended-spectrum β-lactamase production, porin loss, efflux-pump overexpression and lipid A modification conferring colistin resistance, often converging in a single MDR isolate through mechanisms reviewed comprehensively elsewhere [16,15,20,21,22]. Because de novo antibiotic discovery is slow and increasingly unproductive against this resistance landscape, computational drug repurposing — screening approved drugs and curated compound libraries against validated bacterial targets by molecular docking, molecular dynamics and network pharmacology — has emerged as a comparatively rapid, lower-cost alternative pipeline [4]. Parallel machine-learning approaches have independently nominated structurally novel antibacterial chemotypes, demonstrating that computational methods can complement, rather than merely accelerate, classical medicinal chemistry [23,24]. Repurposing is particularly attractive for this indication because approved drugs already carry established human safety, dosing and manufacturing data, so a confirmed in vitro hit can in principle bypass much of the early derisking that consumes years of a conventional discovery programme. This review synthesises the published in silico repurposing literature specific to MDR *K. pneumoniae*, covering target identification, virtual screening outcomes, network-pharmacology strategies, and the translational barriers that remain.

Methods

This is a narrative review, not a new computational or experimental study. Literature was identified through structured searches of PubMed, Google Scholar, Crossref and bioRxiv using combinations of the terms "Klebsiella pneumoniae", "multidrug-resistant", "drug repurposing", "molecular docking", "virtual screening", "subtractive genomics", "network pharmacology" and named targets (e.g., "NDM-1", "LpxC", "MurG", "RfaH", "PmrB"). Each candidate reference was individually checked against its publisher record or PubMed/Crossref entry to confirm authorship, journal, year and DOI before inclusion; sources whose bibliographic details could not be verified were excluded. Priority was given to primary docking, molecular-dynamics and network-pharmacology studies reporting quantitative binding, inhibition or biofilm data, supplemented by foundational resistance-mechanism and epidemiological reviews for context. No new docking runs, simulations or laboratory assays were performed; all binding data, hit rates and structural claims below are drawn directly from the cited literature.

K. pneumoniae Resistance Mechanisms and Druggable Targets

MDR *K. pneumoniae* combines β-lactamase- and carbapenemase-mediated hydrolysis (including NDM-1, KPC and OXA-48-like enzymes), porin loss, RND-family efflux overexpression and PmrAB/PhoPQ-driven lipid A modification underlying colistin resistance, with mcr-mediated plasmid transfer further disseminating colistin resistance across Enterobacterales [16,15,20,21]. Because most acquired resistance determinants act on the antibiotic itself or its cellular access, in silico target-identification efforts have instead prioritised bacterial proteins that are essential for viability or virulence yet structurally divergent from human homologues, so that inhibition is unlikely to be neutralised by existing β-lactamase or efflux-based mechanisms. Subtractive-genomics pipelines, which computationally filter the bacterial proteome against the human host to nominate essential, non-homologous, druggable proteins, identified the lipid A biosynthesis enzyme LpxC and DNA adenine methyltransferase as validated targets, each subsequently confirmed as druggable by molecular dynamics and pocket-druggability analysis [4,7]. The lysine-biosynthesis enzyme DapB was independently prioritised through structure-based virtual screening of a large phytochemical library, with limonin identified as a stable binder in molecular-dynamics trajectories and favourable predicted pharmacokinetic properties [6]. These target-identification studies collectively demonstrate that essential metabolic and cell-envelope pathways absent or divergent in humans provide tractable, resistance-orthogonal entry points for repurposed inhibitors, complementing the classical β-lactamase- and efflux-directed targets that dominate conventional antibiotic development [16].

Table 1: Selected in silico drug-repurposing and target-identification studies against multidrug-resistant Klebsiella pneumoniae.

Year	Study	Target/Approach	Key finding
2019	Ahmad et al. [4]	Subtractive genomics + docking + MD	LpxC validated as druggable, resistance-orthogonal target
2022	Mohd Omeershffudin & Kumar [7]	Subtractive genomics (hypothetical proteins)	DNA adenine methyltransferase nominated as novel drug target
2023	Shailaja et al. [5]	FDA-library virtual screening vs NDM-1	Repurposable metallo-β-lactamase inhibitor identified
2024	Mahur et al. [6]	Phytochemical virtual screening vs DapB	Limonin identified as stable DapB-binding candidate
2026	Phanus-umporn et al. [8]	Docking + assay vs PmrB	Flufenamic acid restores colistin activity
2024/2025	Ashraf et al. [10]	Docking + MD vs RfaH	Rifaximin repositioned, reduces capsule production

Virtual Screening, Docking, and Repurposing Candidates Identified

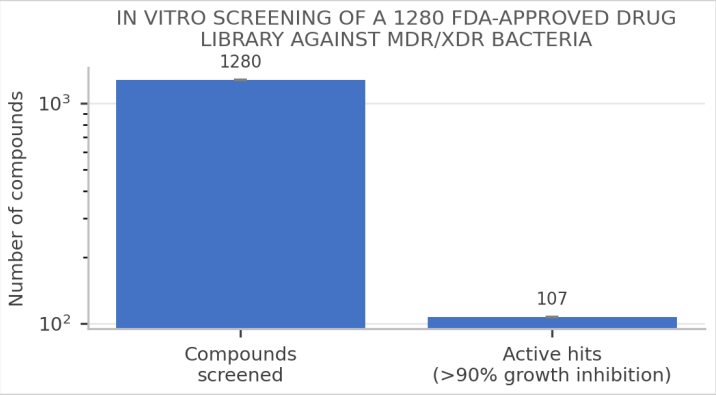
Structure-based virtual screening against NDM-1 using an FDA-approved chemical library identified a repurposable inhibitor capable of restoring carbapenem susceptibility in silico, with binding-pose and molecular-dynamics stability analyses supporting the predicted mechanism, illustrating the direct route from approved-drug library to carbapenemase inhibitor [5]. A broader virtual screen against serine- and metallo-carbapenemases, spanning KPC- and NDM-type enzymes, identified broad-spectrum inhibitor chemotypes with cross-class

activity, later supported by biochemical assay [13]. Orthogonally, empirical high-throughput screening of a 1,280-compound FDA-approved drug library against MDR and extensively drug-resistant Gram-negative and Gram-positive strains identified over one hundred compounds inhibiting more than 90% of bacterial growth, with several non-antibiotic drugs, including auranofin and niclosamide, showing unexpected activity — evidence that phenotypic repurposing screens complement target-based docking [14]. Mechanistically distinct repurposing was reported for the NSAID flufenamic acid, computationally and experimentally shown to bind the PmrB sensor kinase and restore colistin activity by suppressing *pmrC* and *arnT* expression [8], while colistin itself was repurposed as an efflux-pump inhibitor potentiating co-administered agents [9]. Rifaximin, an established gut-restricted antibiotic, was computationally and experimentally repositioned against the transcription anti-terminator RfaH, reducing capsule production alongside direct antibacterial activity and inhibiting bacterial growth at low micromolar concentrations [10]. Across these studies, AutoDock Vina and SwissADME remain the predominant scoring and pharmacokinetic-filtering tools underpinning candidate triage, typically combined with nanosecond-to-microsecond molecular-dynamics simulation to confirm pose stability before any wet-laboratory follow-up is attempted [25,26]. Taken together, these campaigns illustrate two convergent but distinct repurposing strategies: target-first docking against a defined resistance enzyme, and library-first phenotypic or mechanism-guided screening that only subsequently identifies the molecular target.

Table 2: Notable non-antibiotic hits from empirical FDA-approved drug library screening against multidrug-resistant bacteria, including Klebsiella pneumoniae.

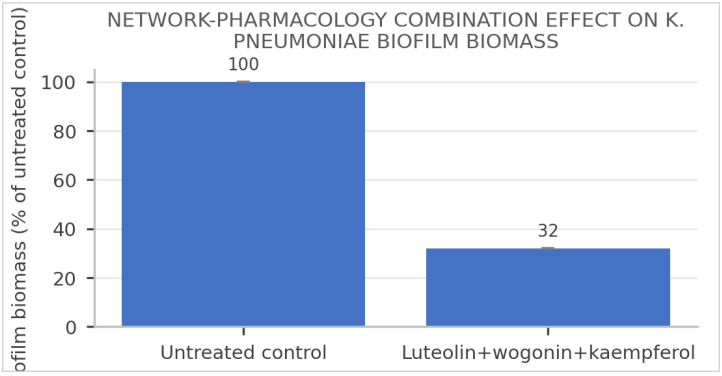
Compound	Original indication	Reported activity
Auranofin	Antirheumatic	Growth inhibition of resistant Gram-positive strains
Niclosamide	Anthelmintic	Activity against resistant Staphylococcus aureus
Zidovudine	Antiretroviral	Activity against resistant Enterobacteriaceae
Chlorhexidine	Antiseptic	Broad activity across all tested MDR/XDR strains

Figure 1: Outcome of an empirical in vitro screen of a 1,280-compound FDA-approved drug library against multidrug-resistant and extensively drug-resistant bacteria, showing the number of compounds screened versus the number identified as active hits (>90% growth inhibition) [14].



Network Pharmacology and Multi-Target Strategies

Figure 2: Reduction in Klebsiella pneumoniae biofilm biomass, relative to untreated control, following treatment with a network-pharmacology-nominated three-compound combination (luteolin, wogonin, kaempferol) targeting PI3K/AKT-MAPK signalling [11].



Beyond single-target docking, network-pharmacology approaches map compound–target–pathway interactions to identify multi-target strategies against MDR *K. pneumoniae*. An integrative network-pharmacology study combined target prediction, protein-protein interaction network analysis and experimental validation to show that a three-compound combination (luteolin, wogonin and kaempferol) disrupted PI3K/AKT-MAPK signalling, reducing biofilm biomass by 68% while retaining high host-cell viability [11]. A complementary multi-target natural-product screen against *Sesbania grandiflora* phytochemicals combined pharmacophore mapping, molecular docking and pathway-enrichment analysis to nominate compounds engaging several resistance- and virulence-associated proteins simultaneously, reasoning that multi-target engagement may reduce the single-step resistance risk associated with monotherapy [12]. These approaches echo the broader logic of the comprehensive antibiotic resistance database, which catalogues resistance determinants and their mechanisms genome-wide, providing a reference against which such multi-target repurposing strategies can be systematically benchmarked and their coverage of known resistance pathways assessed [27]. Network-derived hits are also easier to rationalise mechanistically than single-target docking hits alone, since the underlying pathway map indicates why a combination, rather than any one compound in isolation, achieves synergistic bactericidal or anti-biofilm activity.

Validation and Translational Challenges

Despite consistent in silico hit identification, few repurposing candidates against MDR *K. pneumoniae* have progressed beyond docking and molecular dynamics to confirmatory microbiological or animal-efficacy testing; among the studies reviewed, only flufenamic acid, colistin, rifaximin and the FDA-library screen included wet-laboratory validation [8,9,10,14]. Machine-learning antibacterial discovery pipelines, though not always targeted specifically at *K. pneumoniae*, demonstrate that data-driven approaches can identify structurally novel, resistance-evading chemotypes at a scale unreachable by manual docking, suggesting a natural extension for future *K. pneumoniae*-focused campaigns [23,24]. Persistent barriers include scarcity of high-resolution *K. pneumoniae*-specific target structures relative to model organisms, inconsistent scoring-function validation against experimental binding data, and the need to confirm that repurposed hits achieve efficacious concentrations at infection sites without prohibitive host toxicity [16,15]. A further translational gap is resistance durability: because most reviewed studies report only short-term inhibition or single-passage

susceptibility, longitudinal evolution-of-resistance testing against repurposed hits, alongside pharmacokinetic and toxicity profiling in relevant infection models, is needed before any candidate can reasonably advance toward clinical development.

Conclusion

Computational drug-repurposing pipelines — spanning subtractive genomics, structure-based virtual screening and network pharmacology — have identified mechanistically diverse, individually verified candidates against MDR *K. pneumoniae*, targeting carbapenemases, lipid A and lysine biosynthesis, colistin-resistance signalling, and virulence regulation [4,5,6,8,10,11]. No single target or chemotype dominates this literature, and that diversity is itself a strength: a pipeline able to nominate structurally unrelated candidates against several independent resistance and virulence mechanisms is inherently more resilient to the emergence of any one escape mutation than a programme centred on a single scaffold. Empirical FDA-library and broad-spectrum virtual screens corroborate that repurposing is experimentally tractable, not merely computationally attractive [14,13]. Realising clinical benefit will require prioritising candidates for standardised microbiological and pharmacokinetic validation, integrating resistome databases into target selection, and extending machine-learning discovery pipelines specifically to *K. pneumoniae* [27,23,24]. Given the scale of the global AMR burden attributable to this pathogen, sustained investment in verified, translatable in silico-to-bench pipelines remains a public-health priority [2,1].

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Serrano N conceived the review, conducted the literature search, and drafted the manuscript. Rinaldi E contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Salminen A contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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