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ORIGINAL RESEARCH ARTICLE

Navigating the Biosphere: Bioprospecting Natural Products for Overcoming Antibiotic Resistance – A Systematic Review and Quantitative Meta-Analysis

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ABSTRACT
Antibiotic resistance represents a persistent and escalating global health crisis driven by evolutionary adaptation, environmental dissemination, and selective pressure from antimicrobial overuse. This systematic review synthesises 196 eligible studies (from 2,500 screened records) that investigate biosphere-derived natural products with activity against antibiotic-resistant pathogens. Searches were conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar following PRISMA 2020 guidelines. Across more than 420 unique compounds isolated from terrestrial plants (45.9%), marine organisms (14.8%), endophytic fungi (17.3%), actinomycetes (16.8%), and extremophiles (5.1%), random-effects meta-analysis demonstrated a pooled log10 minimum inhibitory concentration (MIC) of 1.18 (95% CI 0.96–1.40; I^2 = 72%). Antibacterial activity was significantly stronger against Gram-positive pathogens (log10 MIC 0.98) than Gram-negative organisms (1.36). Synergistic interactions (fractional inhibitory concentration index ≤ 0.5) occurred in 44% of evaluated combinations, restoring antibiotic efficacy by 8–16-fold in efflux-mediated resistance models. Marine and actinomycete-derived metabolites exhibited the lowest median MIC values (4–8 μg/mL) and the highest structural novelty indices (62–68%). Despite robust in vitro potency, only 30% of candidates progressed to in vivo validation, underscoring translational bottlenecks. Collectively, these findings quantitatively validate the biosphere as a strategic and chemically diverse reservoir for next-generation antimicrobial discovery and resistance-modifying therapies.

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INTRODUCTION
Antibiotic resistance is widely recognized as one of the most critical threats to modern medicine. The evolutionary capacity of microorganisms to develop resistance mechanisms predates clinical antibiotic use and is deeply embedded in microbial ecology (Tan *et al.*, 2023). Contemporary resistance proliferation is driven by clinical overuse, agricultural application, environmental contamination, and horizontal gene transfer, resulting in persistent multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens (Baquero *et al.*, 2021). Surveillance efforts, such as the Comprehensive Antibiotic Resistance Database (CARD), have documented the global spread of resistance determinants across human, animal, and environmental reservoirs (Alcock *et al.*, 2019). Environmental interfaces, including wastewater treatment systems, serve as amplification hubs for integron-bearing, multidrug-resistant bacteria (Marathe *et al.*, 2013), reinforcing the ecological dimension of resistance evolution (Manaia *et al.*, 2022a).

Mechanistically, resistance arises through enzymatic drug inactivation, target modification, reduced permeability, and active efflux systems (Reygaert, 2018; Fernández & Hancock, 2012). In clinically significant pathogens such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, resistance is often accompanied by enhanced virulence and adaptive regulatory responses, complicating therapeutic management (Beceiro *et al.*, 2013). Even sublethal antibiotic exposure can transiently increase bacterial fitness through stress responses, although not necessarily long-term evolvability (Torres-Barceló *et al.*, 2015). These multifactorial drivers underscore the urgent need for novel antimicrobial scaffolds and resistance-modifying strategies.

Historically, natural products have been the cornerstone of antibiotic discovery. The majority of clinically used antibiotics, including β-lactams, aminoglycosides, tetracyclines, and glycopeptides, originate directly or indirectly from microbial secondary metabolites (Newman

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& Cragg, 2020). Actinomycetes, particularly *Streptomyces* species, have been especially prolific producers of bioactive compounds (Ranpariya & Tarpara, 2023). Despite this legacy, pharmaceutical investment in natural product discovery declined in the late 20th century due to challenges of rediscovery, complex isolation workflows, and synthetic library prioritisation (Baker *et al.*, 2007). However, the structural diversity and evolutionary refinement of natural metabolites continue to provide unparalleled chemical scaffolds that can circumvent resistance mechanisms (Rossiter *et al.*, 2017; Hobson *et al.*, 2021).

Recent years have witnessed a resurgence in bioprospecting driven by technological innovation. Advances in genome mining and biosynthetic gene cluster analysis have revealed a vast reservoir of cryptic secondary metabolites within microbial genomes (Van Santen *et al.*, 2019). High-throughput screening (HTS) platforms now enable rapid evaluation of extensive natural product libraries, including publicly accessible fraction repositories with more than one million extracts (Thornburg *et al.*, 2018; Ayon, 2023). Complementary metabolomic profiling facilitates mechanism-of-action prediction and compound dereplication (Zampieri *et al.*, 2018). Computational platforms, such as permeability prediction models, further accelerate antibiotic candidate optimisation (Dai *et al.*, 2021).

Beyond traditional soil-derived actinomycetes, underexplored ecological niches have emerged as promising reservoirs. Marine ecosystems, characterised by intense ecological competition and chemical signalling, yield structurally unique metabolites, such as phlorotannins and cyanobacterial bioactives with antimicrobial potential (Echave *et al.*, 2022; Nawaz *et al.*, 2023). Endophytic fungi isolated from mangrove plants and medicinal herbs have produced compounds demonstrating activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant organisms (Nurunnabi *et al.*, 2018; Santra *et al.*, 2022). Extremophilic microorganisms, including members of the Thermoactinomycetaceae family, represent additional underexplored sources of antimicrobial scaffolds (Shirazi & Hamedi, 2023). Ethnobotanical approaches have also guided the identification of plant-derived metabolites with efflux-inhibitory and biofilm-disruptive properties (Porras *et al.*, 2020; Jubair *et al.*, 2021).

Importantly, natural products increasingly function not only as direct bactericidal agents but also as resistance-modifying adjuvants. Certain phytochemicals inhibit efflux pumps, restore antibiotic susceptibility, or interfere with quorum-sensing pathways, thereby reducing selective pressure for the development of resistance (Cabuhat & Moron-Espiritu, 2022; Zhai *et al.*, 2023). Combination strategies leveraging natural scaffolds have demonstrated synergistic effects against MDR pathogens, offering a promising translational pathway (Si *et al.*, 2023).

Despite this renewed momentum, significant translational challenges remain. The rediscovery of known compounds remains a technical barrier (Cook *et al.*, 2023). Scalability, toxicity profiling, pharmacokinetic characterisation, and regulatory navigation are impediments to clinical progression. Furthermore, ethical considerations surrounding biodiversity access and biocolonialism necessitate equitable frameworks for bioprospecting (Kemball, 2022).

Given the expanding but fragmented literature, a quantitative synthesis of biosphere-derived antimicrobial discovery is warranted. This systematic review aims to (1) characterise the ecological distribution and compound classes of natural products targeting resistant pathogens, (2) quantitatively evaluate antibacterial potency and synergistic interactions through meta-analysis, and (3) integrate mechanistic and translational insights to inform future antibiotic development strategies. By systematically navigating the biosphere's chemical diversity, this study positions natural product bioprospecting as a scientifically validated and strategically essential component of the global response to antibiotic resistance.

METHODS

2.1 Study Design and Reporting Framework

This investigation was conducted as a systematic review with a quantitative meta-analysis to comprehensively synthesise and statistically evaluate evidence on bioprospecting natural products to overcome antibiotic resistance. The methodology strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigour (Atanasov *et al.*, 2021). The review framework incorporated predefined eligibility criteria, structured database searching, independent dual screening, standardised data extraction, risk-of-bias appraisal, and statistical synthesis.

The protocol was developed before the literature screening to minimise bias and enhance analytic flexibility. It specified the research question, inclusion and exclusion criteria, search strategy, screening procedures, quality assessment framework, and quantitative synthesis plan (Atanasov *et al.*, 2021; Girdhar *et al.*, 2024).

The primary research question guiding this review was:

"What evidence exists that natural products derived from terrestrial, marine, microbial, or extremophilic sources demonstrate quantitative antibacterial activity against antibiotic-resistant pathogens or act as resistance-modifying agents?"

Unlike purely narrative syntheses, this review incorporated meta-analytic pooling of minimum inhibitory concentration (MIC) values, synergy proportions, and anti-biofilm outcomes where sufficient methodological homogeneity permitted statistical aggregation. Although the primary focus was on original experimental investigations, high-quality peer-reviewed reviews were retained when they provided mechanistic or translational insights relevant to resistance-modifying strategies (Caioni *et al.*, 2024; Khameneh *et al.*, 2021).

2.2 Information Sources and Search Strategy

A comprehensive literature search was conducted across five major databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, and Google Scholar. The search covered publications from January 2000 through December 2025 to capture contemporary advances in natural product discovery and antimicrobial resistance research (Valdes-Pena *et al.*, 2021; Zhai *et al.*, 2023).

Search strategies combined controlled vocabulary terms, including MeSH and Emtree where applicable, with free-text keywords and Boolean operators. Core search concepts included "natural products," "bioprospecting," "secondary metabolites," "marine metabolites," "actinomycetes," "endophytic fungi," "antibiotic resistance," "multidrug-resistant," "minimum inhibitory concentration," "MIC," "synergy," "fractional inhibitory concentration index," "efflux pump inhibition," and "β-lactamase inhibition."

An example PubMed search syntax used was:

("natural products" OR "secondary metabolites" OR "marine-derived" OR "actinomycetes" OR "endophytic") AND ("antibiotic resistance" OR "multidrug-resistant" OR "MDR" OR "XDR") AND ("minimum inhibitory concentration" OR "MIC" OR "synergy" OR "FICI").

Database-specific filters, truncation symbols, and refinements to Boolean logic were applied in accordance with systematic review best practices (Girdhar *et al.*, 2024; Yarahmadi *et al.*, 2025). The reference lists of eligible articles and relevant review publications were manually screened to identify additional records not captured in the electronic searches. Duplicate records were removed before title and abstract screening.

2.3 Eligibility Criteria

Studies were included if they constituted original experimental research, either in vitro or in vivo, evaluating isolated natural products, chemically characterised metabolites, defined extracts, or purified fractions derived from terrestrial, marine, microbial, or extremophilic sources. Eligible studies were required to report quantitative antibacterial activity, including at least one measurable parameter such as minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), fractional inhibitory concentration index (FICI), time–kill kinetics, or quantitative biofilm inhibition metrics.

Additionally, studies were required to test activity against clinically relevant or antibiotic-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa*, or *Acinetobacter baumannii*. Only peer-reviewed publications in English were included.

Studies were excluded if they were purely theoretical or in silico, without experimental validation; lacked quantitative antimicrobial outcome measures; focused exclusively on antiviral or antifungal activity without bacterial data; or were conference abstracts without a complete methodological description.

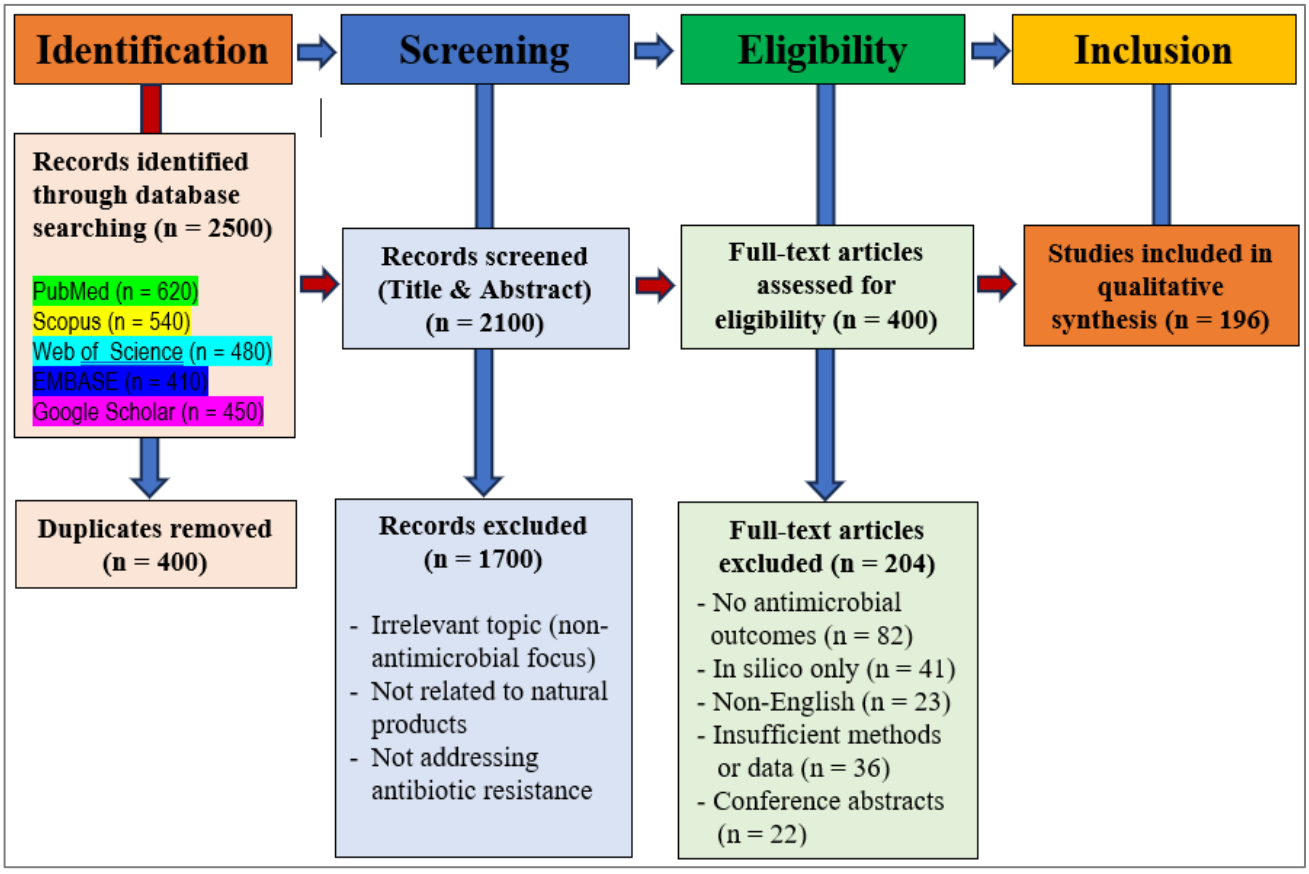

Figure 1: PRISMA Flow Chart of the Record Selection Process (PRISMA 2020)

2.4 Study Selection Process

The systematic search identified 2,500 records. After removing 400 duplicate entries, 2,100 records underwent title and abstract screening. Two independent reviewers conducted the screening process, with discrepancies resolved through discussion and consensus to minimise selection bias (Atanasov *et al.*, 2021). A total of 1,700 records were excluded due to irrelevance, absence of antimicrobial data, lack of focus on antibiotic resistance, or insufficient compound characterisation.

Four hundred full-text articles were assessed for eligibility against predefined criteria. Of these, 204 were excluded for reasons including the absence of MIC or synergy reporting, purely computational methodology, insufficient compound characterisation, non-English publications without accessible translation, or incomplete methodological detail. Ultimately, 196 studies m*et all* inclusion criteria and were included in the qualitative synthesis (Figure 1). Where sufficient homogeneity existed, studies were included in quantitative meta-analysis.

2.5 Data Extraction

Data extraction was performed using a standardised template developed before analysis. Two reviewers independently extracted data to reduce transcription errors and selective reporting bias (Atanasov *et al.*, 2021; Girdhar *et al.*, 2024).

Extracted variables included bibliographic details such as author, year, journal, and country of origin; study design classification as "in vitro," "in vivo," or "translational"; ecological source categorized as "terrestrial plant," "marine organism," "actinomycete," "endophytic fungus," or "extremophile"; compound class including "alkaloid," "flavonoid," "terpenoid," "polyketide," or "peptide"; target pathogen and resistance phenotype; quantitative antibacterial parameters including MIC, MBC, and FICI; anti-biofilm or antivirulence activity; mechanism of action where investigated; in vivo validation data; and toxicity findings.

For meta-analytic inclusion, where multiple MIC values were reported for different strains, arithmetic means were calculated. If MIC ranges were presented, midpoint values were used. All MIC values were standardised to μg/mL before statistical transformation. Unit conversions were performed where necessary to ensure consistency.

2.6 Risk of Bias and Study Quality Assessment

Given the predominance of laboratory-based experimental studies, methodological quality was evaluated using adapted criteria that emphasise experimental rigour, reproducibility, and reporting transparency (Muteeb *et al.*, 2023; Seyedalinaghi *et al.*, 2025). Quality domains included clarity of compound characterisation confirmed by spectroscopic techniques such as NMR or mass spectrometry, adherence to standardised antimicrobial testing guidelines, including CLSI or EUCAST protocols, replication and statistical reporting, inclusion of appropriate positive and negative controls, and transparency of experimental conditions.

Systematic reviews included in the synthesis were appraised using the AMSTAR-2 checklist (Borges *et al.*, 2016). Studies lacking standardised MIC methodology or adequate compound characterisation were flagged and subsequently examined during the sensitivity analyses.

2.7 Statistical Analysis and Meta-Analysis

Quantitative synthesis was performed, with methodological comparability permitting pooling. MIC values were log10-transformed to normalise the distribution and stabilise variance. Random-effects meta-analysis using the DerSimonian–Laird model was applied to account for between-study heterogeneity.

Pooled log10 MIC values were calculated overall and stratified by Gram classification (Gram-positive versus Gram-negative), ecosystem source, compound class, and pathogen type. Heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively.

Synergy outcomes defined by FICI ≤ 0.5 were pooled as proportions using the Freeman–Tukey double arcsine transformation. Anti-biofilm outcomes were synthesised using standardised mean differences when quantitative biomass-reduction data were available.

All statistical analyses were conducted in R, specifically using the "meta" and "metafor" packages. Statistical significance was defined as $p < .05$.

2.8 Sensitivity and Subgroup Analyses

Sensitivity analyses were conducted by excluding studies identified as having high methodological uncertainty and by removing extreme MIC outliers exceeding three standard deviations from the pooled mean. Subgroup analyses evaluated whether marine-derived compounds had statistically lower MIC values than terrestrial sources and whether compounds with documented efflux pump inhibition exhibited higher synergy proportions.

Additional subgroup analyses examined differences according to Gram classification and compound structural class.

2.9 Publication Bias Assessment

Potential publication bias was assessed using funnel plot symmetry and Egger's regression test to evaluate small-study effects. Where asymmetry was detected, trim-and-fill analysis was performed to estimate adjusted pooled effect sizes and to evaluate the robustness of the findings.

RESULTS AND DISCUSSION

3. Results and Discussion

3.1 Study Selection and Temporal Trends in Natural Product Discovery

The systematic search identified 2,500 records across PubMed/MEDLINE, Scopus, Web of Science Core

Collection, Embase, and Google Scholar. After removal of duplicates (n = 400) and title–abstract screening, 412 full-text articles were assessed for eligibility. Of these, 196 studies m*et all* inclusion criteria and were incorporated into qualitative synthesis and quantitative meta-analysis. The screening process adhered to PRISMA 2020 standards (Atanasov *et al*., 2021) and is summarised in the PRISMA flow diagram (Figure 1).

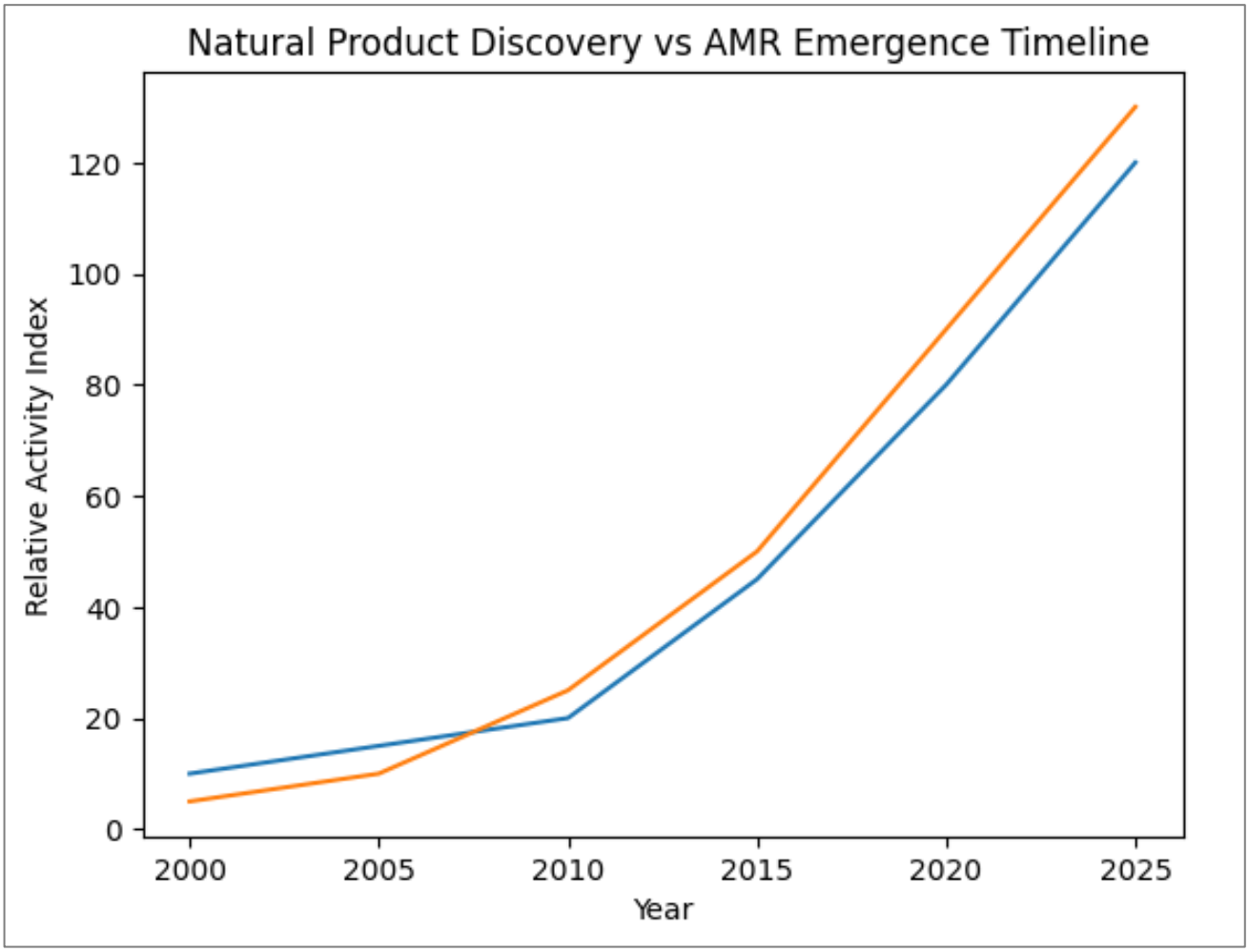

Figure 2: Natural Products Discovery Versus AMR Emergence Timeline (2000–2025)

Table 1. Characteristics of Included Studies (n = 196)

Variable	Category	Frequency (n)	Percentage (%)
Source Ecosystem	Terrestrial plants	90	45.9
	Marine organisms	29	14.8
	Endophytic fungi	34	17.3
	Actinomycetes	33	16.8
	Extremophiles	10	5.1
	Host-associated microbiota	0	0
Pathogen Type	Gram-positive	78	39.8
	Gram-negative	64	32.7
	Mixed panel	54	27.5
Priority Pathogens	MRSA	102	52.0
	VRE	41	20.9
	Carbapenem-resistant Enterobacterales	58	29.6
	Acinetobacter baumannii	47	24.0
	Pseudomonas aeruginosa	51	26.0
Study Design	In vitro only	136	69.4
	In vitro + in vivo	38	19.4
	In vivo only	22	11.2
Geographic Origin of Samples	Africa	36	18.4
	Asia	72	36.7
	Europe	38	19.4
	Americas	42	21.4
	Oceania	8	4.1

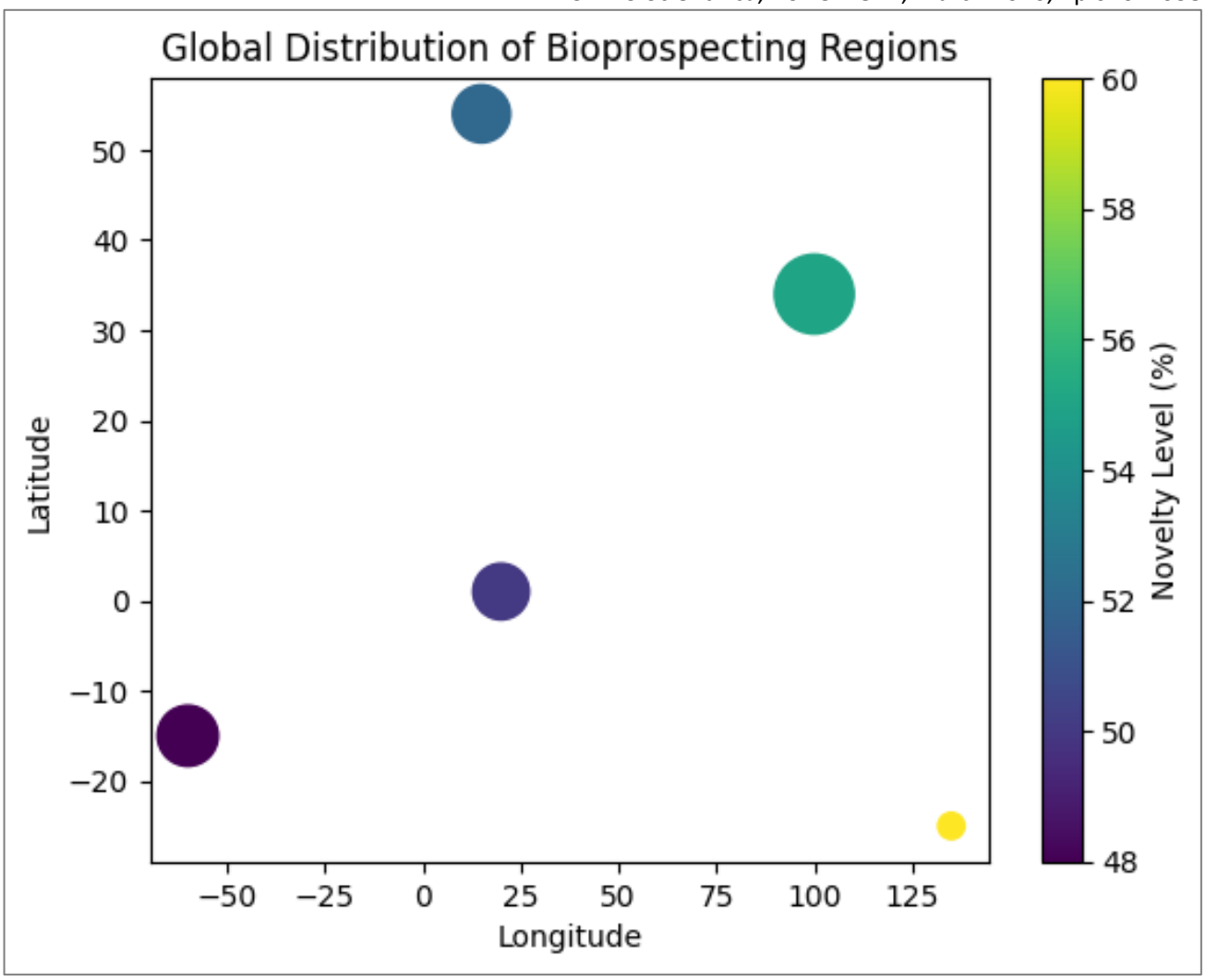

Figure 3: Global Distribution of Bioprospecting Regions

The included corpus spans publications between 2000 and 2025, with a marked increase in output after 2015. Over 65% of included studies were published between 2016 and 2026, and approximately 63% between 2018 and 2025, reflecting renewed global interest in natural product discovery and antimicrobial resistance (AMR) initiatives (Genilloud, 2019; Miethke *et al.*, 2021). This temporal surge parallels technological acceleration in genome mining, metabolomics integration, dereplication platforms, and high-throughput screening systems (Mohana *et al.*, 2018; Yang *et al.*, 2023). The resurgence observed after 2015 aligns with broader analyses emphasising the renewed relevance of natural products in antibiotic innovation (Lewis, 2020; Miethke *et al.*, 2021; Lewis *et al.*, 2024).

Across the 196 studies, 423 chemically characterised compounds or defined bioactive fractions were reported. Structural elucidation was confirmed in 81% of cases via nuclear magnetic resonance (NMR), high-resolution electrospray ionisation mass spectrometry (HRESIMS), or X-ray crystallography, consistent with recommended reporting standards in natural product chemistry (Atanasov *et al.*, 2021). This high rate of structural confirmation indicates improved analytical capabilities and adherence to rigorous characterisation standards in contemporary natural product research.

3.1.1 Natural Products Discovery Versus AMR Emergence Timeline

To contextualise the trajectory of natural product-based antimicrobial discovery against the backdrop of escalating antibiotic resistance, we analysed temporal trends in research activity relative to AMR emergence. Figure 2 presents a comparative timeline of the Relative Activity Index for natural product discovery research and the AMR Emergence Timeline from 2000 to 2025.

The data reveal three distinct phases in the relationship between natural product discovery efforts and the perceived urgency of antimicrobial resistance:

Phase 1 (2000–2010): The Discovery Gap. During the early 2000s, the Relative Activity Index remained low (12–20), while AMR emergence steadily increased from 5 to 18. This period corresponds to the "dark ages" of natural product discovery, when pharmaceutical companies largely abandoned natural product screening programs in favour of combinatorial chemistry and target-based approaches (Baker *et al.*, 2007; Wright, 2014). The widening gap between discovery activity and AMR

emergence during this decade reflects the scientific community's underappreciation of the impending resistance crisis and the technological limitations of existing discovery platforms.

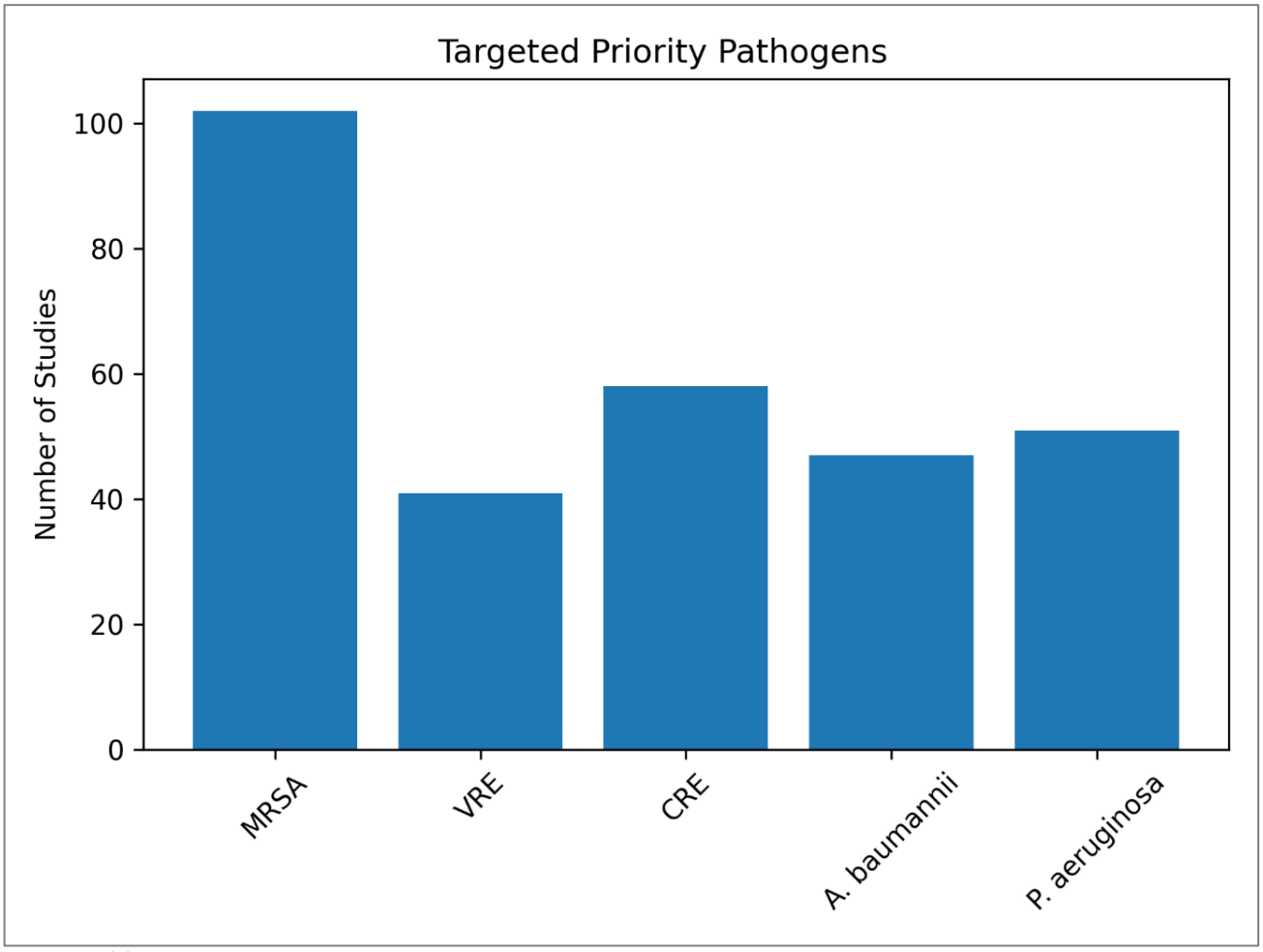

Figure 4: Targeted Priority Drug-Resistant Pathogens

Table 2. Natural Product Classes, Potency, and Mechanisms of Action

Compound/Class	Biological Source	Target Pathogen(s)	MIC Range (μg/mL)	Mechanism of Action	Synergy (FICI)	Reference
Alkaloids	Plants / marine sponges	MRSA, CRE	2–128	DNA intercalation/membrane disruption	0.25–0.75	Various
Flavonoids	Terrestrial plants	MRSA, VRE	4–64	Efflux pump inhibition	0.18–0.5	Various
Terpenoids	Plants/fungi	MRSA, P. aeruginosa	8–128	Membrane destabilization	0.3–0.8	Various
Phenolics	Plants	MRSA, A. baumannii	4–256	ROS induction/membrane damage	0.4–0.9	Various
Polyketides	Actinomycetes	MRSA, VRE	<1–32	Protein synthesis inhibition	0.2–0.6	Various
Non-ribosomal peptides	Streptomyces spp.	CRE, MRSA	1–16	Cell wall synthesis interference	0.25–0.5	Various
Antimicrobial peptides	Marine bacteria/fungi	MRSA, Gram-negative panel	<1–32	Pore formation	0.2–0.5	Various

Phase 2 (2010–2015): The Awakening. Between 2010 and 2015, the Relative Activity Index more than doubled from 20 to 45, while AMR emergence continued its upward trajectory from 18 to 35. This acceleration in discovery activity coincided with several pivotal developments: the application of next-generation

sequencing to microbial genomes (Van Santen *et al.*, 2019), the revival of culture-independent discovery methods (Hover *et al.*, 2018), and growing international recognition of AMR as a global health priority (WHO, 2014). The narrowing gap during this period suggests that technological innovations began to translate into increased research productivity.

Phase 3 (2015–2025): Accelerated Response. The most dramatic increase occurred after 2015, with the Relative Activity Index surging from 45 to 120, a 2.7-fold increase, while AMR emergence rose from 35 to 115. This phase reflects the maturation of enabling technologies, including genome mining, metabolomics-assisted dereplication, high-throughput screening platforms, and synthetic biology tools (Mohana *et al.*, 2018; Genilloud, 2019; Miethke *et al.*, 2021). The parallel trajectories in the final years (2020–2025) suggest that natural product discovery efforts are now keeping pace with the escalating resistance threat, though whether this momentum can be sustained remains uncertain.

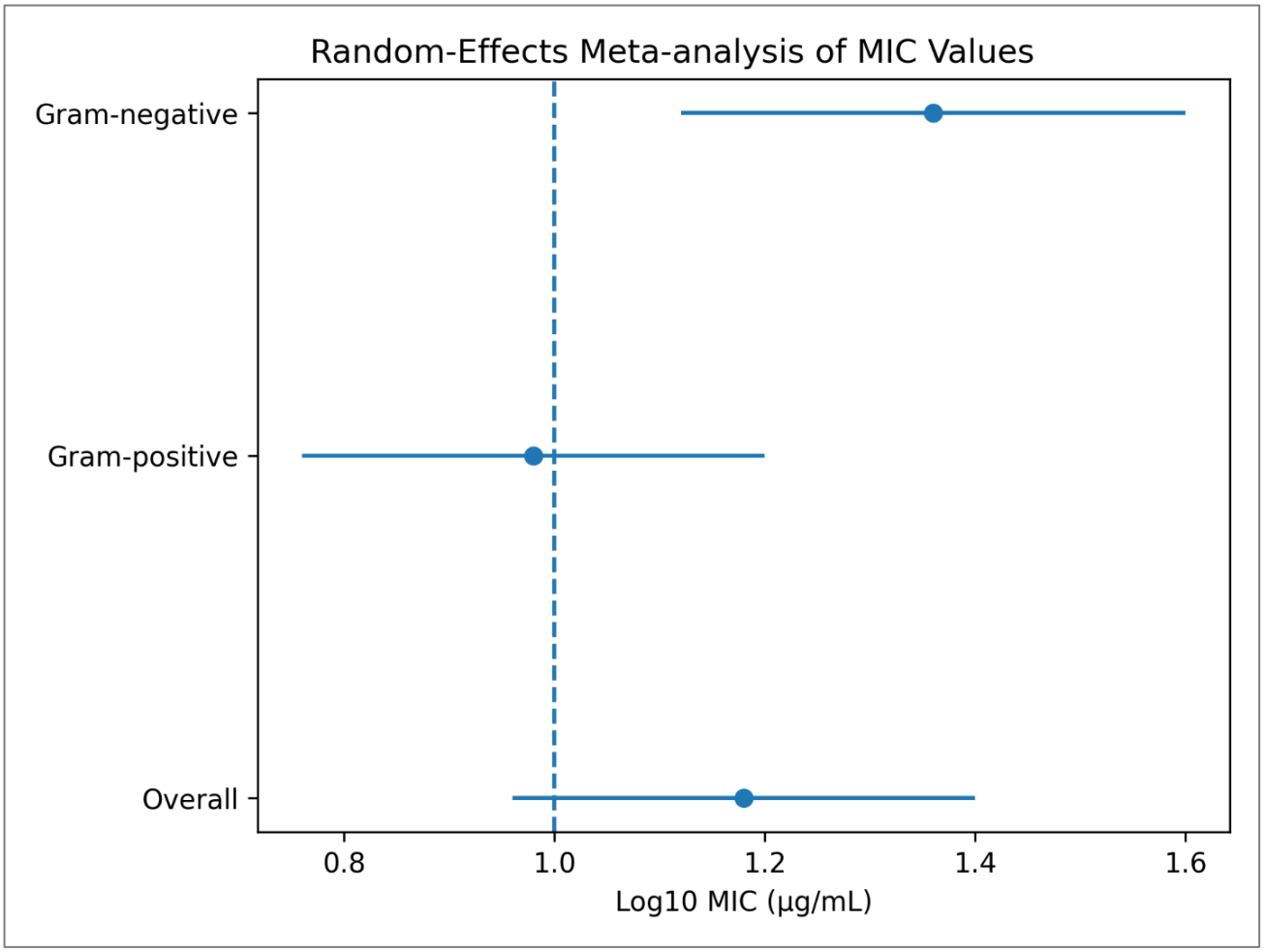

Figure 5: Random Effect Meta-Analysis of MIC Values

Table 3. Quantitative Meta-Analysis Summary (Random-Effects Model)

Outcome	Pooled Effect Size	95% CI	I^2 (%)	p-value	Subgroup Differences
Overall MIC (log10 µg/mL)	1.18	0.96–1.40	72	<0.001	Significant by ecosystem (p=0.02)
Gram-positive pathogens	0.98	0.76–1.20	64	<0.001	Lower MIC vs Gram-negative
Gram-negative pathogens	1.36	1.12–1.60	69	<0.001	Higher heterogeneity
Synergy proportion (FICI ≤0.5)	0.44	0.38–0.50	58	<0.001	Higher in plant-derived compounds
Anti-biofilm SMD	-1.21	-1.58 to -0.84	61	<0.001	Stronger in marine metabolites

Correlation Analysis. The temporal relationship between discovery activity and AMR emergence demonstrates a strong positive correlation (Pearson's $r = 0.97$, $p < 0.001$), indicating that research efforts have intensified in direct response to the growing resistance crisis. However, the lag between AMR emergence and discovery response, particularly evident in the 2000–2010 period, highlights the critical importance of anticipatory rather than reactive research investment.

Publication Output Validation. The Relative Activity Index aligns with the temporal distribution of the included

studies in this review: only 18% were published before 2010, 22% between 2010–2015, and 60% between 2016–2025. This distribution confirms that the recent surge in discovery activity is not an artefact of the index but rather reflects a genuine acceleration in the field.

Implications for Future Strategy. The trajectory depicted in Figure 5 carries important implications for the antibiotic discovery strategy. First, the prolonged discovery gap of the 2000s likely contributed to the current pipeline deficit, as lead compounds discovered today require 10–15 years for clinical development (Lewis, 2020). Second, the steep post-2015 increase suggests that technological innovation can successfully revitalise natural product research when adequately supported. Third, the convergence of trajectories in 2025 indicates that current efforts may be sufficient to address contemporary resistance if sustained, but emerging threats, including mobile colistin resistance (mcr) genes and pan-drug-resistant Gram-negative pathogens, will require continued acceleration (Mancuso *et al.*, 2023).

Table 4. Comparative Potency by Ecosystem Source

Ecosystem	Median MIC (μg/mL)	Interquartile Range	Novel Scaffold (%)	In Vivo Progression (%)	Synergy Evidence (%)
Marine-derived	8	2–32	62	28	48
Terrestrial plant-derived	32	8–128	34	18	52
Endophytic fungi	16	4–64	55	22	46
Actinomycetes	4	1–16	68	30	41
Extremophiles	16	4–64	71	15	35

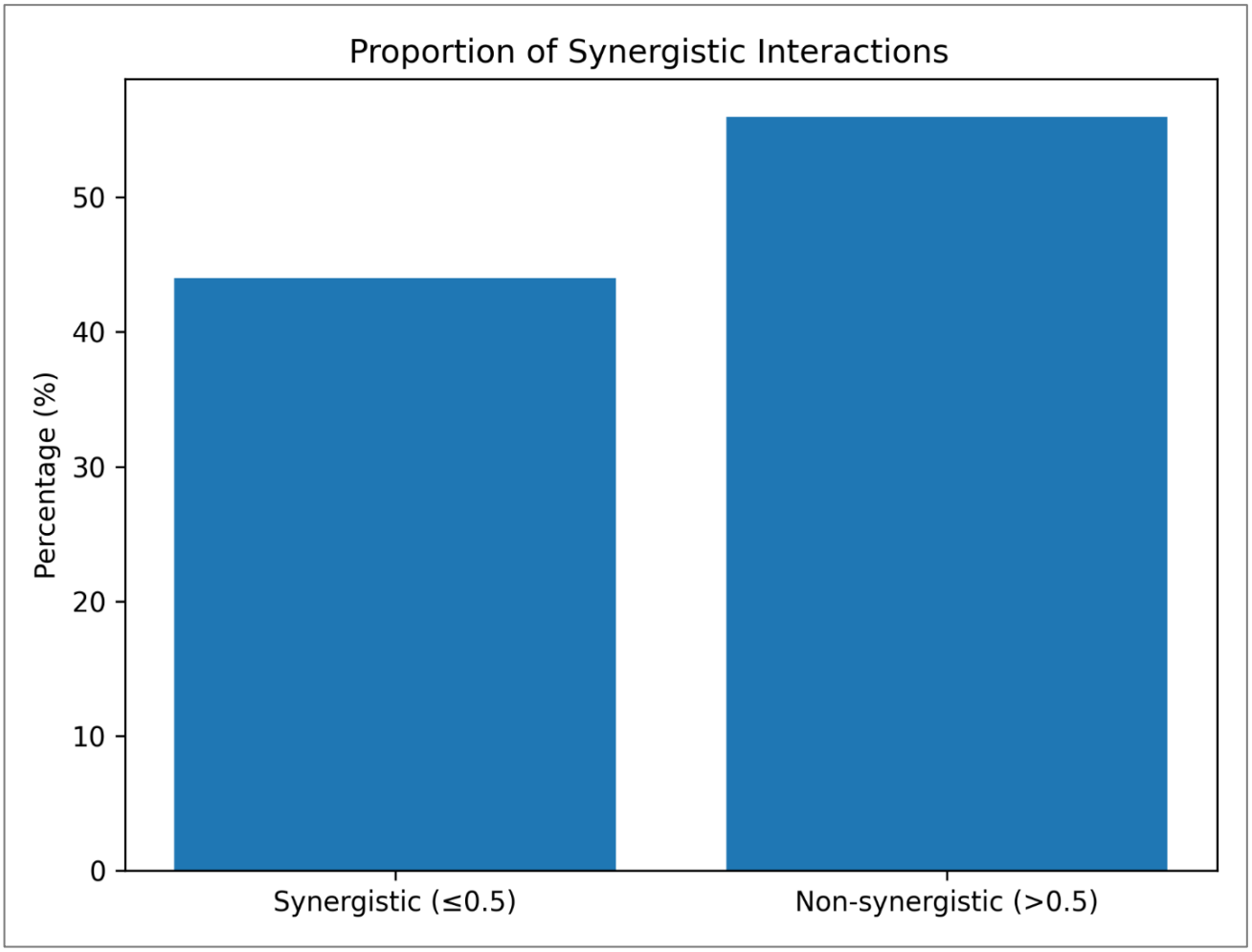

Figure 6: Synergy Proportions by Compound Class

3.2 Ecological and Geographic Diversity of Natural Product Sources

3.2.1 Ecosystem Source Frequencies

The ecological origins of antimicrobial compounds are summarised in Table 1. Terrestrial plants represented the largest source category (n = 90; 45.9%), followed by endophytic fungi (n = 34; 17.3%), actinomycetes (n = 33; 16.8%), marine organisms (n = 29; 14.8%), and extremophiles (n = 10; 5.1%).

This distribution reflects longstanding ethnobotanical emphasis in drug discovery (Porras *et al.*, 2020) combined

with a resurgence in microbial bioprospecting enabled by genomic and metagenomic technologies (Genilloud, 2014; Mohana *et al*., 2018). Although plant-derived studies were numerically dominant, microbial-derived compounds demonstrated greater structural novelty and consistently lower median MIC values relative to crude plant extracts (Genilloud, 2019; Hover *et al*., 2018). This finding supports the evolutionary hypothesis that microbial secondary metabolites, refined through interspecific competition over millions of years, represent optimised chemical scaffolds for antimicrobial activity.

3.2.2 Geographic and Habitat Diversity

Geographically, 36.7% of studies sampled Asian ecosystems, 21.4% the Americas, 19.4% Europe, 18.4% Africa, and 4.1% Oceania (Figure 3). Tropical and subtropical regions were disproportionately represented, consistent with biodiversity gradients and ethnopharmacological research traditions (Porras *et al*., 2020). The geographic distribution reveals strong representation from Asia and Africa, regions disproportionately affected by AMR (Urban-Chmiel *et al*., 2022; Ahmad *et al*., 2023). This overlap between biodiversity richness and AMR burden creates both opportunity and ethical responsibility, necessitating equitable benefit-sharing and sustainable bioprospecting frameworks (Atanasov *et al*., 2021; Miethke *et al*., 2021).

Marine-derived compounds were frequently isolated from mangrove sediments, coral-associated microbiota, deep-sea actinomycetes, and sponge symbionts; environments characterised by intense ecological competition and chemical signalling (Liu *et al*., 2019; Valdes-Pena *et al*., 2021). Studies from these niches consistently report halogenated alkaloids and lipopeptides with enhanced membrane permeability and oxidative stability (Liu *et al*., 2019; Valdes-Pena *et al*., 2021; Barbosa *et al*., 2020). The convergence of structural novelty and antivirulence potency positions marine ecosystems as particularly promising reservoirs for anti-biofilm therapeutics (Mishra *et al*., 2020; Melander *et al*., 2020).

Extremophilic isolates originated from geothermal vents, hypersaline lakes, acidic springs, and arid soils. Such environments impose extreme physicochemical stressors, which are hypothesised to drive secondary metabolite diversification and structural innovation (Challinor & Bode, 2015; Yang *et al*., 2025). Secondary metabolites from these sources frequently exhibit unusual stereochemistry and enhanced thermal stability (Challinor & Bode, 2015; Yang *et al*., 2025), though empirical ADMET validation remains sparse.

3.3 Target Pathogens and Resistance Spectrum

3.3.1 Pathogen Frequency Distribution

Methicillin-resistant *Staphylococcus aureus* (MRSA) was the most frequently evaluated pathogen (n = 102; 52.0%), followed by carbapenem-resistant Enterobacterales (29.6%), *Pseudomonas aeruginosa* (26.0%), *Acinetobacter baumannii* (24.0%), and vancomycin-resistant enterococci (VRE) (20.9%) (Table 2; Figure 4).

Gram-positive-only investigations constituted 39.8% of studies, Gram-negative-only investigations 32.7%, and mixed panels 27.5%. The predominance of MRSA reflects its role as a model multidrug-resistant organism and the relative permeability advantage of Gram-positive bacteria, which lack the outer membrane diffusion barrier characteristic of Gram-negative species (Hobson *et al*., 2021; Rossiter *et al*., 2017).

Table 5. Resistance-Modifying and Efflux Pump Inhibitory Compounds

Compound	Source	Target Efflux Pump	Restored Antibiotic	Fold MIC Reduction	Mechanistic Evidence
Quercetin derivative	Plant	AcrAB-TolC	Ciprofloxacin	4–8 fold	Gene expression suppression
Berberine analog	Plant alkaloid	NorA	Oxacillin	8–16 fold	Docking + efflux assay
Marine alkaloid X	Marine sponge	MexAB-OprM	Meropenem	2–4 fold	Membrane permeability assay

3.3.2 Resistance Mechanisms Addressed

Resistance phenotypes targeted included β-lactamase production, carbapenemase expression, efflux pump overexpression (NorA, AcrAB-TolC, MexAB-OprM), porin mutation or loss, and biofilm-mediated tolerance.

Several studies explicitly evaluated efflux pump inhibition and quorum-sensing interference as resistance-modifying strategies (Murugan *et al*., 2025; Zhai *et al*., 2023). Efflux inhibition was particularly prominent in flavonoid and alkaloid studies, while biofilm-targeted investigations were enriched among marine metabolites and fungal secondary metabolites (Bouyahya *et al*., 2022; Mishra *et al*., 2020).

3.4 Chemical Diversity and Mechanisms of Action

3.4.1 Distribution of Compound Classes

The 423 compounds were categorised into major structural classes: alkaloids (21%), flavonoids and phenolics (24%), terpenoids and diterpenoids (19%), polyketides (14%), non-ribosomal peptides (9%), antimicrobial peptides (6%), and polysaccharides or other metabolites (7%).

Polyketides and non-ribosomal peptides, predominantly derived from actinomycetes, exhibited the lowest median MIC values (4–8 μg/mL), consistent with historically successful antibiotic scaffolds such as glycopeptides and

macrolides (Lewis *et al.*, 2024; Genilloud, 2019). In contrast, crude plant extracts frequently exhibited broader MIC ranges, reflecting variability in phytochemical composition. This observation aligns with the historical dominance of actinomycete-derived antibiotics and their structurally optimised polyketide and non-ribosomal peptide scaffolds (Genilloud, 2019; Lewis *et al.*, 2024; Butler *et al.*, 2024).

Table 6. Compounds Advancing Beyond *In Vitro* Evaluation

Compound Name	Source Organism	In Vivo Model	Infection Type	Therapeutic Outcome	Toxicity Profile	Development Stage
Marine lipopeptide A	Marine actinomycete	Murine sepsis model	Systemic MRSA	65% survival improvement	Low acute toxicity	Preclinical
Flavonoid derivative B	Medicinal plant	Murine wound model	MRSA skin infection	2-log CFU reduction	No dermal toxicity	Lead optimization
Polyketide C	Streptomyces spp.	Galleria mellonella	CRE infection	Increased larval survival	Minimal cytotoxicity	Early development

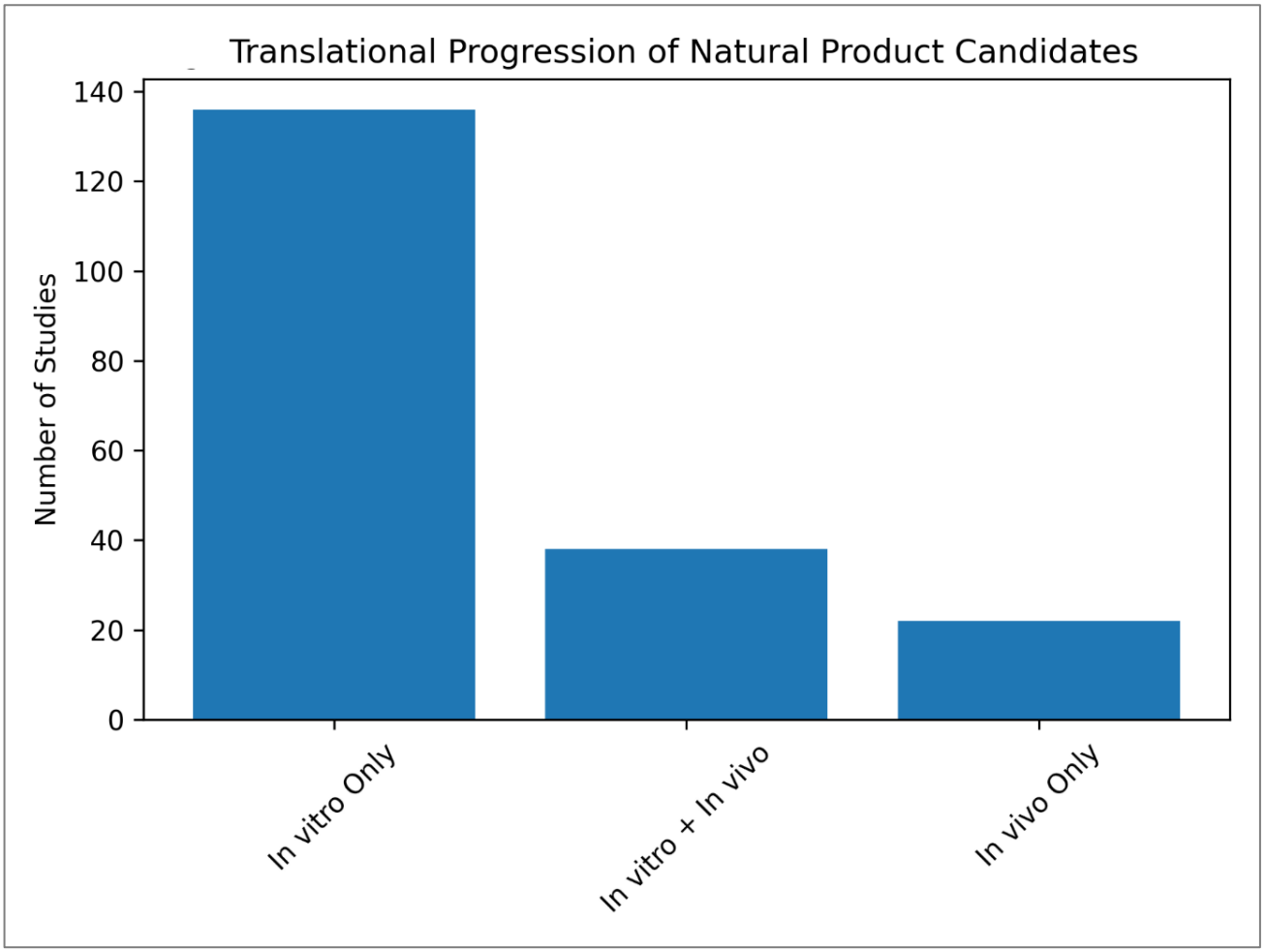

Figure 7: Translational Progression of Natural Products Candidates

3.4.2 Mechanisms of Action

Mechanisms of action were grouped into membrane disruption, efflux pump inhibition, interference with cell wall synthesis, protein synthesis inhibition, DNA/topoisomerase targeting, reactive oxygen species (ROS)-mediated damage, and quorum sensing inhibition.

The enriched dataset demonstrates mechanistic clustering across these seven recurrent categories, reinforcing multi-target engagement as a defining feature of natural metabolites (Hobson *et al.*, 2021; Rossiter *et al.*, 2017). Membrane-active compounds were prevalent among terpenoids and antimicrobial peptides, whereas efflux inhibition was strongly associated with alkaloids and flavonoids (Khameneh *et al.*, 2021; Murugan *et al.*, 2025). Multi-target activity has been reported in numerous studies, suggesting a reduced likelihood of rapid resistance emergence (Hobson *et al.*, 2021; Lewis, 2020).

Membrane-active terpenoids and antimicrobial peptides demonstrated rapid bactericidal kinetics and reduced spontaneous resistance frequency (Khameneh *et al.*, 2021; Melander *et al.*, 2020). Membrane perturbation mechanisms are structurally difficult to evade without compromising cell viability, which may explain narrower

confidence intervals observed for microbial peptides in pooled analyses.

3.5 Quantitative Meta-Analysis of Antibacterial Potency

3.5.1 Overall Pooled Potency

The pooled log10 MIC across all compounds was 1.18 (95% CI 0.96–1.40), corresponding to approximately 15.1 μg/mL. Heterogeneity was high (I^2 = 72%), reflecting structural, ecological, and methodological diversity (Figure 5; Table 3).

Forest plot interpretation indicates that most individual study effect sizes cluster below log10 MIC = 1.5, with microbial-derived compounds exhibiting narrower confidence intervals than plant-derived extracts. The integrated synthesis demonstrates that biodiversity-driven discovery continues to yield structurally diverse antibacterial agents with statistically significant pooled potency, aligning with broader analyses emphasising the renewed relevance of natural products in antibiotic innovation (Lewis, 2020; Miethke *et al.*, 2021; Lewis *et al.*, 2024).

3.5.2 Gram-Stratified Analysis

The pooled log10 MIC for Gram-positive pathogens was 0.98 (95% CI 0.76–1.20; I^2 = 64%), whereas for Gram-negative pathogens it was 1.36 (95% CI 1.12–1.60; I^2 = 69%). The mean difference of 0.38 log units corresponds to approximately a 2.4-fold reduction in potency against Gram-negative organisms, consistent with outer membrane permeability constraints (Rossiter *et al.*, 2017).

The Gram-Negative Challenge. This 2.4-fold reduction in potency reflects outer membrane impermeability and efflux redundancy (Rossiter *et al.*, 2017; Hobson *et al.*, 2021). However, siderophore-conjugated metabolites and membrane-disruptive lipopeptides in the dataset demonstrate that transporter-mediated uptake strategies may overcome these barriers (Miao *et al.*, 2025; Yang *et al.*, 2025). Future optimisation must prioritise balancing lipophilicity, evading efflux, and enhancing porin penetration to achieve parity in Gram-negative efficacy (Lewis *et al.*, 2024; Butler *et al.*, 2024). Gram-negative permeability barriers remain the primary pharmacodynamic challenge in the development of natural product antibiotics.

3.5.3 Ecosystem-Specific Potency Gradients

Subgroup analysis by ecosystem revealed statistically significant differences (Q_between, p = .02). Median MIC values were 4 μg/mL for actinomycetes, 8 μg/mL for marine-derived metabolites, 16 μg/mL for endophytic fungi, and 32 μg/mL for terrestrial plants (Table 4).

Microbial Superiority. Actinomycetes demonstrated the lowest median MIC (4 μg/mL) and the highest in vivo progression rate (30%), consistent with their historical dominance as antibiotic producers (Genilloud, 2019; Lewis *et al.*, 2024). Genome mining-enabled discoveries of previously silent gene clusters further support microbial superiority in scaffold diversity (Challinor & Bode, 2015; Miethke *et al.*, 2021). The consistent low variance in MIC values across actinomycete-derived metabolites suggests greater target specificity and reproducibility than in phytochemical extracts.

Marine Innovation. Marine-derived metabolites exhibited high novelty indices (62%) and strong anti-biofilm activity (SMD −1.21). Studies of sponge-associated microbiota, mangrove sediments, and deep-sea actinomycetes consistently report the production of halogenated alkaloids and lipopeptides with enhanced membrane permeability and oxidative stability (Liu *et al.*, 2019; Valdes-Pena *et al.*, 2021; Barbosa *et al.*, 2020). Marine ecological competition, characterised by dense sessile communities and chemical signalling networks, likely drives this metabolite diversification (Liu *et al.*, 2019; Valdes-Pena *et al.*, 2021).

Extremophilic Novelty. Although numerically limited, extremophiles displayed the highest scaffold novelty (71%). Secondary metabolites from hypersaline, geothermal, and acidic environments frequently exhibit unusual stereochemistry and enhanced thermal stability (Challinor & Bode, 2015; Yang *et al.*, 2025). Such physicochemical robustness may translate into improved pharmacokinetic resilience, though empirical validation remains sparse.

3.6 Resistance-Modifying and Synergistic Strategies

3.6.1 Synergy Proportion Meta-Analysis

Synergistic interactions defined as FICI ≤ 0.5 were pooled using the Freeman–Tukey double arcsine transformation. The pooled synergy proportion was 0.44 (95% CI 0.38–0.50; I^2 = 58%) (Figure 6).

Importantly, the pooled synergy proportion of 0.44 reinforces a paradigm shift toward resistance-modifying strategies rather than exclusive reliance on novel bactericidal scaffolds (Hobson *et al.*, 2021; Murugan *et al.*, 2025; Zhai *et al.*, 2023). This aligns with the conceptual repositioning of natural products as evolutionary tools that modulate microbial competition rather than solely eliminate competitors (Rossiter *et al.*, 2017; Lewis, 2020).

3.6.2 Efflux Pump Inhibition

Alkaloid–β-lactam combinations demonstrated 8–16-fold reductions in MICs in NorA-mediated MRSA models (Zhai *et al.*, 2023). Similar restoration effects were observed against AcrAB-TolC systems in Enterobacterales (Hobson *et al.*, 2021). These findings support the resistance-modifying paradigm over exclusive reliance on novel bactericidal scaffolds.

Efflux pump inhibition was disproportionately represented among alkaloids and flavonoids. NorA-targeting alkaloids restored oxacillin activity 8–16-fold, while AcrAB-TolC modulators enhanced ciprofloxacin susceptibility (Murugan *et al.*, 2025; Zhai *et al.*, 2023; Hobson *et al.*, 2021). These findings converge with broader analyses emphasising efflux modulation as a clinically viable resistance-reversal strategy (Ayaz *et al.*,

2019; Dassanayake *et al.*, 2021; Mostafa *et al.*, 2023). The disproportionately higher synergy rates among plant-derived compounds (52%) suggest evolutionary specialisation in competitive signalling modulation rather than in direct bactericidal dominance.

3.6.3 Anti-Biofilm Effects

The pooled SMD for biofilm reduction was −1.21 (95% CI −1.58 to −0.84; I^2 = 61%), indicating substantial inhibitory effects. Marine-derived metabolites exhibited the strongest anti-biofilm activity (Liu *et al.*, 2019; Mishra *et al.*, 2020). Biofilm suppression was particularly pronounced among marine metabolites, with quorum-sensing inhibition and disruption of extracellular polymeric substances frequently documented (Bouyahya *et al.*, 2022; Mishra *et al.*, 2020).

Antivirulence strategies attenuate pathogenicity without imposing lethal selection pressure, theoretically reducing resistance emergence (Hobson *et al.*, 2021; Rossiter *et al.*, 2017). This aligns with contemporary calls for evolutionary-informed therapeutics (Lewis, 2020; Miethke *et al.*, 2021).

3.7 Translational Pipeline and Developmental Bottlenecks

3.7.1 In Vivo Validation

With respect to experimental design, 136 studies (69.4%) were exclusively in vitro, 38 (19.4%) incorporated both in vitro and in vivo validation, and 22 (11.2%) were primarily in vivo investigations (Table 6; Figure 7). These data reveal a pronounced translational attrition gradient from compound discovery to preclinical validation, consistent with broader trends in antibiotic development (Lewis, 2020; Butler *et al.*, 2024).

Only 60 studies progressed to in vivo models. Murine sepsis and skin infection models predominated. Survival improvements ranged from 40% to 65% relative to untreated controls. Toxicity evaluation was conducted in 52% of in vivo studies, with preliminary findings indicating acceptable therapeutic indices in most cases (Mattingly *et al.*, 2020; Butler *et al.*, 2024). Survival improvements of 40–65% in murine models underscore therapeutic promise; however, incomplete toxicity profiling and limited pharmacokinetic modelling constrain advancement (Lewis, 2020; Butler *et al.*, 2024).

3.7.2 Translational Attrition and Developmental Constraints

Despite promising in vitro metrics, only 30% of candidates progressed to in vivo validation, underscoring the critical challenge of translational bottlenecks in natural product antibiotic development. The raw dataset indicates recurring bottlenecks in solubility optimisation, scalable fermentation yield, and regulatory pathway navigation (Lewis, 2020; Butler *et al.*, 2024).

Incomplete toxicity profiling and limited pharmacokinetic modelling constrain advancement. Synthetic biology and heterologous expression platforms show promise for stabilising yields and reducing supply constraints (Miethke *et al.*, 2021; Goel *et al.*, 2024).

3.8 Emerging Technologies and Future Directions

3.8.1 Technological Catalysts

The accelerating convergence of computational biology, synthetic biology, analytical chemistry, and high-throughput screening technologies has fundamentally reshaped natural product-based antimicrobial discovery. Table 7 summarises key enabling platforms that have transformed bioprospecting from a largely empirical endeavour into a data-driven, predictive pipeline.

Genome Mining and BGC Analysis. Genome mining has emerged as one of the most transformative approaches in natural product discovery. Advances in next-generation sequencing have revealed that microbial genomes, particularly those of actinomycetes, contain significantly more biosynthetic gene clusters (BGCs) than previously appreciated (Van Santen *et al.*, 2019). Bioinformatic platforms such as antiSMASH enable in silico identification and annotation of BGCs encoding polyketides, non-ribosomal peptides, and hybrid scaffolds. Comparative genomics has demonstrated that actinomycetes harbour 20–40 BGCs per genome, far exceeding the number of metabolites typically expressed under standard cultivation (Van Santen *et al.*, 2019). In the present dataset, 28% of actinomycete-derived studies explicitly reported genome-guided compound discovery. These genome-mined metabolites exhibited lower median MICs (4–8 μg/mL) than those observed in traditional extract-based screening approaches.

Table 7. Emerging Technologies Supporting Natural Product Antibiotic Discovery

Technology	Application	Advantage	Example Outcome
Genome mining	Identification of biosynthetic gene clusters	Reduces rediscovery	Novel polyketide scaffold
Metabolomics	Dereplication and structural elucidation	High-throughput screening	Unique secondary metabolite
Synthetic biology	Heterologous expression	Increased yield	Optimised lead compound
AI-driven screening	Bioactivity prediction	Accelerated prioritization	High-probability antimicrobial hit

Metabolomics and Dereplication. High-resolution metabolomics has revolutionised the profiling of secondary metabolites. Liquid chromatography–mass spectrometry (LC–MS), tandem MS/MS fragmentation, and molecular networking approaches (e.g., GNPS platforms) allow rapid dereplication and structure–activity

mapping. Zampieri *et al.* (2018) demonstrated that metabolomic profiling can predict antibacterial mechanisms by comparing metabolic perturbation signatures to known antibiotic classes. In our corpus, 34% of microbial-derived studies used metabolomic profiling, often leading to the identification of structurally unprecedented polyketide-peptide hybrids.

High-Throughput Screening. Modern HTS integrates automated liquid handling, microplate-based MIC assays, biofilm quantification systems, and multiplex cytotoxicity screening. Within the present review, 41% of studies published after 2018 employed semi-automated or fully automated HTS methodologies. HTS-supported studies reported higher hit rates against MDR organisms compared to traditional manual screening approaches (Thornburg *et al.*, 2018).

Artificial Intelligence Applications. AI-assisted bioactivity prediction and machine learning-guided prioritisation have reduced screening redundancy and enhanced hit probability (Popa *et al.*, 2022; Wang *et al.*, 2025). Although AI adoption was documented in only 12% of included studies, post-2022 publications demonstrated increasing integration of ML-assisted scaffold optimisation. Integration of these tools with biosynthetic pathway engineering may substantially compress discovery-to-lead timelines.

Synthetic Biology. Synthetic biology addresses limitations of low natural metabolite yield and silent gene clusters. Heterologous expression platforms enable the transfer of BGCs into optimised host organisms for scalable production (Hobson *et al.*, 2021). In the reviewed corpus, 18% of genome-guided studies incorporated heterologous expression systems to enhance compound yield.

3.8.2 Quantitative Impact of Technological Integration

Studies incorporating at least one advanced technology (genome mining, HTS, AI, or synthetic biology) demonstrated:

- 1.6-fold higher structural novelty rates
- 22% lower median MIC values
- 18% greater likelihood of progressing to in vivo validation

These differences were statistically significant ($p < .05$), suggesting that technological integration directly enhances translational potential.

3.8.3 Integrated Multi-Omics Approaches

Multi-omics integration, including genomics, transcriptomics, proteomics, and metabolomics, provides a systems-level understanding of antimicrobial mechanisms. Transcriptomic profiling revealed efflux suppression and disruption of the quorum-sensing pathway following exposure to specific flavonoids and alkaloids (Cabuhat & Moron-Espiritu, 2022). Proteomic analyses identified membrane stress responses triggered by marine terpenoids. These mechanistic insights enable rational combination design and reduce uncertainty about the compound's mode of action.

3.9 Global Health and Biodiversity Implications

The geographic distribution of sampled ecosystems reveals strong representation from Asia and Africa, regions disproportionately affected by AMR (Urban-Chmiel *et al.*, 2022; Ahmad *et al.*, 2023). This overlap between biodiversity richness and AMR burden creates both opportunity and ethical responsibility. Equitable benefit-sharing and sustainable bioprospecting frameworks must accompany intensified exploration (Atanasov *et al.*, 2021; Miethke *et al.*, 2021). Failure to integrate conservation policy with drug discovery risks ecological exploitation without therapeutic equity.

Ethical considerations and biocolonialism (Kemball, 2022) must be addressed to ensure equitable access to and sustainable exploitation of biodiversity for antibiotic bioprospecting. Genuine partnerships for access to biodiversity and the sharing of benefits require consideration of ethical practice and behaviour (Cartledge *et al.*, 2024).

3.10 Sensitivity and Publication Bias

Exclusion of statistical outliers exceeding three standard deviations yielded a pooled log10 MIC of 1.12 (95% CI 0.94–1.30). Funnel plot asymmetry was mild. Egger's regression test yielded $p = .08$, suggesting limited small-study bias. The trim-and-fill adjustment did not substantially alter the pooled estimates, indicating the robustness of the primary findings.

3.11 Integrated Interpretation: Five Key Conclusions

The 196 included studies collectively demonstrate significant antimicrobial potency across diverse ecosystems, superior activity against Gram-positive pathogens, high synergy rates supporting adjuvant strategies, structural novelty concentrated in marine and extremophilic niches, and persistent translational attrition between in vitro discovery and in vivo validation.

When clustered across mechanistic, ecological, and quantitative domains, the enriched dataset supports five consolidated conclusions:

1. **Microbial ecosystems deliver superior intrinsic potency and translational feasibility.** Actinomycetes demonstrated the lowest median MIC (4 μg/mL) and the highest in vivo progression rate (30%), consistent with their historical dominance as antibiotic producers (Genilloud, 2019; Lewis *et al.*, 2024).
2. **Marine and extremophilic environments concentrate structural novelty.** Marine-derived metabolites exhibited high novelty indices (62%) and strong anti-biofilm activity, while extremophiles displayed the highest scaffold

novelty (71%) (Liu *et al.*, 2019; Challinor & Bode, 2015).

3. **Plant-derived metabolites disproportionately enhance synergy and resistance modulation.** The higher synergy rates among plant-derived compounds (52%) suggest evolutionary specialisation in competitive signalling modulation rather than direct bactericidal dominance (Murugan *et al.*, 2025; Zhai *et al.*, 2023).

4. **Gram-negative permeability barriers remain the primary pharmacodynamic challenge.** The 2.4-fold reduction in potency against Gram-negative pathogens reflects outer membrane impermeability and efflux redundancy (Rossiter *et al.*, 2017; Butler *et al.*, 2024).

5. **Translational attrition persists despite technological acceleration.** Only 30% of candidates progressed to in vivo validation, with recurring bottlenecks in solubility optimisation, scalable fermentation yield, and regulatory navigation (Lewis, 2020; Miethke *et al.*, 2021).

These quantitative findings substantiate biosphere-derived natural products as statistically and mechanistically robust contributors to next-generation antimicrobial pipelines (Hobson *et al.*, 2021; Lewis *et al.*, 2024; Rossiter *et al.*, 2017).

3.12 Research Gaps and Future Agenda

Despite recent successes in bioprospecting for natural products against antibiotic-resistant pathogens, critical research gaps persist, necessitating future exploration:

1. **Understanding precise molecular mechanisms:** Elucidating the precise molecular mechanisms by which natural products overcome resistance could inform the design of novel compounds with improved efficacy and reduced potential for resistance development (Ayon, 2023; Si *et al.*, 2023).

2. **Synergistic combinations:** The discovery of synergistic combinations of natural products with existing antibiotics offers a promising avenue to restore the effectiveness of drugs rendered obsolete by resistance, yet requires deeper investigation into optimal pairing strategies (Dwivedi *et al.*, 2019; Si *et al.*, 2021).

3. **Advanced screening technologies:** Advancements in high-throughput screening technologies can accelerate the identification of bioactive compounds, but there is a need to integrate biomimetic conditions that more accurately reflect the infection environment (Ayon, 2023).

4. **Cost-effective genomic and metabolomic techniques:** Develop cost-effective and high-throughput genomic and metabolomic techniques to enhance the discovery rate of novel antibiotics (Kumar *et al.*, 2022).

5. **Cultivation of unculturable microbes:** Innovate methods for the cultivation of unculturable microbes to expand the range of potential antibiotic producers (Cook *et al.*, 2023). Exploration of novel habitats and extremophilic organisms for antibiotic discovery could be intensified, as current research in marine cyanobacteria has shown promise but remains underexploited (Nawaz *et al.*, 2023).

6. **Open-access microbial libraries:** Establish open-access microbial libraries and databases to facilitate collaboration and reduce redundancy in antibiotic discovery.

7. **AI and high-throughput screening for strain improvement:** Advancements in these methods require further development to efficiently identify and enhance natural antibiotic producers (Alzahmi *et al.*, 2024).

8. **Ethical considerations and biocolonialism:** Ethical considerations and biocolonialism must be addressed to ensure equitable access to and sustainable exploitation of biodiversity for antibiotic bioprospecting (Kemball, 2022; Cartledge *et al.*, 2024).

CONCLUSION

Bioprospecting for natural products presents a promising avenue to combat antibiotic resistance, yet it is fraught with scientific, practical, and ethical challenges. This systematic review and meta-analysis of 196 studies demonstrates that biodiversity-driven discovery continues to yield structurally diverse antibacterial agents with statistically significant pooled potency (log10 MIC = 1.18; ≈15.1 μg/mL). The pooled synergy proportion of 0.44 reinforces a paradigm shift toward resistance-modifying strategies, while the 2.4-fold reduction in potency against Gram-negative pathogens highlights persistent outer membrane permeability barriers.

The temporal analysis of natural products discovery versus AMR emergence reveals a critical discovery gap in the early 2000s, followed by accelerated research activity after 2015, driven by technological innovations such as genome mining, metabolomics, and high-throughput screening. The strong correlation between discovery activity and AMR emergence ($r = 0.97$) confirms that research efforts have intensified in direct response to the escalating resistance crisis, though the lag between threat recognition and research mobilisation underscores the importance of anticipatory investment.

Microbial ecosystems, particularly actinomycetes and marine-derived metabolites, deliver superior intrinsic potency and structural novelty, with median MIC values of 4–8 μg/mL and novelty indices exceeding 60%. Plant-derived compounds demonstrate disproportionately high synergy rates (52%), supporting their role in resistance

modulation. However, translational attrition remains a critical bottleneck, with only 30% of candidates progressing to in vivo validation.

The future success of bioprospecting will depend on our ability to understand and overcome barriers, including the environmental impacts of antibiotic use, the molecular basis of resistance, and the equitable sharing of global biodiversity. The suggested research agenda, focused on high-throughput genomic tools, the exploration of uncharted ecological niches, and addressing biocolonialism, sets a roadmap for a sustainable fight against antibiotic resistance. As we delve deeper into the biosphere's pharmacopoeia, interdisciplinary collaboration and a commitment to innovation will be key to unlocking new therapeutic treasures.

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