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Unlocking Microbial Potential: Innovations in Natural Product Biosynthesis and Therapeutic Applications

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Abstract

MNPs play a pivotal role in diverse fields, spanning medicine, agriculture, and industry. This review paper synthesizes insights from various discussions on microbial natural products, encompassing their sources, bioactive properties, and applications. We explore microbial diversity contributing to natural product synthesis, emphasizing bacteria and fungi as prolific producers. The methods for isolating and characterizing these compounds underscore the interdisciplinary nature of microbial natural product research utilizing various analytical techniques contributing to the structural characterization and dereplication of microbial natural products and enhancing drug discovery processes. Discussions on the potential therapeutic applications reveal antimicrobial, anticancer, and immunomodulatory properties, highlighting the pharmaceutical relevance of these compounds. Additionally, the agricultural and industrial significance of microbial natural products is explored, showcasing their role as biopesticides, biofertilizers, and enzymes in various processes. The importance of databases like NPA and NPBS in advancing MNP research and the complexities of intellectual property and commercialization in the context of patents and licensing are also discussed. The challenges associated with discovering and harnessing microbial natural products, including issues of cultivation and optimization, are also addressed. This abstract provides a comprehensive overview of the multifaceted aspects of microbial natural products, underscoring their significance in scientific, medical, and industrial domains.

Keywords: Microbial Natural Products (MNPs), Databases, Biosynthesis, Antimicrobial Agents, Structural Characterization

INTRODUCTION

Nature has long been a prolific source of pharmaceutical agents, contributing to contemporary drug development. Notably, microorganisms, such as bacteria and fungi have stood out for their chemical diversity, unique structures, and important contributions to drug discovery [1]. The pivotal discovery of penicillin in 1929 marked the onset of the "*Golden Age of Antibiotics*", revolutionizing NP research and leading to the antibiotic era in the 1940s [2]. Since then, MNPs have played an important role in the pharmaceutical industry, yielding over 15,000 antibiotics, with 150 currently on the market [3].

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While initial discoveries were predominantly from terrestrial bacteria, recent exploration in diverse environments, such as marine and extreme habitats, has expanded the repertoire of microorganisms harboring novel bioactive NPs [4]. To improve the efficiency of natural-product programs, ongoing efforts focus on diversifying microbial strains and extract libraries, minimizing genetic and chemical redundancy [5]. Departing from traditional random searches, recent approaches, particularly in microbial symbiotic systems, have unveiled novel chemotypes and biological activities for drug discovery and

development [6].

MNPs, instrumental in discovering antibiotics, continue to offer substantial biodiversity for identifying new drugs across various therapeutic categories [7]. With diverse applications, including antibiotics, anticancer agents, and immunosuppressants, these compounds provide cost-effective medicines, particularly in developing countries, revolutionizing healthcare [8].

This review presents a curated dataset of NPs effective against prominent infectious pathogens, compiled through meticulous manual curation to inspire researchers to explore the intricate interplay between NPs and infections.

BIOSYNTHESIS OF MNPS

The creation of NPs from various sources, such as plants, animals, marine life, and microorganisms is a complex endeavor that has intrigued scientists for many years [9]. The production of MNPs is influenced by the genetic regulation of microbial metabolic pathways, revealing considerable unexplored possibilities [10]. For instance, filamentous fungi can generate a wide array of secondary metabolites through BGCs [11]. These BGCs manage the synthesis of NPs via intricate branching and converging pathways, which increases their structural diversity [12]. Enzymes from different BGCs work together, utilizing reactions like Diels-Alder cycloaddition to create distinctive compounds, and often, a single BGC is responsible for the production of fungal meroterpenoids [13]. Enzymes, such as meroterpenoid cyclases and dioxygenases contribute to the variety of fungal meroterpenoids [14]. Likewise, various microorganisms, including fungi and bacteria, produce α-pyrone-containing NPs [15].

Recent developments have broadened the possibilities for NP synthesis through methylation, facilitated by SAM-dependent methyltransferases (MTs) [16]. Techniques driven by genomics have made it possible to produce metabolites that are usually not expressed under standard laboratory conditions, allowing for a deeper investigation into microbial metabolic capabilities [17]. Enzymes like cytochrome P450s, laccases, and unique cyclases are essential in the dimerization process, speeding up the identification of new dimeric compounds [18, 19].

Improvements in heterologous expression systems, especially with modified strains of *Escherichia coli* and Streptomyces, have enhanced NP production by increasing the availability of precursors and streamlining metabolic pathways [20]. Combinatorial biosynthesis, which uses microorganisms as "cell factories," further expands the frontiers of NP discovery by genetically altering biosynthetic pathways [21]. These innovations, along with genome mining, offer potential for drug discovery and biotechnological applications, transforming our comprehension and use of MNPs [22].

Structural Characterization and Dereplication

Dereplication constitutes a pivotal step in the analysis of extracts derived from microbial fermentation or plant samples, to identify and eliminate known or redundant compounds [23]. Targeted dereplication, integrating genomic and metabolomic data, plays an important role in streamlining structure elucidation efforts and improving the efficiency of NP-based drug discovery [24].

The integration of genomic and metabolomic data offers a valuable approach for targeted dereplication (Table 1). Genomic data allows the prediction of chemical structures by analyzing gene clusters responsible for synthesis, helping in the identification of potential NPs before fermentation studies commence whereas metabolomic data involves the analysis of metabolites produced by microorganisms, enabling automated comparisons of metabolite profiles for library construction [25, 26]. This integrated approach helps researchers identify and isolate new chemical entities, avoiding the re-isolation of known compounds and enhancing discovery efficiency [27].

The exploration of structural characterization and dereplication of MNPs encompasses diverse methodologies and tools, significantly contributing to the ongoing quest for novel bioactive compounds and the advancement of drug discovery from microbial sources (Figure 1).

Table 1. Latest approaches for structural characterization and targeted dereplication.

Method/Database	Approach/Insights	Tools/Platforms	References
acd_lotusv7 Database (derived from LOTUS)	Carbon-13 NMR spectral data predictions; Efficient and free method for structural dereplication	nmrshiftdb2 web interface, Wikidata linkage	[28]
NP-MRD	Deposition of NMR meta-data assignments; Aids in structural characterization; QM calculations	ACD/Labs,RDKit,	[29]
DEREP-NP	DOSY; Predicts molecular weight; Effective in dereplicating known NPs; Distinguishes compounds in mixtures	SMART 2.0; MADByTE	[30]
UNPD	Research in structural diversity and similarity using molecular fingerprints; Valuable insights for groups with limited resources	MaxMin algorithm; DBCS; Tree MAP	[31]
MN Methods	Diverse strategies for identifying and prioritizing secondary metabolites; Integration of MS and NMR data; Advancements in big data approaches	Classical MN, feature-based MN, ion identity MN, building blocks-based MN, substructure-based MN, bioactivity-based MN	[32]
MADByTE	Identification of common structural features in complex extract libraries; Mapping bioactivity to structural networks	Two-dimensional NMR spectra	[33]
CNMRPredict	Combines structural and taxonomic data with predicted carbon-13 NMR data from the LOTUS NP database; an Easily searchable database	ACD/Labs CNMR Predictor and DB software	[34]
DEREPLICATOR+	Algorithm for identifying a wide range of NPs; Molecular networking project for searches against spectral libraries	GNPs molecular networking project	[35]
MS-Based Workflows	Liquid chromatography data-dependent mass spectrometric platform; Tandem mass analysis and molecular networking	MS workflows, molecular networking	[36]

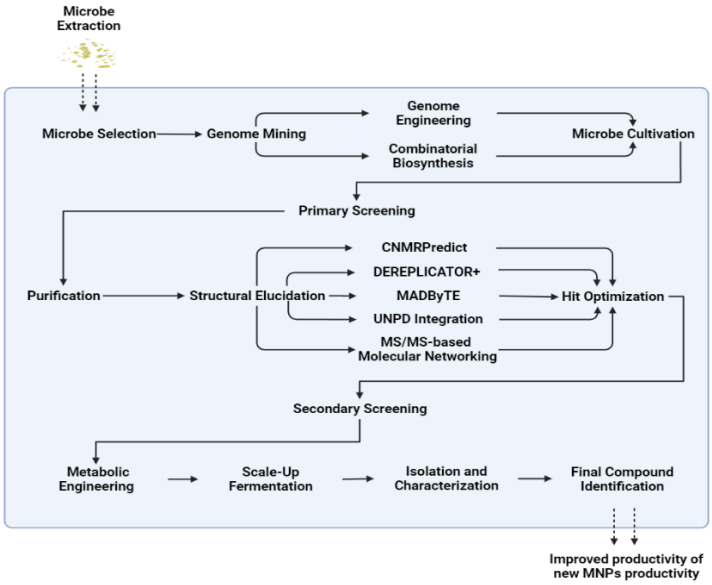

Figure 1. Diverse methodologies are employed for the enhancement of products attributes and the derivation of novel MNPs.

BIOLOGICAL ACTIVITIES OF MNPS

Antibacterial MNPs

Bacteria, particularly adept at producing bioactive NPs, predominantly manifest their secondary metabolites, presenting a rich source for therapeutic exploration [37]. MNPs, encompassing secondary metabolites, exhibit noteworthy therapeutic attributes and biological functions, positioning them as valuable resources for combating various diseases [38]. The imperative to discover new antimicrobial compounds from natural sources is underscored by the challenges posed by ABR and the limitations in fully tapping into the biosynthetic potential of microorganisms [39–46].

Table 2. Prominent Antibacterial MNPs throughout the ages.

Antimicrobial Agent	Source	Mechanism of Action	Clinical Uses	References
Penicillin G and V	Various Penicillium species	Inhibits bacterial cell wall synthesis	Various infections	[47]
Cephalosporins	*Cephalosporium fungus*	Broad spectrum antibiotics	Septicemia, pneumonia, meningitis, etc.	[48]
Vancomycin	*Streptomyces orientalis*	Inhibits bacterial cell wall synthesis	MRSA, other β-lactam-resistant bacteria	[49]
Tetracyclines	Various Streptomyces species	Interferes with bacterial protein synthesis	A wide range of microorganisms	[50]
Chloramphenicol	*Streptomyces venezuelae*	Inhibits bacterial protein synthesis	Gram-positive and Gram-negative bacteria, rickettsia	[51]
Amphotericin B	*Streptomyces nodosus*	Disrupts fungal cell membrane	Candida, Aspergillus, etc.	[52]
Griseofulvin	*Penicillium griseofulvum*	Binds to fungal microtubules	Dermatophytosis	[53]
Streptomycin	*Streptomyces griseus*	Inhibits bacterial protein synthesis	Tuberculosis, sepsis, endocarditis, etc.	[54]
Echinocandin B	*Aspergillus nidulans*	Inhibits fungal cell wall synthesis	Candida species	[53, 55]
Bacitracin	*Bacillus subtilis*	Inhibits bacterial cell wall synthesis	Gram-positive bacteria	[56]
Polymyxins	*Bacillus polymyxa*	Disrupts bacterial cytoplasmic membrane	Gram-negative bacteria	[57, 58]
Neomycins	*Streptomyces fradiae*	Inhibits protein synthesis and DNA polymerase	Broad-spectrum activity	[59]
Nystatin	*Streptomyces noursei*	Disrupts fungal cell membrane	Candida, etc.	[60]
Erythromycin	*Saccharopolyspora erythraea*	Inhibits bacterial protein synthesis	Chest infections, skin diseases, etc.	[61]
Rifamycins	*Amycolatopsis mediterranei*	Inhibits bacterial DNA-dependent RNA synthesis	Tuberculosis	[62]
Gentamicin	*Micromonospora purpurea*	Inhibits bacterial protein synthesis	Urinary tract infections, respiratory tract infections, etc.	[63]
Mupirocin	*Pseudomonas fluorescens*	Inhibits bacterial protein synthesis	Skin infections, MRSA	[64]
Daptomycin	*Streptomyces roseosporus*	Disrupts bacterial cell membrane function	Complicated skin and soft tissue infections	[65]
Platensimycin	*Streptomyces platensis*	Inhibits bacterial DNA-dependent RNA synthesis	Antibacterial activity against Gram-positive pathogens	[66]
Nisin	*Lactococcus lactis*	Bactericidal peptide	Food preservative, selective agent in microbiological media	[67]
Teixobactin	*Uncultured bacteria*	Inhibits bacterial cell wall synthesis	Gram-positive bacterial strains, MRSA, S. pneumoniae, etc.	[68]

Enniatins	*Fusarium tricinctum Corda*	Not specified	Mild antibacterial and antileishmanial activities	[69]
Copsin	*Coprinopsis cinereal*	Bactericidal peptide	Gram-positive bacteria	[70]
Albicidin	*Xanthomonas albilineans*	DNA gyrase inhibitor	Broad spectrum antibacterial activity	[71]
Cystobactamids	*Cystobacter sp.*	Inhibitors of bacterial DNA gyrase	E. coli, A. baumannii, S. aureus, S. pneumonia	[72]

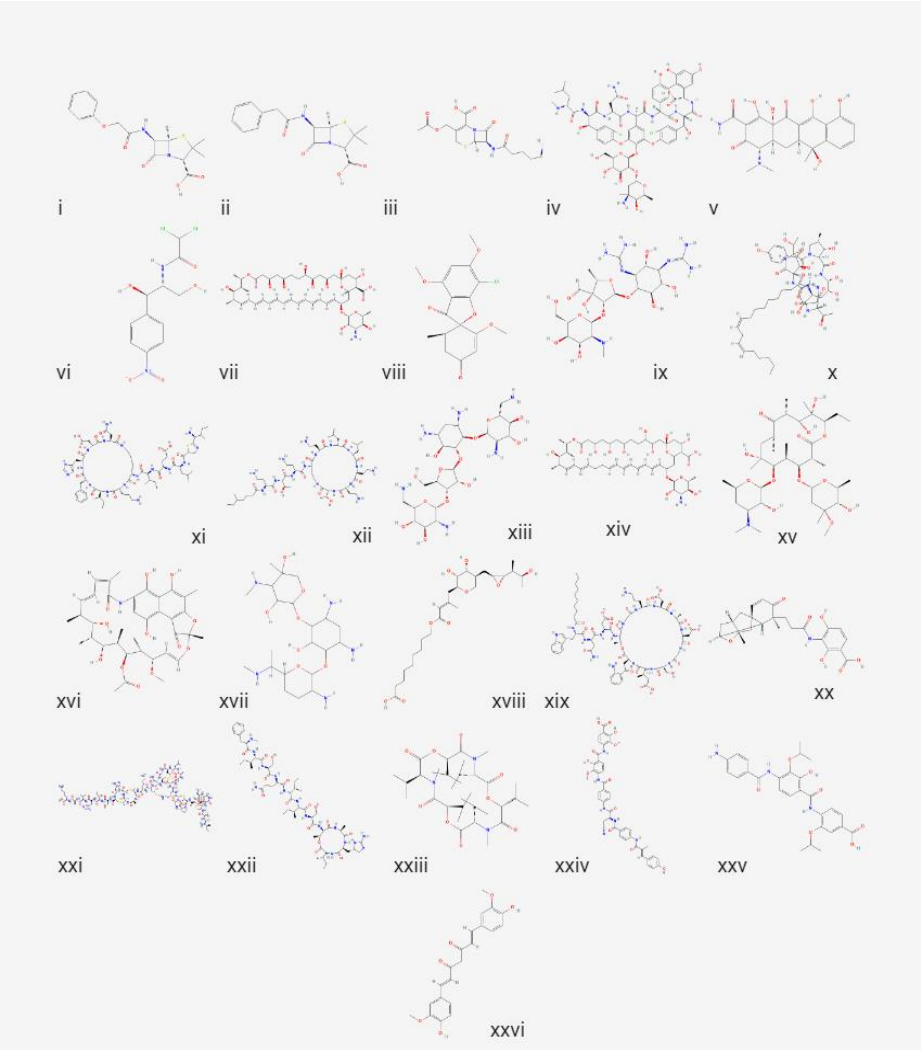

Figure 2. Structures of MNPs with Antibacterial Properties (i) Penicillin V (ii) Penicillin G (iii) Cephalosporins (iv) Vancomycin (v) Tetracyclines (vi) Chloramphenicol (vii) Amphotericin B (viii) Griseofulvin (ix) Streptomycin (x) Echinocandin B (xi) Bacitracin (xii) Polymyxins (xiii) Neomycins (xiv) Nystatin (xv) Erythromycin (xvi) Rifamycins (xvii) Gentamicin (xviii) Mupirocin (xix) Daptomycin (xx) Platensimycin (xxi) Nisin (xxii) Teixobactin (xxiii) Enniatins (xxiv) Albicidin (xxv) Cystobactamids (xxvi) Curcumin.

Europe, with over 67,000 ABR infections costing €1.1 billion, and the United States, with 2.8 million cases, confront the urgency of developing novel antibiotics [40]. Contributing factors to ABR are diverse and include natural genetic modification in bacteria, resulting in the emergence of drug-resistant strains. Over-prescription of antibiotics, including the gratuitous use of broad-spectrum antibiotics, has significantly accelerated ABR. Mechanisms leading to antimicrobial resistance encompass enzymatic inactivation of antibiotics, alteration of antibiotic target sites, decreased intracellular accumulation

and/or efflux of antibiotics, and modification of metabolic pathways or bypassing antibiotic action [41, 42].

The biosynthesis of cryptic bacterial NPs, exemplified by the discovery of the lanthipeptide antibiotic kyamicin, has provided a strategy for addressing ABR by expanding the repertoire of NP scaffolds (Table 2) [43]. Curcumin, derived from *Curcuma longa*, demonstrates multifaceted antibacterial effects by disrupting cell membranes in both Gram-positive and -negative bacteria, inhibiting quorum sensing and cell division, inducing oxidative stress, altering bacterial metabolism, and exhibiting promising synergies with polymyxins and other NPs [44, 45]. Tetracycline, obtained from *Streptomyces spp*., exhibits bacteriostatic activity against malaria by inhibiting protein synthesis. In bacteria, tetracyclines are known to bind constituents of both the 30S and 16S ribosomal RNA subunits, thus blocking prokaryotic translation (Figure 2) [46].

Antifungal and Antiviral MNPs

Extensive research has explored the application of these NPs in drug development to combat a range of viral infections, including hepatitis, herpes simplex, HIV, influenza, respiratory syncytial virus, and SARS-CoV-2 (Table 3) [73]. Various compounds, such as flavonoids, polyphenols, saponins, and essential oils derived from microbial sources, have displayed a broad spectrum of antimicrobial and antiviral activity, positioning them as promising candidates for the prevention and treatment of fungal infections [74]. The quest for alternative antifungal drugs with high efficacy and low resistance rates has led researchers to focus on MNPs, given their structural and bioactive diversity (Figure 3) [75].

Table 3. Prominent antiviral and antifungal MNPs and their mechanisms.

Compound	Source	Virus/Fungus Targeted	Mechanism of Action	References
MM3122	Molecular docking studies with X-ray structure of TMPRSS2	SARS-CoV-2, MERS-CoV	Inhibition of TMPRSS2 enzyme, blocking viral entry	[76]
Labyrinthopeptin A1	Actinomadura namibiensis DSM 6313	HIV, HSV	Inhibition of viral entry post-CD4 binding	[77]
Aspernigrin	Aspergillus niger	SARS-CoV-2	Highest inhibitory activity among isolated naphthopyrones	[78]
Neoechinulin B	Aspergillus amstelodami	HCV	Inhibition of transcriptional activities of the LXR	[79]
Truncateol O	Truncatella angustata	HIV-1	Inhibition of HIV-1	[80]
Truncateol P	Truncatella angustata	H1N1	Inhibition of H1N1	[80]
Sampangine	Annonaceae family (plants)	Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus	Induction of oxidative stress, upregulation of oxidative stress-related genes	[81]

Anticancer/Antitumour MNPs

Most anticancer agents exert their effects on DNA or its precursors, disrupting the synthesis of genetic material and causing damage to both normal and malignant cells (Table 4) [82]. Chirality, particularly in the context of different enantiomers of chiral compounds, plays a pivotal role in anticancer chemotherapy, where distinct pharmacological effects can be observed (Figure 4) [83].

MNPs as Antioxidant and Anti-inflammatory Agents

A deficiency of antioxidant compounds in the daily diet poses a risk for the development of degenerative diseases (Table 5) [84–107]. Inflammation, a nonspecific immunological response by the body, occurs in reaction to trauma, neoplasms, autoimmune attacks, or microbial invasions. The inflammatory site witnesses' various processes, including increased blood supply, leakage of cellular fluid and small molecules, and protein penetration (Figure 5) [108].

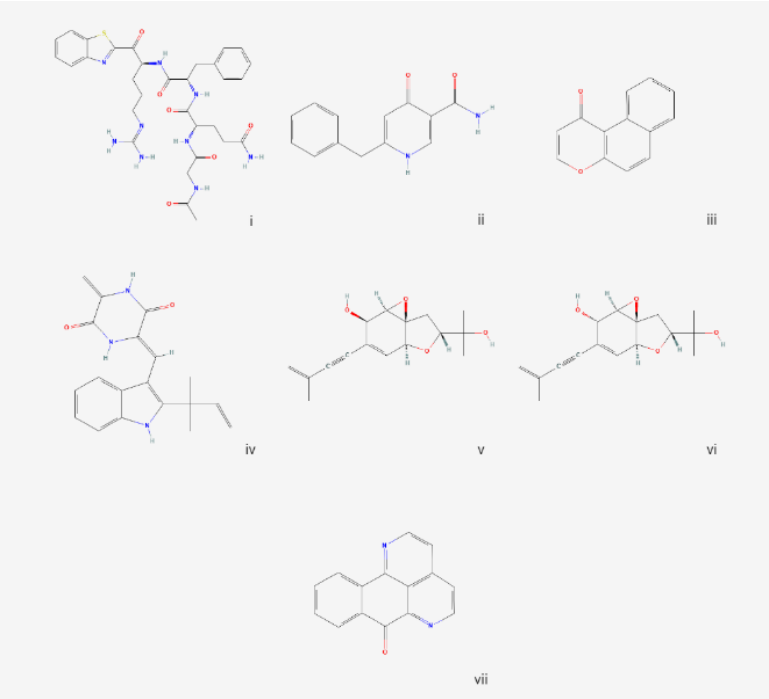

Figure 3. Structures of MNPs with Antiviral and Antifungal Properties (i) MM3122 (ii) Aspernigrin (iii) Naphthopyrone (iv) Neoechinulin B (v) Truncteol O (vi) Truncateol P (vii) Sampangine.

Table 4. Antitumour MNPs for different types of cancer.

Cancer Type	Compounds	Mechanism of Action	References
Brain Cancer	Actinomycin D, Valinomycins, Salinomycin, Komodoquinone A	Enzyme inhibition, Suppression of metabolic regulators in glioma, Blocking the VEGF-VEGFR2-Akt/FAK signaling pathway, Stimulation of differentiation	[84–87]
Lung Cancer	Ethyl acetate extract, Neoantimycin F, Anthraquinones, quercetin-3-O-b-L-rhamnopyranosyl-(1 to 6)-b-D-glucopyranoside, Galvaquinone B, Tuberatolide B	Fragmentation of DNA, Condensation of chromatin, Induction of apoptosis, Reduction in mitochondrial membrane potential, Generation of reactive oxygen species, Activation of caspases, Suppression of ERK1/2 phosphorylation	[88–92]
Cervical Cancer	N-acetyl-deformylantimycin, Geldanamycin, Caffeic acid, Paclitaxel, Adenosine	Degradation of oncoproteins E6/E7 through ROS-mediated ubiquitin-proteasome system activity, Suppression of ERK1/2, STAT3, and the PI3K/AKT/mTOR pathway, Triggering apoptosis in HeLa cells positive for HPV-18	[93–97]
Colon Cancer	Ether extract, Ethyl acetate fraction, Pyrrolo (1,2-a) pyrazine-1,4-dione, hexahydro-3-(phenylmethyl)-, Dobutamine, Bleomycin	Elevation in p53 expression, Halting of the cell cycle, Initiation of apoptosis, Augmentation of p21 and p53 levels, Diminution of cyclin B1, CDK2, CDK4, Intrinsic apoptosis, Cleavage of PARP, Activation of Caspase-3	[98–100]
Blood Cancer	Metabolites, Pure cytotoxic compound, Spicamycin, KRN5500, Daunorubicin, Doxorubicin, Vincristine, Vinblastine	Stimulation of apoptosis, Activation of Caspase-3, Inactivation of AKT, Reduction in Bcl-2 levels, Adjustment of PML localization, Increase in BAX expression, Initiation of apoptosis through p53-dependent mechanisms	[101, 102]
Other Cancers	Mensacarcin, Streptochlorin, Kosinostatin, Novobiocin	Caspase-3/7-mediated apoptosis, Impaired mitochondrial function, Targeted cytotoxicity towards melanoma cells harbouring the BRAFV600E mutation, triggering p53-dependent apoptosis, Eliciting DNA damage, Inducing autophagy and mitophagy	[103–106]

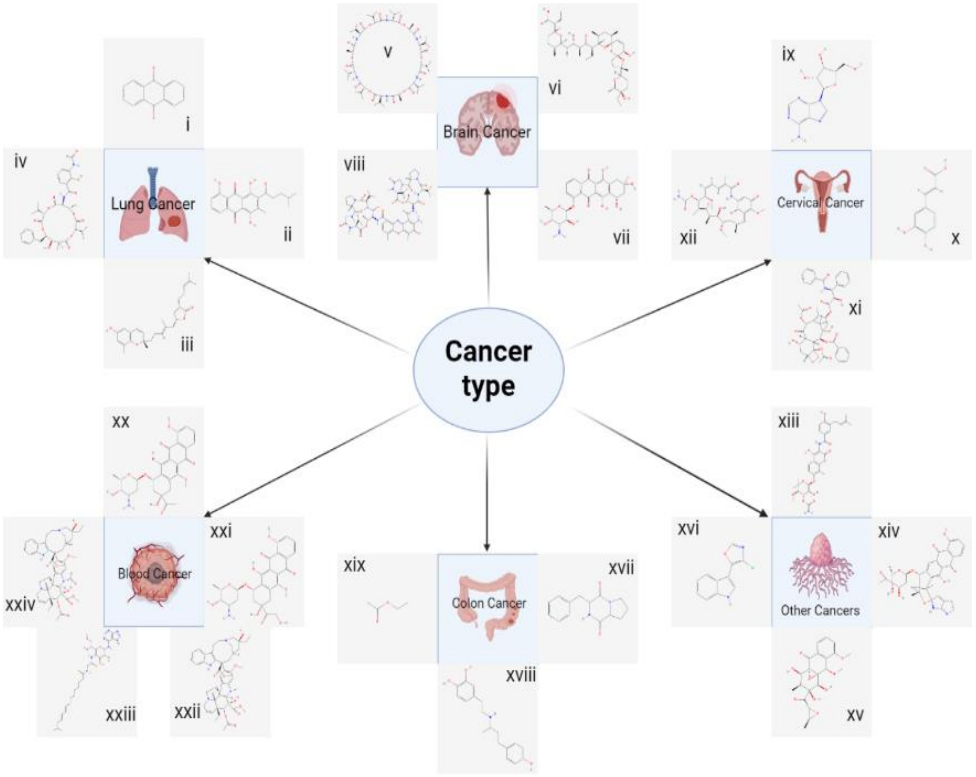

Figure 4. Structures of MNPs with Antitumour Properties for different types of Cancers (i)Anthraquinones (ii) Galvaquinone B (iii) Tuberatolide B (iv) Neoantimycin F (v) Valinomycins (vi) Salinomycin (vii) Komodoquinone A (viii) Actinomycin D (ix)Adenosine (x) Caffeic acid (xi) Paclitaxel (xii) Geldanamycin (xiii) Novobiocin (xiv) Kosinostatin (xv) Mensacarcin (xvi) Streptochlorin (xvii) Pyrrolo [1,2-a] pyrazine-1,4-dione, hexahydro-3-[phenylmethyl]- (xviii)Dobutamine (xix) Ethyl acetate (xx) Daunorubicin (xxi) Doxorubicin (xxii) Vinblastine(xxiii) Spicamycin (xxiv) Vincristine.

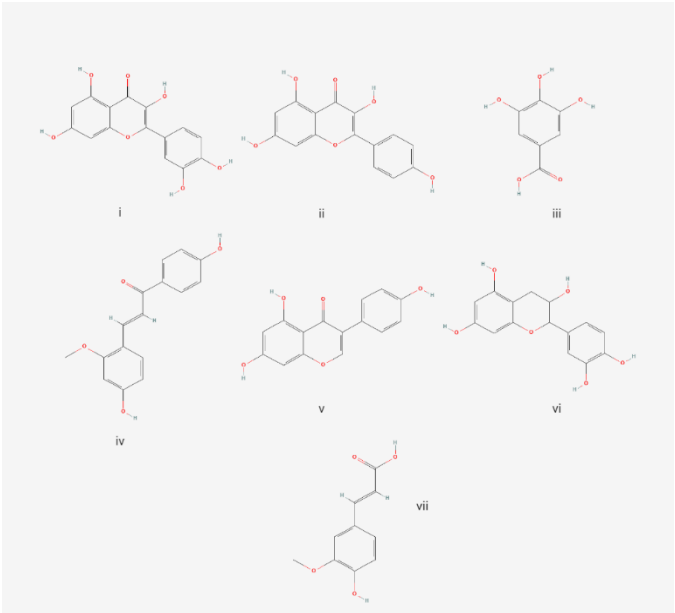

Figure 5. Structures of MNPs with Antioxidant and Anti-inflammatory Properties (i) Quercetin (ii) Kaempferol (iii) Gallic acid (iv) Reterochalcone (v) Genistein (vi) Catechin (vii) Ferulic acid.

Table 5. Some of the Antioxidant and Anti-inflammatory MNPs.

Mechanism of Action	Antioxidant Compound	Description	References
Inhibition of nucleic acid synthesis	Kaempferol	Demonstrates high antibacterial efficacy (MIC50 = 25 μg/ml) targeting E. coli DNA gyrase, inhibiting the crucial enzyme responsible for DNA supercoiling and bacterial proliferation.	[109]
	Polymethoxylated Flavones	Exhibits comprehensive antimicrobial effectiveness against both E. coli and S. aureus, with IC50 values ranging from 1.45 to 1.89 mg/ml.	[109]
	Quercetin	Hinders DNA supercoiling, induces DNA cleavage, and exhibits inhibitory effects on antibiotic-resistant H. pylori bacteria.	[110]
	Glycosylated Flavones	Facilitates topoisomerase IV-dependent DNA cleavage in E. coli, with rutin acting as an inhibitor of topoisomerase IV activity.	[111]
	Catechins	Suppresses ATPase activity (ECG < ECGC < EGCG) of the gyrase B subunit, preventing ATP hydrolysis and influencing DNA supercoiling.	[112]
	Soybean Isoflavone [SI]	Modifies the supercoiling of double-stranded DNA, and inhibits both topoisomerases I and II, thereby impacting nucleic acid synthesis.	[113]
	Genistein	Influences DNA and RNA synthesis, induces bacterial cell elongation, and impedes protein synthesis.	[114]
Disruption of membranes	Sophoraflavanone G	Demonstrates potent antibacterial activity, modifies membrane functions, and reduces membrane fluidity.	[115]
	Catechins	Interacts with bacterial membrane proteins, fatty acid synthase, and beta-lactamase, leading to alterations in membrane fluidity.	[116]
	Epigallocatechin Gallate [EGCG]	Disrupts membranes induce membrane leakage and bring about morphological changes in Gram-negative bacteria.	[117]
	Ferulic and Gallic Acid	Inflicts severe and irreversible damage to membranes, resulting in continual leakage of vital cellular constituents.	[118]
Inhibition of energy metabolism	Reterochalcones	Halts oxygen consumption in targeted cells, and inhibits NADH oxidation in bacterial membranes, thereby impeding the electron transport c	[119–122]

Table 6. MNPs in the food and agriculture industry.

Category	Examples	Applications/Uses	References
Amino acids	Lysine, Methionine, Threonine, Aspartic acid, Glutamate, Serine, Aspartame	Amino acids play a vital role in protein synthesis, serving as essential components in animal feed for nutritional balance. Additionally, certain amino acids function as flavor enhancers and antioxidants in various applications.	[123, 124]
Vitamins	Riboflavin, Cyanocobalamin, β-Carotene	Micronutrients, essential for health, serve as coenzymes facilitating various metabolic processes. Their applications span across diverse industries, including food, pharmaceuticals, and healthcare.	[125, 126]
Enzymes	Nitriles, Amines, Phenylalanine, Ammonia lyase, Sacrosidase	Enzymes exhibit catalytic activities crucial for accelerating biochemical reactions. Their widespread use extends to the food, chemical, and healthcare industries for enhancing processes and product development.	[127]
Organic acids	Acetic acid, Lactic acid, Citric acid, Itaconic acid	Versatile compounds find extensive applications in food, beverages, pharmaceuticals, and various industries due to their diverse functionalities and beneficial properties.	[128–130]
Alcohol	Ethanol, Glycerol	Biofuels derived from renewable sources, alongside serving as chemical feedstock, have applications across a spectrum of industries, contributing to sustainable practices.	[131, 132]
Biopesticides and plant growth regulators	Biofungicides (Trichoderma), Bioinsecticides (*Bacillus thuringiensis, B. sphaericus*), Plant hormones (auxins, gibberellins, cytokinins, abscisic acid and ethylene), Bioherbicides (Phytopthora)	Environmentally friendly alternatives in agriculture include microbial herbicides and bio-funggicides, while plant hormones act as messengers, regulating plant growth for improved yield and health.	[133]

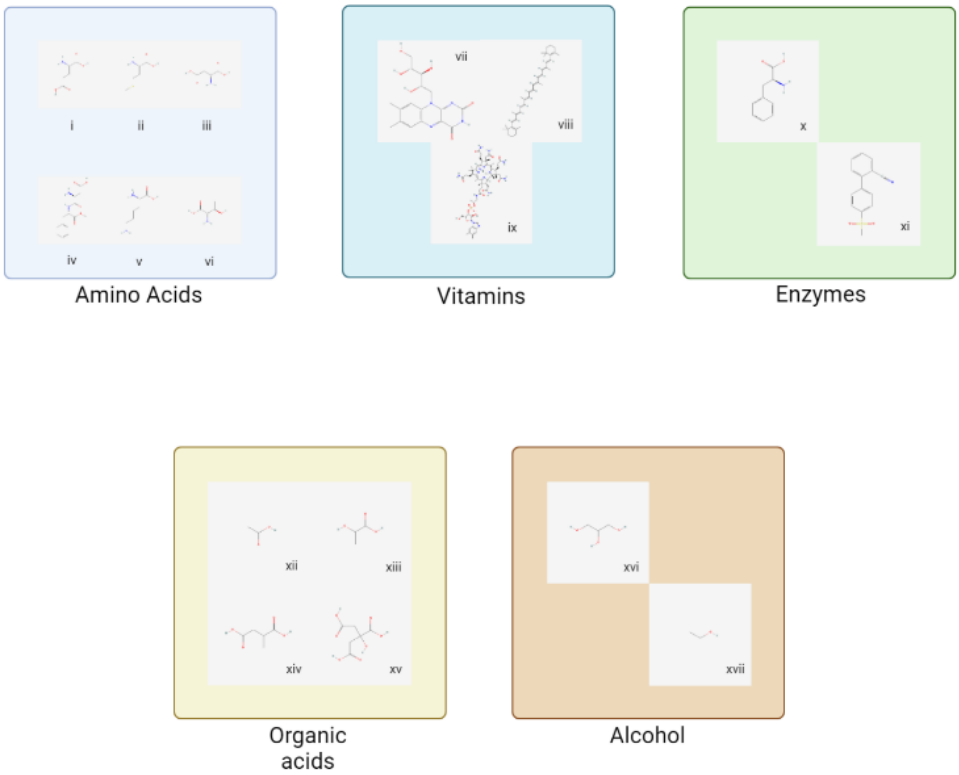

Figure 6. Structures of MNPs that are used in different sectors of Food industries (i) Glutamic acid(ii) Methionine (iii) Asparatic acid (iv) Aspartame (v) Lysine (vi) Threonine (vii) Riboflavin (viii) Beta-Carotene (ix) Cyanocobalamin (x) Phenylalanine (xi) Nitrile (xii) Acetic acid (xiii) Lactic acid (xiv) Itaconic acid (xv) Citric acid (xvi) Glycerine (xvii) Ethanol.

MNPs in the Agriculture and Food Industry

Recent focus has been directed towards the exploration of novel MNPs in the domains of agriculture, food, and beverage research to capitalize on the abundant resources of waste and by-products generated by the agricultural and food industries, serving as rich sources of bioactive compounds, such as phenolic compounds, dietary fibers, amino acids, fatty acids, probiotics, vitamins, minerals, carotenoids, and other phytochemicals (Table 6) [120]. The burgeoning popularity of beverages, driven by perceived health benefits, affordability, and their role in environmental sustainability, has witnessed a surge in recent years [121]. Simultaneously, scientific investigations have zeroed in on the development of vegetable crop varieties with enhanced biological value, characterized by elevated levels of lycopene, beta-carotene, ascorbic acid, and other natural ingredients endowed with antioxidant activity (Figure 6) [122].

DATABASES FOR MNPS RESEARCH

Databases assume a pivotal role in advancing MNPs research, facilitating the systematic annotation, storage, and analysis of data (Table 7) [134]. Notable contributions to this field include the development of databases, such as the NPA and the NPBS database. The NPA stands out as a comprehensive, open-access repository encompassing over 32,000 MNP structures, accompanied by taxonomic descriptions and chemical ontology terms [135].

IP and Commercialization of MNPs

The field of IP and commercialization surrounding MGRs is a vital area that revolves around patents and licensing. The USPTO plays a vital role in issuing patents for naturally occurring components that have been modified. These modifications help distinguish them from their natural counterparts and contribute to the rich diversity of chemical compounds available [136–147]. When it comes to patent eligibility, products must meet specific criteria, with natural phenomena typically excluded from

consideration. Interestingly, a significant number of drugs used worldwide have their origins in natural products or their derivatives. To secure patents for these products, meticulous characterization and isolation processes are vital in focusing on how they can be structurally, biologically, or metabolically altered [148, 149]. Discussions facilitated by the WIPO aim to ensure that bioprospecting agreements are disclosed in patent applications, helping to strike a balance between protecting intellectual property and ensuring that benefits are shared equitably [150].

Table 7. Some of the important databases for MNP research.

Database Name	Year of Establishment	Focus	Number of Compounds	Database Links	Reference
NPASS	2017	NPs from various sources	43,285 NPs [last updated in 2023]	http://bidd.group/NPASS/	[136]
StreptomeDB	2012	Bacterial NPs (Streptomyces)	6,524 NPs [last updated in 2021]	http://www.pharmbioinf.uni-freiburg.de/streptomedb3/	[137]
NPA	2019	Microbially-derived NPs	32,552 NPs [last updated in 2022]	https://www.npatlas.org/	[135]
DNP	1980s	NPs from various sources	3,40,000 NPs [last updated in 2023]	http://dnp.chemnetbase.com/	[138]
Dictionary of Antibiotics	1988	Antibiotic substances	>10,000 NPs [last updated in 2013]	https://www.routledge.com/Dictionary-of-Antibiotics-and-Related-Substances-with-CD-ROM-Second-Edition/Bycroft-Payne/p/book/9781439839522	[139]
ClusterMine360	2013	Nonribosomal Peptide and Polyketide classes	300 BGCs [last updated in 2013]	http://clustermine360.ca	[140]
DoBISCUIT	2013	Gene clusters for secondary metabolite biosynthesis	108 BGCs [last updated in 2016]	https://www.nite.go.jp/en/nbrc/genome/dobiscuit.html	[141]
MIBiG Repository	2015	Experimentally characterized BGCs	2502 [last updated on 2023]	https://mibig.secondarymetabolites.org	[142]
IMG-ABC	1997	Known and predicted bacterial BGCs	28,73,91,62,889 BGCs [last updated in 2024]	https://img.jgi.doe.gov/cgi-bin/abc/main.cgi	[143]
antiSMASH Database	2016	Putative BGCs from high-quality bacterial genomes	152,106 BGCs [last updated in 2018]	https://antismashdb.secondarymetabolites.org	[144]
GNPS	2014	Tandem MS data analysis	< 1,500 public datasets [last updated in March 2022]	https://gnps.ucsd.edu/	[145]
MetaboLights	2012 (overhauled in 2019)	Metabolomics data repository	439,537 data files [last updated in 2023]	https://www.ebi.ac.uk/metabolights/	[146]

Future Perspective and Challenges

The future of drug discovery based on natural products for infectious diseases faces numerous obstacles. A key challenge is the need for effective bioassay systems to evaluate anti-MNPs. Issues include securing dependable sources for natural products, the complexity of bioactive compound structures, and difficulties with high-throughput screening. Progress is impeded by factors, such as a lack of understanding of molecular mechanisms, high costs of development, and concerns regarding patentability [151].

Improvements in DNA sequencing and bioinformatics are expected to reveal the biosynthetic capabilities of microbes, with in silico methods becoming standard in natural product discovery. The move towards in silico bioprospecting, propelled by progressions in sequencing, gene synthesis, bioinformatics, and metabolomics, is revolutionizing the natural product discovery landscape [152]. Addressing the difficulties in synthesizing complex natural products is important for developing next-generation drugs, especially in the urgent fight against multidrug-resistant pathogens and the management of long-term side effects [153].

The changing dynamic of natural product discovery shows the importance of silicon-based bioprospecting. While microbial communities are essential for cleaning up pollutants, challenges remain in characterizing microorganisms that cannot be cultured [154].

The use of natural products for anticaries treatment faces hurdles, such as accurately measuring antimicrobial effectiveness, tackling the difficulties of surface-adsorbed enzymes for disrupting biofilms, conducting clinical trials, exploring complex natural product compositions, and closing research gaps [155].

In the field of herbal medicine, adverse reactions, which were once overlooked, are now a significant concern. There is an urgent need for standardized global regulatory frameworks, highlighting the role of regulatory agencies in ensuring a consistent and high-quality supply of herbal products. Increased vigilance is necessary for monitoring adverse reactions and facilitating the clinical trial process [156, 157].

CONCLUSIONS

MNPs are a significant and largely underutilized resource for development in drug discovery and biotechnology. The complex biosynthetic pathways that govern the creation of these compounds, especially in microorganisms like fungi, underscore the potential for discovering new bioactive materials. Researchers are starting to explore new potential for producing compounds with distinct therapeutic effects through genome mining and combinatorial biosynthesis. The process of eliminating known substances and identifying new ones is vital for making drug discovery more efficient, particularly given the rising issue of antimicrobial resistance. The identification of MNPs with antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory properties present promising solutions to these pressing challenges. However, the field encounters obstacles, such as the necessity for more effective bioassay systems and dependable sources of natural products, especially as bioprospecting increasingly relies on improvements in genomic and bioinformatics technologies. Ethical issues related to bioprospecting and the commercialization of these natural products, particularly concerning intellectual property rights, are major topics that require attention. Finding a balance between safeguarding intellectual property and safeguarding fair benefit-sharing is vital for the sustainable growth of this area. As technologies, like in silico bioprospecting and next-generation DNA sequencing advance, they are likely to transform the discovery and development of new MNP-based medications. However, tackling the intricacies of MNP biosynthesis, high development costs, regulatory challenges, and patentability issues will be essential in the coming years. Ultimately, overcoming these hurdles will be important for fully leveraging the potential of microbial natural products to address urgent global health issues, such as multidrug-resistant pathogens and long-term disease management. The future of MNP research holds exciting opportunities, but its success will rely on ongoing collaboration among scientific innovation, ethical considerations, and regulatory oversight.

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Authors Contribution

All the authors have equally contributed to the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

List of Abbreviations

NP	Natural Product
MNP	Microbial Natural Product
BGC	Biosynthetic Gene Clusters
MT	Methyltransferase
PKS	Polyketide Synthase
GCF	Gene Cluster Families
UHPLC-MS	Ultra High-Performance Liquid Chromatography-Mass Spectrometry
NMR	Nuclear Magnetic Resonance
DOSY	Diffusion-Ordered NMR Spectroscopy
UNPD	Universal Natural Product Database
MN	Molecular Networking
MS	Mass Spectrometry
CNMR	Carbon Nuclear Magnetic Resonance
GNPS	Global Natural Product Social
QM	Quantum Mechanical
DEREP-NP	Database For Rapid Dereplication of Known Natural Products
DBCS	Dissimilarity-Based Compound Selection
ABR	Antibiotic Resistance
LXR	Liver X Receptor
HCV	Hepatitis C Virus
EPS	Extracellular Polymeric Substances
CA	Cycloastragenol
NPA	Natural Products Atlas
NPBS	Natural Products & Biological Sources
DNP	Dictionary of Natural Products
IP	Intellectual Property
MGR	Microbial Genetic Resource
USPTO	U.S. Patent and Trademark Office
WIPO	World Intellectual Property Organization

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