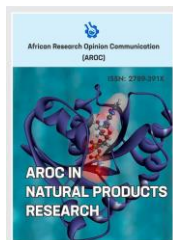


RESEARCH ARTICLE

Therapeutic Potential of Non-Plant-Derived Natural Products in Modern Medicine: A Systematic Review of Mechanisms, Applications, and Innovations

Sodiq M. Balogun¹, Abdulhakeem R. Agboola², Rofiyat O. Raji³, Deborah A. Popoola⁴



¹Department of Bioinformatics and Genomics, University of North Carolina at Charlotte, USA

²Department of Biochemistry, College of Medicine, University of Calabar, Nigeria

³The Ph.D. Program for Translational Medicine, Taipei Medical University, Taiwan

⁴Faculty of Clinical sciences, College of Medicine, Kaduna State University, Nigeria

Corresponding Author: Sodiq M. Balogun
Email: balogun.sodiqm@gmail.com

ABSTRACT

Background: Non-plant natural products have emerged as powerful contributors to modern pharmacotherapy, offering structurally diverse and mechanistically novel compounds for the treatment of complex diseases. This systematic review examines bioactive agents derived from microorganisms, fungi, marine organisms, animal venoms, and minerals, highlighting their therapeutic applications and mechanisms of action across major disease areas, including infections, cancer, neurological disorders, cardiovascular diseases, and immune-mediated conditions. Using PRISMA guidelines, literature published between 2000 and 2025 was screened across PubMed, Scopus, Web of Science, and ClinicalTrials.gov, yielding 48 eligible studies. Notable compounds include penicillin, lovastatin, cyclosporin A, ziconotide, and eribulin, each exemplifying the clinical relevance of non-plant sources. These agents act through diverse mechanisms—such as calcium channel blockade, DNA crosslinking, microtubule inhibition, and immunosuppression—often with greater specificity and potency than plant-derived or synthetic alternatives. Key advantages include modular biosynthesis via PKS and NRPS enzymes, high biological selectivity, and scalable production via microbial fermentation or synthetic biology. However, challenges remain, including toxicity, complex synthesis, and limited natural abundance. Emerging technologies such as genomic mining, nanocarrier delivery systems, and AI-assisted drug discovery offer promising solutions to these barriers. By mapping the landscape of non-plant-derived natural products, this review underscores their value in addressing unmet clinical needs and expanding the drug discovery pipeline beyond traditional botanical sources.

Keywords: Non-plant natural products; Microbial metabolites; Venom peptides; Marine compounds; Cyclosporin A; Ziconotide; Drug discovery; Therapeutic mechanisms

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1. Introduction

Nature has long served as a prolific source of therapeutic agents, with natural products accounting for over 50% of all FDA-approved drugs between 1981 and 2019, either as unmodified natural products, derivatives, or synthetic compounds inspired by natural scaffolds (Newman & Cragg, 2020; Omiyale et al., 2024; Edema et al. 2023; Omiyale et al., 2024). Traditionally, pharmacognosy—the study of medicinal natural products—has focused on higher plants and herbs due to their extensive use in folk medicine and the relative ease of harvesting and processing (Ogunjobi et al., 2020; Ogunjobi et al., 2025). Iconic examples like morphine (from *Papaver somniferum*) and artemisinin (from *Artemisia annua*) have underscored the therapeutic richness of the plant kingdom. However, a growing body of evidence has highlighted the immense pharmaceutical potential of

non-plant natural sources, including microorganisms, fungi, marine organisms, animal venoms, and inorganic compounds (Adegbesan et al. 2021; Ogunlakin et al., 2024).

These sources are responsible for some of the most groundbreaking therapeutic discoveries in modern medicine. For instance, penicillin, isolated from the mold *Penicillium notatum*, marked the beginning of the antibiotic era and has saved countless lives from bacterial infections (Lax & Thomas, 2020). Similarly, cyclosporin A, derived from the fungus *Tolypocladium inflatum*, revolutionized organ transplantation by providing targeted immunosuppression (Borel et al., 1976). Ziconotide, a peptide isolated from the venom of the marine cone snail *Conus magus*, has provided a non-opioid solution for the management of severe chronic pain by selectively blocking N-type calcium channels (Miljanich, 2004).

These non-plant-derived agents often possess structural and functional characteristics that distinguish them from phytochemicals. Unlike plant secondary metabolites that often follow well-known biosynthetic patterns, microbial and marine natural products frequently arise from non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS), enabling the generation of highly complex, macrocyclic, and stereochemically rich molecules (Medema et al., 2015).

This chemical diversity translates into novel mechanisms of action that are especially valuable in addressing therapeutic gaps such as antimicrobial resistance, chronic inflammation, neurodegenerative disorders, and multidrug-resistant cancers. In addition to structural novelty, these compounds also exhibit enhanced specificity and potency, often acting on molecular targets that have proven elusive to synthetic small molecules or plant-based analogs (Onah et al., 2024; Oluyemisi et al., 2021). For example, animal toxins like melittin and conotoxins have evolved to interact with ion channels, receptors, and enzymes with exquisite precision—properties now being harnessed in drug development.

Despite their demonstrated efficacy and market presence, the broader integration of non-plant natural products into pharmacotherapy remains underexplored in the literature. Much of the existing scholarship focuses either on narrow compound classes (e.g., antibiotics, marine alkaloids) or specific disease categories, lacking a unified synthesis of the diverse sources and disease targets that characterize non-plant-derived natural products.

This review systematically evaluates natural products from non-plant biological and inorganic sources in disease treatment. It offers an overview of their major classes and origins, outlines key mechanisms of action, and summarizes pharmacological applications across therapeutic areas such as cancer, infection, and inflammation. Approved drugs and clinical candidates from these sources are highlighted, along with current challenges and future research directions. By mapping this diverse therapeutic landscape, the review aims to support drug discovery and promote the integration of underexplored biological resources into biomedical innovation.

2. Methodology

2.1. Literature Search Strategy

A structured and comprehensive literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility of the review process. The search targeted peer-reviewed studies published between January 2000 and May 2025, drawing from four major electronic databases: PubMed, Scopus, Web of Science, and ClinicalTrials.gov. These databases were selected based on their broad coverage of biomedical, pharmacological, and clinical research.

To identify relevant studies, a range of search terms and Boolean combinations were employed. These

included phrases such as “non-plant natural product,” “microbial metabolite and therapeutic use,” “fungal secondary metabolite and disease,” “marine natural product and clinical trial,” “animal-derived peptide and mechanism,” and “natural compound and not plant and drug.” These terms were chosen to capture the wide array of natural compounds derived from microbial, fungal, marine, animal, and mineral origins, while explicitly excluding those of plant origin. Searches were optimized by using Medical Subject Headings (MeSH) where applicable and applying filters for language (English), study type (in vitro, in vivo, clinical), and relevance to human disease treatment.

In addition to electronic database searches, a manual review of the bibliographies of relevant review articles, meta-analyses, and high-impact primary studies was performed to identify additional literature that may not have been retrieved through automated searches. Grey literature and regulatory documentation from agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO) were also reviewed to gather data on approved and investigational natural product-based therapies from non-plant sources.

This comprehensive search strategy aimed to maximize sensitivity and specificity, ensuring that the included studies reflect the current state of knowledge regarding non-plant-derived natural products used in disease treatment.

2.2. Inclusion and Exclusion Criteria

To ensure the relevance and scientific rigor of the studies included in this systematic review, clearly defined inclusion and exclusion criteria were established prior to the screening process. Studies were eligible for inclusion if they met several criteria. First, they had to be peer-reviewed publications that explicitly described the therapeutic application of natural products derived from non-plant sources, such as microorganisms, fungi, marine organisms, animal products, or minerals. Additionally, studies were considered if they provided mechanistic, pharmacological, or clinical insights—whether based on in vitro experiments, animal models (in vivo), or human clinical trials.

Finally, the review also incorporated data on drugs that have either received regulatory approval (e.g., from the U.S. Food and Drug Administration [FDA] or European Medicines Agency [EMA]) or are currently undergoing clinical evaluation as investigational therapies. In contrast, studies were excluded from this review if the natural products discussed were exclusively of plant origin, as the focus was on non-plant-derived compounds. Articles written in languages other than English were also excluded to ensure consistency in interpretation and reporting.

Furthermore, any publications describing compounds used solely for cosmetic, nutritional supplementation, or veterinary purposes were omitted, as the review was limited to therapeutic applications relevant to human diseases. Following this selection framework,

more than 1,000 records were initially retrieved from the literature search. After removing duplicates and screening titles and abstracts for relevance, 48 studies met the inclusion criteria and were incorporated into the final synthesis.

For quality assurance, all eligible clinical studies were assessed using the Cochrane Risk of Bias Tool, while animal studies were evaluated in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, ensuring that the included evidence met acceptable standards of methodological quality.

3. Major Sources of Non-Plant Natural Products

3.1. Microorganisms

Microbes, especially bacteria and actinomycetes, are prolific producers of bioactive secondary metabolites. The genus *Streptomyces* alone has given rise to over 70% of known antibiotics, including streptomycin, chloramphenicol, and rifampicin. Microbial biosynthetic gene clusters (BGCs) encode complex enzymes like polyketide synthases (PKSs) and non-ribosomal peptide synthetases (NRPSs), enabling the creation of pharmacophores not achievable by chemical synthesis alone.

3.2. Fungi

Fungi such as *Aspergillus*, *Tolypocladium*, and *Penicillium* have been a rich source of both antibiotics and metabolic drugs. Lovastatin, isolated from *Aspergillus terreus*, was the first statin to enter the market, revolutionizing hypercholesterolemia treatment. Cyclosporin A, from *Tolypocladium inflatum*, is a cyclic undecapeptide with potent immunosuppressive effects critical for organ transplant medicine.

3.3. Marine Organisms

The marine environment hosts a chemically diverse ecosystem of sponges, tunicates, mollusks, and cyanobacteria. Compounds such as trabectedin (from sea squirts), eribulin (synthetic derivative of halichondrin B from sponges), and brentuximab vedotin (derived from dolastatin 10) illustrate the therapeutic potential of oceanic natural products. Marine metabolites often possess halogenated structures, sulfated moieties, and macrocyclic frameworks that interact uniquely with cellular targets.

3.4. Animal-Derived Products

Animal venoms, secretions, and endogenous peptides have emerged as potent therapeutic agents. Ziconotide, derived from *Conus magus* (cone snail), is a selective N-type calcium channel blocker used for refractory pain. Snake venom derivatives led to captopril, the first ACE inhibitor. Similarly, **melittin**, a major component of bee venom, exhibits anticancer and anti-inflammatory effects through membrane disruption and apoptosis induction.

3.4.1 Snail-Based Products

Snails, particularly the Giant African land snail (*Archachatina marginata*), have shown significant therapeutic potential. A toxicological assessment by Bashir et al. (2015) revealed dose-dependent alterations in hepatic and renal markers following intraperitoneal administration of haemolymph. While no overt toxicity or mortality occurred, elevated AST, ALT, ALP, and creatinine suggested potential hepatocellular and renal stress, warranting cautious therapeutic use.

GC-MS analysis further identified 26 bioactive constituents—including esters, fatty acids, and alkanes—implicated in antioxidant, anti-inflammatory, and antimicrobial activity, substantiating its traditional medicinal use (Ovioma et al., 2022). Meanwhile, studies by Ademolu et al. (2013) reported downregulation of digestive enzyme activity during aestivation, highlighting the physiological shifts in nutrient metabolism.

Region-specific studies also show significant biochemical variation in snail tissues. For example, Bamidele et al. (2018) found that haemolymph contained higher mineral concentrations than flesh, while snails from warmer climates exhibited elevated lipid and protein levels.

3.4.2 Propolis and Apicultural Products

Nigerian bee products—particularly propolis—have demonstrated a wide range of biomedical effects. Bashir et al. (2015) observed that methanolic extract of *Apis mellifera* propolis significantly increased white blood cells and platelet indices in mice, indicating potent immunomodulatory and thrombopoietic effects.

Shittu & Ibrahim (2015) investigated the toxicological effect of bee stings in *Plasmodium berghei*-infected mice. Their study showed that bee stings ameliorated liver enzyme abnormalities associated with malaria, suggesting potential hepatoprotective and antiparasmodial properties. Enzyme activities like AST, ALT, GGT, and ALP were normalized compared to untreated controls.

Shittu et al. (2015) demonstrated dose-dependent increases in serum AST and potassium levels, coupled with reductions in creatinine, urea, and total protein, following 21-day administration at 300–600 mg/kg. These shifts imply subclinical hepatic and renal stress, despite normal ALT and ALP activity.

Ajibola et al. (2012) emphasized the therapeutic versatility of apitherapy, including bee venom, honey, and propolis, in treating infections, inflammation, and boosting immunity. Shittu et al. (2015, IJTDH) conducted a comparative review on animal-based ethnomedicine in Nigeria, covering snails, bees, crustaceans, and insects, and reaffirmed the pharmacological potential of various non-plant natural products in traditional medicine. Another study on the alteration of liver enzymes by natural therapies in malaria treatment validated biochemical markers as important indicators of efficacy and toxicity of insect-

based treatments (Shittu & Ibrahim, R. (2015). The nutritional and medicinal significance of marine invertebrates and land crabs was discussed in Ajibola et al. (2020), further supporting the dietary role of non-plant sources.

Chemical profiling using GC-MS identified flavonoids, terpenoids, esters, and phenolic compounds, many with known antimicrobial and antioxidant properties (Lawal et al., 2016; Lawal et al., 2018). Propolis extract also showed hepatoprotective activity against CCl₄-induced liver injury, with enzyme levels comparable to silymarin, and confirmed histological preservation of hepatocytes (Shittu et al., 2015).

Additionally, studies comparing Nigerian sweet and bitter honey revealed the presence of medically active phytochemicals—flavonoids, saponins, and steroids—with antioxidant and anti-inflammatory roles (Adeniyi et al., 2016). Yusuf et al. (2021) emphasized the high protein and fatty acid content of *Apis mellifera adansonii*, suggesting its value in immunomodulation and metabolic health.

3.4.3 Insects and Edible Invertebrates

Insect-based products offer considerable nutritional and pharmacological benefits. Lawal et al. (2014) showed that *Musca domestica* larvae extract improved antioxidant enzyme activity in trypanosome-infected rats, reducing oxidative stress via enhanced SOD and catalase activity. Bamidele et al. (2021) reported that adult honey bees across Nigerian ecological zones had high protein, essential minerals, and vitamins—though high phytate levels raised minor bioavailability concerns.

Crickets (*Brachytrupes membranaceus*) analyzed by Idowu et al. (2020) contained up to 55.45% crude protein, high-quality fatty acids, and essential vitamins, underscoring their role in addressing malnutrition. Termites (*Macrotermes bellicosus*) from varied environments consistently displayed strong nutritional profiles, with minimal heavy metal contamination (Idowu et al., 2014; Idowu et al., 2019). Their value in local food systems remains high due to significant protein, vitamin, and mineral contents. Grasshoppers such as *Sphenarium purpurascens* also exhibit excellent nutrient profiles, meeting WHO standards for essential amino acids and healthy fatty acid ratios, further supporting insect consumption for food security (Ramos-Elorduy et al., 2016).

Odeyemi et al. (2011) reported the **nutritional composition of housefly larvae meal**, showing high protein and fat content, supporting its use as an alternative animal protein source in livestock feed. Adenekan et al. (2013) highlighted the nutrient and microbiological safety of edible land snails, confirming their traditional and dietary relevance. The study by Akinmutimi and Onen (2005) established that termites and crickets have high protein and amino acid profiles, showing potential as viable alternative proteins.

3.4.4 Other Non-Plant Sources

A broader view of non-plant natural products shows the influence of environmental and processing factors. Idowu et al. (2022) highlighted the phytochemical richness of termites, including alkaloids and flavonoids. Similarly, Ohiokpehai (2003) emphasized the nutritional potential of edible invertebrates in traditional food systems.

Oladimeji et al. (2020) confirmed that processing methods significantly affect bioactive retention in edible insects, advocating for minimal processing to preserve therapeutic compounds. These insights strengthen the rationale for using methanolic extracts in research and therapeutic applications.

Akintola et al. (2013) demonstrated that marine invertebrates like *Callinectes amnicola*, *Cardisoma armatum*, and *Littorina littorea* are lean protein sources with high mineral content, suitable for low-fat dietary interventions. These species, harvested from Nigerian lagoons, may alleviate micronutrient deficiencies in coastal communities.

3.5. Minerals and Inorganic Natural Compounds

Minerals such as kaolin, bentonite, and arsenic trioxide are traditional remedies still used today. Arsenic trioxide was re-approved by the FDA for treating acute promyelocytic leukemia (APL) due to its ability to degrade PML-RAR α fusion proteins.



Figure 1. Major Sources of Non-Plant Natural Products and Their Therapeutic Applications: This figure illustrates five major sources of non-plant natural products—microorganisms, fungi, marine organisms, animals, and minerals—highlighting key bioactive compounds and their therapeutic applications in antimicrobial, anticancer, immunomodulatory, and antioxidant treatments.

4. Disease-Specific Applications and Mechanisms

4.1. Infectious Diseases

Antibiotics from *Streptomyces* and *Penicillium* remain frontline treatments. Novel antifungals from marine fungi and bacteriocins from probiotics are under study. Many act by inhibiting cell wall synthesis, blocking protein translation, or modulating microbial biofilm formation (Figure 2).

4.2. Cancer

Cancer continues to be a major global health challenge, and natural products from non-plant sources have played an instrumental role in the development of effective anticancer therapies. Several of these compounds, originally discovered from microbes or marine organisms, have unique mechanisms of action that allow them to interfere with key processes in cancer cell proliferation, survival, and metastasis. In particular, many non-plant-derived agents target DNA replication and repair, microtubule dynamics, and transcriptional regulation, leading to cancer cell death and suppression of tumor growth (Figure 2).

One of the earliest and most well-known examples is mitomycin C, a potent alkylating agent produced by the actinomycete *Streptomyces caespitosus*. Mitomycin C functions as a DNA crosslinker, forming covalent bonds between DNA strands, thereby inhibiting DNA replication and transcription. This mechanism induces apoptosis, particularly in hypoxic tumor environments where it is enzymatically activated, making it especially useful in solid tumors such as anal, breast, and gastrointestinal cancers (Tomasz, 1995; Figure 2).

Another clinically significant compound is eribulin mesylate, a synthetic analog of halichondrin B, which was originally isolated from the marine sponge *Halichondria okadai*. Eribulin acts as a microtubule dynamics inhibitor by binding to the plus ends of microtubules, preventing their elongation without affecting depolymerization. This leads to mitotic arrest, disruption of the mitotic spindle, and ultimately, cell death. Eribulin has been approved for the treatment of metastatic breast cancer and liposarcoma, particularly in patients who have progressed after standard anthracycline or taxane therapies (Towle et al., 2001; Cortes et al., 2011).

Trabectedin, derived from the Caribbean Sea squirt *Ecteinascidia turbinata* and now produced synthetically, represents another marine-derived anticancer agent with a multifaceted mechanism. It binds to the minor groove of DNA and causes bending of the DNA helix toward the major groove, which disrupts the binding of transcription factors and DNA repair proteins. Trabectedin is especially effective in modulating the tumor microenvironment by depleting tumor-associated macrophages and has demonstrated clinical efficacy in soft tissue sarcomas and relapsed ovarian cancer (D'Incalci & Galmarini, 2010).

The cytotoxic effects of these agents are often complemented by their ability to induce apoptosis, enforce cell cycle arrest, and inhibit angiogenesis, thereby starving tumors of their blood supply. These multi-targeted actions make non-plant-derived anticancer natural products highly valuable, especially in resistant or refractory cancers. Moreover, their structural complexity and novel modes of action serve as templates for the development of next-generation chemotherapeutic agents and antibody-drug conjugates (ADCs), such as those derived from dolastatin 10, a cytotoxic peptide isolated from sea hares and used in the ADC brentuximab vedotin (Figure 2).

In summary, non-plant-derived natural products have enriched the oncology pharmacopeia with structurally novel and mechanistically distinct compounds. Their continued development, optimization through synthetic chemistry, and incorporation into combination regimens represent promising strategies for enhancing therapeutic efficacy and overcoming resistance in cancer treatment.

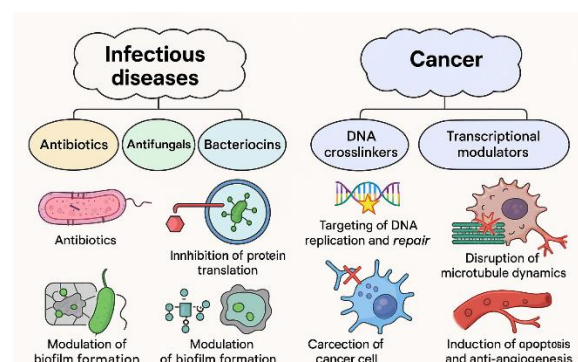


Figure 2. Mechanisms of Action of Non-Plant-Derived Natural Products in Infectious Diseases and Cancer: This diagram outlines how non-plant-derived natural products combat infections and cancer. Antimicrobials disrupt microbial cell walls, protein synthesis, or biofilms, while anticancer agents induce DNA damage, inhibit transcription or mitosis, and promote apoptosis and anti-angiogenesis.

4.3. Neurological Diseases

Neurological and neuropsychiatric disorders—including chronic pain, depression, anxiety, and neurodegenerative diseases—pose a significant global burden, with limited effective therapies and considerable side effects from existing pharmacological treatments. Natural products from non-plant sources have emerged as promising candidates in addressing some of these therapeutic gaps, particularly due to their novel mechanisms of action and ability to target CNS pathways previously considered "undruggable."

One of the most notable examples is ziconotide, a synthetic peptide derived from ω -conotoxin MVIIA, a component of the venom of the marine cone snail *Conus magus*. Ziconotide is a selective blocker of N-type voltage-gated calcium channels (CaV2.2), which are primarily located in the presynaptic terminals of dorsal horn neurons in the spinal cord. By inhibiting

these calcium channels, ziconotide prevents the release of excitatory neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide (CGRP), thereby significantly reducing the transmission of nociceptive signals (Miljanich, 2004). Unlike opioids, ziconotide does not interact with opioid receptors and therefore lacks risks of respiratory depression, tolerance, or addiction, making it an important option for patients with intractable chronic pain, particularly those with cancer-related or neuropathic pain unresponsive to traditional analgesics. It is administered intrathecally due to its peptide nature and poor blood-brain barrier permeability, and has been FDA-approved since 2004 for the management of severe chronic pain in appropriately selected patients (Figure 3).

Another notable non-plant-derived compound with growing interest in psychiatry is psilocybin, a naturally occurring tryptamine alkaloid found in various species of psychoactive fungi, especially those of the *Psilocybe* genus. Psilocybin is a prodrug, rapidly converted in the body to psilocin, which is structurally similar to serotonin and acts primarily as a partial agonist of the 5-hydroxytryptamine 2A (5-HT_{2A}) receptor (Figure 3). Activation of this receptor modulates cortical excitability, alters connectivity in the default mode network, and induces acute alterations in perception and cognition (Vollenweider & Kometer, 2010). What distinguishes psilocybin from conventional antidepressants is its ability to induce rapid, sustained antidepressant and anxiolytic effects after a single or few administrations, often with therapeutic effects lasting for weeks to months. Clinical trials have shown its efficacy in treatment-resistant depression, major depressive disorder, and post-traumatic stress disorder (PTSD), with promising safety and tolerability profiles when administered under medical supervision (Carhart-Harris et al., 2016; Davis et al., 2021).

Both ziconotide and psilocybin represent paradigms of targeted, receptor-specific interventions that avoid the pitfalls of conventional therapies such as opioids or selective serotonin reuptake inhibitors (SSRIs). Their success highlights the therapeutic richness of non-plant natural products in neurology and psychiatry. Continued exploration of marine toxins, fungal alkaloids, and microbial neuroactives may lead to the development of novel drugs for a range of disorders including epilepsy, Alzheimer's disease, and schizophrenia, especially where conventional synthetic drugs have failed (Figure 3).

4.4. Metabolic and Cardiovascular Diseases

Cardiovascular diseases (CVD) and metabolic disorders such as hyperlipidemia, diabetes, and hypertension remain the leading causes of morbidity and mortality worldwide. Non-plant natural products have contributed significantly to the pharmacological management of these conditions, particularly through the discovery of statins and bioactive peptides derived from fungal and animal sources.

One of the most transformative therapeutic breakthroughs in cardiovascular medicine came from fungi. Lovastatin, the first FDA-approved statin, was

originally isolated from *Aspergillus terreus* and acts as a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway responsible for cholesterol biosynthesis (Endo, 1985). By reducing hepatic cholesterol production, statins not only lower low-density lipoprotein (LDL) levels but also improve endothelial function, reduce oxidative stress, and stabilize atherosclerotic plaques. The discovery of lovastatin paved the way for the development of synthetic and semi-synthetic statins such as atorvastatin and simvastatin, which remain the cornerstone of lipid-lowering therapy.

Beyond fungal metabolites, animal venom peptides have gained attention as potential modulators of vascular tone and hemostasis. Several peptides derived from snake venoms, for instance, exhibit ACE-inhibitory activity, and one such peptide led to the development of captopril, the first oral ACE inhibitor for treating hypertension and heart failure (Ondetti et al., 1977). More recently, research has focused on peptides that modulate nitric oxide (NO) pathways, resulting in vasodilation, and on those that inhibit platelet aggregation, thus preventing thrombotic events such as myocardial infarction and stroke. For example, batroxobin, a serine protease from the *Bothrops atrox* venom, promotes clot formation by converting fibrinogen into fibrin in a controlled manner and is used therapeutically in certain bleeding disorders and vascular surgeries (Wang et al., 2016).

The specificity and potency of these compounds, especially in targeting cardiovascular enzymes and receptors, continue to inspire novel drug development. The incorporation of venom-derived pharmacophores into peptidomimetics and nanoformulations is also being actively explored to overcome challenges such as short half-life and immunogenicity.

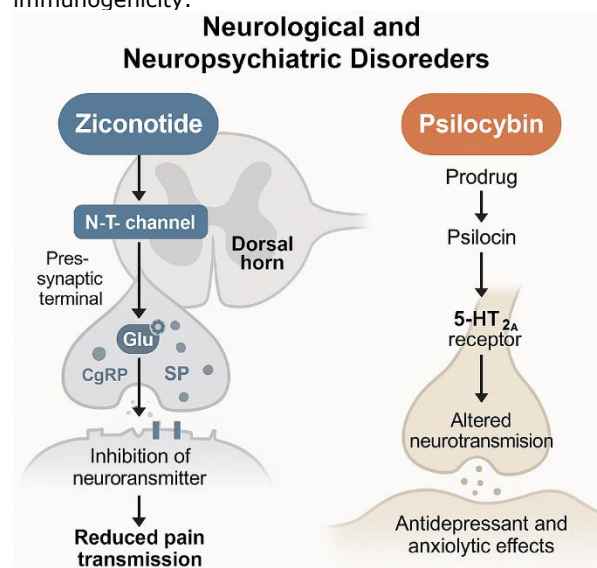


Figure 3. Mechanisms of Ziconotide and Psilocybin in CNS Disorders: Ziconotide blocks N-type calcium channels at spinal presynaptic terminals, inhibiting excitatory neurotransmitter release and reducing pain transmission. Psilocybin, via conversion to receptors in the cortex, altering neurotransmission to produce antidepressant and anxiolytic effects.

4.5. Autoimmune and Inflammatory Diseases

Autoimmune and chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, are characterized by dysregulated immune responses against host tissues. Immunomodulatory natural products from non-plant origins, especially from fungi and venomous animals, have demonstrated significant potential in controlling these conditions by targeting T-cell activation pathways and pro-inflammatory transcription factors.

A landmark example is cyclosporin A, a cyclic undecapeptide produced by the fungus *Tolypocladium inflatum*. Cyclosporin A binds to the intracellular protein cyclophilin, forming a complex that inhibits calcineurin, a calcium/calmodulin-dependent phosphatase critical for T-cell activation. By blocking calcineurin, cyclosporin A prevents the dephosphorylation and nuclear translocation of the nuclear factor of activated T cells (NFAT), thereby inhibiting interleukin-2 (IL-2) transcription and subsequent T-cell proliferation (Borel et al., 1976). This immunosuppressive mechanism has revolutionized organ transplantation and is also utilized in autoimmune disease management.

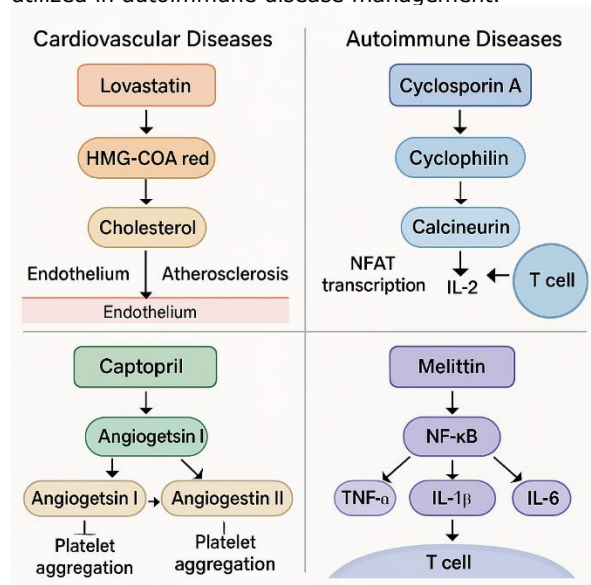


Figure 4: Mechanisms of Non-Plant-Derived Compounds in Cardiovascular and Autoimmune Diseases: Lovastatin inhibits HMG-CoA reductase to reduce cholesterol and prevent atherosclerosis. Captopril blocks angiotensin-converting enzyme, lowering angiotensin II and reducing vascular tension and platelet aggregation. Cyclosporin A suppresses IL-2 production via calcineurin inhibition, dampening T-cell activation. Melittin inhibits NF-κB signaling, reducing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and T-cell-mediated inflammation

In parallel, research into animal venom peptides has uncovered several promising candidates that modulate key signaling pathways involved in inflammation. For instance, melittin, the principal peptide in bee venom, has been shown to inhibit NF-κB, a transcription factor central to the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Park et al., 2004). Additionally, certain scorpion

and spider venom components have demonstrated the ability to influence JAK-STAT signaling, another pivotal pathway in autoimmune pathophysiology.

These bioactive peptides not only suppress pro-inflammatory cytokines but also influence macrophage polarization, mast cell degranulation, and dendritic cell activation, making them attractive candidates for novel biologics and topical formulations. However, challenges such as immunogenicity, delivery barriers, and off-target toxicity must be addressed through synthetic modification, nanoparticle encapsulation, or peptidomimetic strategies.

5. Drug Approvals and Clinical Pipeline

Over 25 drugs derived from non-plant natural products have received FDA or EMA approval. Dozens more are in clinical trials, especially in oncology and antimicrobial resistance research (Figure 1).

Table 1: Non-plant based drug approvals and clinical pipeline

Drug	Source	Indication	Year Approved
Penicillin	<i>Penicillium chrysogenum</i>	Bacterial infections	1943
Lovastatin	<i>Aspergillus terreus</i>	Hypercholesterolemia	1987
Cyclosporin A	<i>Tolypocladium inflatum</i>	Transplant rejection	1983
Eribulin	Marine sponge derivative	Metastatic breast cancer	2010
Ziconotide	<i>Conus magus</i>	Chronic neuropathic pain	2004
Arsenic trioxide	Mineral	Acute promyelocytic leukemia	2000

6. Advantages Over Plant-Derived Compounds

While plant-derived natural products have long served as important sources of therapeutic agents, compounds derived from non-plant sources—including microbes, fungi, marine invertebrates, and animals—offer a set of unique and compelling advantages that position them as powerful alternatives and complements in modern drug discovery. These advantages span the realms of chemical diversity, biological specificity, scalability, and sustainability.

One of the most significant advantages of non-plant natural products is their greater scaffold complexity and chemical diversity, especially among marine and microbial metabolites. Unlike many plant secondary metabolites that adhere to relatively conserved biosynthetic routes (e.g., flavonoid or alkaloid pathways), microbial and marine organisms produce highly diverse molecular frameworks through modular

enzyme systems such as non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS). These systems are capable of assembling large, multi-cyclic, and stereochemically rich molecules that can engage in intricate interactions with biological macromolecules. For example, marine-derived agents like halichondrin B and trabectedin contain unique macrocyclic and spiroketal structures rarely encountered in terrestrial flora, allowing them to interact with DNA, tubulin, and transcriptional machinery in ways not replicable by plant-based analogs (Molinski et al., 2009).

In addition to their structural complexity, non-plant-derived compounds—particularly animal venom peptides—are known for their high biological specificity and potency. These peptides have evolved over millions of years to precisely target vital molecular structures such as voltage-gated ion channels, G-protein coupled receptors, and enzyme active sites, often with sub-nanomolar affinities. For instance, ziconotide from cone snail venom selectively blocks N-type calcium channels without affecting other subtypes, offering potent analgesia without the addictive risks of opioids (Miljanich, 2004). This level of specificity not only enhances therapeutic efficacy but also reduces off-target effects and toxicity, making venom peptides highly attractive candidates for precision medicine.

Another compelling advantage lies in the synthetic modifiability and biosynthetic tractability of microbial and fungal products. Unlike complex plant extractions that often yield low concentrations of active ingredients and are influenced by seasonal variability, microbial and fungal natural products can be produced through controlled fermentation and biotechnological manipulation. Advances in genetic engineering and synthetic biology allow for the optimization of yield, structural modifications, and even the creation of entirely new analogs by rewiring biosynthetic gene clusters (Ziemert et al., 2016).

This scalability and adaptability have led to the successful development of numerous derivatives and semi-synthetic drugs based on microbial scaffolds, such as improved statins and β -lactam antibiotics. From an environmental perspective, non-plant natural product sources often offer a lower ecological footprint. While the overharvesting of medicinal plants can lead to biodiversity loss, habitat destruction, and depletion of slow-growing species, microbial fermentation and invertebrate aquaculture can be sustainably scaled in bioreactors or marine farms.

Furthermore, techniques like metagenomic mining and marine microbial symbiont culturing reduce the need for repeated harvesting of sensitive organisms like deep-sea sponges or endangered amphibians (Piel, 2010).

In summary, the advantages of non-plant-derived natural products are multifaceted: they provide novel chemotypes, enhanced target specificity, technological feasibility for optimization, and ecological sustainability. These features not only diversify the drug discovery pipeline but also address

some of the core limitations of traditional plant-based pharmacognosy, making them essential contributors to the future of therapeutic innovation.

7. Challenges and Limitations

Despite the remarkable therapeutic potential of natural products from non-plant sources, several critical challenges hinder their seamless integration into the mainstream drug development pipeline. These limitations span pharmacological, logistical, and regulatory domains, necessitating multi-pronged strategies for their resolution.

A major concern is toxicity and narrow therapeutic index, particularly for compounds such as melittin (from bee venom) and arsenic trioxide (a mineral-derived drug). Melittin, while demonstrating potent anticancer and anti-inflammatory activity, is known to cause hemolysis, membrane disruption, and non-specific cytotoxicity at therapeutic doses (Raghuraman & Chattopadhyay, 2007). Similarly, arsenicals require careful dosing due to risks of cardiotoxicity, hepatotoxicity, and peripheral neuropathy. The fine balance between efficacy and safety poses significant formulation and dosing challenges, often requiring innovations in targeted delivery systems, such as liposomal encapsulation or antibody-drug conjugates.

Another major obstacle is the limited and unsustainable biosupply of many marine and venom-derived compounds. For example, trabectedin was originally sourced from the tunicate *Ecteinascidia turbinata*, but its natural abundance was so low that one ton of sea squirt biomass was needed to produce just one gram of compound. Although synthetic and semi-synthetic routes have mitigated some supply issues, many bioactive agents from sponges, mollusks, and rare microbes continue to suffer from low yield and high ecological impact, impeding their clinical development (Cragg & Newman, 2013).

Structural complexity is another challenge, as many non-plant-derived compounds contain multiple chiral centers, macrocyclic rings, and labile functional groups that make chemical synthesis exceedingly difficult and cost-prohibitive. Agents such as halichondrin B and dolastatin 10 required decades of research to develop viable synthetic analogs like eribulin and brentuximab vedotin. In addition, maintaining compound stability and bioactivity during synthesis, storage, and delivery remains an ongoing hurdle, especially for peptide- and toxin-based molecules.

The regulatory landscape also poses significant limitations. Natural products with novel mechanisms—especially those derived from venom or previously unexplored microbes—often face stringent toxicological evaluation, lengthy preclinical safety testing, and difficulty in standardization. Unlike synthetic small molecules, whose pharmacokinetics and structure-activity relationships are well-characterized, many natural compounds exhibit batch variability, low oral bioavailability, and immunogenic potential, making them challenging to evaluate within

conventional regulatory frameworks (Butler et al., 2014).

Taken together, these challenges underscore the importance of integrating interdisciplinary approaches—including chemical engineering, formulation science, synthetic biology, and regulatory science—to unlock the full therapeutic value of non-plant natural products.

8. Conclusion

Non-plant natural products continue to redefine therapeutic possibilities. Their contribution spans antimicrobials, cancer therapy, immunomodulation, and neurological care. The rich biosynthetic diversity of microbial, marine, and animal systems provides scaffolds and mechanisms that are both novel and clinically impactful. Strategic investment in research, production technologies, and translational frameworks is vital to fully harness these unique molecular treasures for 21st-century medicine.

9. Future Perspectives

Despite current limitations, the future of drug discovery from non-plant natural sources appears highly promising, particularly in light of technological innovations that are transforming how we identify, optimize, and deliver complex bioactive compounds.

One of the most exciting frontiers is genomic mining and metagenomics, which enable the discovery of cryptic biosynthetic gene clusters (BGCs) in unculturable microorganisms. Advanced bioinformatics tools now allow researchers to predict and reconstruct novel metabolic pathways from environmental DNA sequences, unlocking previously inaccessible compounds from marine sediments, hot springs, and symbiotic microbiomes (Ziemert et al., 2016). These cryptic gene clusters often encode enzymes capable of producing new chemical scaffolds with untapped therapeutic potential, including antibiotics, antitumor agents, and antivirals.

Simultaneously, synthetic biology and metabolic engineering are transforming drug manufacturing by allowing precise manipulation of microbial hosts such as *E. coli* or *Streptomyces*. Researchers can now insert entire BGCs into high-yield hosts, or design chimeric clusters that combine modules from different organisms to generate “unnatural” natural products with improved bioactivity, stability, or pharmacokinetics (Medema et al., 2015). These tools are already being used to produce otherwise scarce compounds like taxol analogs, epothilones, and lipopeptides at industrial scales.

To address challenges of toxicity and delivery, nanotechnology-based carriers are being developed to improve the targeted delivery and controlled release of venom-derived peptides, metalloid-based drugs, and hydrophobic marine alkaloids. Liposomes, dendrimers, and polymeric nanoparticles can reduce off-target effects and prolong the half-life of unstable compounds in systemic circulation. Several venom peptides, including melittin, have shown improved efficacy and safety when loaded into nanoparticles for

cancer therapy and neurodegenerative conditions (Park et al., 2017).

Finally, artificial intelligence (AI) and network pharmacology are revolutionizing target identification and drug repurposing. Machine learning algorithms can analyze vast datasets to predict molecular targets, toxicity profiles, and synergistic combinations, accelerating the preclinical pipeline for natural products. Network-based models further enable the mapping of multi-target interactions, crucial for understanding the systemic effects of complex molecules and designing combination therapies for multifactorial diseases like cancer or Alzheimer's.

In combination, these advancements signal a paradigm shift in how non-plant natural products will be sourced, optimized, and translated into clinical use. Interdisciplinary collaboration among microbiologists, chemists, engineers, computational biologists, and clinicians will be vital in realizing this vision.

Conflict of interests

The authors declare that they have no Conflict of interests.

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