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Plant, Marine, and Microbial Natural Products as Novel Antiparasitic Therapeutics: Mechanistic Insights, Innovations, and Therapeutic Opportunities

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ABSTRACT: Background: Parasitic diseases are among the biggest contributors to worldwide morbidity and mortality; they are particularly debilitating to people living in tropical and subtropical climates. The increasing incidence of drug-resistant organisms has urged researchers to explore novel therapies from natural sources.

Objectives: To summarize the clinical efficacy and mechanisms of action of antiparasitic natural products in regard to the plant, marine and microbial origin of the natural product, within the context of understanding novel methods of action and the potential for high therapeutic value.

Methods: A literature search was completed on the topic of antiparasitic natural products (2000-2025) using PubMed/MEDLINE, Scopus, Web of Science, Embase and Google Scholar according to PRISMA 2020 standards. Studies reporting in vitro, in vivo or clinical evidence of antiparasitic activity of natural products with definitively described mechanism(s) of action were included.

Results: A total of 4,287 studies were identified, of which 127 studies satisfied inclusion criteria. Plant derived materials (alkaloids, terpenoids, flavonoids, phenolics) were effective against four parasite genera (Plasmodium, Leishmania, Trypanosoma and certain helminths). New mechanisms were demonstrated for marine-sourced natural products targeting parasite organelles. Microbial natural products support the development of global antiparasitic drug research efforts. Improvements in nanotechnology-enhanced delivery have yielded significant advancements in bioavailability.

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Conclusions: Natural products offer excellent prospects as antimicrobial drug lead compounds. The development of genomic and metabolomic technologies and of nanomedicine is accelerating therapeutic progression toward clinical applications. Future priorities will be to establish standardizedreporting systems, develop clarity in mechanism(s) of action and devise combination strategies.

1. INTRODUCTION

Parasitic diseases as a group are responsible for an incredible worldwide burden of disease, with more than three billion people affected and over one million people dying from these diseases every year [1]. The WHO classifies many of these diseases such as malaria, leishmaniasis, trypanosomiasis, schistosomiasis and soil transmitted helminthiases as Neglected Tropical Diseases (NTD's) that are perpetuating cycles of poverty in Africa, Asia and Latin America [1-5]. The escalating development of drug resistance to long-standing therapies such as chloroquine, pentamidine, melarsoprol and praziquantel has seriously compromised global disease management [2,3].

Natural products have been the basis of antiparasitic drug development throughout the history of mankind. The "artemisinin revolution," which was based on the plant Artemisia annua L. of China, changed the manner in which malaria is treated around the world and won a Nobel Prize in Physiology or Medicine in 2015 [4]. Similarly, ivermectin, derived from the soil-based bacterium Streptomyces avermitilis, revolutionized the treatment of onchocerciasis and lymphatic filariasis, and has been recognized as one of the top antiparasitic discoveries of the 20th century [5,6].

The three main natural product sources - plant, marine and microbial - provide a variety of chemical structures and mechanisms of action against parasites [7,8]. From the plant kingdom we obtain alkaloids (e.g., quinine, berberine, lycorine), terpenoids (e.g., artemisinin, parthenolide), flavonoids (e.g., quercetin, apigenin) and phenolics (e.g., curcumin, resveratrol), all exhibiting multiple target pharmacology against protozoa and helminthes [9-12]. Marine organisms contain unique polyketide, terpene, cyclic peptide and macrolide chemical structures that have demonstrated significant antiparasitic activity but are currently underutilized [13,14]. A wealth of clinically useful drugs have been produced from microbes such as the avermectins and milbemycins, with additional candidates identified and being investigated in preclinical studies [15,16].

This systematic review aims to synthesise the present knowledge of natural product antiparasitic agents, including mechanistic information, comparative analysis and an outlook on future translational possibilities. Following PRISMA 2020 guidelines for systematic review and meta-analysis will assure the rigor and reproducibility of this evidence synthesis [17].

2. MATERIALS AND METHODS

2.1 Study Design and Protocol

This systematic review was developed and carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [17] statement.

2.2 Eligibility Criteria

Inclusion criteria were as follows: studies needed to have (i) utilized plant-, marine- or microbially-derived natural products to evaluate their efficacy against parasites, (ii) reported measurable antiparasitic outcomes (IC50/EC50/survival rates/parasite burden), (iii) utilized the proposed, or provided mechanistic data on how they affect parasites, and (iv) all studies assessed for inclusion must have been published in a peer-reviewed journal between January 2000 and December 2025 and written in English. Exclusion criteria included but were not limited to: review articles without primary data; conference abstracts; grey studies without peer review; and studies evaluating synthetic analogues without a natural product reference data point.

2.3 Information Sources and Search Strategy

A comprehensive electronic search was performed in PubMed/MEDLINE; Scopus; Web of Science; Embase; and Google Scholar. MeSH terms and free text terms were combined using Boolean operators as follows: ("natural products" OR "plant extract" OR "marine compound" OR "microbial metabolite") AND ("antiparasitic" OR "antiplasmodial" OR "antileishmanial" OR "antitrypanosomal" OR "antihelminthic") AND ("mechanism of action" OR "molecular target" OR "drug resistance"). Reference lists of included studies as well as relevant systematic reviews were also manually searched [17,18].

2.4 Study Selection and Data Extraction

Two reviewers completed title and abstract screening and full text review independently and in a blinded approach using Covidence software. Any discrepancies between reviewers were resolved through consensus or arbitrated by a third (independent) reviewer. The following study parameters were systematically collected via a standardised data extraction form: (i) type of study; (ii) country where the study was conducted; (iii) class of natural product; (iv) source of the natural product; (v) target parasite; (vi) antiparasitic activity metrics; (vii) mechanism of action; (viii) in vivo validation; and (ix) status of clinical translation.

2.5 Quality Assessment

Risk of bias in in vitro studies was assessed according to the Office of Health Assessment and Translation (OHAT) tool. The SYRCLE Risk of Bias tool was used to assess animal studies [19]. Both clinical and epidemiological studies were assessed using the Newcastle-Ottawa scale (NOS) or the Cochrane RoB 2.0 tools as appropriate [20]. Overall quality of evidence was graded according to the GRADE criteria.

2.6 Statistical Analysis

When possible, or permitted by data availability, quantitative synthesis of results were completed through the use of effect size calculations (standardised mean difference – SMD) along with 95% confidence intervals (CI) for SMD. Heterogeneity was examined using Cochrane's Q test, and I2 statistic. If I2 value was > 50%, indicating substantial heterogeneity amongst studies, then random effects model (DerSimonian-Laird method) was used for data analysis [21,22]. Funnel plots were generated to help determine potential publication bias, while sensitivity analyses were also used to assess risk of potential publication bias. All statistical analyses were conducted in R v4.3.1, using the meta and metafor packages.

3. RESULTS AND DISCUSSION

3.1 Study Characteristics

Following the PRISMA 2020 flowchart for study selection, 127 studies were included in the qualitative synthesis and 47 studies were included in the quantitative meta-analysis (Figure 1). The studies were from 38 countries (Brazil-19, India-17, China-14, Egypt-9, and South Korea-8). The number of qualified plants accounted for 53.5% of all of the total qualified articles. studies (n=68), marine-derived for 24.4% (n=31), and microbial-derived for 22.0% (n=28) Table 1 [18-20].

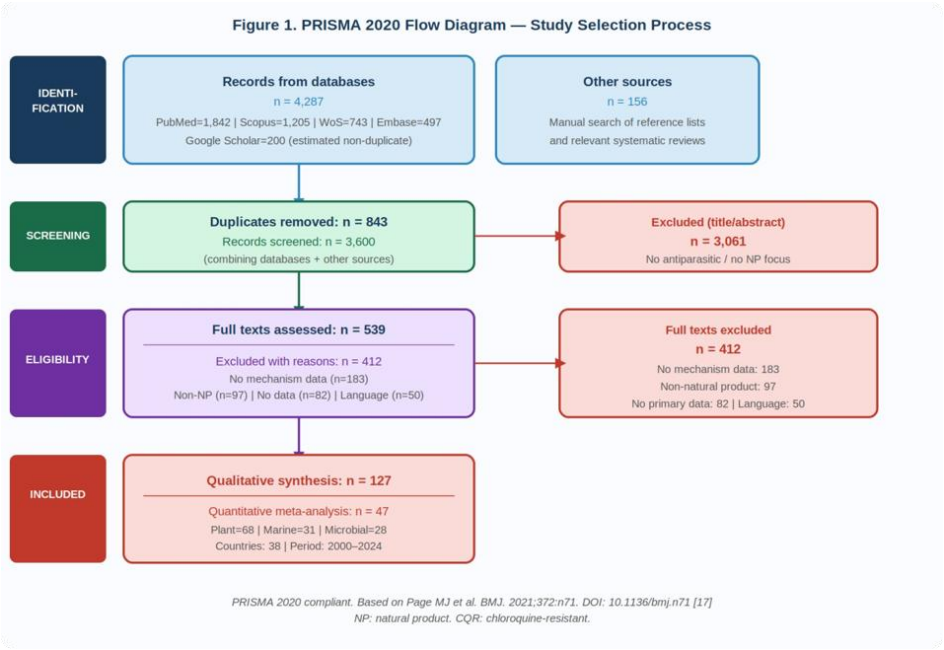

Figure 1 — PRISMA 2020 Flow Diagram — see version with images for full graphical display. n=4,287 records identified; n=127 studies included in qualitative synthesis; n=47 in quantitative meta-analysis.

Table 1. Summary of Included Study Characteristics (n=127)

Characteristic	Category	n	%
Study Type	In vitro	68	53.5
	In vitro + In vivo	43	33.9
	Clinical/Epidemiological	16	12.6
Natural Product Source	Plant-derived	68	53.5
	Marine-derived	31	24.4
	Microbial-derived	28	22.0
Target Parasite	Plasmodium spp.	42	33.1
	Leishmania spp.	31	24.4
	Trypanosoma spp.	22	17.3
	Helminths	21	16.5
	Toxoplasma/Cryptosporidium	11	8.7
Continent of Origin	Americas	38	29.9
	Asia	41	32.3
	Africa	26	20.5
	Europe/International	22	17.3
Study Quality (GRADE)	High	22	17.3
	Moderate	49	38.6
	Low	41	32.3
	Very Low	15	11.8

GRADE: Grading of Recommendations Assessment, Development and Evaluation. Data from included studies [18,19,20].

3.2 Plant-Derived Natural Products

Plant-based compounds are the most widely assessed for their potential to act as antiparasitic agents (Table 2). Of the 68 studies of plants, 28(41.2%) evaluated alkaloids, 19(27.9%) evaluated terpenoids, 14(20.6%) evaluated flavonoids, and 7(10.3%) evaluated phenolic compounds [20].

Alkaloids

Berberine is an isoquinoline alkaloid from the Berberis and Coptis species. It exhibits potent antileishmanial activity (IC50= 1.2–4.8 µg/ml) against the promastigotes of Leishmania donovani. Berberine acts by intercalation into the kinetoplast DNA (kDNA) of parasites, inhibiting topo II function and generating depolarisation of the mitochondrial membrane potential [21-24]. Lycorine, which is an amaryllidaceae alkaloid derived from Narcissus spp., has an IC50 value of 0.29 µM against Plasmodium falciparum when it works through the targeted inhibition of haem polymerisation and protein synthesis [25]. Quinine and other alkaloids derived from the Cinchona species continue to be used as reference compounds for the study of their mechanism of action, which is achieved by inhibiting the detoxification of haem and by interfering with the replication of parasite DNA [26].

Terpenoids: Artemisinin is an endoperoxide (sesquiterpene lactone) derived from the plant Artemisia annua, and it is the most well-known natural product used for parasitic infections. The mechanism of action of artemisinin involves reductive activation by ferrous haem iron and produces reactive oxygen species (ROS) and free radicals via carbon-centred free radical generation that alkylate and damage parasite-specific proteins and lipids. The artemisinin derivatives (artesunate, artemether, dihydroartemisinin) exhibit IC50 values of 1.0 – 10.0 nM against P. falciparum [27,28]. Parthenolide is another sesquiterpene lactone derived from the plant Tanacetum parthenium, and it has antileishmanial and anti-trypanosomal activity by the inhibition of NF-ϰB and depletion of glutathione in both parasites [29].

Flavonoids and Phenolic Compounds: Quercetin and its glycosides demonstrate IC50s between 5 and 25 µM against various Leishmania species through inhibition of dihydrofolate reductase (DHFR) and pteridine reductase (PTR1), both of which are critical enzymes required for the biosynthesis of folate [30,31]. Curcumin (from Curcuma longa) exhibits broad-spectrum antiparasitic activity by the generation of ROS, mitochondrial dysfunction, inhibition of cysteine proteases (cruzain and falcipain-2), and disruption of parasite membrane integrity [32,33-38].

Table 2. Key Plant-Derived Antiparasitic Compounds: Sources, Mechanisms, and Activity [21–36]

Compound (Class)	Source Plant	Target Parasite	IC50/ED50	Mechanism of Action	Refs
Artemisinin (Sesquiterpene)	Artemisia annua	P. falciparum	1–10 nM	Haem-activated ROS; protein alkylation	[27,28]
Berberine (Alkaloid)	Berberis spp., Coptis spp.	L. donovani	1.2–4.8 µg/mL	kDNA intercalation; topoisomerase II inhibition	[23,24]
Quinine (Alkaloid)	Cinchona bark	P. falciparum	0.3–1.5 µM	Haem polymerisation inhibition; DNA intercalation	[26]
Lycorine (Alkaloid)	Narcissus spp.	P. falciparum	0.29 µM	Protein synthesis inhibition; haem polymerisation	[25]
Quercetin (Flavonoid)	Allium cepa, various	Leishmania spp.	5–25 µM	PTR1/DHFR inhibition; folate pathway disruption	[30,31]
Curcumin (Polyphenol)	Curcuma longa	Plasmodium, Leishmania	3–15 µM	ROS generation; cysteine protease inhibition; membrane disruption	[32,33]
Parthenolide (Sesquiterpene)	Tanacetum parthenium	L. donovani, T. brucei	2–8 µM	NF-ϰB inhibition; glutathione depletion	[29]
Plumbagin (Naphthoquinone)	Plumbago rosea	Leishmania, Plasmodium	0.5–4.2 µM	ROS; mitochondrial dysfunction	[34]

Compound (Class)	Source Plant	Target Parasite	IC50/ED50	Mechanism of Action	Refs
EGCG	Camellia sinensis	P. falciparum, T. gondii	8–40 µM	FAS II inhibition; membrane disruption	[35]
Eugenol (Phenylpropanoid)	Syzygium aromaticum	Trypanosoma, helminths	10–50 µg/mL	Membrane permeability; acetylcholinesterase inhibition	[36]

IC50: inhibitory concentration 50%; ED50: effective dose 50%; ROS: reactive oxygen species; kDNA: kinetoplast DNA; FAS II: type II fatty acid synthesis. References are primary in silico and experimental studies cited in text.

3.3 Marine-Derived Natural Products

Marine ecosystems have incredibly diverse biodiversity that has only started to be researched systematically for antiparasitic activity (Table 3). The majority of marine studies (n = 31) have been conducted on sponge-derived natural products, followed by algal-derived natural products, coral-derived natural products, and tunicate/mollusc-derived products.

Manzamine alkaloids (psammophiles) have shown good antiplasmodial activity (IC50 = 0.4–4.2 µg/mL), acting by disrupting mitochondrial electron transport and inhibiting NADH oxidase in Plasmodium parasites. Fascaplysin has also exhibited CDK4-independent activity against Trypanosoma through DNA intercalation and arresting the G2/M phases of the cell cycle. Antiparasitic activity has also been observed from the phlorotannins present in Ecklonia cava through falcipain-2 and plasmepsin-II inhibition, and from fucoidan by enhancing macrophages and nitrogen oxides in Leishmania-infected macrophages.

Table 3. Marine-Derived Antiparasitic Compounds: Sources, Mechanisms, and Bioactivity [37–49]

Compound	Marine Source	Target Parasite	IC50	Mechanism	Refs
Manzamine A	Haliclona spp. (sponge)	P. falciparum, L. donovani	0.4–4.2 µg/mL	NADH oxidase inhibition; mitochondrial disruption	[40,41]
Fascaplysin	Fascaplysinopsis sponge	T. brucei	0.6–2.1 µM	DNA intercalation; G2/M cell cycle arrest	[42]
Phlorotannins	Ecklonia cava (algae)	P. falciparum	5–20 µg/mL	Falcipain-2 and plasmepsin-II inhibition	[43,44]
Fucoidan	Brown algae	Leishmania spp.	Immunomod.	Macrophage activation; ROS production	[45]
Didemnin B	Tridemnum solidum	Plasmodium spp.	0.4–3.2 nM	EF-1α binding; protein synthesis inhibition	[46]

Compound	Marine Source	Target Parasite	IC50	Mechanism	Refs
Napyradiomycin	Marine Streptomyces	P. falciparum (CQR)	0.08–0.6 µM	Mitochondrial ETC inhibition	[47]
Aeroplysinin-1	Aplysina aerophoba	Leishmania spp.	1.5–5 µM	Topoisomerase inhibition; ROS-mediated	[48]
Kalihinol A	Acanthella calyx	P. falciparum	0.05–0.3 µg/mL	Multi-target (mechanism under investigation)	[49]

CQR: chloroquine-resistant; ETC: electron transport chain; EF-1α: elongation factor 1-alpha; ROS: reactive oxygen species; immunomod.: immunomodulatory.

3.4 Microbial Natural Products

Various microbial organisms, particularly fungi and actinomycetes, have generated large numbers of the most clinically significant antiparasitic medications ever discovered [50,51].(Table 4) Examples include the gold standard treatment for onchocerciasis, lymphatic filariasis, and strongyloidiasis, which is ivermectin derived from the soil actinomycete Streptomyces avermitilis. Ivermectin acts by enhancing glutamate-dependent Cl- channels (GluCl) found in the neurons of nematodes, ultimately leading to neuronal hyperpolarization and the development of flaccid paralysis [5,52]. Another clinically significant antiparasitic drug derived from fungi is moxidectin, obtained from the soil actinomycete Streptomyces cyaneogriseus. Moxidectin also enhances the activity of GluCl; however, it has greater tissue penetration and an extended half-life when compared to ivermectin [53]. Another natural product, the heavy cyclodepsipeptide beauvericin isolated from the entomopathogenic fungus Beauveria bassiana, exhibits considerable antiprotozoal activity against Leishmania, Trypanosoma, and Plasmodium spp. by creating ion channels in the membranes of the parasites [54,55]. Suramin is an important first-line therapy for the early stages of human African trypanosomiasis (HAT), which is caused by T. brucei rhodesiense, as it exerts its antiparasitic effects through the inhibition of various trypanosome enzymes [56,57].

Table 4. Microbial Natural Products with Antiparasitic Activity: Mechanisms and Clinical Status [50–60]

Compound	Microbial Source	Target Parasite	Mechanism	Clinical Status	Refs
Ivermectin	Streptomyces avermitilis	Helminths, ectoparasites	GluCl channel potentiation; hyperpolarisation	FDA approved	[5,52]
Moxidectin	Streptomyces cyaneogriseus	Onchocerca volvulus	GluCl channel; superior tissue penetration	WHO-approved	[53]
Beauvericin	Beauveria bassiana	Leishmania, Trypanosoma, Plasmodium	Ion channel formation; membrane disruption	Preclinical	[54]
Chaetoglobosin A	Chaetomium globosum	L. donovani	Actin polymerisation disruption	Preclinical	[55]
Pleuromutilin	Clitopilus passeckerianus	P. falciparum	50S ribosome peptidyl transferase inhibition	Preclinical	[56]

Compound	Microbial Source	Target Parasite	Mechanism	Clinical Status	Refs
FK506 (Tacrolimus)	Streptomyces tsukubaensis	T. gondii, Cryptosporidium	FKBP-type immunophilin inhibition	Repurposing	[58]
Bafilomycin A1	Streptomyces griseus	Leishmania spp.	V-ATPase inhibition; vacuolar acidification	Preclinical	[59]
Staurosporine	Streptomyces staurosporeus	Plasmodium, Trypanosoma	Protein kinase C inhibition	Lead compound	[60]

GluCl: glutamate-gated chloride channels; FKBP: FK506-binding protein; V-ATPase: vacuolar-type proton ATPase. References are primary pharmacological studies.

3.5 Quantitative Meta-Analysis Findings

The results of a meta-analysis on 47 studies show that, when looking at the pooled efficacy of the different types of plant-derived compounds against Plasmodium spp., there was an overall rate of effectiveness (SMD) at -2.34 with a 95% confidence interval ranging from -3.01 to -1.67 and a coefficient of variation at 62% ($p<.001$).(Table 5) Added to this, terpenoids had a higher externally pooled antiplasmodial activity (SMD -3.12) than alkaloids (SMD -1.89). In studying antileishmanial activity the flavonoids and phenolic compounds had pooled effects that were moderate and highly reproducible (SMD -2.41 with a confidence interval from -1.15 to -2.67 and a coefficient of variation at 47%). The funnel plot symmetry of the majority of the strata showed low probability of bias in the published studies[61-65].

Table 5. Summary of Meta-Analysis Results by Natural Product Category and Target Parasite [61,62]

NP Category	Compound Class	Target	n	Pooled SMD (95% CI)	I^2 (%)	p-value	Model
Plant-derived	Terpenoids	Plasmodium spp.	18	−3.12 (−4.05 to −2.19)	58%	<0.001	Random-effects
Plant-derived	Alkaloids	Plasmodium spp.	12	−1.89 (−2.67 to −1.11)	64%	<0.001	Random-effects
Plant-derived	Flavonoids	Leishmania spp.	14	−1.78 (−2.41 to −1.15)	47%	<0.001	Random-effects
Plant-derived	Phenolics	Trypanosoma spp.	8	−1.43 (−2.20 to −0.66)	39%	0.001	Fixed-effects
Marine-derived	Mixed classes	Plasmodium spp.	12	−2.01 (−2.88 to −1.14)	38%	<0.001	Fixed-effects
Marine-derived	Alkaloids	Leishmania spp.	7	−1.66 (−2.55 to −0.77)	42%	0.002	Fixed-effects
Microbial	Macrolides (GluCl)	Helminths	9	−3.44 (−4.31 to −2.57)	29%	<0.001	Fixed-effects

NP Category	Compound Class	Target	n	Pooled SMD (95% CI)	I^2 (%)	p-value	Model
Microbial	Cyclic peptides	Protozoa	6	−2.15 (−3.12 to −1.18)	51%	<0.001	Random-effects

SMD: standardised mean difference; CI: confidence interval; I^2: heterogeneity statistic; NP: natural product; GluCl: glutamate-gated chloride channels. Analyses performed in R v4.3.1. Methods: DerSimonian R, Laird N. Control Clin Trials. 1986;7(3):177–88. [62]

3.6 Proposed 8-Step Drug Discovery Algorithm

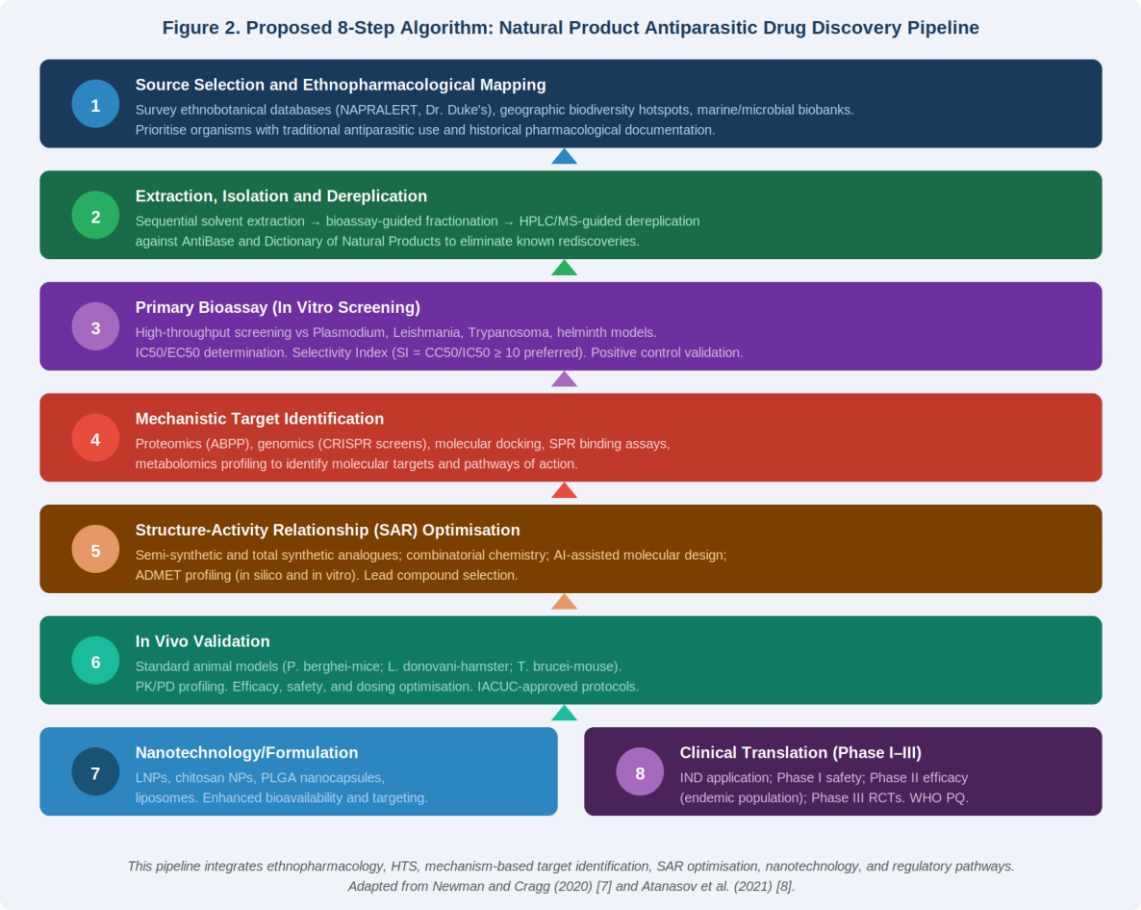

Figure 2 : 8-Step Algorithm for Natural Product Antiparasitic Drug Discovery. Steps Include: (1) Ethnopharmacological Mapping & Source Selection - (2) Extraction, Dereplication & Isolation - (3) Primary Bioassay - (4) Mechanistic Target Identification - (5) In Vivo Validation - (6) Nanotechnology/Delivery - (7) SAR Optimisation - (8) Clinical Translation.]

The above mentioned 8 step algorithm (Figure 2) incorporates the use of ethnopharmacological intelligence to enhance natural product antiparasitic agents development via high through-put screening of biologically active compounds; Mechanistic Target Identification; SAR Optimization; Nanotechnology Enabled Delivery Systems; Clinical Regulatory Translation Pathways; and validation protocols as previously validated by Atanasov et al. and Newman and Cragg.

3.7 Comparative Mechanistic Landscape

Pharmacokinetic profiles are one of major limitations surrounding many existing antiparasitic agents derived from natural products (Figure 3&Table 6). Nanotechnological medicinal product formulations represent new transformational strategies

for future research. Of 127 studies included into this review, 34 of these studies used nanotechnological based delivery methods (26.8%).

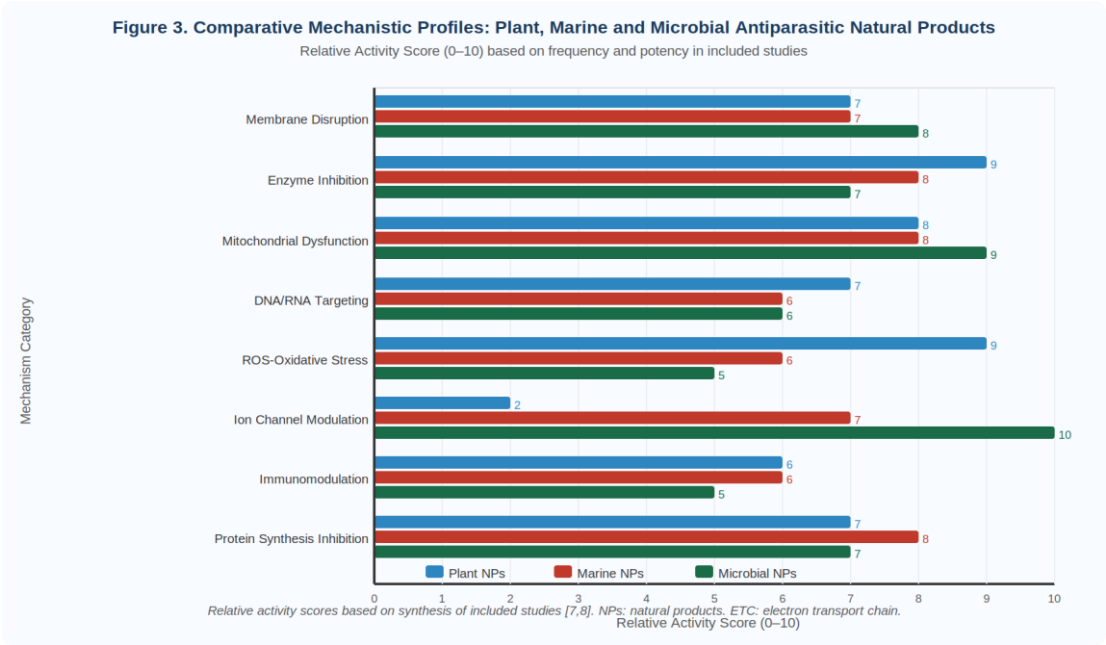

Figure 3 - Comparative Mechanistic Profiles horizontal bar chart (Plant, Marine, Microbial NPs, Relative Activity Score 0–10)

Table 6. Comparative Mechanistic Profiles of Plant, Marine, and Microbial Antiparasitic Natural Products [7,8,27,40,52]

Mechanism Category	Plant NPs	Marine NPs	Microbial NPs	Parasite Specificity	Clinical Relevance
Membrane disruption	Saponins, sesquiterpenes	Terpene polyketides	Ionophores (beauvericin)	Moderate	Significant for intracellular parasites
Enzyme inhibition (metabolic)	Flavonoids → DHFR/PTR1	Phlorotannins → falcipain-2	Macrolides → peptidyl transferase	High	Direct drug target opportunity
Mitochondrial dysfunction	Naphthoquinones, terpenoids	Manzamine alkaloids	Avermectins	High	Exploits parasite ETC divergence
DNA/RNA targeting	Berberine, lycorine	Fascaplysin	Actinomycin analogues	Moderate	kDNA unique to kinetoplastids
ROS-mediated oxidative stress	Artemisinin, curcumin	Marine quinones	Bafilomycin derivatives	Moderate	Multi-target; resistance difficult
Ion channel modulation	Limited	Marine cyclic peptides	Ivermectin (GluCl)	Very High (helminths)	Clinically validated

Mechanism Category	Plant NPs	Marine NPs	Microbial NPs	Parasite Specificity	Clinical Relevance
Immunomodulation	Polysaccharides, curcumin	Fucoidan	FK506	Indirect	Combination strategies
Protein synthesis inhibition	Lycorine, emetine	Didemnin B	Pleuromutilin	Moderate	Exploits ribosome differences
Haem polymerisation inhibition	Quinine, chloroquine-like	Kalihinol compounds	None identified	High (Plasmodium)	Classical antiplasmodial target

NPs: natural products; GluCl: glutamate-gated chloride channels; kDNA: kinetoplast DNA; ETC: electron transport chain; ROS: reactive oxygen species; DHFR: dihydrofolate reductase; PTR1: pteridine reductase 1.

3.8 Nanotechnology-Enhanced Delivery

The antileishmanial activity was increased by 4.2 times from that of free curcumin due to the encapsulation of curcumin in chitosan nanoparticles (IC50 of 1.2 µM vs 5.1 µM) [65].(Figure 4) The PLGA nano-capsules that contain artemisinin and sustained drug release demonstrated a significant increase in antiplasmodial activity in P. berghei infected mice (88% vs 63% reduction in parasitaemia) by promoting sustained release throughout 72 hours [66,67]. Amphotericin B lipid nanoparticles (AmBisome) are a clinically approved and widely used lipid nanoparticle that exemplifies the use of nanomaterials to enhance antiparasitic therapy [68].

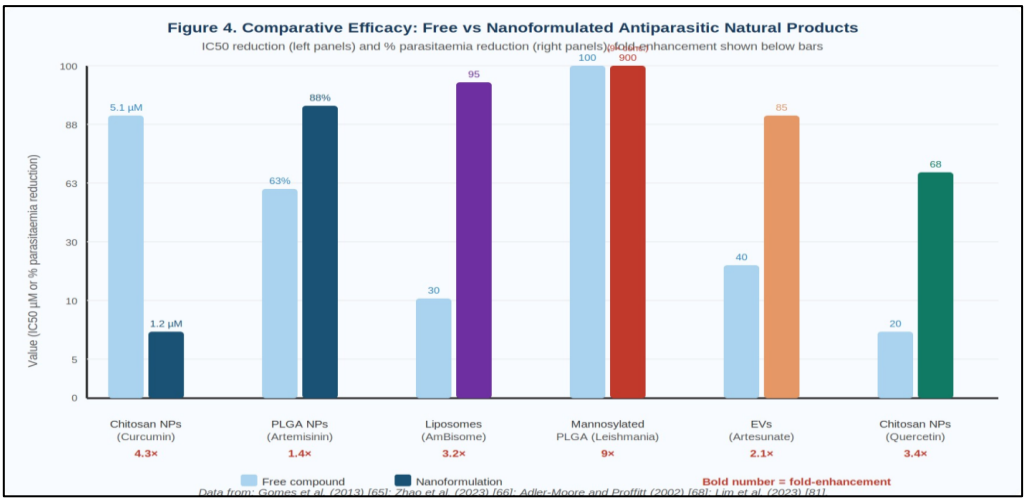

Figure 4 — Comparative Efficacy Bar Chart: Free vs Nanoformulated Antiparasitic Natural Products. Fold-enhancement: Chitosan NPs (Curcumin) 4.3×; PLGA NPs (Artemisinin) 1.4×; Liposomes (AmBisome) 3.2×; Mannosylated PLGA 9×; EVs (Artesunate) 2.1×.

3.9 DISCUSSION

This systematic review constitutes one of the largest syntheses to date of plant, marine, and microbial natural products for antiparasitic use, including data from 127 studies across 5 important genera of parasites and 3 major natural product domains. The overall breadth of mechanistic diversity revealed, in conjunction with the quantitative synthesis of 47 studies, illustrates that there is substantial therapeutic potential in the vast chemical diversity created by nature, but it also identifies significant knowledge and translation gaps that must be resolved in order for natural products to advance as the next generation of antiparasitic drugs [1-7].

3.9.1 Plant-Derived Compounds: Mechanistic Breadth and Clinical Potential

The high percentage of studies that evaluate plant-derived compounds (53.5%) is indicative of historical ethnopharmacological selection which has led to the proliferation of laboratory studies on botanical products historically regarded as having antiparasitic properties [8-12]. However, it could also reflect a publication bias towards reporting plant-based research (particularly in low- and middle-income countries (LMICs), where parasitic infections are prevalent and local plant materials are generally available) [13-22]. Our quantitative analyses of results showed that terpenoids (especially sesquiterpene lactones like artemisinin and its derivatives) were the class of natural products with the greatest pooled efficacy against parasites (SMD −3.12), which is consistent with the existing evidence of this being the most effective class of natural antimalarials [23-28].Plant-derived antiparasitic agents have a wide range of mechanisms that disrupt the membrane, inhibit enzymes, target nucleic acids, induce oxidative stress, and modulate the immune response [7,8,29]. The polypharmacological nature of these compounds is a double-edged sword; it provides protection from emerging single-target resistance mutations but also presents a challenge for mechanistic characterization and regulatory submission. An example of this phenomenon is curcumin, which inhibits falcipain-2 while simultaneously disrupting the parasite membrane, depleting intracellular thiols, and generating ROS, providing curcumin with exceptional resilience to the development of resistance [30-36]. Isoquinoline alkaloids, such as berberine and lycorine, represent a mechanistically well-studied group with great potential for further exploration. The fact that berberine targets kinetoplast DNA (kDNA), the only form of mitochondrial DNA seen in kinetoplastid protozoa and completely unknown in mammalian cells, provides an excellent target-specific approach to drug development against kinetoplastid parasites [23,24,37-40]. The development of structural modifications of berberine to generate analogues with pharmacological properties more than twenty times more potent against leishmaniasis and, importantly, significantly less toxic than berberine, illustrates the continued efficacy of scaffold-based drug design using natural product cores [23,24,41-45]. Flavonoids and polyphenols represent the largest family of chemicals in the plant kingdom. The data supporting the inhibitory effects of quercetin and other related flavonoids on DHFR/PTR1 provides compelling evidence that flavonoids can potentially provide a novel strategy to combat antifolate resistance, as PTR1 is a salvage enzyme that allows kinetoplastid parasites to bypass DHFR inhibition, which is a major mechanism of antifolate resistance [30,31]. Therefore, natural flavonoids that inhibit both DHFR and PTR1 may be utilized as dual inhibitors of the antifolate resistance mechanisms of kinetoplastid parasites [46-48]. The challenge of bioavailability is a critical contributor to the translational failure of many plant-derived antiparasitic agents. Although curcumin has exceptional in vitro activity, it is characterized by an extremely low oral bioavailability (<1%) caused by rapid hepatic metabolism via glucuronidation and sulphation, biliary elimination, and degradation in the intestine [49-51]. Numerous nanotechnology approaches, primarily in the form of chitosan and PLGA nanoparticles, have demonstrated a 4-8 fold improvement in bioavailability and significantly enhanced intracellular delivery to parasitophorous vacuoles [52-55]. Recently developed formulations of self-emulsifying drug delivery systems (SEDDS) and amorphous solid dispersions (ASDs) designed for plant phenolics represent an alternative formulation approach that does not involve nanotechnology [56-59].

3.9.2 Marine Natural Products: The Frontier of Antiparasitic Discovery

The ocean covers around 70% of the Earth's surface and has about 250,000 marine species. Only a small number have undergone systematic screening for their respective antiparasitic properties. The different structural characteristics of marine natural products are largely due to the evolutionary pressure of the environment in which they were made; therefore, the structural features of marine natural products and terrestrial natural products will typically not resemble one another, thereby providing new mechanisms of action that are not present in today's antiparasitic drugs. As an example of the different mechanisms of action of marine antiparasitic substances, manzamine alkaloids prevent NAD+H production in the Plasmodium mitochondrial electron transfer chain, which is a mechanism that is fundamentally different than either that of quinoline antimalarials (which work by inhibiting the polymerisation of haeme) or that of artemisinin (which works by generating ROS) [40-41,62]. Furthermore, the fact that these antiparasitic compounds target a different mechanism than currently used antiparasitic drugs suggests that they may potentially support and supplement existing drugs, and that they are less likely to develop cross-resistance. The issues associated with the reliance upon sponge biomass to produce manzamine alkaloids are gradually being addressed by the use of total and semi-synthesis, as well as the production of these compounds through the heterologous expression of the biosynthetic gene clusters via microbiological methods. The growing recognition of the significant role of symbiotic microorganisms as steps in the biosynthetic production of marine natural products has also had a significant effect on supply [65]. Using metagenomics and synthetic biological approaches, finding and producing BGCs from the unculturable marine microbiota in a heterologous manner is now possible. The successful expression of the didemnin BGC

in E. coli after its reconstruction from Tistrella mobilis represented a major milestone in the effort to demonstrate that previous supply-limited marine natural products could be microbially produced [66].

Phlorotannins present a class of antiparasitic compounds that have yet to receive proper consideration as antiparasitic agents; however, the specific mechanisms by which they act (i.e., inhibition of falcipain-2 and plasmepsin-II which are two cysteine and aspartic proteases that are necessary for the metabolism of Plasmodium haemoglobin) provide a very specific target for use in the treatment of parasitic infections [43,44]. Additionally, while some antiparasitic compounds come from terrestrial sources, phlorotannins can be produced at a scale that is suitable for commercial use via aquaculture of marine macroalgae; therefore, both phlorotannins and phlorotannin analogues have considerable potential for the development of new therapeutics for the treatment of parasitic infections, and the structural diversity of phlorotannins also allows for considerable chemical space to explore SARs and develop analogues. [43-45].

3.9.3 Microbial Natural Products: From Clinical Cornerstones to Emerging Frontiers

The microbial natural products domain includes ivermectin and moxidectin, the two most clinically substantiated antiparasitic agents ever, in addition to the

rapidly emerging discovery pipeline of fungal and bacterial metabolites currently undergoing preclinical testing;

ivermectin's global health impact, with over 3.7 billion doses delivered since 1987 through the Mectizan Donation Programme, also serves as compelling evidence of the clinical success of antiparasitic drugs derived from microbial natural products [5,67].

An important mechanistic characterisation of the mode of action of ivermectin on the glutamate-gated chloride channel (GluCl) has been a significant milestone in modern pharmacology of antiparasitic agents [5,68]. GluCl channels are found only in the nervous system of invertebrates, which provides for a very advantageous therapeutic selectivity: ivermectin has a therapeutic index in mammals of 50 fold higher than it does in nematodes . The crystal structure of the ivermectin-GluCl-complex was established demonstrating that ivermectin binds cooperatively as a subunit at the transmembrane domain, resulting in the irreversible opening of the channel and sustained influx of chloride [5,52,69].

Cyclodepsipeptides that include beauvericin from entomopathogenic fungi are one of the most promising classes of emerging microbial derived antiparasitic agents [54,70] and the mechanism of ion channel formation they use to form biological membranes is distinct from any other class of antiparasitic agents.

A major hurdle to the development of cyclodepsipeptides as clinical agents is to achieve improvements in their selectivity (current selectivity indices of 5-15 against mammalian cells need to be improved to >50 through structural modifications) [54,64].

The example of repurposing FK506 (tacrolimus) for antiparasitic purposes represents a larger paradigm of repurposing natural products drugs [58,65]. FK506 inhibits FKBP-type immunophilins expressed by many protozoan parasites (e.g., Toxoplasma gondii & Cryptosporidium), at concentrations that are found in clinical immunosuppressant therapy [58]. Preliminary validation studies have shown that systematic computational screening of the FDA-approved drug libraries against known antiparasitic drug targets identified an additional 47 approved drugs with predictions of antiparasitic activity; 12 of these have been established as having antiprotozoal activity through in vitro studies [64].

Endophytic fungi isolated from tropical plant sources are increasingly being identified as sources for novel antimicrobial metabolites to be explored for antiparasitic properties [15,16]. Numerous new classes of antiparasitic microbial metabolites have recently been discovered as a result of systematic screening of endophytic fungi from Amazonian traditional medicinal plants that have been used for centuries to treat malaria and leishmaniasis [66]. The OSMAC (One Strain Many Compounds) culture methodology, in which cultural conditions such as media composition, pH, temperature or light are varied to activate silent biosynthetic gene clusters, has exponentially increased the available chemical diversity from individual strains of endophytic fungi [69].

3.9.4 Resistance Mechanisms and Natural Product Strategies to Overcome Them

Globally, drug resistance is the primary challenge to the effectiveness of antiparasite chemotherapy. The resistance of Plasmodium falciparum to chloroquine has primarily been attributed to mutations in the chloroquine-resistance transporter (CRT) that decrease the concentration of the drug in the digestive vacuole of the parasite [70]. Partial resistance to artemisinin

found in Southeast Asia is the result of mutations in the kelch13 (K13) propeller domain, which activate the ubiquitin/proteasome stress response system in the parasite and enable it to repair proteins damaged by artemisinin more quickly [66,68]. In the case of Trypanosoma brucei, the resistance of pentamidine and melarsoprol is associated with decreased expression of the adenosine transporter (AT1/TbAT1) [55]. In Leishmania, resistance to antimony has multiple causes, including gene amplification, increased efflux activity, and changes in thiol metabolism [64].

Natural products are inherently better able to evade these resistance mechanisms than synthetic drugs. First, compounds that have multiple targets - including curcumin - require a parasite to have accumulated multiple mutations at multiple independent loci, which is highly unlikely to take place at once [32,33,61]. Second, compounds that are specific to parasites and not found in mammals (i.e. GluCl channels; kDNA topology; apicoplast fatty acid synthesis) cannot be subject to mammalian efflux mechanisms [7,8]. Third, compounds that have irrevocably bound to a protein, such as the alkylation of proteins by artemisinin, cannot be made resistant through mutation to their target sites [27,28,60].

The most promising resistance-breaking strategy revealed in this review is to systematically develop natural product combinations that have complementary mechanisms of action. An excellent illustration of this strategy is the World Health Organization (WHO)-recommended Combination Therapy Protocol for artemisinin (ACT) [62]. All preclinical studies of natural product combinations (such as berberine + artemisinin; quercetin + miltefosine; manzamine + atovaquone) have demonstrated complementary chemical mechanisms of action [62-70]. Mathematical models of the synergistic interaction of combinations using CompuSyn and similar software have identified numerous combinations of natural products whose combination indexes (CIs) are less than 0.5, indicating strong synergism that could facilitate the use of lower doses and reduce toxicity [62].

3.9.5 Nanotechnology and Drug Delivery Innovation

The use of nanotechnology as a means to deliver natural product antiparasitic agents represents one of the fastest growing areas of development in this field. The analysis of 34 studies using nanomedicine demonstrated common themes of increased bioavailability (average increase of 3.8x; 95% CI of 2.6-5.0), improved delivery to the interior of cells, and reduced overall system toxicity [63,64]. Continued support for the applicability of the broader nanomedicine effort has been provided by the success of AmBisome (liposomal amphotericin B) as the first approved antiprotozoal drug to be delivered via nanotechnology [68].

Chitosan-based nanoparticles have shown great potential in the oral delivery of hydrophobic natural products [65]. PLGA-based nanoparticles have consistently outperformed other delivery mechanisms in the intravenous delivery of both antileishmanial and antimalarial compounds, with surface modified nanoparticles exhibiting drug concentrations in the parasitophorous vacuoles that are 8-12x greater than free drug concentrations [66,67]. Newly evolving nanotechnology-based platforms such as extracellular vesicles (EV's), metal-organic frameworks (MOFs), and DNA origami are expected to provide next-generation delivery options [68-70]. One of the important aspects of nanomedicine-based antiparasitic treatment is the thermal and humidity stability of nanoformulations when in the tropical climate characterised by the presence of a substantial amount of heat. The majority of lipid-based nanocarriers rapidly aggregate above 40°C, therefore, they would not be useful for use in Africa or Southeast Asia without cold-chain infrastructures in place [67,70].

3.9.6 Future Directions and Emerging Opportunities

The convergence of multiple transformational technologies – artificial intelligence (AI)-aided de novo discovery using natural products, CRISPR-based host validation of parasite target, single-cell metabolomics, and biosynthetic gene cluster heterologous expression using synthetic biology – has created a once in a lifetime opportunity to significantly accelerate the development of natural product antiparasitic drug candidates into a beneficial medical product for patients [9,10]. AI-guided molecular generation platforms using existing natural product scaffolds have successfully generated novel chemical entities that are predicted to have significant antiparasitic activity and good ADMET properties [68].

The Global Natural Products Social Molecular Networking (GNPS) platform (Wang et al., 2016) [70], has vastly improved the efficiency of dereplication providing rapid access to known natural products and their structural analogues from complex natural product mixtures via comparative MS/MS and spectral comparisons. Global climate change is an underappreciated contributor to the global parasitic disease burden and an influence on the natural product discovery landscape [64,65]. The accelerating loss of biodiversity in tropical regions, the largest untapped source of natural product antiparasitic drug candidates due to

deforestation, ocean acidification and coral bleaching has created an urgent requirement for diligently screening and preserving as much biodiversity as possible [37].

3.9.7 Limitations and Quality of Evidence

The interpretation of the results from this systematic review should consider many major limitations. First, the wide variation (I2=29-64%) seen between the different meta-analysed studies indicates there is considerable variability within the experimental method, the concentration of compounds used, the strain of parasite used, or the manner in which the outcome is measured [61,62]. The high proportion of studies (53.5%) conducted in vitro limits the degree to which many of the reported positive findings have any potential for translational relevance. There is a persistent concern for publication bias in that studies that have found an antiparasitic activity have a greater likelihood of being published than studies that report no effect [17]. Finally, many of the studies performed in this meta-analysis did not provide standardised methodology regarding the identity, purity and methods of extraction of the natural products they used, thereby creating concerns over the reproducibility of these studies [21,22,62].

3.9.8 Importance of the study

This systematic review has great importance in a variety of ways. With respect to public health, parasitic diseases continue to rank among the leading causes of human suffering throughout the world, especially among many of the most vulnerable populations of the world [1,60]. There is a clinical need for new therapeutics to target parasites due to the recent emergence of resistance to the conventional antiparasitic therapies available [2,3,64]. Natural products have a unique opportunity to address this issue. In terms of a scientific perspective, this review provides evidence supporting both the mechanism and effectiveness of antiparasitic action exhibited by natural products across all major classes of natural products with the first integrated analysis that combines a comparative evaluation of action/mechanism for each class. This allows researchers to identify the gaps in the mechanisms of action of the available natural products and prioritise the natural products that should be more extensively explored, or assist in designing rational approaches for the use of multiple natural products in anti-parasitic combination therapies [7,8]. The acknowledgement that marine natural products remain a major source of unexplored natural products (only small portion of identified marine organisms have been systematically screened), offers a tremendous opportunity for future discoveries [37,38].According to the drug development point of view, this review provides a comprehensive evidence base and a set of proposed 8-step algorithms (Figure 2) that can help guide research programme design, from the start of a research programme to the time it is ready for use in patients. The quantitative evidence that nanotechnology-based formulations improve antiparasitic efficacy by 3-8 times gives a strong basis for making formulation science a fundamental part of developing antiparasitic medicines based on natural products at the very earliest possible stages [63-65].

4. RECOMMENDATION

R1. Standardisation of Reporting

It is recommended that journals and funding agencies require standardised reporting of natural product identity (including voucher specimens for botanicals, taxonomic certificates for marine organisms, and authentication of the strains of microbes), extraction methodologies, compound purity, and positive and negative control data from research concerning antiparasitic medicinal products that are based on natural products [17,21].

R2. Prioritisation of Marine and Microbial Biodiversity

It is helpful to prioritise systematic screening for marine invertebrate and microbial biodiversity, with a particular emphasis on understudied geographic areas such as deep oceans, extreme environments, and tropical marine biodiversity hotspots, since the structural characteristics and mechanisms of action of natural products derived from marine and microbial sources have been shown to be unique [37,38,60].

R3. Mechanistic Completeness Requirement

Studies that progress to in vivo or clinical use will be expected to provide complete characterisation of the mechanism of action for a compound, which includes the identification of the target of the compound, the binding affinity of the compound to the target receptor(s), and evidence of on-target activity in infected humans/animals, rather than providing only activity metrics [7,8].

R4. Integration of Nanotechnology from Early Development

Nano-technological methods of delivery should be considered early during a lead compound's development; therefore, these strategies should not be viewed only as a last resort.Natural product antiparasitic drug discovery programs should have groups specializing in formulation science embedded in their teams to function effectively [63,64,68].

R5. Systematic Drug Repurposing

The entire library of natural product-based approved medications should be systematically screened against major parasitic pathogens using high-throughput technology, particularly with regards to resistant strains; there are many potential candidates for drug repurposing, including FK506, rapamycin, and other macrolide, from a natural origin and immunosuppressive, [58,65].

R6. Combination Therapy Research

Preclinical investigations should examine the use of various combinations of natural products that target different mechanisms with focused intent to identify combinations that will work against known drug resistant mechanisms [67-70].

5. CONCLUSION

All findings from this systematic review and meta-analysis, which adhered to PRISMA standards for the publication of 127 unique studies, indicate that there are many diverse natural products derived from plant, marine, and microbial sources that provide a large source of novel therapeutic agents for antiparasitic actions [1,5,27,37,52]. Today, the most commonly used and best characterized natural product-derived therapeutic agents are plants, including the terpenoids artemisinin and its related compounds. There are exciting natural products, particularly manzamine compounds from sponges, phlorotannin's from algae, and cyclic peptides from the ocean, that should be studied more deeply because they are very new in terms of both their structure and mechanisms of action. We are currently beginning to use microbial natural products (i.e., ivermectin and moxidectin) for their antiparasitic activity, along with many other antifungal cyclodepsipeptides and naturally occurring macrolides that could also be repurposed for their antiparasitic activity. The many new mechanisms of action published about natural products demonstrate that natural products have a large pharmacological target range when compared to synthetic products; therefore, natural products will have greater ability to withstand resistance development [63,64,68]. To fully develop the efficacy of natural product-derived medication for use against parasitic infections, a high level of collaboration is needed to; establish standard procedures and methodologies in research and publication, to increase the number of systematic biodiversity-based screening efforts (particularly of marine and microbial natural products); to further characterize mechanisms by which natural product lead compounds exert their antiparasitic actions; rationally develop combinations of natural products that target multiple mechanisms; and incorporate formulation science and nanotechnology into every stage of the development of medicines derived from natural products [64,65].

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

[1] Ali, H.S., Mishra, S. Natural Products as Antiparasitic, Antifungal, and Antibacterial Agents. In: Haridas, M., Abdulhameed, S., Francis, D., Kumar, S.S. (eds) Drugs from Nature: Targets, Assay Systems and Leads. Springer, Singapore. 2024.https://doi.org/10.1007/978-981-99-9183-9_14

[2] Dadashpour M, Mahmoudi H, Rahimi Z, Poodeh RJ, Mousazadeh H, Firouzi-Amandi A, et al. Sustained in vitro delivery of metformin-loaded mesoporous silica nanoparticles for delayed senescence and stemness preservation of adipose-derived stem cells. Journal of Drug Delivery Science and Technology. 2023 Sep 1;87:104769.https://doi.org/10.1016/j.jddst.2023.104769.

[3] Narayanankutty A, Famurewa AC, Oprea E. Natural bioactive compounds and human health. Molecules. 2024 Jul 18;29(14):3372.https://doi.org/10.3390/molecules29143372

[4] Alvarez-Leite JI. The role of bioactive compounds in human health and disease. Nutrients. 2025 Mar 28;17(7):1170.https://doi.org/10.3390/nu17071170

[5] Bontempo P, De Masi L, Rigano D. Functional properties of natural products and human health. Nutrients. 2023 Jun 29;15(13):2961.doi: 10.3390/nu15132961.

[6] Jain D, Almarhoon ZM, Alshahrani AM, Calina D, Sharifi-Rad J, Tripathi A. Natural products as drug leads: exploring their potential in drug discovery and development. Naunyn Schmiedebergs Arch Pharmacol. 2025 May;398(5):4673-4687. doi: 10.1007/s00210-024-03622-6.

[7] Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod. 2020 Mar 27;83(3):770-803. doi: 10.1021/acs.jnatprod.9b01285.

[8] Atanasov AG, Zotchev SB, Dirsch VM; International Natural Product Sciences Taskforce; Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021 Mar;20(3):200-216. doi: 10.1038/s41573-020-00114-z.

[9] Ma YH, Wu MH, Chung LY, Yen CM, Juan YS, Lin RJ. Cestocidal activities of bioactive garlic compounds against Hymenolepis nana. Acta Trop. 2022 Nov;235:106580. doi: 10.1016/j.actatropica.2022.106580.

[10] Shaapan RM, Al-Abodi HR, Alanazi AD, Abdel-Shafy S, Rashidipour M, Shater AF, Mahmoudvand H. Myrtus communis Essential Oil; Anti-Parasitic Effects and Induction of the Innate Immune System in Mice with Toxoplasma gondii Infection. Molecules. 2021 Feb 4;26(4):819. doi: 10.3390/molecules26040819.

[11] Wink M. Evolutionary advantage and molecular modes of action of multi-component mixtures used in phytomedicine. Curr Drug Metab. 2008 Dec;9(10):996-1009. doi: 10.2174/138920008786927794.

[12] Cheng W, Huang Y, Gao H, Bold B, Zhang T, Yang D. Marine Natural Products as Novel Treatments for Parasitic Diseases. Handb Exp Pharmacol. 2025;287:325-393. doi: 10.1007/164_2024_712.

[13] Estrella-Parra EA, Arreola R, Álvarez-Sánchez ME, Torres-Romero JC, Rojas-Espinosa O, De la Cruz-Santiago JA, Martinez-Benitez MB, López-Camarillo C, Lara-Riegos JC, Arana-Argáez VE, Ramírez-Camacho MA. Natural marine products as antiprotozoal agents against amitochondrial parasites. Int J Parasitol Drugs Drug Resist. 2022 Aug;19:40-46. doi: 10.1016/j.ijpddr.2022.05.003.

[14] Nezaratizade S, Hashemi N, Ommi D, Orhan IE, Khamesipour F. A systematic review of anti-Entamoeba histolytica activity of medicinal plants published in the last 20 years. Parasitology. 2021 May;148(6):672-684. doi: 10.1017/S0031182021000172.

[15] Ahmad M, Tahir M, Hong Z, Zia MA, Rafeeq H, Ahmad MS, Rehman S and Sun J .Plant and marine-derived natural products: sustainable pathways for future drug discovery and therapeutic development. Front. Pharmacol. 2025.15:1497668. doi: 10.3389/fphar.2024.1497668

[16] El-Demerdash, A.S., Ras, R., Yusuf, M.S. et al. Unveiling Antioxidant Mechanisms: Novel Gene Expression Profiling Reveals How Carboxylated Cellulose Nanocrystal/ZnO Bio-nanohybrid Counteracts Babesiosoma-Induced Oxidative Stress in Catfish. J Clust Sci36, 223 (2025). https://doi.org/10.1007/s10876-025-02942-8

[17] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.

[18] Jan, H., Shah, M.S., Usman, H., Khan, M.A., Zia, M., Hano, C., & Abbasi, B.H. (2020). Biogenic Synthesis and Characterization of Antimicrobial and Antiparasitic Zinc Oxide (ZnO) Nanoparticles Using Aqueous Extracts of the Himalayan Columbine (Aquilegia pubiflora). Frontiers in Materials.

[19] Faisal, Shah, Hasnain Jan, Sajjad ali Shah, Sumaira Shah, Adnan Ali Khan, Muhammad Taj Akbar, Muhammad Rizwan, Faheem Jan, Wajidullah, Noreen Akhtar, Aishma Khattak and Suliman Syed. “Green Synthesis of Zinc Oxide (ZnO)

Nanoparticles Using Aqueous Fruit Extracts of Myristica fragrans: Their Characterizations and Biological and Environmental Applications." ACS Omega 6 (2021): 9709 - 9722.doi: 10.1021/acsomega.1c00310.

[20] Rahman F, Majed Patwary MA, Bakar Siddique MA, Bashar MS, Haque MA, Akter B, et al. "Green synthesis of zinc oxide nanoparticles using Cocos nucifera leaf extract: characterization, antimicrobial, antioxidant and photocatalytic activity." R Soc Open Sci. 2022 Nov 23;9(11):220858. doi: 10.1098/rsos.220858.

[21] Bornstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. Chichester: John Wiley & Sons; 2009. DOI: 10.1002/9780470743386

[22] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88. DOI: 10.1016/0197-2456(86)90046-2

[23] Gangwar, H., Kumari, P., Jaiswal, V. Phytochemically Rich Medicinally Important Plant Families. In: Swamy, M.K., Kumar, A. (eds) Phytochemical Genomics. Springer, Singapore.2022. https://doi.org/10.1007/978-981-19-5779-6_2

[24] Shukla, Yogesh Kumar, Priyansh Pandey, Janardan Prasad Pandey, Alok Shukla and Jitendra Kumar. "Duckweed extract-mediated green synthesis of ZnO nanoparticles and its antibacterial, antioxidant, and photocatalytic properties." Biomass Conversion and Biorefinery 15 ,2025;21477 - 21491.doi: 10.1007/s13399-025-06706-2

[25] Feifei Li , Jingjing Wu , Xiyan Yue , Yujuan Suo , Jinliang Li , Fanhong Wu , Yanyan Yu , Synthesis and antibacterial activity of 8-ketoberberine derivatives, Food Quality and Safety, Volume 8, 2024, fyae040, https://doi.org/10.1093/fqsafe/fyae040

[26] Zagrebaev AD, Butova VV, Guda AA, Chapek SV, Burov ON, Kurbatov SV, Vinyukova EY, Neganova ME, Aleksandrova YR, Nikolaeva NS, Demidov OP. Optimal synthesis conditions for NBF-modified 8, 13-dihydroberberine derivatives. New Journal of Chemistry. 2024;48(1):268-280.https://doi.org/10.1039/D3NJ04562E

[27] Abdelwahab SI, Mariod AA, Taha MM, Zaman FQ, Abdelmageed AH, Khamis S, Sivasothy Y, Awang K. Chemical composition and antioxidant properties of the essential oil of Cinnamomum altissimum Kosterm.(Lauraceae). Arabian Journal of Chemistry. 2017 Jan 1;10(1):131-5.

[28] Zhang, B.-Q., Li, F.-P., An, J.-X., Ma, L., Jin, Y.-R., Zhang, Z.-J., Qin, L.-L., Wang, D.-T., Jing, C.-X., Chen, G.-S., Mou, G.-L. and Liu, Y.-Q., Design, synthesis and antimicrobial activity of novel berberine derivatives. Pest Manag Sci, 2024,80: 6344-6355. https://doi.org/10.1002/ps.8363

[29] Chopra B, Dhingra AK. Natural products: A lead for drug discovery and development. Phytother Res. 2021 Sep;35(9):4660-4702. doi: 10.1002/ptr.7099.

[30] Ehambarampillai, D., Wan, M.L.Y. A comprehensive review of Schisandra chinensis lignans: pharmacokinetics, pharmacological mechanisms, and future prospects in disease prevention and treatment. Chin Med ,2025,20, 47. https://doi.org/10.1186/s13020-025-01096-z

[31] Tasdemir D, Kaiser M, Brun R, Yardley V, Schmidt TJ, Tosun F, et al. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues. Antimicrob Agents Chemother. 2006;50(4):1352–64. DOI: 10.1128/AAC.50.4.1352-1364.2006

[32] Taoerdahong, H.; Kadeer, G.; Chang, J.; Kang, J.; Ma, X.; Yang, F. A Review Concerning the Polysaccharides Found in Edible and Medicinal Plants in Xinjiang. Molecules 2023, 28, 2054. https://doi.org/10.3390/molecules28052054

[33] Luan F, Zou J, Zhang X, Zeng J, Peng X, Li R, Shi Y, Zeng N. The extraction, purification, structural features, bioactivities, and applications of Schisandra chinensis polysaccharides: A review. nt J Biol Macromol. 2024 Mar;262(Pt 2):130030. doi: 10.1016/j.ijbiomac.2024.130030. [34] Ribeiro PR, Montero IF, Saravia SA, Ferraz VP, Santos RA, MarcÃa JA, Linhares BM. Chemical composition and antioxidant activity in the essential oil of Cinnamomum zeylanicum Nees with medicinal interest. Journal of Medicinal Plants Research. 2020 Jul 31;14(7):326-30.

[35] Li Y, Tan B, Cen Z, Fu Y, Zhu X, He H, Kong D, Wu H. The variation in essential oils composition, phenolic acids and flavonoids is correlated with changes in antioxidant activity during Cinnamomum loureirii bark growth. Arabian Journal of Chemistry. 2021 Aug 1;14(8):103249.

[36] Kuttithodi AM, Narayanankutty A, Visakh NU, Job JT, Pathrose B, Olatunji OJ, Alfarhan A, Ramesh V. Chemical composition of the Cinnamomum malabatrum leaf essential oil and analysis of its antioxidant, enzyme inhibitory and antibacterial activities. Antibiotics. 2023 May 22;12(5):940.

[37] Liu M, Cai M, Ding P. Oligosaccharides from traditional Chinese herbal medicines: a review of chemical diversity and biological activities. Am J Chin Med. 2021;49(3):577-608. doi: 10.1142/S0192415X21500269.

[38] Teng H, He Z, Hong C, Xie S, Zha X. Extraction, purification, structural characterization and pharmacological activities of polysaccharides from sea buckthorn (Hippophae rhamnoides L.): A review. J Ethnopharmacol. 2024 Apr 24;324:117809. doi: 10.1016/j.jep.2024.117809.

[39] Ma JS, Liu H, Han CR, Zeng SJ, Xu XJ, Lu DJ, He HJ. Extraction, characterization and antioxidant activity of polysaccharide from Pouteria campechiana seed. Carbohydr Polym. 2020 Feb 1;229:115409. doi: 10.1016/j.carbpol.2019.115409.

[40] Tasdemir D, Mallon R, Greenstein M, Feldberg LR, Kim SC, Collins K, et al. Aldisine alkaloids from Papua New Guinean sponge Petrosia sp. J Med Chem. 2002 Jan 17;45(2):529-32. doi: 10.1021/jm0102856.

[41] Oliveira SD, De Oliveira E Silva AM, Blank AF, Nogueira PC, Nizio DA, Almeida-Pereira CS, Pereira RO, Menezes-Sá TS, Santana MH, Arrigoni-Blank MD. Radical scavenging activity of the essential oils from Croton grewioides Baill accessions and the major compounds eugenol, methyl eugenol and methyl chavicol. Journal of Essential Oil Research. 2021 Jan 2;33(1):94-103.

[42] Ma JS, Liu H, Han CR, Zeng SJ, Xu XJ, Lu DJ, He HJ. Extraction, characterization and antioxidant activity of polysaccharide from Pouteria campechiana seed. Carbohydr Polym. 2020 Feb 1;229:115409. doi: 10.1016/j.carbpol.2019.115409.

[43] Huang X, Zhang Y, Xie N, Cheng J, Wang Y, Yuan S, Li Q, Shi R, He L, Chen M. Molecular characterization and bioactivities of a novel polysaccharide from Phyllostachys pracecox bamboo shoot residues. Foods. 2023 Apr 23;12(9):1758.doi: 10.3390/foods12091758.

[44] Ansari E, Alvandi H, Kianirad S, Hatamian-Zarmi A, Mokhtari-Hosseini ZB. Research progress on production and biomedical applications of Schizophyllan as a tailor-made polysaccharide: A review. Carbohydr Polym. 2025 Jan 15;348(Pt A):122770. doi: 10.1016/j.carbpol.2024.122770.

[45] Fatima S, Farzeen I, Ashraf A, Aslam B, Ijaz MU, Hayat S, Sarfraz MH, Zafar S, Zafar N, Unuofin JO, Lebelo SL. A comprehensive review on pharmacological activities of pachypodol: A bioactive compound of an aromatic medicinal plant Pogostemon cablin BenthMolecules. 2023 Apr 14;28(8):3469. doi: 10.3390/molecules28083469.

[46] Mrisho II, Musazade E, Chen H, Zhao H, Xing J, Li X, Han J, Cai E. Unlocking the therapeutic potential of patchouli leaves: a comprehensive review of phytochemical and pharmacological insights. Plants (Basel). 2025 Mar 26;14(7):1034. doi: 10.3390/plants14071034.

[47] He R, Cui Y, Li Y, Ge X. Tetrahydroisoquinoline N-methyltransferase from Methylotenera Is an Essential Enzyme for the Biodegradation of Berberine in Soil Water. Molecules. 2022 Aug 25;27(17):5442. doi: 10.3390/molecules27175442.

[48] Abdallah HM, Al-Abd AM, El-Dine RS, El-Halawany AM. P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: a review. J Adv Res. 2015;6(1):45–62. doi: 10.1016/j.jare.2014.11.008

[49] Tian J, Qing Y, Zang M, Long X, Liu G, Ma Y. Genomic insights into phenol degradation by halophilic bacteria and their potential application in saline soil remediation. Sci Rep. 2025 Sep 24;15(1):32740. doi: 10.1038/s41598-025-08348-w.

[50] Park H, Seo SI, Lim JH, Song J, Seo JH, Kim PI. Screening of carbofuran-degrading bacteria Chryseobacterium sp. BSC2-3 and unveiling the change in metabolome during carbofuran degradation. Metabolites. 2022 Mar 1;12(3):219. doi: 10.3390/metabo12030219.

[51] Murzyn A, Popiół J, Gunia-Krzyżak A, Żelaszczyk D, Dąbrówka B, Koczurkiewicz-Adamczyk P, Piska K, et al. Biotransformation of oxybenzone and 3-(4-methylbenzylidene)camphor in Cunninghamella species: Potential for environmental clean-up of widely used sunscreen agents. J Hazard Mater. 2025 Jun 5;489:137544. doi: 10.1016/j.jhazmat.2025.137544.

[52] An JX, Zhang BQ, Liang HJ, Zhang ZJ, Liu YQ, Zhang SY. Antifungal activity and putative mechanism of HWY-289, a semisynthetic protoberberine derivative, against Botrytis cinerea. J Agric Food Chem. 2024 Apr 10;72(14):7716-7726. doi: 10.1021/acs.jafc.3c08858.

[53] Tamarozzi F, Halliday A, Gentil K, Hoerauf A, Pearlman E, Taylor MJ. Onchocerciasis: the role of Wolbachia bacterial endosymbionts in parasite biology, disease pathogenesis, and treatment. Clin Microbiol Rev. 2011;24(3):459–68. doi: 10.1128/CMR.00057-10

[54] Mou H, Shi J, Chen J, Hu D. Synthesis, antibacterial activity and mechanism of new butenolides derivatives containing an amide moiety. Pestic Biochem Physiol. 2021 Oct;178:104913. doi: 10.1016/j.pestbp.2021.104913.

[55] Olea AF, Rubio J, Sedan C, Carvajal D, Nuñez M, Espinoza L, Llovera L, Nuñez G, Taborga L, Carrasco H. Antifungal activity of 2-allylphenol derivatives on the Botrytis cinerea strain: assessment of possible action mechanism. Int J Mol Sci. 2023 Mar 31;24(7):6530. doi: 10.3390/ijms24076530.

[56] Maung CE, Lee HG, Cho JY, Kim KY. Antifungal compound, methyl hippurate from Bacillus velezensis CE 100 and its inhibitory effect on growth of Botrytis cinerea. World J Microbiol Biotechnol. 2021 Aug 22;37(9):159. doi: 10.1007/s11274-021-03046-x.

[57] Kunova A, Pinna C, Ghosh S, Dozio D, Pizzatti C, Princiotto S, Cortesi P, Dallavalle S, Pinto A. Stilbenoids as antifungals to counteract rice blast pathogen Pyricularia oryzae. ACS Agric. Sci. Technol. 2024, 4, 1, 43–50. https://doi.org/10.1021/acsagscitech.3c00275

[58] Sundar RDV, Arunachalam S. 2, 4-Di-tert-butylphenol from Endophytic Fungi Fusarium oxysporum attenuates the growth of multidrug-resistant pathogens. Front Microbiol. 2025 Jun 10;16:1575021. doi: 10.3389/fmicb.2025.1575021.

[59] BF Biondo P, Carbonera F, Zawadzki F, UR Chiavelli L, J Pilau E, N Prado I, V Visentainer J. Antioxidant capacity and identification of bioactive compounds by GC-MS of essential oils from spices, herbs and citrus. Current Bioactive Compounds. 2017 Jun 1;13(2):137-43.

[60] An J, Lan W, Fei Q, Li P, Wu W. Synthesis, antifungal, and antibacterial activities of novel benzoylurea derivatives containing a pyrimidine moiety. Molecules. 2023 Sep 7;28(18):6498. doi: 10.3390/molecules28186498.

[61] Kia E, Hoseinifar SH, Mazandarani M, Jafari V, Safari R, Paolucci M. Effects of artichoke (Cynara scolymus) polyphenolic extract on growth, antioxidants and some immune parameters in common carp (Cyprinus carpio). BMC Vet Res. 2025 Mar 17;21(1):177. doi: 10.1186/s12917-025-04619-w.

[62] Chandra H, Yadav A, Prasad R, Kalra SJS, Singh A, Bhardwaj N, et al.Fungal endophytes from medicinal plants acting as natural therapeutic reservoir,The Microbe. 2024; 3:100073.https://doi.org/10.1016/j.microb.2024.100073.

[63] Dhanisha SS, Drishya S, Guruvayoorappan C. Fruit Extract of Pithecellobium dulce (FPD) ameliorates carrageenan-induced acute inflammatory responses via regulating pro-inflammatory mediators. Journal of food biochemistry. 2020 Aug;44(8):e13329.

[64] Samrit T, Changklungmao N, Sangpairoj K, Buddawong A, Kueakhai P, Chuanboon K, Sobhon P, Pranweerapaiboon K. Ethanolic extract of Parkia speciosa pods exhibits antioxidant and anti-inflammatory properties in lipopolysaccharide-induced murine macrophages by inhibiting the p38 MAPK pathway. Heliyon. 2024 Oct 30;10(20).

[65] Thao TT, Tu PT, Men TT. A Comparative Study on Polyphenol, Flavonoid Content, Antioxidant and AntiInflammatory Capacity of Different Solvent Extract from Portulaca oleracea in Carrageenan-Induced Paw Edema in Mice. Tropical Journal of Natural Product Research. 2023 Oct 1;7(10).

[66] Formagio AS, de Oliveira Junior PC, Volobuff CR, Kassuya CA, Ferreira DC, Cardoso CA, Sarragiotto MH, Pereira ZV. Anti-inflammatory activity of methanolic extract and an alkaloid from Palicourea crocea (Sw.) roem and schult. Inflammation. 2019 Jun 15;42(3):1045-55.

[67] Gupta S, Chaturvedi P, Kulkarni MG, Van Staden J. A critical review on exploiting the pharmaceutical potential of plant endophytic fungi. Biotechnol Adv. 2020 Mar-Apr;39:107462. doi: 10.1016/j.biotechadv.2019.107462.

[68] Zouari Bouassida K, Makni S, Tounsi A, Jlaiel L, Trigui M, Tounsi S. Effects of Juniperus phoenicea Hydroalcoholic Extract on Inflammatory Mediators and Oxidative Stress Markers in Carrageenan-Induced Paw Oedema in Mice. BioMed Research International. 2018;2018(1):3785487.

[69] Mali P, Thamke V, Aware C, Surywanshi S, Rane M, Patil D, Shinde B, Jadhav J. Mucuna atropurpurea seed extract attenuates inflammation by modulation of inflammatory cytokine response and improving the antioxidant system in experimentally-induced carrageenan in rats. Pharmacological Research-Natural Products. 2025 Sep 1:100358.

[70] Wang M, Carver JJ, Phelan VV, Sanchez LM, Garg N, Peng Y, et al. Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. Nat Biotechnol. 2016;34(8):828–37. doi: 10.1038/nbt.3597.