

Mini Review

Elatol as a Marine-Derived Lead Compound for Infectious Disease Therapy: Antiparasitic, Antibacterial, Antifungal and Antiviral Perspectives

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Abstract

The increasing prevalence of antimicrobial resistance and the limited therapeutic options available for several neglected infectious diseases highlight the need to identify structurally diverse bioactive molecules. Marine organisms represent a valuable source of chemically complex secondary metabolites, among which the halogenated sesquiterpene elatol has attracted attention because of its broad spectrum of anti-infective activities. Elatol, particularly the enantiomeric forms isolated from *Laurencia* species and associated marine organisms, has demonstrated activity against protozoan parasites, helminths, free-living amoebae, bacteria, fungi and viruses. Its antiparasitic effects are especially relevant, with reported activity against *Trypanosoma cruzi*, *Leishmania amazonensis*, *Schistosoma mansoni* and *Naegleria fowleri*. Mechanistic studies suggest that mitochondrial dysfunction, oxidative imbalance, membrane damage, impairment of adhesion and induction of cell-death pathways may contribute to its biological effects. However, the available evidence remains predominantly based on *in vitro* assays, crude extracts or incompletely characterized stereo chemical forms. Differences in potency between enantiomers, variability among producing species and the limited information regarding pharmacokinetics, selectivity, metabolism and *in vivo* efficacy represent major barriers to therapeutic development. This article critically discusses the anti-infective potential of elatol, emphasizing its most relevant biological activities, possible mechanisms of action and the experimental steps required to advance this marine natural product from a promising bioactive compound toward a validated drug-discovery lead.

Keywords: Elatol, *Laurencia*, Marine natural products, Antiparasitic activity, Antimicrobial resistance, *Trypanosoma cruzi*, *Leishmania amazonensis*, *Naegleria fowleri*, Drug discovery

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Introduction

Infectious diseases remain a major global health problem, particularly in regions where access to effective therapies is limited and antimicrobial resistance is increasing. The therapeutic challenge is particularly significant for neglected tropical diseases, opportunistic infections and pathogens for which current treatments are associated with toxicity, poor efficacy, complex administration or emerging resistance. These limitations have stimulated the search for new chemical scaffolds capable of acting against pathogens through mechanisms that differ from those of conventional anti-infective drugs [1, 2].

Marine organisms are an important source of structurally unusual secondary metabolites [3]. Their chemical diversity is associated with ecological interactions involving predation, competition, fouling, microbial infection and chemical defence [4]. Among marine-derived

metabolites, halogenated compounds are of particular interest because the incorporation of bromine or chlorine can influence lipophilicity, molecular conformation, membrane interaction and target recognition [5].

Elatol is a halogenated sesquiterpene mainly associated with red algae of the genus *Laurencia* and related marine organisms [5, 6]. Historically, its biological evaluation has been heavily focused on its ecological role as a marine chemical defense and its general cytotoxicity against cancer cell lines [5]. However, within the pharmacological domain, its potential as a broad-spectrum anti-infective agent; encompassing antiparasitic, antibacterial, antifungal and antiviral activities; represents its most extensively documented therapeutic application [7-9]. Despite this promise, its biological profile remains heterogeneous and strongly dependent on the producing organism, extraction procedure, chemical composition, stereochemistry and experimental model [5].

Therefore, the main objective of this article is to critically evaluate the therapeutic potential of elatol against infectious diseases, distinguishing between demonstrated biological activity, plausible mechanisms and aspects that remain insufficiently investigated.

Chemical and pharmacological considerations

Elatol is a halogenated sesquiterpene characterized by a chemically constrained hydrophobic framework and the presence of a brominated functionality [6]. These structural features may facilitate interactions with biological membranes and hydrophobic regions of proteins. However, the same physicochemical properties that may favour membrane penetration can also contribute to nonspecific toxicity, poor aqueous solubility, high plasma-protein binding or extensive metabolic transformation [10].

An important limitation in the elatol literature is the incomplete reporting of stereochemistry. Different studies have evaluated (+)-elatol, (–)-elatol or compounds for which the enantiomeric identity was not clearly specified. This is not a minor analytical issue. Enantiomers can differ substantially in molecular recognition, target affinity, metabolism, distribution and toxicity [11, 12]. Consequently, biological results obtained with different stereo chemical forms should not automatically be considered interchangeable.

A second limitation concerns the frequent use of crude extracts or fractions containing elatol as a major constituent [7, 13]. Although such preparations may show relevant activity, the observed effects cannot necessarily be attributed exclusively to elatol. Synergistic or antagonistic interactions with other metabolites may contribute to the biological response. For drug-development purposes, activity should therefore be confirmed using chemically authenticated and stereo chemically defined elatol.

Antiparasitic activity

Activity against *Trypanosoma cruzi*

Among the most compelling findings reported for elatol is its activity against the protozoan parasite *Trypanosoma cruzi*, the causative agent of Chagas disease. The reviewed studies reported different sensitivities according to the parasite developmental stage. Elatol showed an IC_{50} of approximately 45.4 μM against epimastigotes, whereas substantially higher potency was observed against trypomastigotes and amastigotes, with reported IC_{50} values of approximately 1.38 and 1.01 μM , respectively [14]. This stage-dependent activity is relevant because trypomastigotes are involved in transmission and dissemination, whereas intracellular amastigotes are responsible for parasite persistence and tissue damage. A compound that is active against both extracellular and intracellular forms may offer a pharmacological advantage over agents that act predominantly at one stage [15].

Mechanistic observations suggest that elatol induces mitochondrial dysfunction and redox imbalance. Reported effects include mitochondrial membrane depolarization, increased mitochondrial superoxide production, loss of membrane and DNA integrity, formation of autophagic vacuoles and reduction in cell volume. These findings are consistent with the involvement of oxidative stress, mitochondrial damage and regulated cell-death pathways [8, 16]. Nevertheless, the mechanistic interpretation should remain cautious. Mitochondrial depolarization and reactive oxygen species production may represent primary molecular events or secondary consequences of membrane disruption. Further studies using genetically or pharmacologically validated targets are required to establish whether mitochondria are the principal target or one component of a broader cytotoxic process.

Activity against *Leishmania amazonensis*

Elatol has also demonstrated activity against *Leishmania amazonensis*, a causative agent of cutaneous and mucocutaneous leishmaniasis. Reported IC_{50} values were approximately 4.0 μM against promastigotes and 0.45 μM against amastigotes [17]. The greater activity against the intracellular amastigote stage is particularly interesting because this form is responsible for infection of mammalian macrophages.

Some studies reported no evident toxicity to host macrophages under the experimental conditions employed [17, 18]. However, this observation should not be interpreted as definitive evidence of therapeutic selectivity. Selectivity indices depend on the host-cell model, exposure time, assay endpoint and concentration range. In addition, macrophages are not the only relevant cells for evaluating systemic toxicity.

Comparisons among studies are complicated by differences in the enantiomeric identity of elatol. In another investigation, activity was reported in $\mu\text{g/mL}$ rather than μM , with values of approximately $9.7 \pm 1.2 \mu\text{g/mL}$ against promastigotes and $4.5 \pm 0.9 \mu\text{g/mL}$ against amastigotes [18]. Such differences highlight the need for standardized assays using the same stereo chemical form, parasite strain, host-cell system and experimental endpoint.

The antileishmanial potential of elatol may be associated with its ability to affect parasite membranes, redox homeostasis or intracellular survival. However, direct evidence for a defined molecular target is currently limited. Future studies should determine whether elatol interferes with mitochondrial function, thiol metabolism, sterol biosynthesis, membrane integrity or parasite-macrophage interactions.

Activity against helminths and free-living amoebae

Elatol has also been investigated against the trematode *Schistosoma mansoni*. Reported effects include mortality of cercariae and inhibition of oviposition in adult worms. Molluscicidal activity against *Biomphalaria glabrata*, the intermediate host of *S. mansoni*, has also been described. These observations suggest that elatol could have dual relevance by affecting both parasite stages and transmission-related organisms [19]. However, molluscicidal activity raises important ecological and toxicological questions. A compound intended for environmental application must be evaluated against non-target aquatic organisms, including fish, crustaceans, algae and beneficial invertebrates. The therapeutic and environmental applications of elatol should therefore be considered separately.

Particularly notable activity has been reported against the free-living amoeba *Naegleria fowleri*, an etiological agent of primary amoebic meningoencephalitis. The (+) -enantiomer showed IC_{50} values of approximately 1.08 and 1.14 μM against two reference strains, whereas the (–) -enantiomer was markedly less potent, with IC_{50} values close to 37–38 μM . This difference provides strong evidence that stereochemistry can substantially influence anti-amoebic activity [20].

The reported inhibition of trophozoite adhesion to extracellular matrix proteins is particularly relevant. Adhesion is an important step in host colonization and tissue invasion, and its inhibition may reduce pathogenicity even when complete parasite killing is not achieved [21]. Nevertheless, the anti-adhesion effect should be confirmed using physiologically relevant extracellular matrix models and, ideally, *in vivo* infection systems.

Antibacterial and antifungal potential

Elatol has demonstrated antibacterial activity against a range of marine and human-associated bacteria. Studies have reported inhibition of several marine bacterial species and a subset of human pathogenic isolates, including *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Salmonella species*, *Proteus mirabilis* and *Flavobacterium helmiphilum* [22]. In another study, elatol inhibited *Escherichia coli*, *Salmonella typhi* and *Vibrio cholerae*, with reported MIC and MBC values of approximately 100 and 250 $\mu\text{g/mL}$, respectively [23].

These results indicate that elatol possesses antibacterial activity, but its potency is variable and generally lower than that of many clinically established antibiotics. In addition, activity differs considerably among *Laurencia* species and extracts. Some preparations showed little or no activity against particular pathogens, whereas others exhibited moderate or strong effects [7, 24].

The variability may reflect differences in elatol concentration, co-occurring metabolites, stereochemistry, extraction solvent, bacterial strain and assay methodology. Accordingly, antibacterial activity should not be generalized to all *Laurencia* extracts or to all elatol preparations [5].

Antifungal effects have also been reported. Elatol-containing preparations showed moderate activity against *Ustilago violacea*, *Fusarium oxysporum* and *Candida albicans*, and stronger activity against *Mycotypha microspora* and *Eurotium repens* [22, 25]. Extracts containing elatol also inhibited *Colletotrichum lagenarium* in some experimental settings but were inactive against *Aspergillus flavus* [26].

These findings support the possibility of developing elatol-derived compounds for selected fungal or agricultural applications. Nevertheless, the distinction between fungistatic and fungicidal activity, the activity against resistant clinical isolates and the toxicity toward mammalian cells remain insufficiently characterized.

Antiviral activity

The antiviral evidence for elatol is less extensive than the antiparasitic evidence but remains promising. An extract of *Laurencia dendroidea* in which (–)-elatol was a major constituent showed selective antiherpetic activity against acyclovir-resistant herpes simplex virus. Inhibition values of approximately 97.5% for HSV-1 and 43.8% for HSV-2 were reported, with a CC_{50} of approximately 48.2 $\mu\text{g/mL}$ [27].

These observations are relevant because resistance to acyclovir and related nucleoside analogues represents a clinical problem, particularly in immune compromised patients [9]. However, the use of an extract complicates the attribution of antiviral activity specifically to elatol. The activity must be reproduced using purified, stereo chemically defined compound and compared with the complete extract.

Computational studies have also examined possible interactions between elatol and viral proteins, including SARS-CoV-2 RNA-dependent RNA polymerase [28]. Such studies may help generate hypotheses regarding possible molecular interactions, but docking scores cannot establish antiviral efficacy [29]. Weak or moderate predicted binding should not be interpreted as evidence of therapeutic potential without biochemical and cellular confirmation.

Future antiviral studies should include time-of-addition experiments, viral entry and replication assays, evaluation of viral resistance, cytotoxicity in relevant host cells and confirmation using authentic virus systems where appropriate.

Challenges for therapeutic development

Despite its broad biological profile, several barriers must be overcome before elatol can be considered a realistic therapeutic candidate.

First, the current evidence is dominated by *in vitro* studies. Activity in cell-based assays does not necessarily predict efficacy in animals or humans. Elatol must be evaluated in appropriate infection models to determine whether effective concentrations can be achieved at the site of infection without unacceptable toxicity.

Second, pharmacokinetic information is scarce. Key parameters such as absorption, plasma stability, tissue distribution, metabolic half-life, bioavailability and excretion remain insufficiently defined. The hydrophobic and halogenated nature of elatol may limit aqueous solubility and systemic exposure [30].

Third, selectivity requires more rigorous assessment. Cytotoxicity should be examined in multiple human cell types, including hepatocytes, renal cells, cardiomyocytes and relevant immune cells. Genotoxicity, mitochondrial toxicity and effects on inflammatory pathways should also be investigated.

Fourth, the influence of stereochemistry must be systematically addressed. Both enantiomers should be prepared or isolated in pure form and compared using standardized assays. Their relative potency, toxicity, metabolic stability and pharmacokinetic behaviour may differ substantially [5, 11, 12].

Finally, sustainable supply is essential. Large-scale harvesting of *Laurencia* species is unlikely to represent a suitable long-term strategy. Cultivation of producing organisms, microbial production, semi-synthesis or total synthesis should be explored to guarantee reproducible supply and reduce ecological pressure [31].

Conclusions and future perspectives

Elatol represents a chemically distinctive marine natural product with a broad anti-infective profile. Its most compelling activities have been reported against protozoan parasites, particularly *T. cruzi*, *L. amazonensis* and *N. fowleri*. The compound also shows antibacterial, antifungal and antiviral effects, although these activities are more variable and require additional validation.

The available evidence suggests that mitochondrial dysfunction, oxidative imbalance, membrane damage and inhibition of parasite adhesion may contribute to its biological effects. However, these mechanisms remain incompletely defined and should not yet be considered validated molecular modes of action [5].

The therapeutic relevance of elatol will depend on moving beyond descriptive bioactivity studies toward a structured drug-discovery programme. Such approach should include stereo chemically controlled compound preparation, target-based mechanistic studies,

standardized potency and selectivity assays, pharmacokinetic characterization, formulation development, *in vivo* efficacy and toxicological evaluation.

At present, elatol should be considered a promising marine-derived lead compound, rather than a clinically validated anti-infective drug. Its development may be particularly attractive for infections associated with drug resistance or limited therapeutic options, provided that future studies establish a sufficient therapeutic window, reproducible activity and acceptable pharmacological properties.

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