

Pharmacological potential of *Ulva* species: a valuable resource

Abstract

With the emergence of new diseases, the increase of pathogenic strains resistance and the apprehensiveness of synthetic compounds side effects, there is a constant need to find natural and low toxicity drug candidates. Seaweeds are rich source of original and bioactive natural substances. In particular, species of the genus *Ulva* have been demonstrated to metabolize biomolecules with pharmacological potential. This mini review present some of the biological properties reported for *Ulva* spp.

Keywords: green seaweed; *Ulva*, antibacterial, anti-inflammatory, cytotoxic, antiviral, Antiprotozoal, antioxidant

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Introduction

Ulva Linnaeus genus (Ulvaceae, Ulvales) is an ubiquitous genera widely distributed in oceans and estuaries. Currently, 128 species (accepted taxonomically) have been listed all around the world.¹ Individuals of this genus are characterized by a broad range of environmental tolerance, high growth rate and photosynthetic activity leading to a relatively abundant natural biomass. Additionally, in a rich nutrient environment, these species can proliferate into green tides, making available important amounts of biomass.² On the other hand, the successful results obtained for *Ulva* spp. cultivation in integrated multitrophic aquaculture (IMTA) systems³ or in land based aquaculture coupled with waste water bioremediation [4] allows promising development for sustainable raw material supply. This last decade, scientific interest for this taxonomic genus has increased.⁵ The cosmopolitan nature of *Ulva* spp., its development patterns and plasticity, among other reasons make it a good model organism to study algal growth, development and morphogenesis.⁶ From an economic perspective, the use of *Ulva* species for different applications has been largely described: bioremediation,⁷ bioenergy,⁸ food and feed.⁹ A biorefinery approach for industrial exploitation of *Ulva* constituents have been proposed.¹⁰ To realize an economically feasible value chain, cascading valorization of both protein and non-protein seaweed constituents is required. We here present a mini review of pharmacological perspectives for species of the genus *Ulva*.

Antibacterial and antifungal

The constant increase of pathogenic microbes resistance to existing antibiotics led to the continual need to find new antibacterial candidates. Marine algae derivatives seem to be good candidates in novel, antibacterial drug discovery.¹¹ Antimicrobial properties of *Ulva* species have been widely studied. Crude extracts of *Ulva* spp. samples often displayed positive antibacterial and/or antifungal activities for samples collected from different parts of the world.¹²⁻¹⁴ In some studies, the active compound have been isolated and identified. As for example, two guaiane sesquiterpenes derivatives from *Ulva fasciata* have been described with significant antibacterial activity against *Vibrio parahaemolyticus*.¹²

Recently¹⁵ demonstrated that time of harvesting of the algae can influence the antibacterial activity. In fact, these authors reported that

U. lactuca methanolic extracts inhibit a range of clinically relevant *Staphylococcus* strains. Moreover, the study showed that lunar phase of macroalgae harvest significantly impacts antimicrobial activity, suggesting that antimicrobial properties can be maximized by manipulating time of algal harvest.

It's worth to mention the use of *Ulva* extracts to synthesize nanoparticles.^{16,17} This technique, is a novel and innovative area of research for biomedical applications. As for example, the study of antifungal potency of silver (Ag-NP) synthesized by *Ulva rigida* aqueous extract tested on different human pathogens and with significant activity obtained on *Aspergillus fumigates*.¹⁸

Anti-inflammatory

Anti-inflammatory activity of species from *Ulva* genus have been reported in different studies. *Ulva rigida* collected from Tunisian coasts showed a significant inhibition of phospholipase A2 activity (PLA2 of *Apis mellifera*). The bioassay guided fractionation of dichloromethane/methanol extract led to the isolation and identification of sulfoquinovosyldipalmitoyl glyceride as the active molecule with an IC50 of 125µM.¹⁹

A steroid, the 3-O-β-D glucopyranosyl-stigmasta-5,25-dien isolated from *Ulva lactuca*, showed topical antiinflammatory activity when tested on the mouse ear oedema assay.²⁰ Organic extracts of *Ulva conglobata* displayed neuroprotective and anti-inflammatory effects on murine hippocampal and microglial cells.²¹ *U. reticulata* presented potent analgesic and anti-inflammatory effects in both acetic acid-induced writhing and hot plate-induced pain models, without significant toxic effect at highest possible doses.²² More recently, sulfated polysaccharide fraction from *Ulva lactuca* (collected from atlantic coasts from Brazil) displayed significant analgesic and anti-inflammatory action.²³ The authors demonstrated that the antinociceptive and anti-inflammatory action occurs through a peripheral mechanism: the bradykinin pathway.

Cytotoxic

There are several studies that demonstrate the cytotoxic potential of *Ulva* species. Methanol extract of *Ulva fasciata* collected from Indian coasts exhibited significant cytotoxic activity on hepatocyte carcinoma cells lines (Hep-G2) with optimum inhibition obtained at

170µg/ml.²⁴ Additionally, ethanolic extract of *Ulva rigida* collected from Marmara Sea shores possess a strong antigenotoxic, chemo-protective effects on mutagenic agent MMC *in vitro*.²⁵ These authors conclude that the obtained results for *U. rigida* extract (antigenotoxic and anti-clastogenic) are of great significance in radioprotection and thus may be useful in human pathological conditions. More recently, cytotoxic activity against three human cancer cell lines (HepG2, MCF7, and Hela) have been attributed to ulvan fraction extracted from *Ulva lactuca* collected from Vietnam coasts.²⁶

Antiviral

First mention of antiviral properties of *Ulva* spp. have been made in early nineties,²⁷ with a bioactive sphingosine from *Ulva fasciata* collected from West coast of India. The extract showed antiviral activity against Semeliki Forest Virus (SFV) at 20mg/mouse/7 days.

Ulva rigida water extracts inhibited significantly the reproduction of influenza virus (A/Aichi (H3N2)) also in fertile eggs.²⁸ The study pointed that *Ulva rigida* extract reduced the mortality rate of white mice in experimental influenza infection when applied orally and extended the time of survival. Extracts of *Ulva fasciata*, collected from Brazilian coasts have been evaluated on the replication of human metapneumovirus (HMPV).²⁹ The results demonstrated that the majority of the extracts possess virucidal activity and therefore have the ability to interact with the extracellular viral particles and prevent the infection. Ulvan, that are sulfated polysaccharide, have been described to have antiviral properties. The ulvan antiviral activity was tested using syncytia formation against paramyxovirus infection, exhibiting significant activity with an IC₅₀ of 0.1µg/ml.³⁰ In addition, significant antiviral activities against Herpes simplex virus type-1 from *U. armoricana* extract have been described.³¹ The revealed activities were correlated to high amounts of rhamnose, uronic acids and sulfate groups which are the main constituents of ulvans.

Antiprotozoal

Even though antiprotozoal properties of seaweeds is understudied, some interesting findings can be reported for *Ulva* spp. Seaweed crude extracts of *Ulva reticulata* and *Ulva rigida* have been documented to exhibit strong *in vitro* activity against the promastigote form of *Leishmania major* with IC₅₀ of 64.75µg/ml and 65.69µg/ml respectively.³² Leishmanicidal potential of different marine and fresh macrophytes have been reported³³ highlighting the antiprotozoal potential of *Ulva lactuca* extract. In fact, *U. lactuca* displayed the most potent activity against axenic amastigotes of *Leishmania donovani* with IC₅₀=5.9ml/ml and efficiently inhibited the FabI enzyme. The antiprotozoal activity of four green marine algae collected from British coasts, among which two *Ulva* species (*U. intestinalis* and *U. lactuca*) have been prospected.³⁴ All crude extracts showed positive antiprotozoal activity against *Trypanosoma brucei rhodesiense* while a moderate trypanocidal activity against *Trypanosoma cruzi* have been obtained for *U. lactuca* extract.

Other

Last but not least, the antioxidant property of species of the genus *Ulva* has to be described since this makes them candidates for several pathologies in which the oxidative stress is incriminated (neurological disorders, atherosclerosis, hypertension, acute respiratory distress, idiopathic pulmonary fibrosis, asthma, cancer, etc.). The antioxidant properties of *Ulva* spp. have been studied from species collected from different parts of the world.^{10,35,36} As for example, the antioxidant

activity, contents of total phenolics and flavonoids were quantified in the methanolic extracts of four *Ulva* species.³⁷ *Ulva clathrata* demonstrated the greater antioxidant potential with a low IC₅₀ of 0.881mg/ml corresponding also to the highest phenolic and flavonoid content (5.080mg GAE/g and 33.094mg RE/g respectively). In addition, the free radical scavenging effects of hot water extract of *Ulva reticulata* obtained on animal model studies highlighted the possible use of this species to reduce hepatic oxidative stress.³⁸

Conclusion

This mini review just sketches the potential of *Ulva* species for pharmacological use. This report reinforces the claims that seaweeds, and in particular species of the genus *Ulva*, can be used in health industry. Additionally, *Ulva* species, with their wide range of application fields, their relatively abundant natural biomass, that can also be cultivated in a sustainable way, constitute good candidates for Blue Biotechnology development.

Conflicts of interest

Author declare that there is no conflict of interest.

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