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*Proceeding*

# Algal extracts as preventive mechanism for mycotoxins development†

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**Abstract:** Macroalgae and microalgae are two sources of natural ingredients that are of interest for industrial sectors because of their multiple potential applications. Algal extracts are known to be rich in valuable compounds such as fatty acids, minerals, and secondary metabolites, among others. Bioactivities disclosed for these biocompounds include their antifungal capacity through the growth inhibition of foodborne pathogens and spoilage microorganisms such as Aspergillus sp., Fusarium sp. or Penicillium sp. Apart from their antifungal activity, algal extracts can minimize the toxicity of mycotoxins through two molecular mechanisms: their antioxidant and their chelating properties. Antioxidants may reduce the toxic effect of mycotoxins whereas algae bioadsorption due to their rich composition in macromolecules (polysaccharides or proteins) may have the capacity to bind mycotoxins, prevent their metabolism, and facilitate their systemic release. These three mechanisms involved in the antifungal activity of micro- and macroalgal extracts will be critically assessed along this review in order to disclose their potential application as key tools in food industry and public health. The use of algae extracts as antifungals and detoxifiers may underline their use of natural additives with no side effects associated that may represent an alternative to extend foodstuffs shelf-life and prevent the occurrence of mycotoxins, especially aflatoxin B1, aflatoxin M1 and ochratoxin A. Therefore, this review is aimed to evaluate the multiple benefits that algal extracts may provide to reinforce food safety, reduce food disposal and prompt the utilization of underused biomass such as algae.

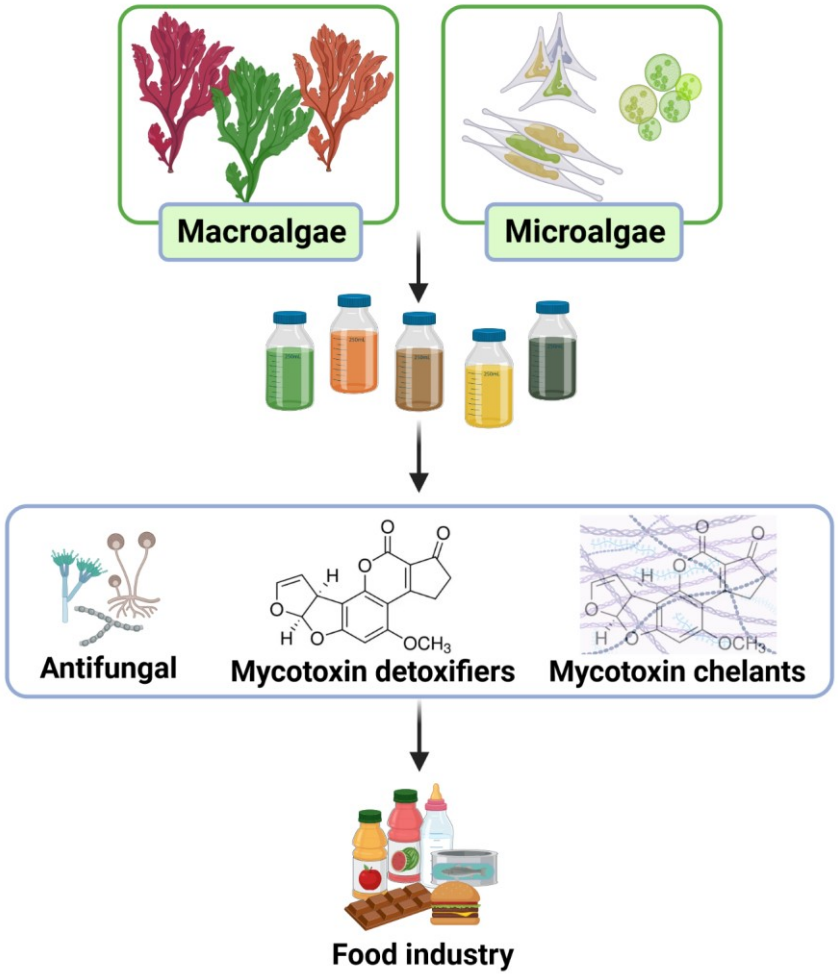
**Keywords:** algae; seaweed; additive; preservative; mycotoxins; shelf-life; food safety

## 1. Introduction

Marine macroalgae and microalgae have served as nutritional or medical ingredients for thousands of years [1]. Nowadays, science is trying to fully understand their chemical composition to optimize all their associated properties since it is well established that algae biomass is a rich and underexploited source of bioactive compounds [2]. The photosynthetic nature of both macroalgae and microalgae have attracted the attention of industrially sectors. By one hand, they can be easily harvested or cultured. By other hand, their photosynthetic capacity points to their biochemical richness. Indeed, algae matrixes are well-known to be rich in valuable compounds such as proteins, polysaccharides, fatty acids, minerals, vitamins and secondary metabolites, such as phenolic compounds or pigments among others [3]. This rich chemical profile is associated to a wide range of bioactivities such as antioxidant, anti-inflammatory, anti-cancer or antifungal, among others [4]. Their antifungal capacity may inhibit the growth of foodborne pathogens and spoilage microorganisms such as the mycotoxin producers *Aspergillus* sp., *Fusarium* sp. or *Penicillium* sp. The growth inhibition of these fungal species may have two synergic benefits: avoid food spoilage and prevent toxin exposure to mycotoxins. Among them, aflatoxins

and ochratoxin A are included as some of the most relevant mycotoxins regarding food safety and regulation frameworks [5]. Apart from the antifungal capacity of algae biomolecules they may provide two additional benefits in already contaminated with mycotoxins food matrixes. They may minimize the toxicological effects of the mycotoxins through their antioxidant, anti-inflammatory, anti-cancer properties. Besides, their rich content in minerals and macromolecules such as polysaccharides or globular proteins may point them as potential detoxifier agents.

Therefore, this review is aimed to present the three pathways involved in the antifungal and detoxifying capacities of algae biomolecules regarding three specific mycotoxins (aflatoxins B1and M1 and ochratoxin A) and three specific genera of fungus (*Aspergillus* sp., *Fusarium* sp. and *Penicillium* sp.).




## 2. Antifungal activity

Different algae species have showed antifungal activity against *Aspergillus* sp., *Fusarium* sp. or *Penicillium* sp. although the inhibition growth degree is highly dependent on several factors. Among the most relevant parameters involved in the variability of the antifungal response are included the fungal and algae species selected, the algae concentration and application mode, or the solvent used for the biocompounds extraction. Indeed, this vast variability of published results strongly hinders their comparison.

Five brown algae were assessed as inhibitors of the mycelial growth of *Aspergillus flavus*. The dried biomass of *Sargassum despiense, Turbinaria decurrens, Dilophus ligulatus, Cystoseira myrica* and *Padina pavonica* was added into the culture medium at six different concentrations were tested (10, 30, 50, 100, 150 and 200 g/mL). The most effective species were *T. decurrense, D. ligulatus,* and *P. pavonia.* Indeed, the use of the essential oils extracted

from these three algae (0.2 mg/mL) fully inhibited the growth of *Aspergillus flavus* and so the formation of aflatoxin. Their unsaponifiable matter (0.2 mg/mL) showed a 6-days delay of the mycelial growth and even though it did not totally inhibit when cultured was further extended it depressed aflatoxin formation at rates higher than 70%. Finally, even though the inhibition capacity of fatty acids (0.2 mg/mL) was less aggressive with rates between 25 and 37% the reduction of aflatoxin formation reached values higher than 85% [6]. Later, published works showed results using at least one of these previously tested species. Even though, results are based on the utilization of algae extracts instead of the addition of the algae powder into the culture medium. For instance, the aqueous extracts of *Halimeda opuntia, Jania rubens* and *T. decurrens* was prepared at concentration of 100 mg/mL. All three extracts showed effective growth suppression against *Aspergillus parasiticus* and *A. flavus* with percentages of inhibition that oscillated around 76 to 78 %. Besides, all three extracts showed very relevant detoxifying properties displaying total or nearly total (>90%) elimination of aflatoxins [7]. Another work used two same algae species but different organic solvents and extract concentration. Authors used petroleum ether for extracting biomolecules from *H. opuntia* and *T. decurrens* and ethyl acetate for extracting *Padina pavonica*. All three extracts were finally suspended in dimethyl sulfoxide (DMSO) at 50 mg/ml although different concentrations were applied for each assay. The *H. opuntia* extract at 3 mg/mL was the most promising one since it retarded the most the fungal growth and showed inhibition areas of 16 mm for *A. flavus* and 22 mm for *A. niger* while the respective inhibition zones that *P. pavonica* displayed were 9 and 7 mm and those of *T. decurrens* were 10 mm for both fungi [8]. Other effective antifungal algae species is *Sargassum muticum*. Its methanolic extract at 300 mg/mL showed inhibition growth of 4 pathogenic fungi: *Fusarium moniliforme* (30 mm), *Pythium ultimum* (26 mm), *A. flavus* (24 mm) and *Macrophomina phaseolina* (23 mm) [9].

Apart from macroalgae, microalgae were also demonstrated to be effective antifungal agents, such as biocompounds present in *Nannochloropsis* sp. and *Spirulina* sp. Free phenolic acids, with the chlorogenic acid as the most abundant representative, displayed an efficient reduction of mycelial growth three *Fusarium* species: *F. graminearum*, *F. meridionale* and *F. asiaticum*. The growth of this *Fusarium* complex fungal pathogens was effectively reduced when using free phenolic acids of *Spirulina* sp.at a rate of 0.5 cm/day ($EC_{50}$ of 34 μg/mL) and at a rate of 0.8 cm/day for *Nannochloropsis* sp ($EC_{50}$ of 50 μg/mL) [10]. Similarly, a methanolic extract of *Spirulina* sp. in a 1:5 (w:v) ratio was tested as antifungal agent against *Penicillium verrucosum*. The phenolic content, mainly represented by gallic and caffeic acids, inhibited the growth of *P. verrucosum* mycelia from the first day and reached its maximal value (20%) at the 9$^{th}$ day of incubation. Even though this result was not too high, it was higher than the one reached by calcium propionate (16%). Indeed, *Spirulina* phenolic extract was more effective than this chemical preservative since it did not inhibit *P. verrucosum* growth until the 5$^{th}$ incubation day. Besides, phenolic compounds from *Spirulina* maintained the ochratoxin concentration under 0.5 ng/g for 5 days and reduced its presence in 56% and 29% at the 7$^{th}$ and 9$^{th}$ day against the control, respectively [11].

## 3. Detoxifying bioactivities

The restoration capacity of algae biocompounds has been demonstrated *in vivo* against different mycotoxins. Along this section we present an example of the assessment of restoration of three different animal models when applying diverse algae extracts as co-treatment of aflatoxins B1, M1 or ochratoxin A. Despite this vast variability in the experimental approaches, results are mainly coincident in regards of restoration parameters.

*Ulva prolifera* extracts obtained through an aqueous enzymatic treatment were analytically determined and have a minimal content of 48% of polysaccharides with a MW around 5,000 Da. The most abundant representatives include rhamnose, glucuronic acid, glucose, galactose, and xylose. The co-administration of 2,500 mg/kg of *U. prolifera* polysaccharides and 100 μg/kg of aflatoxin B1 to male broilers improved the reduction of

weight that bursa of Fabricius had suffer in animals only treated with aflatoxin B1 and restored the apoptotic cells found at this immune organ. Regarding the molecular pathways, the administration of *U. prolifera* polysaccharides reversed the disequilibrium caused by aflatoxin B1 both at Nrf2 and mitochondrial apoptotic signaling pathways. Therefore, *U. prolifera* polysaccharides upregulated the activities and expression of antioxidant enzymes (superoxide dismutase, catalase or glutathione peroxidase) and associated proteins (Nrf2, HO-1, p38MAPK, Bcl-2) while downregulated the expression of proteins associated to apoptosis (caspase-3 and Bax) [12].

The aqueous extract obtained from *Amphora cofeaeformis* was evaluated as antifungal but also its capacity to revert the toxic effect of aflatoxin M1. *A. cofeaeformis* extracts displayed antifungal capacity against all tested fungi but it was stronger against *Fusarium culmorum* and *F. graminearum* than against *Aspergillus ochraceus* and *Aspergillus flavus.* Besides, in this work male albino rats treated with aflatoxin M1 (80 μg/kg) and *A. cofeaeformis* extracts (20 mg/kg) reverted many of the negative effects exerted by aflatoxin M1. For instance, the use of *A. cofeaeformis* extracts ameliorated the toxic effects that aflatoxin M1 had on feed intake, body weight, and relative liver weight. In a similar way, liver and kidney in animals treated with aflatoxin M1 showed strong alterations along the specific indicators (aspartate and alanine transaminases, urea, and creatinine). Animals co-treated with *A. cofeaeformis* extracts did not recover the normality in these indicator levels, but they were deeply amortiguated Besides, as it was described for broilers treated with *U. prolifera,* rats treated with *A. cofeaeformis* showed an amelioration on the aflatoxin M1-affected levels of glutathione transferase, catalase, super oxidase dismutase, and a decrease in the levels of malondialdehyde. Finally, at histopathological level the aflatoxin M1 tissue affections (hepatocytes-necrosis foci and congested blood sinusoids) were nearly reversed in animal co-treated with *A. cofeaeformis* extracts [13].

The efficiency of the pigment astaxanthin obtained from *Haematococcus pluvialis* was tested against the ochratoxin A-induced renal oxidative stress and its mechanism of action. The animal model used, C57BL/J mice, was treated with 100 mg/kg/day of astaxanthin and 2h later with ochratoxin A at 5 mg/kg/day. The reduction in the body weight induced by ochratoxin A in mice was restored in the group treated with both ochratoxin A and astaxanthin. This group also showed a reduction in the levels of the specific renal markers, serum uric acid and blood urea nitrogen, that ochratoxin A had previously raised. Along the histological results, the tissular anatomy was restored in the group treated with ochratoxin A and astaxanthin with no glomerular swelling, renal cystic space visible, no cellular degeneration in the tubular epithelium and decreased necrosis. Similarly, at cellular level, the disorder that ochratoxin A caused in the mitochondrial cristae and nucleus were not detected when astaxanthin was also administered. In terms of apoptotic markers, the levels augmented by ochratoxin A were significantly reduced in the group additionally treated with astaxanthin. In this sense, and as observed in the other animal models, the levels of the antioxidant enzymes (superoxide dismutase, catalase or glutathione peroxidase) were reduced while malondialdehyde was increased due to the administration of ochratoxin A. However, the additional administration of astaxanthin reversed these responses. Finally, and as previously pointed out, the binomial treatment of the mycotoxin with an antioxidant booster, normalize the effects that the unique treatment with ochratoxin A had altered. Indeed, astaxanthin triggered the upregulation of the mRNA levels of the NRF2 signaling pathway and downregulated those of KEAP1 [14].

**3.Physical detoxification**

Algae are a well-known source of minerals and minerals are well-known adsorbent agents. Among the most studied marine organisms, diatoms (Diatomeae) stand out due to their unique properties. These marine unicellular microalgae have silicon dioxide ($SiO_2$) shells that create cavities and canals that provide them with high porosity. Even though diatoms have low cation exchange capacity 42.75 mEq/100 their small particle size (<12 μm for 95% of total mass) confer them with high adsorption rates. Based on these features

they have been widely applied as natural adsorbent agents with detoxifying capabilities against mycotoxins. For instance, when diatoms were used as adsorbent agents for aflatoxins, they showed an index of 95% independently of the pH used. However, for ochratoxin A this index was reduced to 67% and it just adsorbed the toxins when tested under acid conditions (pH 3) [15]. Even though, diatoms have been further tested as adsorbent agents, other species are commencing to be tested. That is the case of *Eucheuma cottonii* one of the main industrial sources of κ-carrageenan. Therefore, their remaining residues which are mainly composed of insoluble dietary fiber are considered to get reused for different applications. In this work, residues of *E. cottonii* were finely pulverized at different particle sizes (from ~45 μm to ~420 μm) and tested as adsorbent agents against aflatoxin B1. Adsorption rates fluctuated between 62% and 88% depending on the particle size. The maximal adsorption was obtained with ~150 μm *E. cottonii* and so further assessments were performed using different concentrations of the alga and toxin, incubation times, temperatures and pH conditions. The best adsorption rate for 2 μg/mL of aflatoxin B1 was obtained with *E. cottonii* of ~150 μm particle size at a concentration of 20 mg/mL incubated for 15 min at a pH of 7 and a temperature of 25°C [16]. Similarly, the seaweed *Lithothamnium calcareum* was demonstrated to have adsorption capacity for aflatoxin B1. In this work two approaches were followed. Firstly, when toxin concentration was fixed (1 μg/mL) it was observed a linear pattern. Higher algal concentrations triggered higher adsorption rates, independently of the pH (2 mg/mL of *L. calcareum* absorbed 77% of aflatoxin B1). Secondly, the concentration of aflatoxin B1 was determined based on the amount of seaweed (μg toxin per mg *L. calcareum*). In this scenario, the lowest seaweed content 0.5 mg/mL provided the maximal adsorption with a value of 0.78 μg/mg at pH 6 and a value of 0.62 μg/mg at pH 3 [17]. Finally, a recent work has suggested a synergic solution to remove *Chlorella* sp. from water by using the filamentous of *Aspergillus niger* as coagulants. The adhesion of algal and fungi cells was induced by electrostatic forces that lead to a flocculation rate of 70-80%. This removal of microalgae from water bodies may represent an alternative and double solution to prevent eutrophic issues but also to flocculate mycotoxic fungi from drinking waters by simple precipitation [18].

Besides, algae are well-known sources of macromolecules such as proteins or polysaccharides. And even though, β-D-glucans had been suggested to interact and bind mycotoxins, those from yeast origin have mainly tested whereas no algae results have been found so far [19]. However, other molecules obtained from algae have been pointed out as potential binders of mycotoxins. Their main role as binders was the reduction of the mycotoxins' bioavailability and bioaccessibility and so they hinder their systemic absorption. In a previously cited work, an extract of *A. cofeaeformis* that contained at least nine phenolic compounds with catechin and p-coumaric as the major representatives, was used to fortify milk. Authors suggest that the *A. cofeaeformis*-fortified milk may trap aflatoxins which would limit the toxin bioavailability [13]. Another report pointed to chlorophyll and chlorophyllin as two natural inhibitors of the intake of aflatoxin B1. Indeed, their administration provide chemoprotective effects in rat liver and colon exposed to aflatoxin B1. One of the mechanisms described to be involved is the physical blockage that chlorophyllin induced by forming tight complexes with aflatoxin B1. This scaffold was suggest to reduce the bioavailability and to minimize the tumor incidence [20].

**Table 1.** Summary of antifungal activities of different macroalgae and microalgae species.

| **Macroalgae** | | | |
|---|---|---|---|
| **Chlorophyta** | | | |
| **Species** | **Compound Assays** | **Bioactivity** | **Ref** |
| *Ulva prolifera* | Polysaccharides *In vivo* (broilers) | Reversion of histological and cellular effects of AFB1 in bursa of Fabricius | [12] |

| | | | |
|---|---|---|---|
| *Caulerpa prolifera* | *In vivo* (Sprague Dawley rats) | Improvement of food intake, body weight, decrease of inflammation markers at hepatic level | [17] |
| *Halimedia opuntia* | Aqueous extract | Inhibition growth of *A. parasiticus* and *A. flavus.* Aflatoxins detoxifier. | [7] |
| *H. opuntia* | Petroleum ether extract | Inhibition growth of *A. flavus* (16 mm) and *A. niger (*22 mm*)* | [8]. |
| **Rhodophyta** | | | |
| *Laurencia obtusa* | *In vivo* (Sprague Dawley rats) | Improvement of food intake, body weight, decrease of inflammatory serum and hepatic levels | [17] |
| *Jania rubens* | Aqueous extract | Inhibition growth of *A. parasiticus* and *A. flavus.* Aflatoxins detoxifier. | [7] |
| *Eucheuma cottonii* | Insoluble dietary fiber | Adsorbent agent against AFB1 (62 – 88 %) | [16] |
| *Lithothamnium calcareum* | Algae | Adsorbent agent against AFB1 (77 %) | [17] |
| **Phaeophyta** | | | |
| *S. despiense, T. decurrens, D. ligulatus, C. myrica* and *P. pavonica* | Fatty compounds from essential oils | Fully inhibition of *Aspergillus flavus* growth and aflatoxin1 formation | [6] |
| *T. decurrens* | Aqueous extract | Inhibition growth of *A. parasiticus* and *A. flavus.* Aflatoxins detoxifier. | [7] |
| *T. decurrens* | Petroleum ether extract | Inhibition growth of *A. flavus* (9 mm) and *A. niger (*17 mm) | [8]. |
| *P. pavonica* | Ethyl acetate extract | Inhibition growth of *A. flavus* and *A. niger (*10 mm) | [8]. |
| *S. muticum* | Methanolic extract | Inhibition growth of *F. moniliforme*, *Pythium ultimum*, *A. flavus* and *Macrophomina phaseolina* (>23 mm) | [9] |
| **Microalgae** | | | |
| *Nannochloropsis* sp. and *Spirulina* sp. | Phenolic content: chlorogenic acid | Reduction growth of *F. graminearum, F. meridionale* and *F. asiaticum*. | [10] |
| *Spirulina* sp. | Phenolic content: gallica and caffeic acids | Inhibition of mycelia growth of *Penicillium verrucosum* | [11] |
| *Amphora cofeaeformis* | Aqueous extract *In vivo* (male albino rats) | Inhibition growth of *F. culmorum, F. graminearum, A. ochraceus* and *A. flavus.* Reversion of AFM1 effects (body weight, liver and kidney alterations) | [13] |
| *Haematococcus pluvialis* | Astaxanthin *In vivo* (C57BL/J mice) | Reversion of OTA effects (body weight, kidney and cellular alterations: oxidative and apoptotic signals) | [14] |
| *Chlorella* sp. | Algae culture | Removal by coagulation of *A. niger* from water bodies | [18]. |

[1] Abbreviations: AFB1: aflatoxin B1; AFM1: aflatoxin M1; OTA: ochratoxin A

## 4. Conclusions

Nowadays, customers claim for a stronger presence of natural additives and preservatives in commercial products due to the side effects associated to chemical molecules. Food industry is continuously seeking for innovative and natural compounds that may serve as alternative food preservatives and offer a better safety profile. In this context, macroalgae and microalgae represent two underused, sustainable and natural matrixes to obtain a huge variability of molecules with already demonstrated bioactivities. Among them, the antimicrobial capacity has been repeatedly tested although their specific utilization as antifungals

for combatting mycotoxins has been not so much exploited. Nevertheless, algae have been proved to represent a real approach to prevent the growth of *Aspergillus* sp., *Fusarium* sp. and *Penicillium* sp. and to minimize the synthesis of aflatoxins and ochratoxin A. Besides, the inclusion of algae extract as part of animal feed has been observed to provide strong protection against the negative effects of the mycotoxins. These results seem to be reachable independently of the mycotoxin involved and the animal model tested. Finally, the application of algae as complexing agents that reduce the bioavailability and bioaccessibility was found to have positive effects both in *in vitro* and *in vivo* assays. Therefore, based on the findings the application of algae as food or feed preservatives or additives seems to provide multiple benefits to reinforce food safety and reduce food disposal.

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