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Metabolites from invasive pests inhibit mitochondrial complex II: A potential strategy for the treatment of human ovarian carcinoma?

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ABSTRACT

The red pigment caulerpin, a secondary metabolite from the marine invasive green algae *Caulerpa cylindracea* can be accumulated and transferred along the trophic chain, with detrimental consequences on biodiversity and ecosystem functioning. Despite increasing research efforts to understand how caulerpin modifies fish physiology, little is known on the effects of algal metabolites on mammalian cells.

Here we report for the first time the mitochondrial targeting activity of both caulerpin, and its closely related derivative caulerpinic acid, by using as experimental model rat liver mitochondria, a system in which bioenergetics mechanisms are not altered. Mitochondrial function was tested by polarographic and spectrophotometric methods.

Both compounds were found to selectively inhibit respiratory complex II activity, while complexes I, III, and IV remained functional. These results led us to hypothesize that both algal metabolites could be used as antitumor agents in cell lines with defects in mitochondrial complex I. Ovarian cancer cisplatin-resistant cells are a good example of cell lines with a defective complex I function on which these molecules seem to have a toxic effect on proliferation. This provided novel insight toward the potential use of metabolites from invasive *Caulerpa* species for the treatment of human ovarian carcinoma cisplatin-resistant cells.

1. Introduction

Recent researches suggest that the study of well-defined chemical entities contained by invasive species can contribute both to a better understanding of the biological processes associated with marine invasions and to propose a possible exploitation of vast invasive biomasses to obtain valuable chemicals of interest in pharmacology [1]. Some of those studies concerned about the compound caulerpin (CAU), a bioactive bisindolic alkaloid (Fig. 1) introduced in the Mediterranean along with both the invasive alga *Caulerpa taxifolia*, a species included in the list of the 100 world's worst invasive species listed by the International Union for Conservation of Nature (IUCN), and its congeneric *Caulerpa cylindracea* (previously known as *Caulerpa racemosa* var. *cylindracea*). *C. cylindracea*, in particular, has become the favorite food of a native fish species of considerable commercial importance, the edible white sea bream *Diplodus sargus*. It is noteworthy that, as a consequence of the *C. cylindracea*-based diet, the fish accumulates CAU in its tissues [2–5].

Although CAU, which is one of the main lipophilic components of the above invasive algae, already showed a panel of biological activities [[1], and references therein], there are still no clear evidence of a direct impact of CAU on the fish health, and/or potential risks for the human health as a result of fish consumption. More specifically, it has been observed that, in *D. sargus*, the exposure to *C. cylindracea* modulates the activity of peroxisomal Acyl-CoA oxidase, the first and rate-determining step of the peroxisomal β-oxidation of fatty acids, causing an alteration in lipid metabolism [6]. The increased activity of Acyl-CoA oxidase, observed in fish with medium and high content of CAU, could also mechanistically explain changes observed in the fatty acids levels of fish naturally

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