Metabolites from invasive pests: a threat to the functioning of marine ecosystems and an opportunity for the treatment of ovarian cancer

Mitochondria are cellular cytoplasmic organelles, which take part in a variety of cellular metabolic functions. However, these organelles are generally known as the energy-generating powerhouses of the cell, because they play a fundamental role in the production of the main energy carrier molecule, such as the adenosine triphosphate (ATP). ATP is produced through a sophisticated mechanism requiring the coordinated operation of two main components, both located in the inner mitochondrial membrane: the respiratory chain, constituted by complexes I, II, III and IV, and the ATP-synthase.

In addition to their basic role in ATP synthesis, mitochondria are a major source of reactive oxygen species (ROS), which are key mediators of cellular physiology and pathology. Changes in ROS concentration may have deleterious consequences since ROS, when low, are unable to regulate several biochemical reactions; when high, they are unable to provide a controlled regulation of cellular functioning and produce a condition known as oxidative stress.

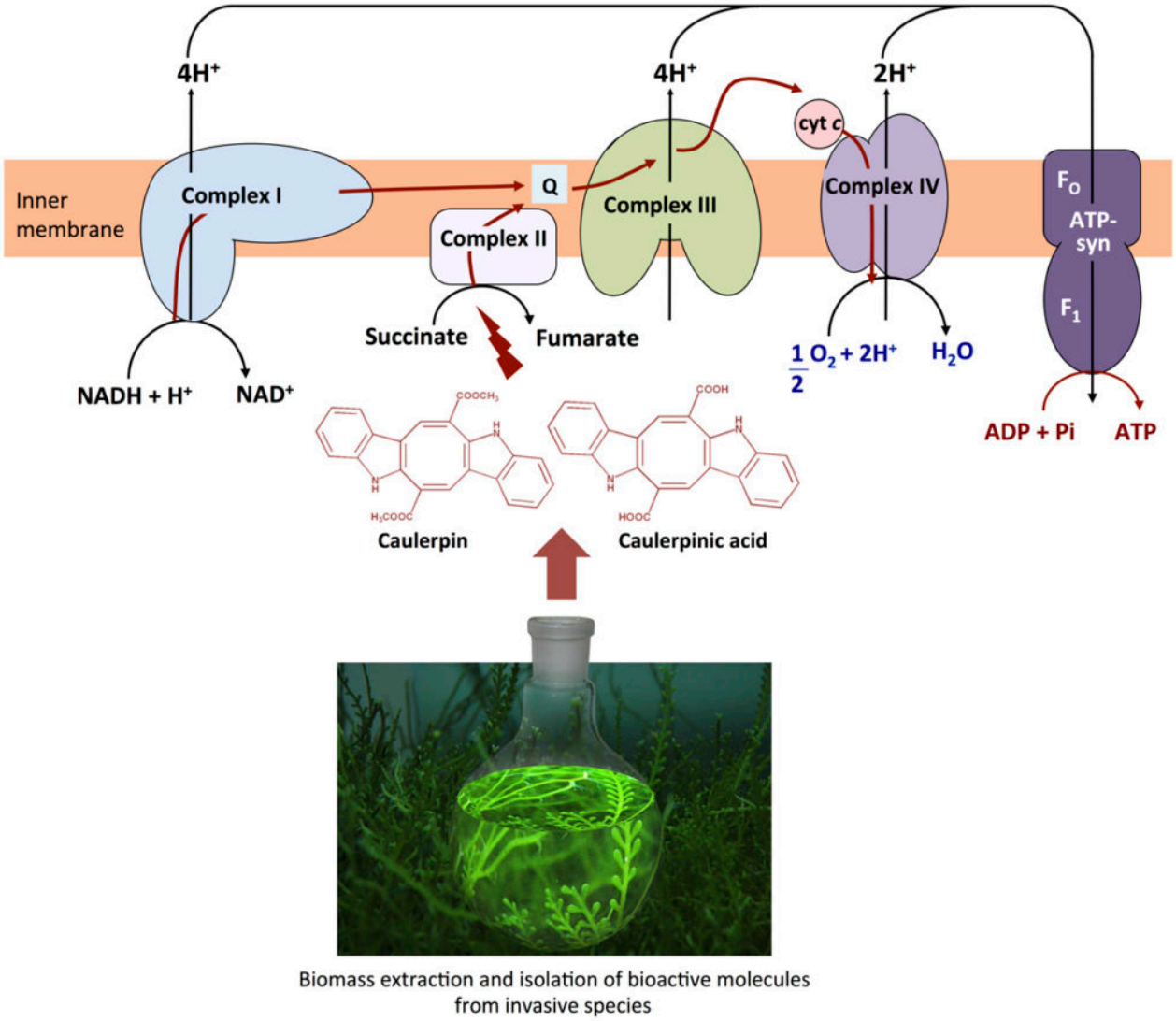

Fig. 1.

In this study we have explored the role of mammalian mitochondria as potential pharmacological targets of secondary metabolites of *Caulerpa cylindracea*, an alien green algal species, which invaded the Mediterranean Sea over the last twenty years, causing the most severe change of sea-bottom landscape occurred in the last decades.

Caulerpa cylindracea produces secondary metabolites that possess several biological activities; the most abundant of these metabolites is the red pigment caulerpin, an alkaloid that has the potential to cause alteration in mitochondrial functionality. Previous studies demonstrated that caulerpin accumulates in the tissues of sea-bream *Diplodus sargus* (as a consequence of the *Caulerpa cylindracea*-based diet) inducing an alteration in lipid metabolism and a condition of

oxidative stress.

Starting from these evidences, we investigated the mitochondria targeting activity of both caulerpin, and its closely related derivative caulerpinic acid. Mitochondria isolated from rat liver have been selected as model system in which physiological mechanisms of cellular energy production are not altered, in order to elucidate whether and how algal molecules affect mitochondrial function. Both compounds were found to selectively inhibit respiratory complex II activity, while complexes I, III and IV remained functional (Fig. 1). Moreover, in this experimental model, inhibition of complex II by algal metabolites did not stimulate ROS release.

The obtained results lead us to hypothesize an effect of algal metabolites in completely blocking mitochondria respiration and, in turn, energy production and proliferation in cells with defects in mitochondrial complex I. Ovarian cancer cells resistant to cisplatin, a chemotherapy drug, are a good example of cell lines with a defective complex I function, on which algal molecules seem to have a toxic effect on proliferation. We found that, also in these cells, caulerpin and caulerpinic acid impair mitochondrial respiration at level of complex II. Differently from cells sensitive to cisplatin, the most used anticancer drug, only cisplatin-resistant cells showed a significant increase in mitochondrial ROS production, suggesting that algal metabolites could be good candidates for the treatment of chemoresistant cancer cells. The effect exerted by caulerpin was stronger than that exerted by caulerpinic acid.

Therefore, by exploring the molecular mechanism by which algal compounds affect mitochondria function, our study provide a preliminary insight into the potential use of *Caulerpa cylindracea* metabolites, which can be accumulated and transferred along the trophic chain with detrimental consequences on biodiversity and ecosystem functioning, for the prospective treatment of human ovarian cancer treatment. This should encourage researchers toward a possible pharmacological exploitation of high added value chemical products from invasive pests huge biomasses, paving the way for making the control of invasive species profitable.

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