



## Essay

## Rethinking the role of dietary antioxidants through the lens of self-medication



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The regulation of oxidative status is critical because fluctuations in the production of aerobic by-products relative to the antioxidant capacity of the organism can have strong fitness consequences. Towards this end, organisms can use endogenous antioxidant defences, which are efficient at combating oxidative attacks but may be costly and need time to be activated. As food items vary in their antioxidant content, animals have the possibility to optimize their oxidative status, rapidly and at a low cost, by selecting food in their environment according to its antioxidant content. However, the actual role of dietary antioxidants remains contentious because their consumption entails inconsistent effects. We propose that this inconsistency stems from the lack of methodical examination of the cost–benefit ratio related to antioxidant intake, which should reflect the actual need for antioxidants by organisms. We apply the framework of self-medication to the regulation of oxidative status, which necessarily implies assessing the physiological needs of consumers. We formulate conditions under which self-medication is likely to occur, and show that most conditions are met for the regulation of oxidative stress. Linking self-medication to oxidative ecology therefore provides a novel mechanistic framework on how oxidative stress can be regulated; it highlights the transient nature of food selection upon the regulation of oxidative status, and thereby shows why indiscriminant supplementation of dietary antioxidants is likely to be misguided.

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Using oxygen as the terminal electron acceptor in the reduction of carbon-based fuels has allowed organisms to produce much more energy than with any anaerobic pathway, and thus has given aerobic organisms a tremendous adaptive advantage (Sessions et al. 2009). The use of oxygen is also associated with the production of reactive oxygen species (ROS) that are involved in many essential physiological pathways such as immune defence or cellular signalling (Dröge 2002; Dowling & Simmons 2009). However, the chemical instability of ROS constitutes a major undesirable side-effect of the aerobic metabolism, as they may cause damage to lipids, proteins and DNA, leading to cellular and organismal ageing (Haenold et al. 2005). These damaging effects are highly fitness relevant as they can be related to reduced fertility and survival (Aitken & Roman 2008; Noguera et al. 2012), and therefore need to be accurately controlled.

Organisms can avoid oxidative damage by adjusting the synthesis and the use of endogenous antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) to the production of

ROS. They may also be able to modify the quality of cellular structures by replacing components susceptible to oxidative damage (e.g. polyunsaturated fatty acids) by more resistant components (e.g. monounsaturated fatty acids; Pamplona & Costantini 2011). Even if these strategies may be efficient in combating ROS excesses, they are nevertheless likely to incur a cost to the organism owing to the synthesis of new molecules from endogenous resources. This could explain why only organisms in good condition may be able to mount appropriate levels of antioxidant defences to counteract ROS production (Garratt & Brooks 2012; Fletcher et al. 2013), and thus avoid situations of oxidative stress (i.e. imbalance between ROS production and antioxidant defences, Costantini & Verhulst 2009). Moreover, the activation of this endogenous antioxidant machinery is likely to take time and may therefore be inappropriate for a rapid response to a rapid increase in ROS production. This probably explains why an acute oxidative challenge leads to a transient increase in oxidative damage that disappears after a while (Han et al. 2008), presumably once endogenous antioxidant defences are activated. To compensate for the cost and latency inherent to an endogenous antioxidant response, organisms have the possibility to use another line of defence: ingesting exogenous dietary antioxidants such as vitamin C, carotenoids, vitamin E or polyphenols (Catoni et al. 2008a).

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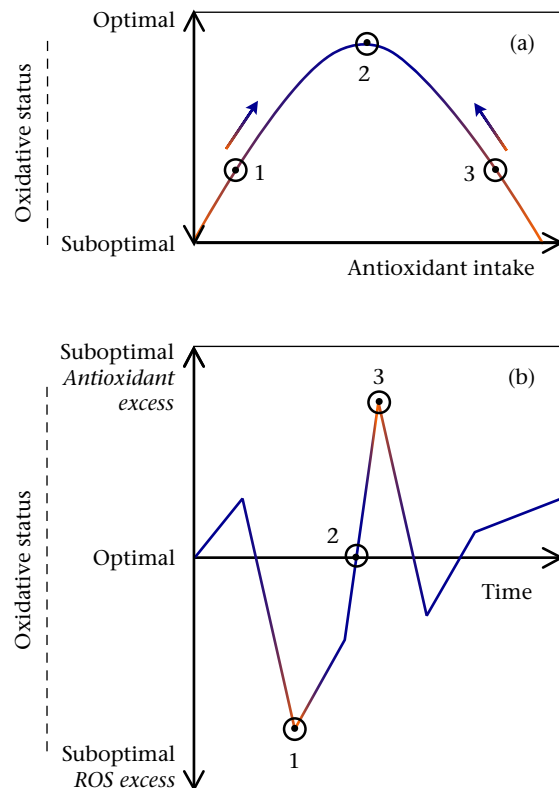
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Because food items vary in their antioxidant contents, the consumption of specific food items can affect the oxidative status of animals (Cohen et al. 2009). Only a few studies have investigated food selection in relation to its content in dietary antioxidants, and some have shown that animals clearly preferentially consume food with high antioxidant content (Schaefer et al. 2008; Catoni et al. 2008b; Senar et al. 2010; Zhang et al. 2012) while others do not (Johnson et al. 2006; Larcombe et al. 2008; Catoni et al. 2011; Giraudeau et al. 2012; Alan & McWilliams 2013). Yet, these studies are currently difficult to interpret because antioxidant supplementation in the diet has produced mixed results. For example, supplementing animals' diet with antioxidants has contradictory effects on growth (De Ayala et al. 2006; Larcombe et al. 2010), muscular performance (Blount & Matheson 2006; Larcombe et al. 2008) and survival (Le Bourg 2001; Gems & Doonan 2009). These contradictory results can primarily be explained by three factors. First, organisms may reduce their endogenous defences in response to a high intake of dietary antioxidants (Selman et al. 2006; Ristow et al. 2009). Second, the consumption of dietary antioxidants that may exceed that physiological compensation can be associated with deleterious effects (Bouayed & Bohn 2010), suggesting that consuming dietary antioxidants can lead to stronger deviation from optimal oxidative status than not consuming them at all (Fig. 1). Third, the supplementation of one class of antioxidants alone, without the recycling action of other antioxidants (through their reduction potential), may be inefficient at correcting oxidative stress and may even worsen it (Catoni et al. 2008a; Monaghan et al. 2009). These three facts are at the basis of the controversy on the significance of dietary antioxidants. We propose that the main limitation for resolving the contentious effects of dietary supplementation is the lack of control by investigators of the organisms' actual needs for antioxidants. Considering the consumption of dietary antioxidants from the perspective of self-medication, which necessarily implies knowing the need for antioxidants of the organism, is therefore expected to contribute to advancing the controversy on the significance of dietary antioxidants.

## SELF-MEDICATION AND OXIDATIVE STRESS

### Concept of self-medication

Organisms regularly face suboptimal physiological states that they can correct with a variety of behavioural and physiological strategies. For instance, to combat infection, animals can employ behavioural avoidance, social immune mechanisms, self-medication, behavioural thermoregulation, anorexia, symbiont-mediated immunity or fecundity compensation (Parker et al. 2011). The use of a specific strategy depends on the balance between the associated benefits and costs relative to other strategies. This suggests that a prerequisite for self-medication to evolve and be used by organisms is that it has to be less costly than other strategies, such as the use of endogenous immune defences during infection. Self-medication occurs in many taxa (from insect larvae to great apes and elephants) presumably because of this relative low cost (Povey et al. 2008; Forbey et al. 2009; Singer et al. 2009; Hart 2011; Parker et al. 2011). Yet, this does not mean that self-medication is devoid of any costs. For instance, medicating resources may be of poor nutritive value compared to food items usually consumed by animals, as is the case for self-medicating great apes (Huffman 1997). In that case, self-medication is expected to be costly, as self-medicating animals would need to devote time and energy to search for and consume medicating resources of poor nutritive value (and potentially rare in the environment) at the expense of feeding on their usual energy-rich resources. Therefore, food selection for pharmaceutically active



**Fig 1.** Variation in oxidative status as a function of (a) antioxidant intake and (b) time. Blue indicates optimal oxidative status or tolerable variation from the optimum. Orange indicates situations when the deviation from the optimum is excessive so that the oxidative status needs to be corrected. '1' illustrates a situation of oxidative stress caused by an excessive production of ROS (relative to the antioxidant capacity), '2' illustrates a situation associated with optimal oxidative status (i.e. balanced antioxidant defences relative to ROS production), and '3' illustrates a situation of oxidative stress caused by an excessive intake of dietary antioxidants (relative to ROS production). The optimization of the oxidative status can therefore occur through opposite strategies: in '1', the consumption of food items rich in antioxidants is expected to be increased to correct oxidative stress (arrow 1), while in '3', food items rich in antioxidants are expected to be counterselected (arrow 3). In '2' no changes in the intake of dietary antioxidant should occur. This example illustrates the lability of oxidative status, and therefore the transient need for antioxidants, which may make self-medication unnoticed by investigators if the oxidative status of the studied organisms is not accurately assessed.

compounds is expected to overrule food selection for energy requirements only when the benefits of ingesting pharmaceutically active compounds exceed those of ingesting energy-rich resources. However, because food items typically vary in various dimensions (e.g. several macronutrients, many micronutrients), pharmaceutically active compounds of poor nutritive value can also be found in combination with energy-rich compounds within the same food item (thus making the detection of self-medicating strategies less obvious by observers). Therefore, the notion that medicating resources are of poor nutritive value is a possible but not necessary condition for self-medication.

A further requirement for self-medication to evolve is that it needs to entail fitness benefits. For instance, infected woolly bear caterpillars, *Grammia incorrupta*, wood ants, *Formica paralugubris*, or monarch butterflies, *Danaus plexippus*, which all use plant derivatives to combat pathogens, have a higher survival rate than infected individuals with no possibility of self-medication (Chapuisat et al. 2007; Singer et al. 2009; Lefèvre et al. 2010). However, even though the consumption of milkweed increases the life span of monarch butterflies when they are infected by protozoan parasites, it decreases their life span in the absence of

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