

Invited Review

The good and bad of antioxidant foods: An immunological perspective

Johanna M. Gostner^a, Kathrin Becker^b, Florian Ueberall^a, Dietmar Fuchs^{b,*}^a Division of Medical Biochemistry, Biocenter, Innsbruck Medical University, Innsbruck, Austria^b Division of Biological Chemistry, Biocenter, Innsbruck Medical University, Innsbruck, Austria

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ABSTRACT

Maintenance of redox homeostasis plays a central role in both health and preventing disease, and antioxidant foods are thought to exert protective effects by counteracting oxidative stress. The term “dietary antioxidant” implies a classical reducing or radical-scavenging capacity, but more data on the *in vivo* bioactivity of such compounds are needed. Indeed, several dietary antioxidants activate signaling cascades that lead to effects that extend beyond radical scavenging, such as the induction of endogenous cryoprotective mechanisms and detoxification. Currently, the overall uptake of antioxidants with diet exceeds actual needs, as food additives that include vitamins, colorants, flavoring agents, and preservatives are often also relatively strong antioxidants. Chronic antioxidative stress favors adverse effects, such as the suppression of T helper (Th) type 1 immune responses and consequent activation of Th2 responses that support the development of asthma, allergies, and obesity. In this context, we discuss the immunoregulatory pathway of tryptophan breakdown by enzyme indoleamine 2,3-dioxygenase (IDO), which represents a central regulatory hub for immune, metabolic, and neuroendocrine processes. Activation of IDO-mediated tryptophan metabolism is strongly redox-sensitive and is therefore susceptible to modulation by dietary components, phytochemicals, preservatives, and drugs.

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1. Introduction

Regular consumption of fruits and vegetables has been thought to minimize the risk of developing chronic diseases because of their rich bioactive compound contents, such as vitamins, minerals, phenolics, terpenoids, etc. Following the use of antioxidant-rich plant extracts in traditional medicines, in which botanical remedies have been used for both the treatment of ailments and severe disorders (Schmidt et al., 2008), a wealth of data regarding phytochemical-enriched dietary supplements and nutraceuticals are now available, which suggest the achievement of well-being and health promotion (Schmidt et al., 2007). Several of the beneficial effects of plant secondary metabolites, such as flavonoids and polyphenols, have been attributed to their antioxidant activities, including the potential to counteract inflammation (Gupta et al., 2013; Romano et al., 2013). Recently, there is interest in using spices and herbs not only for their flavoring properties, but also for their health-modulating properties, as they have been shown to interfere with signaling processes that are important for cell survival, drug metabolism, immune responses, and metabolic homeostasis (Aggarwal, 2010; Kaefer and Milner, 2011; Sung et al., 2011).

Another source of food-derived antioxidants are the additives contained in foodstuffs and drinks, such as vitamins, colorants, flavoring agents, and preservatives, which are added to enhance the shelf life of products or impact consumer behavior. Limiting microbial proliferation or preventing the oxidation of molecules in the microenvironment implies that such additives will affect all surrounding cells and biomolecules in an unbiased manner, although with different sensitivities. Therefore, adverse effects on human health cannot be excluded generally (EMEA, 2003). Indeed, recent data have linked excessive antioxidant uptake to the suppression of T helper (Th) type 1 immune responses thereby promoting Th2 reactions, leading to the potential to develop allergies and asthma (Zaknun et al., 2012).

The term “antioxidant” implies that a compound can quench radicals or diminish the oxidation of other molecules. The preservation of compound’s antioxidant activity until its internalization in cells is of importance, but in particular many phytochemicals are only partially bioavailable, so they might not reach relevant concentrations within a cell. Additionally, within a cell, the compound must not be converted into an inactive metabolite (Del Rio et al., 2013). Otherwise, although each compound might only be present at a low concentration, effective potentiation can be achieved by additive and synergistic interactions of the many phytochemicals present, such as in foods or multicomponent botanical preparations (Wink, 2008). Another assumption is that internalization is not a strict prerequisite for the activity of a compound, as *in vivo* bioactivity may have already started in the gastrointestinal tract (GIT), where

* Corresponding author. Division of Biological Chemistry, Biocenter, Innsbruck Medical University, Innrain 80, Austria. Tel.: +43 5129003 70350; fax: +43 512 9003 73110.

E-mail address: Dietmar.fuchs@i-med.ac.at (D. Fuchs).

compounds are present at high concentrations (Halliwell et al., 2000). But their chemical fate still remains to be discussed, as some dietary antioxidants are prone to oxidative degradation in the GIT, thereby abrogating antioxidant capacity or even obtaining pro-oxidative properties (Halliwell et al., 2005).

Phenolic compounds, as well as sulfites, are known for quenching free radicals and reducing electrophiles, such as peroxy (ROO•) radicals and hydroperoxides (ROOH) (Scott, 1997). Antioxidants, which contain a phenol ring structure and one or more hydroxy groups, can act as reactive oxygen species (ROS) scavengers by forming phenoxyl radical (PhO•) intermediates that are more stable because of the aromatic structure, and serve to discontinue or slow down radical-driven reactions (Burton et al., 1985). PhO• are involved in a number of cellular processes. Redox properties of flavonoids have been shown to be increased in the presence of a 3'-hydroxyl group at the C ring (Burda and Oleszek, 2001). The 3'- and 4'-hydroxy groups at the B ring were shown to be related to transition metal binding, which could enhance antioxidant capacity by preventing Fenton reactions (Kostyuk and Potapovich, 2009), although complexation is strongly pH-dependent (Mira et al., 2002). Otherwise, transition metals have also been shown to initiate phenolic oxidation (Lambert and Elias, 2010). Thus, such molecules can act in either an anti- or a pro-oxidant manner, depending on concentrations and reaction environment (Galati et al., 2002; Sakihama et al., 2002).

Highly reactive free radicals, such as hydroxyl (HO•), alkoxyl (RO•), and carbon-centered radicals (R•), react with a similar rate constant with many molecules in the nearby environment. The only efficient protection from free radicals is to avoid their formation, rather than eliminating them (Forman et al., 2014).

As previously mentioned, the term antioxidants, when used to describe diet, can be misleading as the effect of an antioxidant in its microenvironment depends upon various factors, including chemical reactivity, intra- or extra-cellular localization, concentration, mobility, interactions with other radicals, absorption, distribution, metabolism, and excretion (ADME), as well as the fate of the produced intermediate (Kostyuk and Potapovich, 2009). To generate an appropriate classification scheme, antioxidants can be grouped into categories based on their mode of action, source (endogenous/exogenous, non-enzymatic/enzymatically produced), or solubility (hydrophobic/hydrophilic) (Gutteridge and Halliwell, 1994; EMEA, 2003; Vertuani et al., 2004). Also, it is possible to distinguish primary antioxidants, which belong to the classical chemical antioxidants, from secondary antioxidants, such as antioxidant synergists or antioxidant inducers. Classical chemical antioxidants include molecules that block chain reactions by reacting with free radicals, and reducing agents that have a lower redox potential than the molecule they protect. Antioxidant synergists are substances that can enhance the effect of other antioxidants in a mixture, such as the scavenging of free oxygen. Also chelation of transition metals can be a preventive mechanism, for example by counteracting the Fenton reaction.

Additionally, alternative mechanisms have been suggested to contribute to the bioactivity of dietary antioxidants, including the capacity to target signaling pathways. Dietary antioxidants can act secondarily through preventive actions or the induction of protective signaling cascades and prevent free radical formation (Dinkova-Kostova and Talalay, 2008; Sarkar et al., 2009; Stevenson and Hurst, 2007). Such modes of action result in longer-lasting cellular changes by modifying gene expression. Certain compounds have been shown to enhance endogenous antioxidant potential by upregulating the expression of cytoprotective, detoxifying, and antioxidant genes (Dinkova-Kostova and Talalay, 2008; Stevenson and Hurst, 2007). Notably, ROS and pro-oxidant molecules can also act as messengers that activate protective strategies, such as nuclear factor kappa B (NF-κB), a key transcription factor in the regulation

of inflammation (Schreck and Baeuerle, 1991) or nuclear factor (erythroid-derived 2)-like 2 (Nrf2)/antioxidant response element (ARE)-mediated signaling, a primary pathway activated to protect cells against oxidative and xenobiotic damage (Niture et al., 2014).

2. Oxidative stress, antioxidants, and homeostasis

Normally, free radicals are involved in the maintenance of cell function, and the regulation of oxidative processes is essential to maintain homeostasis (Dröge, 2002). Because of extensive oxygen metabolism in the respiratory chain, mitochondrial oxidases are the main enzymatic source of ROS formation under physiological conditions (Le Bras et al., 2005). Other enzymatic sources include monoamine oxidases, lipoxygenases, cytochrome P-450 enzymes, and xanthine oxidoreductase. Free radical and non-radical reactive species derived from non-enzymatic sources include hydroxyl ions (OH⁻) and radicals (HO•) that originate from hydrogen peroxide (H₂O₂) in the presence of ferrous iron (Fe²⁺) in the Fenton reaction (Fenton, 1894; Winterbourn, 1995) or peroxynitrite (ONOO⁻), which is formed from nitric oxide (•NO) and a superoxide anion (•O₂⁻) (Szabó, 2003).

During the respiratory burst reaction, phagocyte NADPH oxidase (NOX) generates high amounts of •O₂⁻/H₂O₂ as an effective pathogen eradication strategy (Rossi and Zatti, 1964). Other NOX enzymes are widely expressed among several cell types and tissues, and their activity can be activated by various stimuli, such as hormones and cytokines. Notably, NOX is the only enzyme family that produces ROS as its major function, making these enzymes to interesting drug targets (Altenhöfer et al., 2012). Large amounts of reactive species production are essential during an antimicrobial response, but at low levels, small redox molecules, such as ROS and reactive nitrogen species (RNS), are also important signaling molecules (Gostner et al., 2013; Wink et al., 2011; Winterbourn, 2008). For example, H₂O₂ can modulate the activity of various transcription factors, such as NF-κB, activator protein 1 (AP-1), Nrf2, hypoxia-inducible factor-1 (HIF-1), tumor protein p53 (TP53), and many others (Marinho et al., 2014).

To protect cellular structures from the harmful effects of reactive species, antioxidant molecules act as redox buffers in different cellular compartments, such as glutathione/glutathione disulfide (GSH/GSSG), cysteine/cystine (Cys/CySS), or thioredoxins (Trx) (Kemp et al., 2008). Additionally, enzymatic systems, such as superoxide dismutase (SOD), catalase, or glutathione peroxidase, are able to inactivate ROS (Dröge, 2002). A variety of small molecule antioxidants, such as ascorbate, uric acid, and vitamins, are also involved in the neutralization of reactive species. Besides these antioxidant molecules generated via endogenous metabolic routes, redox-active compounds are exogenously supplied by the diet.

The maintenance of redox homeostasis under changing conditions is assured by the concerted action of various interlocking pathways and feedback mechanisms on cellular and organismal levels. Both strongly oxidative milieu and increased reductive stress can lead to pathological consequences (Poljsak and Milisav, 2012). Concentrations of antioxidants that are too low can permit elevated levels of reactive metabolites, whereas increased levels of antioxidants can hamper essential oxidation steps required for normal metabolism or antimicrobial defense. Thus, elevated antioxidant status can enhance the risk of infection (Gostner et al., 2013; Zaknun et al., 2012).

3. Impact of dietary antioxidants on immunoregulatory circuits

The impact of dietary antioxidants on the immune system has been frequently discussed in the literature, mostly regarding the reduction of inflammation resulting from the anti-inflammatory

potential of several phytochemicals and other dietary constituents (Gostner et al., 2014a; Izzi et al., 2012; López-Varela et al., 2002). However, as immunoregulation is strongly connected to metabolic and neuroendocrine processes (Haroon et al., 2012), the modulation of immunological circuits by antioxidants can also induce adverse outcomes, which we discuss below using the catabolic pathway of tryptophan as an example (Schröcksnadel et al., 2006).

The breakdown of the essential amino acid tryptophan to kynurenine can be accelerated during inflammation in response to interferon γ (IFN- γ)-dependent signaling cascades in monocytes/macrophages, and dendritic cells, as well as some other cell types, such as fibroblasts or endothelial cells (Byrne et al., 1986; Werner et al., 1987). The responsible rate-limiting enzyme for the conversion of tryptophan during inflammation is indoleamine 2,3-dioxygenase (IDO1), which can be induced both at the expression and activation levels via redox-sensitive mechanisms (Thomas and Stocker, 1999). Lowering tryptophan levels is an antiproliferative strategy directed against invading pathogens and tumor cells; however activation and proliferation of T cells are also controlled by tryptophan levels. Thus, IDO activity represents a negative feedback loop for immunoregulation (Brandacher et al., 2006; Munn and Mellor, 2013). Measurements of the kynurenine to tryptophan ratio (Kyn/Trp) has been used to indicate accelerated IDO activity in various pathological settings related to chronic immune activation, such as infections, autoimmune diseases, malignant disorders immunodeficiency, anemia, and mood disorders (Fuchs et al., 1991; Schröcksnadel et al., 2006). Simultaneous estimations of oxidative stress markers, such as neopterin, which is produced by the enzyme GTP-cyclohydrolase I (GCH) upon IFN- γ stimulation, or the measurement of cytokine receptors or IFN- γ itself, have been used to link tryptophan breakdown to inflammation-induced IDO activity (Murr et al., 2002; Widner et al., 1997). This is necessary, as also tryptophan 2,3-dioxygenase (TDO) can degrade tryptophan. TDO is expressed in the liver and is regulated by tryptophan levels or glucocorticoids (Knox, 1966).

During immune response, IFN- γ released by T cells induces high output of ROS by human macrophages. For oxidative cleavage of the indole ring structure of tryptophan by the heme enzyme IDO, followed by consequent formation of a ternary complex of iron in its ferrous [Fe(II)] form, oxygen and a substrate are required. Thus, IDO activity requires an antioxidant environment, as the enzyme must be maintained its reduced form (Werner and Werner-Felmayer, 2007). Notably, some radical-scavenging activity can arise from IDO itself when $\bullet\text{O}_2^-$ is used as a reductant of its ferric [Fe(III)] iron; within the tryptophan breakdown pathway, this results as a consequence of the formation of the redox-active kynurenine metabolites 3-hydroxyanthranilic acid and 3-hydroxykynurenine (Thomas and Stocker, 1999). However, the radical-scavenging activity of IDO is thought to be highly concentration-dependent, as the presence of H_2O_2 and absence of tryptophan also result in inhibition of dioxygenase activity and activation of IDO peroxidase function, which leads to protein oxidation (Freewan et al., 2013).

Antioxidant overload can inhibit both IDO expression and function (Schröcksnadel et al., 2007). This could be demonstrated in mitogen-stimulated peripheral blood mononuclear cells *in vitro* by using Kyn/Trp to estimate IDO activity (Jenny et al., 2011a) for several phytochemicals such as resveratrol (Wirleitner et al., 2005), the lignans trachelogenin, arctigenin and matairesinol (Kuehn et al., 2013), the terpene alcohol linalool and the monoterpenes α -pinene and limonene (Gostner et al., 2014b), for food preservatives such as sodium benzoate, sodium sulfite or propionic acid (Maier et al., 2010; Winkler et al., 2006a) and the colorants curcumin (Maier et al., 2010) and beet root extract (Winkler et al., 2005) as well as for anti-inflammatory drugs e.g. aspirin and salicylic acid (Schröcksnadel et al., 2005), chloroquine (Gostner et al., 2012a, 2012b), immunosuppressants tacrolimus and cyclosporine A (Schröcksnadel et al.,

2011), etc. Suppressive effects were also observed upon treatment of cell cultures with complex botanical extracts of a variety of different plants such as *Crinum latifolium* (Jenny et al., 2011b; Zvetkova et al., 2001), *Uncaria tomentosa*, *Hypericum perforatum* (Winkler et al., 2004a, 2004b) or *Carthamus tinctorius* (Kuehn et al., 2013), lavender oil (*Aetheroleum Lavanduli*) (Gostner et al., 2014b), and also for beverages such as cacao (Jenny et al., 2009), coffee (Gostner et al., 2014c), or beer whereby the solved ingredients but not the alcohol content was primarily responsible for the suppressed tryptophan breakdown rate in stimulated cells (Winkler et al., 2006b). For several of the above mentioned extracts and compounds, also decreased neopterin levels were observed in stimulated cells, indicating suppressive activities on pro-inflammatory, IFN- γ mediated pathways.

Interestingly, for some phytochemicals, biphasic responses were observed such as for resveratrol which efficiently reduced neopterin and Kyn/Trp levels in stimulated cells, but induced IDO activity at low concentrations in unstimulated PBMC (Wirleitner et al., 2005). Divergent effects depending on the stimulation status of the cells could be observed also with extracts from *Hypericum perforatum* (Winkler et al., 2004a, 2004b), *Crinum latifolium* and *Camellia sinensis* extracts (Zvetkova et al., 2001), which increased neopterin level especially at low concentrations in unstimulated cells, while reducing them in stimulated ones. Such effects could probably account for the immunomodulatory effects reported for some of these extracts.

The effects of dietary antioxidants on immunological circuits are highly dependent not only on the immune status of the consumer, but also on the nature of the antioxidants. For example, in a study of the effects of black tea drinking on tryptophan metabolism, increased circulating concentrations of kynurenine and the Kyn/Trp ratio were reported, which could indicate an induction of IDO activity in apparently healthy individuals (Gostner et al., 2015).

Notably, nitric oxide ($\bullet\text{NO}$) is a potent antioxidant molecule that is involved in the regulation of many biological processes, although it is itself a radical, although with low reactivity (Wink et al., 2011). $\bullet\text{NO}$ can block the active site heme of IDO by forming a Fe(II)-NO-tryptophan adduct (Thomas et al., 2007). This reversible enzyme inhibition is an important mechanism for regulating IDO activity during an immune response. Importantly, $\bullet\text{NO}$ binding is sensitive to several factors, such as the abundance of tryptophan, $\bullet\text{NO}$ itself, and the cellular redox state (Samelson-Jones and Yeh, 2006). $\bullet\text{NO}$ can be produced from L-arginine by nitric oxide synthases (NOS). Inflammatory conditions enhance $\bullet\text{NO}$ production by inducible NOS (iNOS), which can be activated upon cytokine or lipopolysaccharide stimulation in several cell types (Förstermann et al., 1994). Furthermore, in rodents, $\bullet\text{NO}$ signaling is also involved in the negative regulation of IDO expression in murine IFN- γ -primed macrophages, but not in microglial cells (Alberati-Giani et al., 1997). However, as human macrophages produce low levels of tetrahydrobiopterin (BH_4), a cofactor required for NOS function (Werner et al., 1991), $\bullet\text{NO}$ levels may thus not originate from iNOS, which explains the lower nitrate (NO_3^-)/nitrite (NO_2^-) levels in human plasma compared with those in rodents (Schneemann et al., 1993).

Several plant-derived products have been reported to modulate endothelial NOS (eNOS) activity, thereby positively influencing endothelial function both *in vitro* and *in vivo* (Parks and Booyse, 2002; Schmitt and Dirsch, 2009). For example, red wine polyphenols have been shown to increase eNOS expression and $\bullet\text{NO}$ release in human umbilical vein endothelial cells (Leikert et al., 2002). Additionally, in lipopolysaccharide-stimulated murine cells and in rodents, resveratrol and similar compounds reduced $\bullet\text{NO}$ production by interfering with iNOS expression and/or activity (Huang et al., 2011; Qureshi et al., 2012). A number of other plant phenolic compounds have been reported to reduce $\bullet\text{NO}$ production (Conforti and Menichini, 2011), and several of those compounds were reported to additionally suppress other pro-inflammatory pathways, such as NF- κB -dependent signaling (Nam, 2006). Thus, depending on the

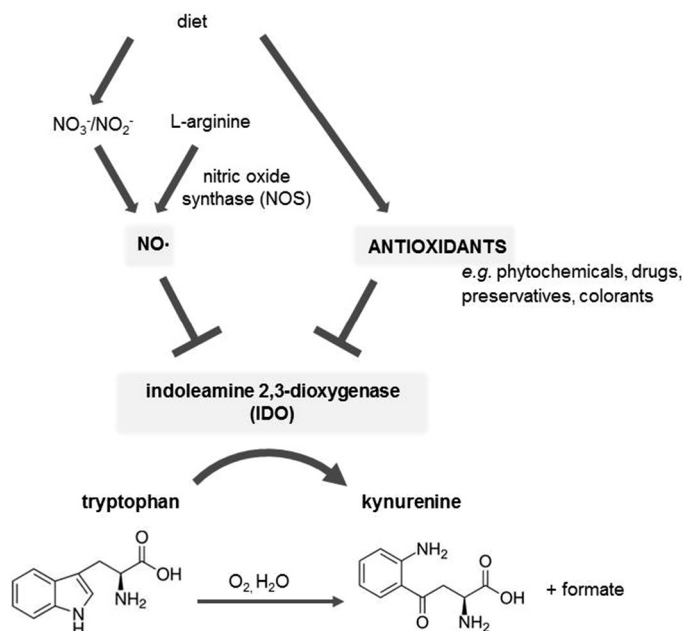


Fig. 1. Expression and activity of indoleamine 2,3-dioxygenase (IDO) is increased during inflammation, most prominently in response to the major T helper type 1 cytokine interferon- γ . Breakdown of the essential amino acid tryptophan to kynurenine is linked to important antiproliferative and immunoregulatory activities. Several classes of antioxidants have been reported to interfere with IDO activation, in which both direct inhibition and suppression of upstream activation signals might play a role. Nitric oxide ($\bullet\text{NO}$), in addition to being an antioxidant itself, acts as a potent inhibitor of IDO activity by blocking the active site. Plant- and diet-derived nitrate (NO_3^-)/nitrite (NO_2^-) represent an alternative source of $\bullet\text{NO}$ to the classical L-arginine- $\bullet\text{NO}$ pathway that is mediated by nitric oxide synthase (NOS). Both non-enzymatic and enzymatic reactions might play a role when using $\text{NO}_3^-/\text{NO}_2^-$ as a source of $\bullet\text{NO}$, whereby these activities could be derived from either endogenous enzymes and antioxidants, the plant material itself, or bacteria found, e.g. in the oral cavity.

model organism, cell type, and inflammatory status, phytochemicals can interfere with $\bullet\text{NO}$ production by modulating the expression and activity of different types of NOS (Fig. 1).

Recent accumulating evidence suggests that dietary nitrate $\text{NO}_3^-/\text{NO}_2^-$ sources also contribute to $\bullet\text{NO}$ concentrations in the human body. $\bullet\text{NO}$ -related bioactivity has been reported for several herbal therapeutics and preparations (Jiang et al., 2012; Tang et al., 2009). Also foods can contain large amounts of $\text{NO}_3^-/\text{NO}_2^-$ (Weitzberg and Lundberg, 2013). Indeed, diets rich in vegetables can lead to daily intakes of more than 1000 mg nitrate per day, which far exceeds the existing recommendations of acceptable daily intake values (Hord et al., 2009). Both dietary $\text{NO}_3^-/\text{NO}_2^-$ are rapidly absorbed and contribute to systemic exposure (Hunault et al., 2009; van Velzen et al., 2008). These anions can be recycled *in vivo* to $\bullet\text{NO}$, whereby either different enzymatic reactions can be involved to obtain $\bullet\text{NO}$ from $\text{NO}_3^-/\text{NO}_2^-$ (Lundberg et al., 2008) or non-enzymatic reduction can occur in the presence of antioxidants, such as ascorbate (Carlsson et al., 2001) or certain polyphenols (Peri et al., 2005). Such non-classical $\bullet\text{NO}$ formation can be activated either endogenously after uptake or with the help of microbiota in the oral cavity (Lundberg et al., 2004), or can occur before uptake within the plant extract itself, as $\text{NO}_3^-/\text{NO}_2^-$ reductase activity has been reported for several herbal extracts (Jiang et al., 2012).

High levels of food-derived $\text{NO}_3^-/\text{NO}_2^-$ have been associated with an increased risk of gastrointestinal cancer and the development of methemoglobinemia in infants. However, obtaining proof for direct causal relationships in epidemiological studies is difficult, and our current data call into question whether high nitrite levels are the

sole cause of hemoglobinemia (Hord et al., 2009). Additionally, the role of diet- or drinking water-derived $\text{NO}_3^-/\text{NO}_2^-$ for cancer development remains the subject of debate (Powelson et al., 2008). Moreover, in several types of cancers, increased expression of NOS has been reported (Ambs et al., 1998; Rao, 2004). Otherwise, recent studies report about health-promoting effects of fruit- and vegetable-rich foods that contain large amounts of $\text{NO}_3^-/\text{NO}_2^-$, such as the Mediterranean Diet or Dietary Approaches to Stop Hypertension (DASH) diet patterns. Diet-related vasodilatory and blood pressure-lowering effects might also depend on diet-derived $\bullet\text{NO}$ sources (Hord et al., 2009). It is important to remember that because of the multiple components in a diet, distinguishing an effect of compounds that induce $\bullet\text{NO}$ formation via endogenous NOS from dietary $\text{NO}_3^-/\text{NO}_2^-$ that fuels the endogenous $\bullet\text{NO}$ pool can be difficult.

The suppression of Th1 type immune responses is a prerequisite for the anti-inflammatory activities of drugs and compounds; however, the chronic prevalence of a reductive milieu and the resulting suppression of Th1 type reactions can favor the development of Th2 type responses, as a consequence of the cross-regulatory nature of Th1 and Th2 responses (Lucey et al., 1996). Th2 type responses are associated with the development of allergies and asthma. Reductive stress from excessive intake of antioxidant food supplements, preservatives, and colorants is suspected to favor switching from a Th1 to a Th2 type response (Gostner et al., 2013; Zaknun et al., 2012). Indeed, sensitivities to preservatives are frequently observed, such as e.g. to diet-derived sulfites, and patients can present a wide spectrum of symptoms that affect the skin, GIT, and respiratory tract (Vally et al., 2009).

Although a diet rich in fruits and vegetables is generally considered to be a health-promoting source of natural antioxidants, there are growing numbers of reports of fruit allergies or hypersensitivities, most often against kiwi, tomato, or citrus fruits; moreover, increased susceptibilities to atopic diseases, such as asthma, are frequently observed in these patients (Mattila et al., 2003; Roehr et al., 2004). However, to what extent this observation is relevant for the general population remains to be elucidated, and such food-related symptoms have only been confirmed in a minority of the cases that have been analyzed (Roehr et al., 2004). An association of dietary antioxidants with a higher prevalence of rhinitis (Bakolis et al., 2010) and hay fever (Nagel et al., 2003) has been documented. By contrast, other studies have described a beneficial influence of fruits and raw vegetables that lowers the risk of asthmatic symptoms, such as wheezing (Wong et al., 2004). In a meta-analysis of 31 studies of the potential interactions between dietary patterns and asthma, Lv et al. (2014) could not confirm an association between certain diets and asthma prevalence in adults, or link a maternal diet with asthma or wheezing in offspring. However, a major limitation of these data is the absence of randomized control trials.

Interestingly, natural antioxidant polyphenols have been shown to modulate both mast cell degranulation and cytokine gene expression, thus interfering with two important immune cell effector functions (Chen et al., 2000). Accordingly, antioxidants could be responsible for specific allergic reactions in certain individuals (Cochrane et al., 2009; Gillman and Douglass, 2010; Ozol and Mete, 2008; Zaknun et al., 2012). Recent findings have indicated that infant vitamin supplementation can also contribute to an increased risk of allergic diseases (Hyppönen et al., 2004; Milner et al., 2004).

In addition to IDO, many other key molecules of the immune and stress response pathways have been shown to be modulated by dietary antioxidants and phytochemicals. Although we do not discuss these pathways in detail, the most important include the NF- κB signaling, expression of cytokines such as tumor necrosis factor (TNF) and other pro-inflammatory biomarkers (Aggarwal, 2010; Gupta et al., 2014; Kaefer and Milner, 2011; Sung et al., 2011), as well as Nrf2-dependent signaling (Forman et al., 2014).

4. Impact of dietary antioxidants on psychoneuroendocrine circuits

Despite allergic reactions, behavioral symptoms have also been linked to exposure to preservatives. McCann et al. (2007) suggested that food additives could be involved in the development of hyperactivity or attention deficit hyperactivity disorder (ADHD) in children. Food additives have been shown to cause non-immunoglobulin E-dependent histamine release from circulating basophils (Stevenson et al., 2010). Although many factors can influence the development of ADHD and only limited evidence was provided by the study of McCann et al. (Weiss, 2012), several follow-up examinations and discussions have been carried out to evaluate the acceptable daily intake of certain food colorants and sodium benzoate (EFSA, 2008). Although most of the concerns were not substantiated, the findings of McCann et al. (2007) might still be relevant for specific individuals who are especially sensitive to one or more additives, as reports of adverse reactions to exposure to food colors in children continue to accumulate (Stevens et al., 2013).

Changes in immune status that lead to dysregulated tryptophan metabolism have also been associated with the development of mood disturbances and depression (Sperner-Unterwieser et al., 2014), as tryptophan is the precursor for synthesis of the neurotransmitter serotonin. Low concentrations of circulating tryptophan have been linked to depressive symptoms in several inflammation-associated diseases, such as cancer (Kurz et al., 2011) and HIV-infection (Schroeksnadel et al., 2008), as well as with age-associated inflammation (Capuron et al., 2011).

Antioxidant preservatives can also exert suppressive effects on leptin-dependent satiety circuits (Mangge et al., 2013). Ciardi et al. (2012) showed that preservatives, such as sodium sulfite, sodium benzoate, and the colorant curcumin, could inhibit leptin release in lipopolysaccharide-stimulated murine adipocytes. Leptin is an important modulator of appetite regulation and energy homeostasis, and the inhibitory effect of preservatives on leptin might contribute to the development of an obesogenic phenotype. For example, by interfering with signaling pathways downstream of leptin, curcumin can reduce leptin-induced increases of intracellular glucose levels by suppressing the membrane translocation of glucose transporter 4 (GLUT4) and accelerating the conversion of glucose to glucose-6-phosphate in hepatic stellate cells *in vitro* (Tang and Chen, 2010) (Fig. 2).

The impact of dietary antioxidants on eating behavior and weight is complex. By reducing the concentrations of circulating tryptophan, disturbed serotonergic transmission can favor carbohydrate intake. Indeed, it has been demonstrated that serotonin synthesis is associated with appetite control and the proportion of carbohydrate-rich food consumption in several human and animal studies (Wurtman, 1983; Wurtman et al., 1980). In overweight adults,

leptin concentrations have been shown to be correlated with tryptophan breakdown before and after an extreme short-term diet (Strasser et al., 2015). Furthermore, accumulating evidence suggests that increased reductive stress in childhood and adolescence could contribute to the development of overweight or obese states, as it has been shown that male overweight and obese juveniles exhibit significantly reduced kynurenine and Kyn/Trp serum levels, while these parameters are increased in adults with metabolic syndrome (Mangge et al., 2014). Additionally, neopterin levels were not increased in obese young individuals (Mangge et al., 2011), which further strengthens the hypothesis that oxidative stress can occur during disease progression. Finally, obesity and adiposity, which are both major risk factors for type 2 diabetes, manifest as chronic pro-inflammatory diseases, and beneficial effects have been reported from dietary approaches that focused on phytochemical-rich nutrition, as antioxidant defenses are lower in these patients than in normal weight counterparts (Vincent et al., 2010).

5. Discussion

Redox-regulated pathways that modulate immunological, metabolic, and neuroendocrine processes are highly cross-regulated, thus any evaluation or prediction of antioxidant activity *in vivo* is challenging. Such predictions become even more complex when attempting to unravel the effects of antioxidants contained in mixtures, such as in the diet or supplements. Also, for several phytochemicals, low bioavailability has hindered the direct translation of effects observed *in vitro* into *in vivo* findings (D'Archivio et al., 2010; Manach et al., 2005).

The overrepresentation of antioxidants in food might lead to reductive stress and associated development of adverse effects. Dietary antioxidants can interfere with normal satiety regulation, thereby promoting the intake of food rich in calories and favoring the development of obesity. However, other lifestyle factors, such as physical exercise, also play a role. Beneficial and health-promoting effects associated with particular plant-derived antioxidants, herbs, or spices are suggested to be of relevance to lower oxidative stress conditions, while the development of allergies, asthma, and obesity has been discussed in relation to antioxidant overload.

Significant efforts have been made to develop antioxidant therapies for several oxidative stress-related diseases, which are accompanied by low levels of circulating antioxidants (Murr et al., 2009); however, success has been limited and sometimes outcomes have even been contradictory, such as for vitamin E supplementation in cardiovascular disease (Saremi and Arora, 2010). Several recent reports have found a potential association between cancer development and antioxidant and vitamin supplementation (Ebbing et al., 2009; Roswall et al., 2012). Thus, it remains important to evaluate antioxidant supplementation during therapy, and patients would likely benefit from more detailed monitoring of individual needs (Violi et al., 2004).

Studies of specific individual nutritional needs and the monitoring of antioxidant status would aid the establishment of antioxidant therapies, especially during chronic diseases. Thereby, measurements of neopterin concentrations or the Kyn/Trp ratio could be a suitable way to monitor the activation status of the immune system *in vivo* in a rapid and reliable manner (Fuchs et al., 1991; Schröcksnadel et al., 2006).

Although larger studies are still needed, we speculate that avoiding excessive uptake of dietary preservatives could help to reduce background antioxidant levels, and could likely increase the response rate to therapeutically administered antioxidants. However, it will be difficult to decipher the exact role of single antioxidants in circulation, as understanding synergistic interactions and induction of signaling cascades will be important.

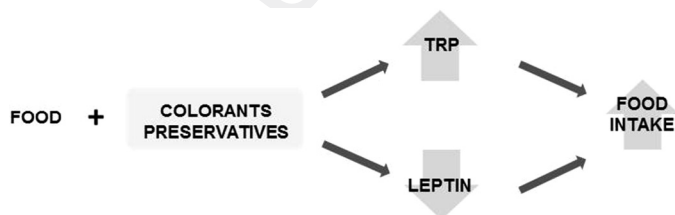


Fig. 2. Dietary antioxidants, such as the preservatives sodium sulfite and sodium benzoate or the colorant curcumin, have been shown to interfere with signaling cascades that regulate food intake (Ciardi et al., 2012). Blocking IDO activity stabilizes peripheral tryptophan levels, and simultaneous reductions of leptin release negatively interfere with satiety regulation. Both of these effects trigger food intake, thus promoting the development of obesity.

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Conflicts of interest

None.

Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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