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Original Article

Association of antioxidant nutraceuticals and acetaminophen (paracetamol): Friend or foe?

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ABSTRACT

Acetaminophen (paracetamol or APAP) is an analgesic and antipyretic drug that can induce oxidative stress-mediated hepatotoxicity at high doses. Several studies reported that antioxidant nutraceuticals, in particular phenolic phytochemicals from dietary food, spices, herbs and algae have hepatoprotective effects. Others, however, suggested that they may negatively impact the metabolism, efficacy and toxicity of APAP. The aim of this review is to discuss the pros and cons of the association of antioxidant nutraceuticals and APAP by reviewing the *in vivo* evidence, with particular reference to APAP pharmacokinetics and hepatotoxicity. Results from the murine models of APAP-induced hepatotoxicity showed amelioration of liver damage with nutraceuticals coadministration, as well as reductions in tissue markers of oxidative stress, and serum levels of hepatic enzymes, bilirubin, cholesterol, triglycerides and inflammatory cytokines. On the other hand, both increased and decreased APAP plasma levels have been reported, depending on the nutraceutical type and route of administration. For example, studies showed that repeated administration of flavonoids causes down-regulation of cytochrome P450 enzymes and up-regulation of uridine diphosphate glucuronosyltransferases (UGT). Moreover, nutraceuticals can alter the levels of APAP metabolites, such as mercapturate glucuronide, sulfate and cysteine conjugates. Overall, the reviewed in *vivo* studies indicate that interactions between APAP and nutraceuticals or plant foods exist. However, the majority of data come from animal models with doses of phytochemicals far from dietary ones. Human studies should investigate gene-diet interactions, as well as ethnic variability in order to clarify the pros and cons of co-administering antioxidant nutraceuticals and APAP.

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1. Introduction

There is a growing interest in the scientific community in nutraceuticals, in particular phenolic phytochemicals from dietary food, spices, herbs and algae due to their ability to mitigate oxidative stress, the latter being associated with both disease risk and drug toxicity [1–4]. Dietary phenolic compounds, including flavonoids and non-flavonoids, have well-established preventive effects against oxidative stress-related diseases, including cardiovascular, neurodegenerative diseases and cancers [3,4]. Flavonoids, present in fruits, vegetables, grains and other plant foods, include several subclasses, such as anthocyanins of red fruits, flavonols of tea, cocoa and dark chocolate, flavanones of orange and grapefruit juices, flavones of artichokes, black olives, celery and whole-grain, flavanols of spinach and onions and isoflavones of soy products [4,5].

Several studies used murine models to test the hepatoprotective effects of natural products [6,7]. For example, the nutraceutical *Spirulina platensis*, a filamentous microalga belonging to the class of *Cyanobacteria*, ameliorated the deltamethrin-induced hepatotoxicity through its antioxidant activity [2]. This effect was evident in its ability to lower the level of the peroxidation marker malondialdehyde (MDA), while increase the content of reduced glutathione (GSH) and the activities of glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT) [2].

Acetaminophen (APAP), also known as paracetamol, is the most frequently used analgesic and antipyretic drug. However, it can induce oxidative stress-mediated hepatotoxicity at high doses [6,7]. In the Western countries, APAP overdose is the commonest cause of acute liver injury (ALI) [8]. Despite the hepatoprotective effects of nutraceuticals, it has been reported that flavonoids within phenolic phytochemicals may negatively impact the metabolism, efficacy and toxicity of drugs [5,9], including APAP [10]. Both inductions and inhibitions of the detoxification enzyme glutathione S-transferase (GST) have been reported for flavonoids, depending on their structure, suggesting potential toxicological consequences [10]. Furthermore, flavonoids could interfere with drugs' bioavailability through different mechanisms, such as competition with cytochrome P450 (CYP) enzymes, esterases, uridine diphosphate glucuronosyltransferases (UGT) and transporters, such as P-glycoprotein, multi-drug resistance-associated proteins (MRP), organic anion transporting polypeptides (OATP), breast cancer-resistance protein (BCRP) and monocarboxylate transporters (MCT) [5].

Differences between the long-term supplementation and acute administration have been observed, probably because in addition to being substrates of phase I, II and III drug metabolism/transport systems, flavonoids are also able to modulate their expression through the activation protein-1 (AP-1), the nuclear factor kB (NF-kB), the nuclear factor erythroid 2-related factor 2 (Nrf2), the aryl hydrocarbon receptor (AhR) and the pregnane X receptor (PXR) [9].

In this work, we aimed to discuss the pros and cons of the association of antioxidant nutraceuticals and APAP by reviewing the *in vivo* evidence, with particular reference to APAP pharmacokinetics and hepatotoxicity.

2. Acetaminophen pharmacokinetics, hepatotoxicity and oxidative stress

APAP is a weak acid with pKa ≈ 9.5, is almost entirely neutral at physiological pH and is rapidly absorbed from the duodenum [11]. It is extensively metabolized in humans, with a half-life in blood of 1.5–3 h after a therapeutic dose. APAP metabolism occurs mainly in the liver through sulfation (25–35% of a therapeutic dose) and glucuronidation (50–70% of a therapeutic dose), by sulfotransferase (SULT, SULT1A1, 1A3/4, and possibly 1E1) and UGT (UGT1A1 and 1A6) enzymes, respectively [11]. Sulfate (Sul)-APAP is excreted in urine and glucuronide (Glu)-APAP in both bile and urine. Despite conjugation is the major route at therapeutic doses, CYP metabolism is important in high-doses induced hepatotoxicity [8].

Biliary excretion of APAP conjugates requires transporters i.e. results from murine models suggested that biliary excretion of both Glu-APAP and Sul-APAP is dependent on MRP2 and BCRP in the canalicular hepatocyte membrane, whereas MRP3 is involved in the basolateral excretion of Glu-APAP and Sul-APAP (in addition to MRP4) [11]. On the other hand, GST is responsible for the enzymatic conjugation of APAP and GSH, while MRP2 is involved in the biliary excretion of GSH-APAP [11]. After a therapeutic dose of APAP, about 5–15% is excreted in urine as a mercapturate (Mer)-APAP or cysteine (Cys)-APAP conjugate (two products of GSH-APAP). The production of these conjugates occurs after phase I metabolism of APAP, which is predominantly mediated by CYP2E1, but other CYP (CYP1A2, 2D6, and 3A4) enzymes have been shown to activate APAP *in vitro* as well [11].

The metabolic activation of APAP produces reactive oxygen species (ROS) and the N-acetyl-p-benzoquinone imine (NAPQI) that reacts readily with the nucleophilic sulfhydryl groups and depletes GSH [6,11–13]. NAPQI can bind to sulfhydryl groups, spontaneously reacting with GSH and it can also bind to hepatic proteins. The latter is the critical initiating event in cell death, observed during APAP-induced liver injury and GSH depletion. Although agents that prevent or scavenge mitochondrial ROS and peroxynitrite are the most promising for APAP hepatotoxicity [12], the importance of GSH defence against the reactive metabolite (NAPQI) led to introducing N-acetylcysteine (NAC) as an antidote for APAP hepatotoxicity in clinical practice [11].

Moreover, NAPQI forms mitochondrial protein adducts, increasing the production of superoxide radicals. The latter can react with nitric oxide to produce the potent oxidant peroxynitrite [6]. Then, the activation of the mitogen activated protein kinase (MAPK), c-Jun-N-terminal kinase (JNK), the nuclear DNA fragmentation, cell death and the subsequent inflammatory response all amplify the injury [12,13]. Adduction of ATP synthase and GPX compromises the generation of ATP through the electron transport chain and interferes with the mitochondrial activity. Further, an inflammatory response is induced by damage-associated molecular patterns (DAMP), released by damaged hepatocytes, activating the resident liver macrophages (Kupffer cells), cytokine/chemokine production and immune cell recruitment [6,13].

Serum alanine aminotransferase (ALT) activity is currently the widely used biomarker for hepatocyte injury, induced by

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