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Review 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

APAP [8]. However, to confirm the absence of liver injury, patients require an ALT measurement at least 24 h after the overdose was ingested. Furthermore, changes in ALT occur in other conditions (fatty liver disease, viral hepatitis, myocardial damage or extreme exercise).

From that, to assess the risk of hepatotoxicity after a single overdose (within 1–2 h), a nomogram is used that plots blood APAP concentration against time after overdose (4 h after overdose absorption is believed to be complete) [8]. On the other hand, APAP-protein adducts persist much longer in serum and their half-life was found to be 1–2 days after an overdose for both children and adults and Cys-APAP has been suggested as a good marker of APAP overdose [8,11]. However, selection of a specific threshold is required because these adducts can be detected in serum after therapeutic doses and a combination of $\geq$1.1 μM Cys-APAP peak concentration and >1000 U/L ALT has been proposed [11]. Other promising markers for APAP hepatotoxicity in humans include circulating mitochondrial DNA (mtDNA), microRNA-122 (miR-122), cleaved Keratin-18 (apoptosis) and full length K18 (necrosis), the chromatin-binding protein [high-mobility group box-1 (HMGB1)] and the mitochondrial enzyme glutamate dehydrogenase (GLDH), whereas the Kidney injury molecule-1 (KIM-1) has been suggested as a marker of secondary injury to the proximal tubular epithelia after APAP overdose [8].

3. Dietary antioxidants and acetaminophen interactions in animal models

Interactions between APAP and antioxidants could affect both its pharmacokinetics and toxicity. Many studies investigated these effects in mice [14–22] and rats [23–30] (Table 1). A dose-dependent increase in the survival rate of APAP-intoxicated mice was observed when *Citrus natsudaidai* was administered for 3 days before APAP treatment [17] and a reduction in the APAP-induced histological damages has been reported for many plant extracts administered before [19,20,24,28,29] or after [21,22,25] APAP intoxication. The reduction of centrilobular necrosis and portal veins congestion on histopathological examination, observed with *Auricularia polytricha* treatment was accompanied by improvements in plasma total proteins [24]. Besides, inhibition of the APAP-induced increase in serum levels of hepatic enzymes, bilirubin and/or lipids has been observed after treatment with *Ganoderma amboinense* [15], Pineapple vinegar (*Ananas comosus*) [16], *A. polytricha* [24], *Lentinula edodes* [22], *Citrullus colocynthis* fruits [27], *Citrus macroptera* [28], *Opuntia robusta* and *Opuntia streptacantha* [29], *Pouteria campechiana* [30], *Carica papaya* leaf and unripe fruit [25], *Spirulina platensis* [18], green tea polyphenols (GTP) [20] and black tea extract (BTE) [21]. In the cases of *S. platensis* [18] and GTP [20], decreases in interleukin (IL)-8 [18] and tumor necrosis factor (TNF)-α [20] serum levels were also observed.

However, green tea extract (GTE) had opposite effects when administered either before APAP by 3 h or once for three days followed by APAP on day 4, or following it by 6 h. The pre-treatment inhibited the APAP hepatotoxicity via reducing its protein covalent binding, whereas the post-treatment increased the APAP-hepatotoxicity via GSH depletion [14]. On the contrary, a single i.p dose of BTE, 90 min after APAP injection increased GSH [21] and Pineapple vinegar (*A. comosus*) by oral gavage for 14 days after seven days of APAP intake increased GSH and GPX [16]. Improvement of the redox status (i.e. increase in antioxidant systems and/or decrease in ROS and peroxidation markers) was also observed with other extracts [15,18,27,29,30]. Therefore, the majority of studies that used antioxidant extracts reported reductions of APAP-induced hepatic injury, except for GTE and GPT that gave contrasting results (Table 1).

Murad and colleagues [21] reported that treatment with thearubigins (TRs) was more hepato-protective than BTE, the latter containing also catechins [3,4]. Other pure nutraceuticals, such as caffeic acid (CA) [31], chlorogenic acid (CGA) [32], eriodictyol [33], ferulic acid (FA) [34], naringenin [35], quercetin [36], resveratrol (RSV) [37–39], rosmarinic acid (RA) [40], syringic acid (SA) [41] have been tested in murine models of APAP-induced hepatotoxicity (Table 2). Caffeic acid [31], naringenin [35], RSV [37] and TRs [21] in mice, as well as RA [40] and SA [41] in rats, reduced APAP-induced histological damages in the liver. This protection was observed both when phytochemicals were administered before [35,40,41] or after [21,31,37] APAP treatment.

In addition, mitigation of oxidative stress (increased antioxidants [21,32–35,40,41] or decreased oxidation markers [35,38,40]), anti-inflammatory effects (reduction of inflammatory cytokines) [31,34,38] and improvements in serum liver enzymes and/or bilirubin levels [21,35,38,41] have been reported for many phytochemicals. For naringenin, a dose-dependent effect has been found for intragastric doses ranging between 200 and 800 mg/kg [35]. However, these doses are far from dietary intakes (lemon, orange and grapefruit juices 5–60 mg/100 ml of flavanone; intake of flavanones 70–100 mg/d) and the bioavailability of polyphenols is low [3,4].

Of note, intragastric eriodictyol administration was of less hepatoprotective value than i.p. administration [33]. Among the studies conducted in murine models (Tables 1 and 2), some used i.p. administration and/or doses greater than 100 mg/kg and the results of these studies should be evaluated with caution. Despite these limitations, overall the results on murine models suggest that extracts (Table 1) or phytochemicals (Table 2) from plant foods can be hepatoprotective against APAP injury. Within the molecular targets, early growth response 1 protein (Erg 1) [31], Toll-like receptor-4 (TLR4) [34], NF-kB [34], p53 [39], cyclooxygenase (COX)-II [20], BCL2 associated X protein (Bax) [20] and JNK [39] were down-regulated, whereas Nrf2 [32], cyclin D1 [39] and proliferating cell nuclear antigen (PCNA) [39] were upregulated.

On the other hand, few studies investigated the effect of antioxidant extracts (Table 1) and phytochemicals (Table 2) on APAP pharmacokinetics and metabolism. Opposite (positive and negative) effects on APAP plasma concentration were observed for *Brassicaceae* (kale) [23] and *Citrus paradise* (Grapefruit) juice (GFJ) [26], respectively. However, GFJ was administered to Sprague–Dawley rats as a single dose through oral gavage, either 28 or 20 h or 30 min before APAP treatment [26], whereas kale was consumed by specific pathogen-free Sprague–Dawley rats for seven days before APAP, inducing mRNA expression of UGT [23]. These results can be due to various factors, such as the differential response

Table 1 – Protective effects of plant extracts against APAP hepatotoxicity and metabolism.

Animal model	Treatment	Duration	Outcomes	Ref.
Mice, B6C3F1 mice (males), receiving a single oral dose of APAP (150–300 mg/kg)	Green tea extract (GTE) (500 or 1000 mg/kg, via oral gavage)	Either before APAP by 3 h or following it by 6 h or once for three days, followed by APAP on the 4th day	GTE after APAP: ↑ hepatotoxicity GTE before APAP: ↓ hepatotoxicity	[14]
Mice, BALB/c (males), receiving daily APAP at 250 mg/kg via oral gavage for seven days	Pineapple vinegar (*A. comosus*) at 0.08 and 2 ml/kg (oral gavage)	14 days after seven days of APAP intake	↓ serum AST, ALT, and triglycerides ↑ tissue GSH and GPX ↓ tissue CYP and iNOS	[16]
Mice, BALB/c (males), receiving a single i.p dose of APAP (350 mg/kg)	*Ganoderma amboinense* powder (1% and 2% daily, mixed with the standard oral diet)	6 weeks (pretreatment), followed by APAP i.p injection	↓ tissue MDA and ROS ↑ tissue GSH and GPX ↓ serum AST and ALT	[15]
Mice, ICR (males), receiving a single i.p dose of APAP (150 mg/kg)	*Spirulina platensis* (SP) extract (3, 6 and 9%, oral)	7 days, before APAP injection	SP 6 and 9%: ↓ tissue ROS ↓ serum AST, ALT and IL-18	[18]
Mice, ICR (males), receiving a single oral APAP (300 mg/kg)	*Citrus natsudaidai* (CN: 300 and 1000 mg/kg, orally)	3 days, followed by APAP dose 2 h later	↑survival rate of APAP-intoxicated mice from 0% to 16.7% (300 mg/kg CN) and 33.3% (1000 mg/kg CN)	[17]
Mice, Kunming (males), receiving a single i.p dose of APAP (1000 mg/kg) on the 6th day of the experiment	Tea polyphenols (TP) (100, 200 and 400 mg/kg, intra-gastric)	6 days, before APAP injection	↓ histological damages ↓ tissue CYP2E1 and CYP1A2	[19]
Mice, Specific-pathogen-free (SPF) BALB/c (males), receiving a single i.p dose of APAP (750 mg/kg)	Green tea polyphenols (GTP) (0.25%, in diet)	5 days, before APAP injection	↓ histological damages ↓tissue COX-II and Bax. ↓ serum ALT and TNF	[20]
Mice, Swiss albino (males), receiving i.p APAP (300 mg/kg)	Black tea extract (BTE) (3% and 4.5%, i.p.)	A single dose, 90 min after APAP injection	↓ histological damages ↑ tissue GSH ↓ serum ALT	[21]
Mice, Wistar (males and females), receiving oral APAP at 1 g/kg per day	*Lentinula edodes* methanolic extract (200 mg/kg, orally)	7 days, 3 h after APAP treatment (for seven days)	↓ histological damages ↓ serum AST, ALT, ALP and bilirubin	[22]
Rats, Specific pathogen-free Sprague–Dawley (males), receiving a single oral dose of APAP (25 mg/kg)	*Brassicaceae* (kale) extract (2 g/kg orally)	7 days, followed by a single APAP on the last day	↑ plasma APAP ↑ tissue UGT	[23]
Rats, Sprague Dawley (males), receiving a single oral dose of APAP (2 g/kg) on the 15th day of the experiment	*Auricularia polytricha* (AP) aqueous extract (250 and 500 mg/kg, orally once daily)	14 days, followed by APAP on the 15th day	↓ histological damages ↑ serum total proteins ↓ serum AST, ALT, ALP, LDH, and total cholesterol	[24]
Rats, Sprague–Dawley (males and females), receiving a single oral dose of APAP at 600 mg/kg	*Carica papaya* leaf (CPL) and unripe fruit (CPF) aqueous extracts (100 and 300 mg/kg, each orally)	Following APAP adminstration by 2, 6 and 10 h	↓ histological damages ↓serum AST, ALT, ALP and direct bilirubin	[25]
Rats, Sprague–Dawley (males), receiving a single dose of APAP (10 mg/kg) via oral gavage	*Citrus paradise* (Grapefruit) juice (GFJ) (10 mg/kg, oral)	A single dose, either 28 or 20 h or 30 min before APAP adminstration	↓ serum APAP	[26]
Rats, Wistar (males) and albino mice (both sexes), receiving a single oral dose of APAP (2 g/kg)	*Citrullus colocynthis* fruits (MECCF) methanolic extract (300 mg/kg, orally)	7 days, APAP was provided 30 min after the last MECCF dose	↓ tissue MDA ↑ tissue SOD and CAT ↓ serum AST, ALT and ALP	[27]

(*continued on next page*)

Table 1 – (continued)

Animal model	Treatment	Duration	Outcomes	Ref.
Rats, Wistar (males), receiving oral APAP (500 mg/kg) daily for seven days	*Citrus macroptera* fruit ethanolic extract (EECM) (250, 500, and 1000 mg/kg, orally)	30 days, in the last seven days, it was co-administered with APAP	↓ histological damages ↓ serum AST, ALT, ALP, LDH, total cholesterol, and triglycerides (in particular, 1000 mg/kg dose)	[28]
Rats, Wistar (males), receiving oral APAP (250 mg/kg) thrice (once every five days)	*Pouteria campechiana* fruit aqueous extract (PCAE) at 50 mg/kg Total phenolic content: 115 ± 1.23 mg GAE/g and a DPPH scavenging activity of 71.6% at 250 µg/ml	Once daily for 15 days (during which APAP was administered once every five days)	↑ hepatocyte GSH, SOD and CAT ↓serum AST and ALT	[30]
Rats, Wistar (males), receiving intra-peritoneal (i.p) APAP at 500 mg/kg (single dose)	*Opuntia robusta* (*Or*) and *Opuntia streptacantha* (*Os*) fruit extract (800 mg/kg, orally)	5 days, before APAP adminstration	↓ histological damages ↑ tissue GSH ↓ serum AST, ALT, and ALP	[29]

ALP: alkaline phosphatase; ALT: alanine aminotransferase; APAP: acetaminophen; AST: aspartate aminotransferase; Bax: BCL2 associated X protein; CAT: catalase; COX: cyclooxygenase; CYP: cytochrome P450; GPX: glutathione peroxidase; GSH: glutathione; IL: interleukin; iNOS: inducible nitric oxide synthase; LDH: lactate dehydrogenase; MDA: malondialdehyde; ROS: reactive oxygen species; SOD: superoxide dismutase; TNF: tumor-necrosis factor; UGT: UDP-glucuronosyl-transferases. Ref.: reference.

to different phytochemicals, nutraceuticals' metabolism by gut bacteria, competition for drug metabolism/transport system in the short term and/or gene expression modulation in the long term. When Wistar rats received a combined oral dose of APAP and quercetin or chrysin for 21 days, plasma APAP increased, suggesting that competitive inhibition prevails in this condition [36]. On the other hand, in mice, Pineapple vinegar (*A. comosus*) [16], tea polyphenols (TP) [19], CGA [32], eriodictyol [33], FA [34] and RSV [39] reduced the APAP metabolism and/or the expression of CYP enzymes.

4. Human evidence

Few studies investigated the effects of nutraceuticals and plant foods on APAP pharmacokinetics in humans [42–46] (Table 3). The calculated parameters included maximum concentration (C_{max}), time of maximum concentration (T_{max}), area under the time versus concentration curve (AUC) and the plasma half-life. All studies were conducted on healthy subjects and the majority (4/5) of them followed a crossover design. The only longitudinal study reported that the consumption of tablets, containing Spanish black radish, camu camu (*Myrciaria dubia*), acerola (*Malpighia emarginata*), honey and manoic root (tapioca) for 4 weeks reduced plasma AUC of both unchanged APAP and APAP metabolites, such as Glu-APAP, Sul-APAP and NAPQI-GSH [42]. Urinary Sul-APAP and Mer-APAP, but not Glu-APAP were higher after 4 weeks of supplementation, when compared to week 0 and urine levels of unchanged APAP increased by 18% (near significance) [42]. Authors suggested that the supplement increased the detoxification of a 1000 mg dose of APAP by the up-regulation of both phase I and phase II enzymes.

On the other hand, Chen et al. [43] reported that the consumption of watercress (*Nasturtium officinale R. BY.*), a cruciferous vegetable, 10 h before APAP (1000 mg) test did not influence glucuronidation and sulfation metabolic pathways as all the pharmacokinetic parameters regarding Glu-APAP and Sul-APAP remained unchanged. Although the APAP pharmacokinetics were unchanged, the plasma concentrations of oxidative metabolites (Cys-APAP and Mer-APAP) increased, as well as their urinary excretion [43]. Moreover, two days of consuming a standardized herbal extract, containing curcuminoids and piperine did not affect the plasma APAP, Glu-APAP and Sul-APAP levels following a single 325 mg oral dose of APAP, although curcuminoids and piperine were measurable in plasma after enzymatic deconjugation with glucuronidase/sulfatase [44]. All urinary pharmacokinetic parameters of unchanged APAP (Sul-APAP, Cys-APAP and Mer-APAP) did not differ between treatment and placebo groups, whereas the decrease in urinary T_{max} and the increase in urinary AUC of Glu-APAP were near to significance ($p = 0.09$ and $p = 0.06$) [44].

Large inter-individual differences in plasma T_{max} have been found after intake of APAP 1500 mg and the C_{max} was reached earlier for six subjects (0.5 h) and much later for two subjects (2 h) with a mean of 65 minutes (min) [45]. The T_{max} was not significantly different between the rosehip drinks with or without lactobacillus Lp299v, but it was higher (100–110 min) compared to water (65 min) [45]. Reductions in

Table 2 – Protective effects of pure nutraceuticals against APAP hepatotoxicity and metabolism.

Animal model	Treatment	Duration	Outcomes	Ref.
Mice C57BL/6 (males), receiving a single oral dose of APAP (300 mg/kg)	Caffeic acid (CA) (10 and 30 mg/kg, oral)	A single dose, 1 h following APAP intake	↓ histological damages ↓ liver MDA, Erg 1 ↓ serum AST, ALT, IL-6, IL-1b and TNF	[31]
Mice ICR (males), receiving a single intragastric dose of APAP (300 mg/kg)	Chlorogenic acid (CGA) (10 or 40 mg/kg, orally)	7 days, followed by a single APAP dose, 1 h after the last dose	↓ hepatic CYP2E1 and CYP1A2 ↑tissue peroxiredoxin, epoxide hydrolase and Nrf2	[32]
Mice Kunming (males), receiving a single i.p dose of APAP (250 mg/kg)	Eriodictyol (50 or 200 mg/kg, intragastric/i.p., then intravenously)	30 min before APAP injection an intragastric/i.p. dose of eriodictyol. Then another dose was given intravenously at APAP injection.	↓ APAP metabolism via hepatic CYP2E1 and CYP3A11 ↑tissue GSH, SOD, CAT, GR and GPX	[33]
Mice BALB/c, receiving a single i.p dose of APAP (350 mg/kg)	Ferulic acid (FA) (10, 30, or 100 mg/kg, orally)	3 doses of FA at 8 h interval before APAP injection	↓ APAP metabolism through hepatic CYP2E1 ↑ tissue SOD and CAT ↓ hepatic TLR4 and NFkB ↓plasma IL-1B and TNF-α	[34]
Specific-pathogen-free (SPF) MT knockout mice (males), receiving a single subcutaneous dose of APAP (250 mg/kg)	Naringenin (200, 400, and 800 mg/kg, intragastric)	4 days before APAP injection	↓ histological damages ↓ tissue MDA ↑tissue GSH/GSSG ↓ serum AST, ALT, and LDH (dose-dependent)	[35]
Rats Wistar (males), receiving a daily oral dose of APAP (100 mg/kg)	Quercetin (5, 10 and 20 mg/kg, oral) or chrysin (50, 100 and 200 mg/kg, oral)	21 days, combined dose of APAP and quercetin or Chrysin	↑ plasma APAP	[36]
C57Bl/6 mice (males), receiving a single i.p APAP dose (300 mg/kg)	Resveratrol (RSV) (50 mg/kg, i.p.)	A single dose, 90 min after APAP	↓ histological damages ↓tissue peroxynitrite, mitochondrial release of endonuclease enzymes and DNA damage	[37]
Mice BALB-c (males and females), receiving a single i.p dose of APAP (900 mg/kg)	Resveratrol (RSV) (30 mg/kg, i.p.)	A single dose, following APAP injection	↓ tissue MDA and MPO ↓ serum AST, ALT, and TNF-α	[38]
Mice C57BL/6 (males), receiving a single i.p dose of APAP (400 mg/kg)	Resveratrol (RSV) (25, 50, and 100 mg/kg, intragastric)	7 times at 12 h interval, then APAP injection 15 min after last RSV dose	↓ hepatic CYP2E1 and CYP1A2 ↓ tissue p53 and JNK ↑ hepatic cyclin D1 and PCNA	[39]
Wistar rats (males), receiving a single i.p dose of APAP (500 mg/kg)	Rosmarinic acid (RA) (10, 50 and 100 mg/kg, intragastric)	7 days before APAP	↓ histological damages ↓ tissue MDA ↑ tissue TAC	[40]
Rats Wistar (males), receiving a single i.p dose of APAP (750 mg/kg)	Syringic acid (SA) (25, 50, and 100 mg/kg, oral)	6 days, followed by APAP injection on the 7th day	↓ histological damages ↑ tissue SOD and CAT ↓serum liver enzymes and bilirubin	[41]
Mice Swiss albino (males), receiving a single i.p dose of APAP (300 mg/kg)	Thearubigins (TRs) (50, 60, and 70 mg/kg, i.p)	A single dose, 90 min after APAP injection	↓ histological damages ↑ tissue GSH ↓ serum ALT	[21]

ALT: alanine aminotransferase; APAP: acetaminophen; AST: aspartate aminotransferase; CAT: catalase; CYP: cytochrome P450; Egr1: early growth response 1 protein; ERK: extracellular-regulated protein kinase; GSH: glutathione; GPX: glutathione peroxidase; GR: glutathione reductase; GSH/GSSG: glutathione-to-oxidized glutathione ratio; IL: interleukin; JNK: c-Jun N-terminal protein kinase; LDH: lactate dehydrogenase; MDA: malondialdehyde; MPO: myeloperoxidase; NF-kB: nuclear factor kappaB; Nrf2: nuclear factor erythroid-2-related factor 2; PCNA: proliferating cell nuclear antigen; SOD: superoxide dismutase; TAC: total antioxidant capacity; TLR4: Toll-like receptor-4; TNF: tumor-necrosis factor. ↓: decrease; ↑: increase; Ref.: reference.

Table 3 – Effects of nutraceuticals and plant foods on APAP pharmacokinetic in humans.

Study design (subjects)	Treatment	Duration	APAP pharmacokinetic	Ref.
Longitudinal (19 healthy)	Tablets (6 daily)One tablet: 370 mg of Spanish black radish, 15.33 mg camu camu, 18.61 mg acerola, honey, manoic root	4 weeks before APAP	APAP (1000 mg) test: ↓ APAP, Glu-APAP, Sul-APAP and NAPQI-GSH (plasma) ↑ Mer-APAP and Sul-APAP (urine) ≈ APAP (urine) ↔ Glu-APAP (urine)	[42]
Crossover (10 healthy)	Watercress homogenates (equivalent to 50 gm watercress)	10 h before APAP	APAP (1000 mg) test: ↓ Cys-APAP and Mer-APAP (plasma and urine) ↔ APAP, Glu-APAP and Sul-APAP (plasma and urine)	[43]
Crossover (8 healthy)	Herbal extract (standardized 4 g curcuminoids plus 24 mg piperine)	2 days before APAP	APAP (325 mg) test: ↔ APAP, Glu-APAP and Sul-APAP (plasma) ↔ APAP, Sul-APAP, Cys-APAP and Mer-APAP (urine) ≈ Glu-APAP (urine)	[44]
Crossover (18 healthy)	Drinks: rosehip with or without Lp299v (200 ml)	Simultaneously with APAP	APAP (1500 mg) test: ↓ APAP (plasma, versus water, no differences within drinks)	[45]
Crossover UGT polymorphisms (66 healthy)	Diet: F&V ≈ 10 servings daily	14 daysbefore APAP	On day 7 and 14 APAP (1000 mg) test: ↑ APAP (saliva, greater on day 7, UGT1A6*2/*2 and UGT2B15*1/*2 genotypes) ↑ Glu-APAP (urine, among women, most pronounced on day 14) ↓ Sul-APAP (urine, most pronounced on day 7)	[46]

APAP: acetaminophen; Cys: cysteine; F&V: fruit and vegetable; Glu: glucuronide; Lp299v: lactobacillus Lp299v; Mer: mercapturate; NAPQI-GSH: N-acetyl-p-benzoquinone imine-glutathione; Sul: sulfate; UGT: uridine diphosphate glucuronosyltransferases. ↓: decrease; ↔: unchanged; ≈: near to significance increase; ↑: increase. Ref.: reference.

C_{max} and AUC were also observed with both rosehip drinks compared to water, especially in the time period up to 90 min. Therefore, the probiotic seems not to influence the rosehip effect on APAP pharmacokinetics [45].

Among the factors that may account for the inter-individual differences in APAP pharmacokinetics, Navarro et al. [46] investigated the diet-gene interactions in a crossover study. Healthy subjects, having different polymorphisms in the UGT family, received 1000 mg of APAP orally on days 7 and 14 of each 2-week feeding period and collected saliva and urine over 12 h [46]. A high (≈10 servings daily) fruit and vegetable (F&V) diet, including cruciferous vegetables (broccoli, cabbage, and daikon radish sprouts), soy foods (soy milk, veggies slices, tofu, and roasted soy nuts), and citrus fruits (grapefruit and orange juices, orange/grapefruit segments, and dried orange peel) was found to induce UGT, compared to a diet devoid of F&V, with a 2-week washout period between the diet periods [46]. Sex, genotype and/or diet differences were observed in salivary APAP pharmacokinetics and urinary excretion of APAP and its metabolites, expressed as percentage of the ingested dose [46]. Overall, salivary APAP C_{max} was higher after F&V diet, but when stratified by genotype, the effect was significant among subjects having UGT1A6*2/*2 or UGT2B15*1/*2 genotypes, whereas an increase in T_{max} was observed only in subjects with the UGT2B15*2/*2 genotype. Besides, C_{max} of salivary APAP was higher in women than in men. In women, urinary % APAP was higher, while % Glu-APAP was lower. Moreover, there was a strong sex-diet interaction with significantly higher % Glu-APAP among women, but not among men, consuming the F&V diet, compared with the basal diet. No statistically significant relationship was found between menstrual phase difference and % Glu-APAP response to F&V supplementation. However, the mean difference in % Sul-APAP between the basal and F&V diets was greater among the women who were not in the same phase of cycle during both diets at day 7, was lower with the F&V than with the basal diet in both groups of women and was no longer significant by day 14. However, overall the % Sul-APAP was lower with the F&V diet relative to the basal diet (Table 3).

As for salivary APAP, diet-gene interactions were found in urinary APAP metabolites [46]. After F&V diet, subjects with UGT1A6*1/*1 had higher % APAP and lower Glu-APAP/APAP ratio than those with UGT1A6*1/*2 and UGT1A6*2/*2 genotypes. On the other hand, despite having a higher Glu-APAP/APAP ratio, UGT2B15*1/*1 individuals had approximately a 2-fold higher F&V to basal diet percentage of difference in ratio response, compared with the UGT2B15*1/*2 and UGT2B15*2/*2 individuals. Therefore, diet-genotype interactions exist, as evidenced by the observed increase in APAP glucuronidation and decrease in Sul-APAP formation after selected F&V consumption [46]. Overall, human studies indicate that interactions occur between APAP and nutraceuticals or plant foods. These interactions depend on both subjects' characteristics and source of phytochemicals.

5. Conclusion

To recapitulate, the reviewed studies indicate that interactions exist between nutraceuticals or plant foods and APAP. Major data came from animal models (Tables 1 and 2),

where both extracts and pure compounds exerted hepatoprotective effects, probably due to their anti-oxidant and anti-inflammatory activities. Furthermore, after treatment with food extracts or pure compounds, modulation of CYP and UGT was found in mice and rats, respectively. In humans (Table 3), both nutraceuticals and the consumption of F&V diet, known to affect phase I and/or phase II metabolism systems, alter APAP pharmacokinetics. In particular, a gene-diet interaction was observed for UGT polymorphisms [46]. Pharmacogenetic profiles have been suggested to have a role in the inter-individual differences in APAP metabolism, the related differences in susceptibility to toxicity and the efficacy of APAP in therapeutics [47].

Although little is known about the influence of race/ethnicity on the metabolism of APAP, Zurlinden et al. [48] recently suggested, by using subpopulation-specific, physiologically-based pharmacokinetic (PBPK) models for Western Europeans and East Asians, that differences in glucuronidation capacity could account for the observed differences in the APAP AUC between the two ethnic groups. Furthermore, it has been reported that faecal bacteria diversify in different ethnic groups [49]. In this context, results from the pseudo germ-free rat model, induced by bacitracin, streptomycin and neomycin treatment, indicated that microbial metabolism affected the plasma concentration of APAP metabolites [50]. In particular, lower AUC(Sul-APAP)/AUC(APAP) ratio and higher AUC of APAP and APAP-glutathione were found in pseudo germ-free rats, compared to the control rats [50]. Therefore, human cross-ethnic studies are needed to evaluate the possible differences in the metabolism, efficacy and toxicity of APAP.

Abbreviation list

AhR	aryl hydrocarbon receptor
ALI	acute liver injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP-1	activation protein-1
APAP	acetaminophen
AST	aspartate aminotransferase
AUC	area under the time versus concentration curve
Bax	BCL2 associated X protein
BCRP	breast cancer-resistance protein
BTE	black tea extract
CA	caffeic acid
CAT	catalase
CGA	chlorogenic acid
C_{max}	maximum concentration
COX	cyclooxygenase
CYP	cytochrome P450
Cys	cysteine
DAMP	damage-associated molecular patterns
Egr1	early growth response 1 protein
ERK	extracellular-regulated protein kinase
F&V	fruit and vegetable
FA	ferulic acid
GFJ	Grapefruit juice
GLDH	glutamate dehydrogenase
Glu	glucuronide
GPX	glutathione peroxidase
GR	glutathione reductase
GSH/GSSG	glutathione-to-oxidized glutathione ratio
GSH	glutathione
GST	glutathione S-transferase
GTE	green tea extract
GTP	green tea polyphenols
HMGB1	high-mobility group box-1
IL	interleukin
iNOS	inducible nitric oxide synthase
JNK	c-Jun N-terminal protein kinase
KIM-1	Kidney injury molecule-1
LDH	lactate dehydrogenase
Lp299v	lactobacillus Lp299v
MAPK	mitogen activated protein kinase
MCT	monocarboxylate transporters
MDA	malondialdehyde
Mer	mercapturate
miR	microRNA
MPO	myeloperoxidase
MRP	multi-drug resistance-associated proteins
mtDNA	mitochondrial DNA
NAC	N-acetylcysteine
NAPQI	N-acetyl-p-benzoquinone imine
NAPQI-GSH	N-acetyl-p-benzoquinone imine-glutathione
NF-kB	nuclear factor kappaB
Nrf2	nuclear factor erythroid 2-related factor 2
OATP	organic anion transporting polypeptides
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PXR	pregnane X receptor
RA	rosmarinic acid
ROS	reactive oxygen species
RSV	resveratrol
SA	syringic acid
SOD	superoxide dismutase
Sul	sulfate
SULT	sulfotransferase
TAC	total antioxidant capacity
TLR4	Toll-like receptor-4
T_{max}	time of maximum concentration
TNF	tumor-necrosis factor
TP	tea polyphenols
TRs	thearubigins
UGT	uridine diphosphate glucuronosyltransferases

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