Toxicology Letters 236 (2015) 154–167

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Mini review

Natural products—friends or foes?

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HIGHLIGHTS

- Food supplements may change the pharmacokinetic profile of drugs.
- Food supplements may change the efficacy of drugs.
- Food and food supplements might induce toxic outcomes in combination with drugs.

ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form 3 May 2015
Accepted 11 May 2015
Available online 14 May 2015

Keywords:
Food supplements
Diet components
Food–drug interactions
Toxic outcomes

ABSTRACT

A trend in the general population has been observed in recent years regarding the orientation toward preventive measures in health; in this context the increased interest from the users and researchers concerning the active effect of food supplements on the health state and on longevity, is noticeable. All over the world, the consumption of natural foods and of vegetal supplements has increased spectacularly over the last 5–10 years. The decreased prevalence of cardio-vascular diseases associated with Mediterranean diet, as well as the French paradox convinced researchers to scientifically document the beneficial outcomes pointed out by traditional use of plants, and to try to develop supplements that would have the same positive effects as these noticed for diet components.

The intense research dedicated to this topic revealed the fact that food supplements are linked to some problematic aspects, such as toxicological side effects when associated with classical synthetic drugs. The food supplement–drug interactions are submitted to complex issues regarding pharmacokinetic interactions leading to changes in absorption, distribution, metabolism and excretion processes with direct impact on effect and toxicological potential.

The present review based on recent literature aims at discussing the food–drug interactions with direct impact on efficacy and toxicity of drugs.

Contents

Abbreviations: ADME, absorption, distribution, metabolism and excretion; ROS, reactive oxygen species; MDA, malondialdehyde; OATP, organic anion transporting polypeptide; QQ, quercetin–quinone; GSH, glutathione; RLE, rat lung epithelial cells; LDH, lactate dehydrogenase; ABC, ATP binding cassette; P-gp, P-glycoprotein; MRP 2, multidrug resistance- associated protein 2; TMD, transmembrane domain; NBD, nucleotide-binding domain; BCRP, breast cancer resistance protein; SGLT1, Na^+- dependent Na1/glucose co-transporter 1; HCC, hepatocellular carcinoma cells; UGT, UDP-glucuronyltransferase; SULT, sulfotransferase.

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http://dx.doi.org/10.1016/j.toxlet.2015.05.009
0378-4274/

1. Introduction

Recent research pointed out an increasing interest concerning the health benefits of a diet rich in natural products and/or vegetal/food supplements. Certain controversies regarding the role of food stuff in promoting health have been registered worldwide both in the research community and in the common population. All over the world, the consumption of natural foods and vegetal supplements has increased spectacularly over the last 5–10 years.

The consumers from developed countries manifest an interest regarding the active role of food on the health state and longevity, specifically on preventing cardio-vascular diseases as well as malignant diseases. Vegetable based diets are considered to reduce the incidence of some chronic diseases (atherosclerotic based cardio-vascular disease, hypertension, type 2 diabetes mellitus, malignancies, hepatic disorders, etc.). For example, the Mediterranean diet, rich in flavonoids, is nowadays considered an effective tool for improving the general health status. In addition, the French paradox is discussed with respect to the ability of red wine polyphenols to reduce the incidence of cardio-vascular disease even in a population consuming a lipid rich diet.

However, as a coin has two sides, there are also some problematic issues, regarding the toxicological aspects that are obviously linked to the use of vegetal supplements and vegetal components of diet, especially when associated with classical medicines. In addition, there are complex issues regarding pharmacokinetic interactions leading to changes of important ADME (absorption, distribution, metabolism and excretion) processes under the effect of natural compounds from diet or food supplements.

Subjects usually consuming rich polyphenols diet are characterized by concentrations of the respective compounds ranging between 2.5 and 10 μM; subjects using natural supplements can reach blood levels of over 20 μM polyphenols. (Tribolo et al., 2008; Winterbone et al., 2009; Margina et al., 2013). Several reports underlined the pro-oxidant effects induced by polyphenols (generally known for their antioxidant effects), whereas some natural compounds have a major influence on P-glycoprotein-mediated transport, thus interacting with anti-cancer therapies. Compounds encountered in cruciferous vegetables (such as polyphenols) modulate the activity of other membrane transporters such as glucose transporter. Moreover, some vegetal extracts generally used in traditional medicine (Devil's claw) or even tea components (epigallocatechin gallate) are listed as inhibitors of CYP enzymes, thus interfering with drug metabolism.

Another important aspect is related to the capacity of some fruit juices (*e.g.*, grapefruit juice) to inhibit the activity of enzymes involved in drug metabolism, thus having an important impact on the pharmacokinetic data and toxicity of these drugs. Other fruit juices (apple, orange) have an inhibitory effect on organic anion transporting polypeptide (OATP) 2B1, thus interfering with the absorption process. As a result concerns are raised regarding the potential interactions of vegetal supplements in patients undergoing chronic therapy, possibly leading to changes of bioavailability, distribution, metabolism, elimination and toxicity of the drugs. The present review aims at discussing certain food–drug interactions with direct impact on efficacy and toxicity of drugs.

2. Polyphenols–antioxidants becoming pro-oxidants

Flavonoids are natural polyphenols, best known as pigments responsible for a diversity of colors found in vegetables (yellow, orange, red, etc.—their name being derived from the Latin word *flavus*, meaning yellow). They are secondary plant metabolites, important for the plant physiology, ensuring the growth, development and defense mechanisms of the plant. Even if their bioavailability is low, dietary intake of flavonoids is correlated with important health benefits (Fraga et al., 2010; Weng and Yen, 2012; Karewicza et al., 2011; Androutsopoulos et al., 2010).

Most of the polyphenolic compounds are found in plants and foods in their glycosylated forms; at the intestinal level, they undergo different biotransformations (depending on the nature of the sugar residue), generally hydrolysis, either in the small intestine (with enzymes such as lactase phlorizin hydrolase or β-glucosidase) or in the colon (under the effect of gut microbiota), the sugar moieties are cleaved and the aglycones are absorbed (Marín et al., 2015). For certain compounds, there are particular features for the biotransformation. For example, flavan-3-ols, (such as (−)-epicatechin), are not glycosylated but acylated with gallic acid and are absorbed at the enterocyte level without any deconjugation or hydrolysis. The absorbed compounds may further undergo hepatic transformations and then reach target organs, *via* blood toward urine excretion.

The bioavailability of polyphenols is also strongly influenced by the nature of the attached sugar, due to interindividual differences regarding the microbiota and digestive enzymes and/or the "associated food matrix" (*e.g.*, dietary fiber divalent minerals, viscous and protein-rich meals, digestible carbohydrates, dietary lipids, etc.). All these factors are reviewed elsewhere (Scholz and Williamson, 2007; Bohn, 2014).

It is important at this point to stress that the bioavailability of hydroxylated flavonoids is a major factor that determines their biological activity *in vivo*. The general consensus suggests that hydroxylated flavonoids, such as quercetin, are subjected to extensive phase II biotransformation reactions that reduce the concentration of the free aglycone in plasma. Since hydroxylated flavonoids are present in very small amounts in their aglycone form in dietary products, the form of flavonoid glucosides is the predominant form of flavonoid compounds that enter the body through food or beverages (Androutsopoulos et al., 2010). Flavonoid glucosides contain one or more sugar groups attached to phenolic hydroxyl groups by a glycosidic bond (Androutsopoulos et al., 2010). The enzyme lactate phlorizin hydrolase (LPH) located in the brush border of the small intestine is capable to catalyze the hydrolysis of certain glucosides, such as quercetin glucosides, to their aglycone (Androutsopoulos et al., 2010; Murota and Terao, 2003). Further conjugation reactions by UGT or SULT enzymes may occur before the