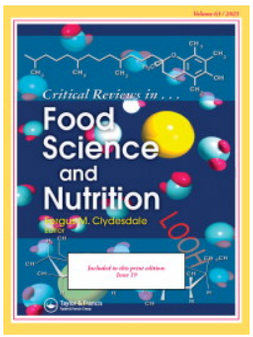

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REVIEW

Food supplement vitamins, minerals, amino-acids, fatty acids, phenolic and alkaloid-based substances: An overview of their interaction with drugs

Maria Lopes[a,b], Manuel A. Coimbra[c,d], Maria do Céu Costa[d,e,f] and Fernando Ramos[a,b,d]

[a]Faculty of Pharmacy, Azinhaga de Santa Comba, University of Coimbra, Coimbra, Portugal; [b]REQUIMTE/LAQV, R. D. Manuel II, Apartado 55142, Oporto, Portugal; [c]LAQV/REQUIMTE, Department of Chemistry, University of Aveiro, Aveiro, Portugal; [d]Economic and Food Safety Authority (ASAE) Scientific Council, Rua Rodrigo da Fonseca, Lisboa, Portugal; [e]CBIOS—Universidade Lusófona's Research Centre for Biosciences & Health Technologies, Lisboa, Portugal; [f]NICiTeS, Polytechnic Institute of Lusophony, ERISA-Escola Superior de Saúde Ribeiro Sanches, Lisboa, Portugal

ABSTRACT

Food supplements are a widespread group of products ingested as a diet complement, whose consumption has recently skyrocketed due to the consumers' concern with their well-being. Among food supplements, vitamin- and mineral-based ones are the top sellers, and the demand of others, such as those containing polyphenols, is increasing. Owing to their alleged natural characteristics, consumers take the safety of food supplements for granted, and use them even when taking medicines. Thus, their potential interactions with drugs have been sparsely evaluated. This manuscript aims to bring forth an up-to-date overview of the most important knowledge involving the interactions between food supplements and drugs, relevant to be aware by nutritionists and other healthcare professionals. To this end, an extensive bibliographic review was conducted focusing on peer reviewed data from experimental *in vivo* evidence and clinical studies whenever major clinical interactions have been reported. Elder people and polymedicated or chronic patients are especially vulnerable to the therapeutic ineffectiveness and toxicity caused by these types of interactions. Drugs used to treat cardiovascular, autoimmune, nervous, and oncological diseases are commonly involved in important clinical interactions with food supplements, many with a narrow therapeutic margin.

KEYWORDS

Adverse effects; drugs; food supplements; interactions; safety

1. Introduction

The use of food supplements, despite being a common and growing practice, is a complex and controversial subject that poses great challenges for health professionals, scientists and regulators (Bilia and Costa 2021). Safety, as well as quality and effectiveness, are the three major concerns associated with the use of food supplements. To ensure compliance with these three requirements, appropriate regulation and enforcement are crucial. In the European Union (EU) and the United States of America (USA), food supplements are legally regarded as "food" or "an especial category of food" and are regulated by general food law and specific legislation, in particular, by Directive 2002/46/EC (European Commission (EC)), 2002) and Dietary Supplement Health and Education Act (DSHEA) (U.S. Food and Drug Administration (FDA)), 1994), respectively. In the EU, the publication of the Directive 2002/46/EC was decisive in the regulation of the food supplement market, namely, in terms of the harmonization of legislation between member states. According to this directive, food supplements are concentrated sources of nutrients, particularly vitamins and minerals, or other substances with nutritional or physiological properties, whose consumption is intended to complement the regular diet and correct any nutritional deficiencies or maintain an adequate intake of specific nutrients. Concerning USA legislation, only the terminology used is slightly different, "dietary supplement," as it refers to the same type of products and the main focus is to ensure the safe use by consumers. As food supplements are legally considered food, unlike medicines, there is in general no need for prior approval by regulatory bodies, as producers and suppliers are those responsible for ensuring their safety and compliance with the requirements of the legislation (van Regnault et al. 2021). These substances can be tablets, capsules, pills, or liquids in measured doses (European Commission (EC)) 2002). In terms of the prevalence and patterns of use, for example, in the USA, according to the 2017–2018 National Health and Nutrition Examination Survey (NHANES), 57.6% of adults (≥20 years) have used food supplements in the preceding 30 days. The consumption of these products was found to be higher in women than men (63.8% versus 50.8%), and it increased with age in both sexes, being higher among women aged 60 years or over (80.2%). Also, the consumption of multiple supplements increased with age, with 25% of adults aged 60 and over reporting the intake of four or more supplements. The most consumed products

CONTACT Fernando Ramos fjramos@ci.uc.ptframos@ff.uc.pt Faculty of Pharmacy, Azinhaga de Santa Comba, University of Coimbra, Coimbra, Portugal.

are multivitamin-mineral supplements, followed by vitamin D and omega-3 fatty acid supplements. Others reported to be heavily consumed are vitamin C, calcium, and plant-based supplements (Mishra et al. 2021). In the USA, about half of supplement consumers have a college degree or more and above-average salaries (Food Standards Agency 2018). They also tend to adopt healthier lifestyle habits (Bailey et al. 2013; Food Standards Agency 2018). The most commonly reported reasons for supplementation are the overall health improvement and maintenance. In general, women tend to use calcium supplements to improve bone health, whilst men are more likely to consume supplements to improve or maintain cardiovascular health as, for example, to lower cholesterol. Older adults (≥60 years) tend to use supplements to improve vision, cardiovascular and osteoarticular health. Among all adults surveyed, only 23% reported supplement use based on the recommendations of a healthcare professional (Bailey et al. 2013). Concerning American children and adolescents (≤19 years), during 2017–2018, about one-third used food supplements. It was found that the consumption of supplements in this age group tends to increase with higher family income and level of education (Stierman et al. 2020). As for the UK, according to the 6th Health of the Nation Survey, 69% of all adults reported taking food supplements in 2019, 41% of which on a daily basis. Only 17.6% of individuals who took supplements did so for a vitamin deficiency, whilst 45.5% did so for overall good feeling and health purposes. Furthermore, about two-thirds of the individuals surveyed plan to take more supplements as they get older, and half of the parents reported that supplements are part of their child's diet. The vast majority (41.8%) bought their supplements from supermarkets, and only 18.9% bought them from a pharmacy. About 17% of people purchased the supplements online, which is particularly worthy of attention given the substantial risks associated with this option. When choosing supplements, most people obtained information through personal research (38.1%) and recommendations from family and friends (27.6%). In 2019, the most consumed supplements in the UK were multivitamins, vitamin C, fish oil/cod liver oil, B complex vitamins and iron (Health Food Manufacturers' Association 2019). This behavior seems to be observed all over the world. In Jordan, in 2019, a prevalence of use of food supplements of 62.1% is to be found. The most commonly consumed products were multivitamins, vitamin D, and vitamin C. About half of the individuals surveyed believed supplements have no side effects, and information about these products was mostly gathered from unreliable sources, such as social networks. Besides, the vast majority has not taken supplements under the guidance of a healthcare professional (Basheer et al. 2021). That said, the food supplement market is undoubtedly a fast-growing one, exhibiting a global market increase of 6.3% between 2014 and 2018, and of 6.7% in North America (USA + Canada) in the homologous period (PwC Deals 2020). In 2018, the market value of food supplements rose to €26 billion in North America and to almost €10 billion in Western Europe (PwC Deals 2020). In 2020 the global food supplements market was valued at €119.7 billion and is expected to reach €129.6 billion in 2021 (Grand View Research 2021). The phenomenon of increasing demand for food supplements is largely due to the growing concern of consumers about their health and well-being, the greater ease of access to food supplements as compared to that of medicines, and the perception that they may have the same effect with a much lower health risk of possible side effects. The aging of the population in developed countries, the adoption of alternative lifestyles such as vegetarianism and veganism, and the desire to improve sports performance are also important drivers of this trend. Furthermore, aggressive marketing and the wide range of products available make their consumption very appealing (Sirico et al. 2018). All in all, the consumption of food supplements is regarded as a preventive measure for health care. In 2019–2021, with the emergence of the pandemic COVID-19 disease caused by SARS-CoV-2, and the widespread news that vitamins, namely vitamin C and D, and certain minerals such as zinc (Shakoor et al. 2021), and other substances such as quercetin (Saeedi-Boroujeni and Mahmoudian-Sani 2021) could help in dealing with the disease, the consumption of food supplements has exceeded all expectations. For instance, in the USA, during the first wave of the COVID-19 pandemic, from March 1 to April 5, 2020, there was a 44% ($435 million) increase in food supplement sales compared to the homologous period in the previous year (Lordan 2021). Likewise, in the UK, according to the Health of the Nation Survey 2021, there has been an increase of 20% in the consumption of food supplements since 2019. More than 70% of the adult population are using supplements, and a third reported having started to use these products as a consequence of the COVID-19 pandemic. In the UK, daily consumers of supplements increased to 20 million people, from 16.5 million in 2019, where the most popular supplements now are vitamin D followed by vitamin C (Health Food Manufacturers' Association 2021). In Slovenia, the use of supplementation increased from 33% in April 2020 (during the first COVID-19 lockdown) to 56% in December 2020 (during the second COVID-19 lockdown) (Žmitek et al. 2021). In Poland, a cross-sectional study based on Google trend analysis reported that during the COVID-19 in March 2020 the interest in and consumption of vitamin and mineral-based food supplements increased. Actually, upon the pandemic outbreak, sales of some types of supplements reached growth rates in the order of three digits (Hamulka et al. 2021). Thus, the current pandemic situation is expected to lead to even greater use of food supplements in the near future. The topic of consumption of food supplements is hence more pressing than ever.

Under normal circumstances, the need for the various nutrients is satisfied by a regular diet including a wide and balanced range of foods and complying with the energetic and nutritional requirements of a healthy person (Sirico et al. 2018). Yet, under certain conditions, i.e., the increase in physiological needs, inadequate supply of nutrients from food sources, or certain specific pathological disorders, the use of food supplements can be justified and advantageous. Notwithstanding, considering the multiple physiological effects of these substances on the different metabolic

pathways, the decision to use a food supplement should be carefully based on a risk-benefit analysis, especially in times where food supplements self-prescription is ever more common.

The amount of specific nutrients can exceed the recommended daily intake (RDI) by as high as 31 times owing to the indiscriminate use of food supplements, which is indeed alarming. Mild to moderate adverse effects, such as abdominal pain, diarrhea, constipation, vomiting, nausea, and headache, have often been reported. There is a real risk of more serious adverse effects such as hepatotoxicity, nephrotoxicity, neurotoxicity, and haematological toxicity, which can even lead to death and cannot be overlooked (Sirico et al. 2018).

A common, serious, and often overlooked problem is the risk of the interaction of food supplements with medicines, which is the focus of this paper. When several pharmacological agents are co-administered, chemical or pharmacological interactions can occur, which may impact the effectiveness of the drugs, leading to a decrease or increase in their action or potentiation of adverse reactions (Gupta et al. 2017). The result depends on the physicochemical nature of the drugs individually and also on how they interact pharmacokinetically and pharmacodynamically. The impact on pharmacokinetics comprises changes in drug absorption, distribution, metabolism, and elimination. The rate and extent of absorption can be affected by the induction or inhibition of the carrier proteins in the intestine, phenomena of chelation, changes in gastric pH, or modifications in gastrointestinal motility (Boccanegra et al. 2020; Karalliedde et al. 2010). Changes in blood flow or permeability of vessels, competition for binding with plasma proteins, modulation of or competition for carriers affect drugs distribution (Boccanegra et al. 2020; Karalliedde et al. 2010). Metabolism can be substantially altered through the induction and inhibition of metabolizing enzymes or competition for the same clearance routes (Karalliedde et al. 2010). Drugs metabolism occurs in two major phases: phase I, in which enzymes such as those of cytochrome P450 (CYP450) system oxidize their substrates, which change reactivity and increase water solubility (Couto et al. 2021); and phase II, where uridine diphosphate glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) conjugate phase I reaction products through glucuronidation or sulfation to facilitate excretion (Couto et al. 2021; Fatunde and Brown 2020). CYP3A, which metabolizes about 60% of all drugs, is a CYP450 enzyme subfamily predominantly involved in phase I of biotransformation. CYP2D6 is responsible for the metabolism of 25% of all drugs, including antiarrhythmics, beta-blockers, and anticancer drugs. CYP2C9 is the second most abundant CYP450 subfamily and metabolizes anticoagulant drugs such as warfarin, whilst CYP2C19 is responsible for clopidogrel metabolism. Excretion can be impacted by inducing or inhibiting carrier proteins, as well as by lessening blood flow to the excretion organs. P-glycoprotein (P-gp)—an efflux transporter—organic anion-transporting polypeptides (OATPs) and organic cation transporters (OCTs) play a major role in the transport of many molecules (Boccanegra et al. 2020; Karalliedde et al. 2010). Pharmacodynamic interaction mechanisms include additive, synergistic and antagonistic effects.

The mechanisms of interaction between drugs and between drugs and food supplements are essentially the same. However, these mechanisms are more complex in the latter case since many compounds often of a very different nature are involved (Gupta et al. 2017). Antioxidant supplements, such as those of the currently very popular resveratrol and quercetin, are an example of the intricate nature of food supplements, as they are usually manufactured from extracts of plants, which additionally contain a large number of other compounds. Hence, it is highly unlikely that the results of interaction studies performed based on the pure bioactive components be consistent with those obtained based on the extracts (Choi and Chin 2021). This renders the identification of potential interactions arising from their consumption a major challenge. In this context, it should be emphasized that it cannot be assumed that a food supplement constituted by a mixture of ingredients is safe simply because its individual constituents are so. There are multiple examples of combinations of compounds that individually exert different biological effects from those that occur when combined (Gershwin et al. 2010). In addition, the chemical composition of a given extract may vary, even when made from different plants with the same binomial name. This is due to the influence of aspects such as location, growing conditions, harvest time, transport and storage conditions, and extraction methodology (Choi and Chin 2021; Waidyanatha et al. 2018). Other aspects, such as the presence of contaminants and the occurrence of adulteration, can create additional problems in the evaluation of potential supplement-drug interactions (Choi and Chin 2021; Lopes et al. 2020; Waidyanatha et al. 2018). Therefore, considering that in general the most commonly used supplements contain multiple vitamins in a single formula, often combined with minerals and small amounts of plant extracts, the potential for interactions seems almost infinite. It is, hence, crucial to identify which of these are clinically relevant.

Health professionals tend to underestimate the practice of self-consumption of food supplements, as patients rarely declare such practice (Silva et al. 2018; Spanakis et al. 2021), what is particularly worrying in certain groups of individuals. For example, it is estimated that between 50% and 80% of the patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) do not report their self-medication to the health professionals and about 80% of them are using at least one food supplement (Bordes et al. 2020). In the case of children, which have immature gastric, immune and nervous systems, the adverse events tend to be more severe than in healthy adults. Older adults are also at great risk for food supplement-drug interactions. These individuals are major consumers of food supplements and are often polymedicated. Moreover, they exhibit pharmacokinetic (e.g., hepatic and renal dysfunction) and pharmacodynamic changes (e.g., exaggerated responses), which are part of the normal aging process, and increase their susceptibility to serious adverse effects (Delafuente 2008; Karalliedde et al. 2010). Patients polymedicated with drugs with a narrow therapeutic index

(e.g., tacrolimus, cyclosporin, digoxin, warfarin, phenytoin, pimozide, theophylline, quinidine, or ergotamine) are equally a risk group. In fact these molecules are associated with more serious clinical interactions and minor changes in concentrations enough to cause important side effects. This becomes particularly worrying when considering the existence of genetic polymorphisms, that is, individuals who are "fast and ultra-fast metabolisers" whilst others are "poor metabolisers." For the same dose, the latter achieve a higher plasmatic concentration of the drug or supplement than the former. Patients with infections are also more predisposed to food supplement-drug interactions because the presence of endotoxin or interferon causes a global induction of CYP450 activity. In smokers, the metabolism of drugs and supplements can also be increased, since smoking causes the induction of CYP1A2, CYP2E1 and UGTs (Karalliedde et al. 2010).

Hence this work is designed to be a reference for health professionals and those in the food science and technology sector, surveying the most clinically relevant interactions between food supplements and drugs. A critical analysis of the literature published in or after 2000 in this field was carried out, with focus on data from clinical studies, including data from animal trials whenever these reported interactions with potentially serious clinical outcomes. Overall, this review covers the interactions between drugs and food supplements, that is with vitamins and minerals, the most frequently used components, and comprehending also amino acids, fatty acids and phenolic compounds which, although less reported in interaction studies, have an emerging use. The group of alkaloid compounds is, for the first time, treated as such within the scope of assessment of food supplement-drug interactions. The legal framework of food supplements is briefly presented, as well as the main determinants behind the consumption of these products, the risks and benefits of their use, groups of individuals most likely to suffer from food supplement-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms. Once these are exposed, selected interactions of particular relevance are highlighted. Strategies to avoid the occurrence of this type of interactions are also discussed. Detailed information on the major potential interactions is also given in an easy to consult format.

Although information on food supplements has been growing, most of it is of a strong laudatory nature and lacks a solid scientific basis. Furthermore, information relating to potential risks of interaction with medicines is scarce and very dispersed, which makes the work of professionals who deal with this issue highly challenging. This manuscript intends to fulfill the arising need of trustworthy information by introducing the fundamental concepts needed for a better understanding of the problem and by providing updated information presented in a concise manner.

2. Vitamin-based supplements

Vitamins are the most consumed food supplement in many countries (Dickinson et al. 2014; Rogovik, Vohra, and Goldman 2010; Sirico et al. 2018). They are a group of organic substances crucial to the proper functioning of the human organism, even if only in small doses. When ingested at excessive levels, they can trigger well documented adverse effects (Rogovik, Vohra, and Goldman 2010; Sirico et al. 2018). Furthermore, vitamins interact with a large number of drugs. Vitamins A, D, E, and K (the chemical names of the aforementioned vitamins are shown in Table 1), which are fat-soluble, and hence not being easily excreted, tend to accumulate and cause serious adverse effects, demanding great care in their use. The antagonistic effect of vitamin K on anticoagulants such as warfarin—a drug with a narrow therapeutic margin—is worthy of mention. Water-soluble vitamins, such as B1, B2, B5, B7, B12, and C (Table 1), exhibit considerable potential for interactions with drugs, but mostly with reversible and not-so-serious adverse effects, since they are easily excreted. Vitamins B3 and B9 (Table 1) are noteworthy exceptions as, although soluble in water, they are associated with important toxicity and potential for interaction with drugs, wherefore their administration requires close attention (Rogovik, Vohra, and Goldman 2010).

Vitamins are safe in doses within the recommended daily intake (RDI), whether short and long-term; however important adverse effects can arise when taking high doses of a single vitamin (Sirico et al. 2018). The RDI for vitamin A is 300–700 µg/day (~1000–2000 IU) for children and 700–900 µg/day (~2300–4300 IU) for adults (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)), 2012). While these doses of vitamin A are not associated with toxic effects, higher doses, i.e., 12,000 µg/day (~40,000 IU), can result in important hepatotoxicity, leading to the appearance of symptoms such as headache, vertigo, nausea, blurred vision, muscle pain, lack of coordination, skin peeling and alopecia. Severe overdose can even cause coma and death (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)), 2012). Likewise, vitamin D, a potent sterol hormone, is increasingly recognized as a fundamental part of human health, with growing evidence that its benefits go far beyond bone health, being increasingly consumed and prescribed in the form of supplements. This great popularity of vitamin D today is certainly a reflection of people's increased awareness of and concern about the possible consequences of low vitamin D levels (Cianferotti et al. 2015). Yet, this ample use of these vitamin D treatments has also brought about a substantial increase in the number of reports of vitamin D intoxication. Vitamin D toxicity involves the occurrence of hypercalcaemia and includes manifestations ranging from the mildest, such as thirst and polyuria, to the most severe ones, such as seizures, coma and death. Cases of intoxication are usually a consequence of inadequate prescription, consumption of unauthorized preparations, as well as the use of high-dose formulations without the supervision of a healthcare professional (Taylor and Davies 2018). Within this context, it is important to note that the marked increase in vitamin D prescription worldwide in the last decade may be due to an overzealous correction of vitamin D deficiency by physicians, often without prior confirmation of a real deficit (Kaur, Mishra, and Mithal 2015). Furthermore, data from the study by Wan et al. (2019) suggest that guidelines on

Table 1. Interactions between drugs and vitamin-based supplements (↗ – Increase; ↘ – decrease).

Vitamin	Interactions			
	Effects on the drug	References	Effects on the vitamin	References
A (3-dehydroretinol, retinol, retinoids, retinyl acetate, retinyl palmitate, beta-carotene)	**Metabolism (↘) | Plasma levels (↗) | Adverse effects (↗):** Warfarin (anticoagulant): increased bleeding risk. The interaction mechanism should be related to the CYP2C19 inhibition. Caution in co-administration with drugs that affect haemostasis. **Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Acetaminophen (nonnarcotic analgesic and antipyretic drug). **Adverse effects (↗) | Effectiveness (↘):** Simvastatin (antihyperlipidemic): increased risk of hepatotoxicity. **Adverse effects (↗):** Isotretinoin, acitretin, tretinoin, bexarotene, tazarotene, etretinate (retinoid derivatives): increased risk of hepatoxicity. Vitamin A can potentiate liver dysfunction. Caution in co-administration with hepatotoxic drugs (e.g., acetaminophen, isoniazid, carbamazepine, methotrexate, amiodarone, or methyldopa). Tetracyclines (antibiotics): increased risk of intracranial hypertension. Paclitaxel (anticancer drug): increased risk of bone marrow suppression. **Effectiveness (↗|↘):** Contradictory results for anticancer drugs.	(Berginc and Kreft 2014; Cheung et al. 2001; Mouly et al. 2017; Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010; Seifried et al. 2003; Williamson, Driver, and Baxter 2009)	**Absorption (↗) | Plasma levels (↗):** Zinc (mineral). **Plasma levels (↗):** Isotretinoin, acitretin, tretinoin, bexarotene, tazarotene, etretinate (retinoid derivatives); statins (antihyperlipidemics); antipsoriatics. Estrogens (oral contraceptives/hormone replacement therapy). The interaction mechanism should be related to the mobilization of hepatic vitamin storage. **Absorption (↘) | Plasma levels (↘):** Neomycin (antibiotic); colchicine (uricosuric drug); cholestyramine, colestipol (bile acid sequestrants); aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium carbonate (antacids); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); orlistat (anti-obesity drug); olestra (fat substitute). **Absorption (↘) | Plasma levels (↘) | Excretion (↗):** Laxatives. These drugs reduce the transit time in the intestine, causing diarrhea and, consequently, an increase in the fecal loss of fat-soluble vitamins. **Plasma levels (↘):** Medroxyprogesterone (oral contraceptive/hormone replacement therapy). Vitamin A deficiency causes decreased immunity to infections. In severe situations, it can lead to xerophthalmia and night blindness. **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics.	(Berginc and Kreft 2014; Meletis and Zabriskie 2007; Mohn et al. 2018; Mouly et al. 2017; Thurnham 2004; Williamson, Driver, and Baxter 2009)
B1 (Thiamin mononitrate, thiamin hydrochloride)	**Excretion (↗):** Furosemide (loop diuretic). **Effectiveness (↘):** Chemotherapy drugs.	(Berginc and Kreft 2014; Goldman, Vohra, and Rogovik 2009; Rogovik, Vohra, and Goldman 2010)	**Absorption (↘) | Plasma levels (↘):** Aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium carbonate (antiacids). The interaction mechanism should be related to the change in gastric pH. Metformin (antidiabetic): increased risk of lactic acidosis. The interaction mechanism should be related to the inhibition of intestinal ThTR-2–mediated thiamin transport. **Metabolism (↗) | Plasma levels (↘) | Excretion (↗):** Estrogen, progesterone (oral contraceptives/hormone replacement therapy); theophylline (bronchodilator). **Cell availability (↘) | Excretion (↗):** Antihypertensive drugs in general. **Tissue delivery (↘):** Digoxin (cardiotonic and antiarrhythmic drug); **Transport across the blood-brain barrier (↘):** Phenytoin (antiepileptic drug). **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/ inhibitor of platelet aggregation). **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics. Vitamin B1 deficiency causes peripheral neuropathy.	(Berginc and Kreft 2014; Goldman, Vohra, and Rogovik 2009; Karalliedde et al. 2010; Mouly et al. 2017; Noland and Drisko 2020; Vora et al. 2020)

B2 (Riboflavin, riboflavin 5′-phosphate sodium, vitamin G, lactoflavin)	**Effectiveness (↗):** Imipramine, desipramine, amitriptyline, nortriptyline (antidepressants); phenothiazines (antipsychotics); phenytoin (antiepileptic). **Absorption (↘) | Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Effectiveness (↘):** Quinacrine (antimalarial drug/antibiotic). **Metabolism (↗):** Anticancer drugs. **Cancer cell delivery (↘) | Effectiveness (↘):** Methotrexate (anticancer drug). **Effectiveness (↘):** Doxorubicin (anticancer); sulfamethoxazole (sulphonamide antibiotic) and other sulpha-containing drugs.	(Berginc and Kreft 2014; Goldman, Vohra, and Rogovik 2009; Noland and Drisko 2020; Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010)	**Absorption (↘) | Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Tetracyclines (antibiotics); imipramine, amitriptyline, chlorpromazine (antidepressants); thioridazine, haloperidol, molindone, chlorpromazine (antipsychotics); barbiturates (antiepileptics). **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Estrogen, progesterone (oral contraceptives/hormone replacement therapy). **Absorption (↘) | Excretion (↗):** Probenecid (uricosuric drug). **Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Boron (mineral). **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation). **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics. Vitamin B2 deficiency states are associated with the occurrence of cheilosis, glossitis, and normochromic anemia.	(Berginc and Kreft 2014; Karalliedde et al. 2010; Mason 2008; Noland and Drisko 2020)
B3 (Niacinamide, niacin, nicotinic acid, nicotinamide, vitamin PP)	**Metabolism (↘) | Plasma levels (↗) | Excretion (↘) | Adverse effects (↗):** Carbamazepine, primidone, valproic acid, clobazam (antiepileptics). **Action (↗) | Adverse effects (↗):** Warfarin (anticoagulant)**;** acetylsalicylic acid, ibuprofen, naproxen (nonsteroidal anti-inflammatory drugs/inhibitors of platelet aggregation): increased bleeding risk. Acetylsalicylic acid may also potentiate gastritis induced by niacin. Clonidine (antihypertensive): risk of exacerbation of orthostatic hypotension. Statins (antihyperlipidemics): increased risk of myopathy and rhabdomyolysis (only at daily doses of niacin > 1 g/day). **Effectiveness (↘):** Insulin, metformin, sulfonylureas, acarbose, nateglinide, repaglinide, pioglitazone, rosiglitazone (antidiabetic drugs). Allopurinol, probenecid, sulfinpyrazone (uricosuric drugs). Niacin can increase uric acid plasma levels due to inhibition of uricase or decreased uric acid excretion. Niacin can potentiate liver dysfunction. Caution in co-administration with hepatotoxic drugs (e.g. acetaminophen, isoniazid, carbamazepine, methotrexate, amiodarone, or methyldopa).	(Baxter 2009; Berginc and Kreft 2014; Caballero, Finglas, and Toldrá 2016; Goldman, Vohra, and Rogovik 2009; Hadeler and Maderal 2021; Heemskerk et al. 2014; Karalliedde et al. 2010; Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010; Song and FitzGerald 2013)	**Metabolism (↘) | Plasma levels (↗) | Excretion (↘) | Adverse effects:** Primidone (antiepileptic). **Plasma levels (↗) | Excretion (↘):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation). The interaction mechanism should be related to the competition for conjugation with glycine, which functions as a detoxification mechanism. **Absorption (↘):** Ibuprofen, naproxen (nonsteroidal anti-inflammatory drugs). The interaction mechanism should be related to the competitive intestinal transport and the occurrence of lesions in the gastrointestinal mucosa. **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation). **Plasma levels (↘) | Body stores (↘):** Isoniazid (antituberculosis drug); valproic acid (antiepileptic); estrogen, progesterone (oral contraceptives/hormone replacement therapy); long-term administration of antibiotics. Depleting vitamin B3 stocks leads to peripheral neuropathy and pellagra.	(Berginc and Kreft 2014; Karalliedde et al. 2010; Kipsang et al. 2019; Mouly et al. 2017; Noland and Drisko 2020)

(*Continued*)

Table 1. (Continued)

	Interactions			
Vitamin	Effects on the drug	References	Effects on the vitamin	References
B5 (D-Pantothenic acid, dexpanthenol, D-pantothenate sodium, D-pantothenate calcium)	**Action (↗):** Antimalarial drugs; antihyperlipidemics. More studies are required.	(Miller and Rucker 2020)	**Transport across the placenta (↘):** Primidone, carbamazepine (antiepileptics). The interaction mechanism should be related to the competition for sodium-dependent multivitamin transporters. **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/ inhibitor of platelet aggregation). **Plasma levels (↘) | Body stores (↘):** Estrogen, progesterone (oral contraceptives/hormone replacement therapy); tetracyclines (antibiotics). Vitamin B5 deficiency causes paraesthesia, namely "burning feet" syndrome.	(Berginc and Kreft 2014; Karalliedde et al. 2010; Miller and Rucker 2020)
B6 (Pyridoxine hydrochloride, pyridoxine 5′-phosphate, pyridoxine dipalmitate)	**Effectiveness (↗):** Nortriptyline, amitriptyline, desipramine, imipramine (antidepressants). Antidiabetic drugs. Supplementation with pyridoxine may have an advantageous effect on glucose tolerance, through the activation of either apokynureninase or kynureninase. **Adverse effects (↘):** Estrogen, progesterone (oral contraceptives/ hormone replacement therapy). Pyridoxine supplementation when using these drugs can be advantageous in that it can have an antidepressant effect and also contribute to the normalization of glucose tolerance. **Metabolism (↗) | Plasma levels (↘) | Effectiveness (↘):** Levodopa (antiparkinson's drug). This effect occurs only in the absence of dopa-decarboxylase inhibitors, which is not a common clinical practice. A pyridoxine derivative is a cofactor in the reaction of peripheral conversion of levodopa to dopamine, which therefore reduces the amount available for conversion in the CNS. Dopa-decarboxylase inhibitors suppress the peripheral conversion reaction. Hydralazine (antihypertensive). The interaction mechanism should be related to the formation of inactive complexes between pyridoxine and the drug. **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Effectiveness (↘):** Phenytoin, fosphenytoin, phenobarbital, primidone (antiepileptics).	(Baxter 2009; Conner 2013; Karalliedde et al. 2010; Noland and Drisko 2020)	**Absorption (↘) | Plasma levels (↘)** Corticosteroids; theophylline (bronchodilator). **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Estrogen, progesterone (oral contraceptives/hormone replacement therapy); primidone, phenytoin, carbamazepine, oxcarbazepine, topiramate, levetiracetam, gabapentin, phenobarbital (antiepileptics). **Plasma levels (↘) | Excretion (↗):** Isoniazid (antituberculosis drug). **Cell availability (↘) | Excretion (↗):** Antihypertensive drugs in general. **Plasma levels (↘):** Phenelzine, tranylcypromine (antidepressants); levodopa, carbidopa, benserazide (antiparkinson's drugs); cycloserine (antibiotic); penicillamine (antirheumatic drug). **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/ inhibitor of platelet aggregation). **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics; hydralazine (antihypertensive); isoniazid, ethionamide (antituberculosis drugs). The interaction mechanism should be related to the formation of inactive complexes between pyridoxine and the drug. Depleting vitamin B6 stocks leads to peripheral neuropathy and pellagra.	(Berginc and Kreft 2014; Conner 2013; Karalliedde et al. 2010; Mouly et al. 2017; Noland and Drisko 2020; Rojo-Sebastián, González-Robles, and Yébenes 2020)

B7 (D-biotin, coenzyme R, vitamin H, W factor)			**Absorption (↘) | Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Primidone, phenytoin, carbamazepine, topiramate, phenobarbital (antiepileptics). **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/ inhibitor of platelet aggregation). **Plasma levels (↘) | Body stores (↘):** Tetracyclines (antibiotics).	(Berginc and Kreft 2014; Karalliedde et al. 2010; Noland and Drisko 2020)
B9 (Acid folic, 5-methyltetrahydrofolate, folacin, folate, L-methylfolate)	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Methotrexate (anticancer/immunosuppressant); ibuprofen (nonsteroidal anti-inflammatory drug); zinc (mineral). Cimetidine, ranitidine (histamine type-2 receptor antagonists). The interaction mechanism should be related to a phenomenon of precipitation and reduction of facilitated diffusion. **Metabolism (↘) | Plasma levels (↗) | Excretion (↘) | Adverse effects (↗):** Capecitabine (anticancer drug). A patient died possibly due to this interaction. **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Effectiveness (↘):** Primidone, phenobarbital, phenytoin, carbamazepine, oxicarbamazepine, levetiracetam (antiepileptics). The use of folic acid in high doses may antagonize the effects of anticonvulsants. **Plasma levels (↘) | Excretion (↗):** Metformin (antidiabetics); antihypertensives; diuretics. **Effectiveness (↘):** Mafenide, sulfadiazine, sulfacetamide, sulfisoxazole, trimethoprim, dapsone, chloramphenicol (antibiotics); proguanil, pyrimethamine, sulfadoxine (antimalarial drugs); methotrexate (anticancer/immunosuppressant). These drugs act as antagonists of folic acid. There is an important risk with prolonged use or high doses.	(Baxter 2009; Berginc and Kreft 2014; Fernández-Villa, Aguilar, and Rojo 2019; Karalliedde et al. 2010; Mason 2008; Mouly et al. 2017; Ramos et al. 2014)	**Absorption (↘) | Erythrocyte uptake (↘):** Isoniazid (antituberculosis drug). **Absorption (↘) | Plasma levels (↘):** Cholestyramine, colestipol (bile acid sequestrants); corticosteroids; valproic acid (antiepileptic); cimetidine, ranitidine (histamine type-2 receptor antagonists); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); metformin (antidiabetic); pancreatin (pancreatic enzymes); zinc (mineral). **Absorption (↘) | Plasma levels (↘) | Intracellular cycling (↘):** Methotrexate (anticancer/immunosuppressant); sulfasalazine, mesalazine (aminosalicylates); triamterene (diuretic); colchicine (uricosuric). **Absorption (↘) | Metabolism (↗) | Plasma levels (↘) | Cell transport (↘) | Excretion (↗) | Body stores (↘):** Primidone, phenytoin, carbamazepine, oxicarbamazepine, topiramate, levetiracetam, gabapentin, phenobarbital (antiepileptics). **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Estrogen, progesterone (oral contraceptives/hormone replacement therapy); acetylsalicylic acid, ibuprofen, naproxen (nonsteroidal anti-inflammatory drugs/inhibitors of platelet aggregation). **Excretion (↗)** Methyldopa (antihypertensive). **Plasma levels (↘) | Body stores (↘):** Mafenide, sulfadiazine, sulfacetamide, sulfisoxazole, trimethoprim, dapsone, chloramphenicol (antibiotics); proguanil, pyrimethamine, sulfadoxine (antimalarial drugs); methotrexate (anticancer/immunosuppressant). These drugs act as antagonists of folic acid. Tetracyclines, cycloserine (antibiotics). Vitamin B9 deficiency can lead to the occurrence of megaloblastic anemia and cognitive dysfunction.	(Baxter 2009; Berginc and Kreft 2014; Conner 2013; Karalliedde et al. 2010; Mason 2008; Noland and Drisko 2020)

(*Continued*)

Table 1. (Continued)

	Interactions			
Vitamin	Effects on the drug	References	Effects on the vitamin	References
B12 (Cyanocobalamin, hydroxocobalamin, methylcobalamin)			**Absorption (↗) | Plasma levels (↗):** Metronidazole (antibiotic). The interaction mechanism should be related to the fact that metronidazole decreases the number of bacteria, which consequently reduces the probability of vitamin B12 binding. Prednisolone (corticosteroid). The interaction mechanism should be related to the stimulation of acidic gastric secretion. **Absorption (↘) | Plasma levels (↘):** Aminoglycosides, aminosalicylic acid, (antibiotics); cholestyramine, colestipol (bile acid sequestrants); acetylsalicylic acid (nonsteroidal anti-inflammatory drug/ inhibitor of platelet aggregation); aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium carbonate (antacids); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); sulfasalazine, mesalazine (aminosalicylates); colchicine (uricosuric); methyldopa (antihypertensive); biguanides, thiazolidinediones (antidiabetics); cimetidine, ranitidine (histamine type-2 receptor antagonists); vitamin C. Thiazides (diuretics). These drugs cause hyperkalaemia, which interferes with the absorption of vitamin B12. **Absorption (↘) | Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics; steroids; anticancer drugs. Zidovudine (antiretroviral). This interaction is particularly problematic because it adds to other issues that cause low levels of vitamin B12 in HIV-positive people. **Absorption (↘) | Metabolism (↗) | Plasma levels (↘) | Cell transport (↘) | Excretion (↗) | Body stores (↘):** Primidone, phenytoin, carbamazepine, oxicarbamazepine, topiramate, levetiracetam, gabapentin, phenobarbital (antiepileptics). **Absorption (↘) | Plasma levels (↘) | Excretion (↗):** Metformin (antidiabetic). **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Body stores (↘):** Estrogen, progesterone (oral contraceptives/hormone replacement therapy). **Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/ inhibitor of platelet aggregation). **Action (↘):** Chloramphenicol (antibiotic). Chloramphenicol can cause severe and potentially fatal bone marrow depression, which is the opposite action of vitamin B12. **Inactivation:** Nitrous oxide (anesthetic). When used in prolonged anesthesia.	(Baxter 2009; Conner 2013; Karalliedde et al. 2010; Mohn et al. 2018; Mouly et al. 2017; Noland and Drisko 2020; Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010; Tamura et al. 2000; van Oijen et al. 2004; Williamson, Driver, and Baxter 2009; Wulffele et al. 2003)

C (L-ascorbic acid, sodium-L-ascorbate, potassium-L-ascorbate, calcium-L-ascorbate, L-ascorbyl 6-palmitate)	**Absorption (↗) | Plasma levels (↗):** Iron (mineral) and iron-containing drugs; chromium (mineral). **Absorption (↗) | Plasma levels (↗) | Excretion (↘) | Adverse effects (↗):** Aluminum-containing antacids: increased risk of encephalopathy in patients with renal failure, and constipation in patients in general. **Plasma levels (↗):** Tetracyclines (antibiotics); estrogens (oral contraceptives/hormone therapy replacement). **Excretion (↘) | Action (↗) | Adverse effects (↗):** Acetaminophen (non narcotic analgesic and antipyretic drug). Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation). The interaction mechanism should be related to the fact that the acidification of urine by vitamin C can increase the reabsorption of salicylates in the renal tubules. **Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Propranolol (antihypertensive); fluphenazine (antipsychotic). **Absorption (↘) | Metabolism (↗) | Plasma levels (↘) | Effectiveness (↘):** Indinavir (antiretroviral): risk of the development of drug resistance. The interaction mechanism should be related to the induction of CYP3A4. **Excretion (↗):** Antidepressant drugs. The interaction mechanism should be related to the fact that low pH urine hinders the passive reabsorption of the drug. Desferrioxamine (chelator). The excretion of iron promoted by desferrioxamine is increased by taking vitamin C. Mexiletine (antiarrhythmic). **Effectiveness (↘):** Doxorubicin and other free radical anticancer drugs. The interaction mechanism should be related to the potent capacity of vitamin C to neutralize free radicals. Simvastatin (antihyperlipidemic). Vitamin C may block the response of HDL to simvastatin-niacin therapy. Warfarin (anticoagulant). **Adverse effects (↗):** Acetazolamide (diuretic): increased risk of formation of kidney stones.	(Berginc and Kreft 2014; Bordes et al. 2020; Cheung et al. 2001; Karalliedde et al. 2010; Mason 2008; Mouly et al. 2017; Ramos et al. 2014)	**Absorption (↗):** Iron (mineral) and iron-containing drugs. **Absorption (↘) | Plasma levels (↘):** Hydrocortisone (corticosteroid). **Plasma levels (↘):** Tetracyclines (antibiotics); fluphenazine (antipsychotic); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors). **Absorption (↘) | Plasma levels (↘) | Excretion (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation). **Metabolism (↗) | Plasma levels (↘) | Excretion (↗):** Estrogens (oral contraceptives/hormone therapy replacement). **Excretion (↗):** Phenobarbital, primidone (antiepileptics); diuretics. Vitamin C deficiency is associated with the occurrence of mucosal bleeding, lethargy, and hyperkeratosis.	(Baxter 2009; Berginc and Kreft 2014; Conner 2013; Karalliedde et al. 2010; Mason 2008; Ramos, Figueiredo, and Caramona 2018)

(*Continued*)

Table 1. (Continued)

Vitamin	Interactions			
	Effects on the drug	References	Effects on the vitamin	References
D (1,25-Dihydroxycholecalciferol, 25-hydroxycholecalciferol, dihydrotachysterol, alfacalcidol, paricalcitol, calcitriol, calcifediol, calcipotriene, cholecalciferol, ergocalciferol)	**Absorption (↗) | Plasma levels (↗) | Adverse effects (↗):** Magnesium (mineral): increased risk of hypermagnesaemia, especially in patients with renal insufficiency. Aluminum-containing drugs. The interaction mechanism related to the fact that the proteins involved in the transportation of calcium from the intestinal lumen, through the epithelial cells, into the bloodstream, can also bind to aluminum and transport it. As vitamin D stimulates the expression of these carrier proteins, an increase in the intestinal absorption of aluminum may occur, which can lead to the appearance of toxic effects, especially in patients with renal failure who take aluminum-based phosphate binders and vitamin D as chronic pharmacological therapy. Calcipotriene (synthetic vitamin D3 derivative): increased risk of hypercalcaemia. Even though calcipotriene is used topically, if absorbed in considerable quantities it can have a systemic effect. **Adverse effects (↗):** Thiazides (diuretics): increased risk of hypercalcaemia. The interaction mechanism is related to the fact that thiazides decrease the excretion of calcium. Calcium (mineral): increased risk of hypercalcaemia. **Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Bisphosphonates (antiresorptive drugs). **Metabolism (↗) | Plasma levels (↘) | Excretion (↗) | Effectiveness (↘):** Lercanidipine (antihypertensive). The interaction mechanism should be related to the CYP3A4 induction. Warfarin (anticoagulant): increased risk of portal vein thrombosis. The interaction mechanism should be related to the CYP2C9 induction. **Action (↗) | Adverse effects (↗):** Insulin and oral antidiabetics: increased risk of hypoglycemia. **Effectiveness (↘):** Digoxin (cardiotonic and antiarrhythmic): increased risk of severe cardiac arrhythmias as a result of the occurrence of hypercalcaemia. Verapamil (antihypertensive): increased risk of hypercalcaemia, which can lessen the effectiveness of verapamil in atrial fibrillation. Calcitonin (calcium metabolism modifier). Antagonistic effect.	(Berginc and Kreft 2014; Hu et al. 2019; Karalliedde et al. 2010; Mason 2008; Mouly et al. 2017; Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010)	**Plasma levels (↗):** Calcipotriene (synthetic vitamin D3 derivative). **Absorption (↘) | Plasma levels (↘):** Prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone (corticosteroids); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); bile acid sequestrants; laxatives. **Absorption (↘) | Metabolism (↗) | Plasma levels (↘):** Phenobarbital, phenytoin (antiepileptics); theophylline (bronchodilator); orlistat (anti-obesity drug). **Cell availability (↘):** Statins (antihypertensives). **Osteoclastic bone resorption (↗):** Clorazepate, diazepam (anxiolytics). **Transformation to active forms (↘):** Antituberculosis drugs; corticosteroids; cimetidine (histamine type-2 receptor antagonist); antiepileptics. The lack of vitamin D leads to the occurrence of osteomalacia and osteoporosis.	(Baxter 2009; Berginc and Kreft 2014; Conner 2013; Mouly et al. 2017; Orces, Montalvan, and Tettamanti 2020; Ramos, Figueiredo, and Caramona 2018)

E (Alpha-tocopherol, beta-tocopherol, delta-tocopherol, gamma-tocopherol)	**Absorption (↗) | Plasma levels (↗):** Cyclosporin (immunosuppressant). **Action (↗) | Adverse effects (↗):** Warfarin (anticoagulant); acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation): increased bleeding risk. Insulin (antidiabetic): increased risk of hypoglycemia. **Adverse effects (↗):** Ibuprofen, naproxen (nonsteroidal anti-inflammatory drugs): increased bleeding risk. Tipranavir (antiretroviral): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis. **Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Propranolol (antihypertensive). **Effectiveness (↘):** Digoxin (cardiotonic and antiarrhythmic): increased risk of cardiac arrhythmias. Simvastatin (antihyperlipidemic). Antioxidant supplements may block the response of HDL to simvastatin-niacin therapy. Iron (mineral). Vitamin E supplementation can impair the response to iron treatment in those individuals with anemia caused by lack of iron. **Effectiveness (↗|↘):** Contradictory results for anticancer drugs.	(Berginc and Kreft 2014; Bordes et al. 2020; Chan 2001; Cheung et al. 2001; Mason 2008; Mouly et al. 2017; Pastori et al. 2013; Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010; Seifried et al. 2003)	**Absorption (↗) | Plasma levels (↗):** Cyclosporin (immunosuppressant). **Absorption (↘) | Plasma levels (↘):** Cholestyramine, colestipol (bile acid sequestrants); sucralfate (gastrointestinal protectant); statins (antihyperlipidemics); laxatives. **Plasma levels (↘) | Body stores (↘):** Estrogens (oral contraceptives/hormone therapy replacement); chlorpromazine (antipsychotic); desipramine (antidepressant); phenobarbital, phenytoin, carbamazepine (antiepileptics); gemfibrozil (antihyperlipidemic); orlistat (anti-obesity drug); olestra (fat substitute). Vitamin E deficiency states lead to the occurrence of ataxia, peripheral neuropathy, and hemolytic anemia.	(Baxter 2009; Berginc and Kreft 2014; Karalliedde et al. 2010; Mason 2008)
K (K1—Phytonadione, K2—menaquinone, K3—menadione, K4—menadiol acetate, K5 – 4-amino-2-methyl-1-naphthol)	**Effectiveness (↘):** Warfarin (anticoagulant). Antagonistic effect. Caution in co-administration with drugs that affect haemostasis.	(Berginc and Kreft 2014; Kurnik et al. 2004; Rogovik, Vohra, and Goldman 2010)	**Absorption (↘) | Plasma levels (↘):** Cholestyramine, colestipol (bile acid sequestrants); sucralfate (gastrointestinal protectant); colchicine (uricosuric); orlistat (anti-obesity drug); laxatives. **Intracellular cycling (↘):** Warfarin (anticoagulant); cephalosporins (antibiotics). **Metabolism (↗) | Plasma levels (↘):** Barbiturates (antiepileptics). **Plasma levels (↘) | Body stores (↘):** Antibiotics in general. Vitamin K deficiency causes spontaneous hemorrhage and hypothrombinaemia.	(Berginc and Kreft 2014; Noland and Drisko 2020; Ramos, Figueiredo, and Caramona 2018)

vitamin D supplementation are not being consistently followed, particularly in the case of children.

At this point, it is important to stress that food supplements, for example, multivitamins, are very often advised by health professionals, such as physicians, pharmacists, nutritionists, and nurses, a recommendation which requires specialized knowledge and an effective communication with patients, if proper use is to be ensured. In a study conducted by Holt (2014), the habits of self-consumption and recommendation to patients of food supplements by general practitioners (GPs) and pharmacists in New Zealand were evaluated. It was noted that GPs and pharmacists often take supplements themselves and routinely recommend them to their patients. Among GPs, 66% reported recommending multivitamins to their patients, 76% vitamin D and 30% vitamin C, while among pharmacists 52% indicated recommending multivitamins, 19% vitamin D and 52% vitamin C. It was difficult to conclude whether the recommendations were based on robust scientific evidence, as these supplements were recommended for a variety of situations . There is no solid scientific evidence to support the use of multivitamins to improve health in general, however, in the case of the existence of a real or suspected nutritional deficiency, their use may be sensible, which was the most stated reason for their recommendation (Holt 2014). In another work, Dickinson et al. (2011) assed the use of food supplements by cardiologists, dermatologists and orthopedists. It was found that 57%–75% of physician specialists use these products—most commonly multivitamins, the maintenance of their own good health being the most often mentioned reason, while 66%–91% recommend supplements to their patients . Furthermore, recommending supplements to their patients is also related to their field of expertise . When asked about their views on supplements, 55% of cardiologists, 69% of dermatologists, and 75% of orthopedists said they thought it to be "a good idea for patients to take multivitamins." In terms of vitamins, cardiologists indicated that their patients often ask about vitamin E, dermatologists about vitamins E and D, and orthopedists cite vitamin D as the one their patients seek most (Dickinson et al. 2011). In dermatology, vitamins B3 and B7 are also frequently prescribed (Hadeler and Maderal 2021; Waqas et al. 2020). Regarding the latter, it is worth mentioning the study by Waqas et al. (2020), in which biotin recommendation practices by USA clinics and their knowledge about the interference of this vitamin in laboratory tests were evaluated. It was found that 43.9% prescribe biotin, mainly for hair and nail issues, and 39.5% recommend other biotin-containing supplements. Most physicians were aware that there are no randomized trials proving that vitamin B7 helps in the treatment of dermatological conditions, and that it interferes with thyroid function tests and troponins. Yet, few knew about the interference with both HIV and hepatitis serology, beta human chorionic gonadotrophin, and vitamin D levels. Finally, 19.5% had no knowledge of whatever interference. Nearly half of clinicians did not alert to the need to interrupt biotin supplementation prior to laboratory testing, which suggests that knowledge of interferences may not be reflected in the medical practice. It should be underlined that the Food and Drug Administration (FDA) advised that biotin interference with laboratory tests can lead to incorrect diagnosis and even patient death (Waqas et al. 2020). All in all, these studies highlight the need to increase healthcare professionals' awareness of the risks and benefits of recommending food supplements. It is worthy of note that in the study by Dickinson et al. (2011) most clinicians mentioned not having received any formal education or training on food supplements and expressed interest in acquiring more knowledge, namely in continuing education programs. Therefore, it is essential to expand the training of healthcare professionals regarding to food supplements, with special emphasis on the topic of interactions.

Concerning the potential for interaction of vitamins with medicines, a detailed list is shown in Table 1. It should be noted that the data discussed throughout this review are gathered mostly from clinical studies, and occasionally from in vivo animal trials when potentially major clinically relevant interactions are detected.

Supplements with vitamin A, which are much sought after by those with vision problems, interact with drugs such as warfarin (anticoagulant), simvastatin (antihyperlipidemic), and acetaminophen (analgesic and antipyretic), potentiating their adverse effects, that is, increasing the risk of bleeding from the first one, and of hepatotoxicity in the case of the last two drugs (Ramos et al. 2014). This can be especially important owing to the fact that both warfarin and simvastatin are often used chronically, the first being additionally a drug with a narrow therapeutic index. Thus, in general, the simultaneous use of supplements with vitamin A, warfarin and simvastatin should be avoided whenever possible. Also, the co-administration of retinoids and vitamin A- containing supplements it not recommended owing the additive effects and increased risk of vitamin A toxicity (Rogovik, Vohra, and Goldman 2010).

With regard to vitamin B3, when used concomitantly with anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory drugs (NSAIDs) in general (Rogovik, Vohra, and Goldman 2010), this vitamin can also increase the risk of bleeding, as well as decrease the effect of antidiabetics (Heemskerk et al. 2014; Song and FitzGerald 2013) and uricosuric drugs (Rogovik, Vohra, and Goldman 2010; Song and FitzGerald 2013). Furthermore, thanks to their cholesterol lowering effect, vitamin B3 supplements are often used in the treatment of dyslipidemia, but their concomitant use with statins may increase the risk of severe myopathies (Ramos et al. 2014). Awareness of these potential interactions is therefore necessary.

Vitamin D supplements, widely used for the prevention and treatment of osteoporosis, may increase the risk of portal vein thrombosis when co-administered with warfarin (anticoagulant) (Levy et al. 2017), as well as decrease the efficacy of digoxin and increase aluminum absorption, an element well known for its toxicity to nerve and kidney cells (Ramos et al. 2014; Rogovik, Vohra, and Goldman 2010). In general, vitamin D doses above 50 μg/day for adults are not recommended (Rogovik, Vohra, and Goldman 2010). In the case of patients taking digoxin, high vitamin D doses can induce hypercalcemia which increases the risk of fatal

cardiac arrhythmias. When digoxin and vitamin D co-administration is really necessary, calcium levels should be regularly monitored. Also, patients with renal failure and taking aluminum-containing phosphate binders, should be closely monitored, owing to the high risk of toxicity by the increased aluminum levels (Rogovik, Vohra, and Goldman 2010). Recently, Orces, Montalvan, and Tettamanti (2020) conducted a study to assess the effect of statins on serum vitamin D concentrations among older adults. It was found that the mean of 25-hydroxyvitamin D [25(OH)D] and D3 [25(OH)D3] levels were, regardless of treatment duration, 4.4 nmol/L and 3.3 nmol/L higher amongst individuals taking statins. Interestingly, in the analysis of subgroups, this association was stronger in those patients with a daily intake of vitamin D < 400 IU, and attenuated among those with intakes ranging from 400 to 800 and >800 IU per day (Orces, Montalvan, and Tettamanti 2020). Based on the fact that cholesterol and vitamin D share a common precursor—7-dehydrocholesterol (7-DHC)—it is plausible that the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) may contribute to an increase in 7-DHC concentrations, thus yielding a suitable base for the 25(OH) D synthesis. Furthermore, the competition between vitamin D and statins for CYP3A4 metabolism is another mechanism that may contribute to the increase of 25(OH)D concentrations (Orces, Montalvan, and Tettamanti 2020). This is a newly identified potential interaction for which we should be on the alert.

Considering vitamin E, it can intensify the effects of anticoagulants, antiplatelet agents and NSAIDs, increasing the risk of bleeding (Mouly et al. 2017; Pastori et al. 2013; Rogovik, Vohra, and Goldman 2010) and can also potentiate the action of insulin (Mason 2008), increasing the risk of hypoglycemia crises. On the other hand, it can reduce the effectiveness of drugs such as simvastatin (Cheung et al. 2001). These potential interactions require attention and caution, especially with regard to treatment with anticoagulants/antiplatelets. If supplementation with vitamin E is effectively necessary during anticoagulant treatment, the international normalized ratio (INR) should be carefully monitored for one to two weeks after the start and end of supplementation with the vitamin (Karalliedde et al. 2010). Large doses of vitamin E, i.e., above 100 U/day, should be absolutely avoided in patients taking anticoagulants (Karalliedde et al. 2010).

Vitamin K is not commonly available alone as a supplement, but rather as a component of some multivitamin formulas (Mason 2008). Warfarin therapy requires close monitoring to prevent bleeding and maintain the required therapeutic levels, and it is well known that high vitamin K intake can decrease warfarin's effectiveness significantly (Rogovik, Vohra, and Goldman 2010). On the other hand, a poor vitamin K status tends to increase sensitivity to slight fluctuations in vitamin K intake, as shown in the study by Kurnik et al. (2004). In this work a multivitamin containing vitamin K in small doses (25 μg/day) was administered for 4 weeks to individuals at stable anticoagulation, which lead to subtherapeutic INRs, demanding an increase in the dose of warfarin in individuals with vitamin K depletion, that is with vitamin K plasma levels <1.5 mg/L, but not in patients with plasma levels of vitamin K > 4.5 mg/L. Hence, the most important measure is to ensure that patients maintain a regular balanced diet, as warfarin interactions with food generally do not cause clinically significant changes (Kurnik et al. 2004). Instead, supplementation should be strictly on the recommendation of an appropriately trained healthcare professional.

The few examples discussed above clearly demonstrate that the potential of interaction of vitamins with drugs is vast. Within this scope, it should be underlined that the consumption of vitamin supplements is not only very frequent in adults, but also among younger people, who are known to be especially vulnerable (Elliott 2019). In this sense, to determine the frequency and types of potential interactions between vitamins and drugs in children arriving at a pediatric emergency department Goldman, Vohra, and Rogovik (2009) conducted a cross-sectional study involving nearly 1800 families. It was found that 11% of children who used vitamin-based supplements had had potential vitamin-drug interactions in the previous trimester, and among these, 37% had had more than one potential interaction . The most common interaction detected was between vitamin C and acetaminophen. It is well established that vitamin C decreases the renal clearance of acetaminophen, which can lead to supratherapeutic plasma concentrations of this drug, and consequently result in the occurrence of hepatotoxicity . Acute paracetamol intoxication is quite problematic for clinicians, especially in the pediatric context, owing to its insidious evolution to severe hepatitis that can culminate in death. Another frequently identified interaction was that of vitamins B3 and E with ibuprofen (NSAID), which can increase the risk of bleeding (Goldman, Vohra, and Rogovik 2009). Recently, in a study by Elliott (2019), food supplements commercialized in Canada for children were assessed concerning their nutrient levels. The median dose found was superior to the appropriate intake (AI) recommendations set by the Institute of Medicine and Health of Canada for vitamins A, B1, B2, B6, B7, B9, B12, and C. Several studies have warned of the dangers of excessive intake of both vitamins A and B9 in children, since these vitamins are widely used as fortifiers in foods commonly consumed by them. Hence, it is relatively easy to exceed the AI, which adds to the high potential that these vitamins exhibit for clinically relevant interactions with drugs, as discussed, and exponentially increases the risk of problems (Elliott 2019).

In light of the above, the real need for supplementation stresses the need for its follow-up. For instance, the depletion of the body's vitamin reserves caused by some drugs, such as estrogens and antiepileptics, justifies an increase in vitamin intake through supplementation. Recently, Rojo-Sebastián, González-Robles, and Yébenes (2020) conducted a study in which the effect of levodopa/carbidopa therapy on the levels of vitamin B6 of patients with Parkinson's disease was evaluated. It was observed that this drug can negatively impact the serum levels of the aforementioned vitamin. This finding highlights the need for monitoring these patients, and for an eventual

supplementation. In that case, preference should be given to mono-vitamin formulas, since multi-vitamin ones represent an increased risk of potentially dangerous interactions.

3. Mineral-based supplements

Minerals are inorganic elements, which act as cofactors for enzymes, thus influencing overall energy metabolism. Supplements based on minerals are, like those based on vitamins, widely used, often even in conjunction with vitamins, either by self-medication or on the recommendation of health professionals.

Among the various minerals, calcium supplements have been reported as the most consumed, especially by women, to prevent osteoporosis, a condition prevalent in women (Dickinson et al. 2014; Skeie et al. 2009). In this sense, Dickinson et al. (2011) investigated the use of food supplements by various medical experts, and 63% of surveyed orthopedists reported that their patients frequently asked about the use of calcium supplements. Moreover, 93% of these experts consider that patients with a family history of osteoporosis or bone issues should consider using a calcium supplement (Dickinson et al. 2011). Likewise, in a study conducted by Holt (2014), self-consumption and recommendation to patients of supplements by GPs and pharmacists were assessed, and 30% of GPs were reported to recommend calcium supplements to their patients, and 42% to recommend supplements of magnesium. Among pharmacists, 10% were reported to recommend calcium supplements and 67% magnesium supplements. Interestingly, the prevention or treatment of nocturnal cramps was one of the common reasons for recommending patients to use magnesium, although the currently available scientific evidence is clearly insufficient (Holt 2014). In another research, Hetherwick, Morris, and Silliman (2006) evaluated the attitudes of California dietitians toward food supplements and found that their majority use and recommend food supplements, respectively 69% and 74%. The supplements most recommended by these professionals were calcium, multivitamins combined or not with minerals, and also vitamins E and C, and iron. To ensure appropriate nutrient intake, to prevent the manifestation of osteoporosis, to help with wound healing, to prevent anemia, and to preserve an overall good health were among the most commonly cited explanations for using and recommending such supplements. In this context, it is important to emphasize that although the consumption of mineral supplements is generally safe under the recommended conditions, the excess thereof can lead to toxicity. For instance, calcium is an essential mineral, but in very high doses it can contribute to the development of atherosclerosis . Similarly, high doses of iron can cause serious issues with iron storage in patients with haemochromatosis (Soni et al. 2010). In addition, it should be noted that the current evidence from randomized clinical trials does not support the use of vitamin and/or mineral supplements to reduce the risk of non-communicable diseases such as cancer, cardiovascular diseases, and type 2 diabetes (Zhang et al. 2020). Even with regard to osteoporosis, studies on the effects of calcium and vitamin D supplementation report results that are not entirely consistent (Zhang et al. 2020). However, in the absence of a clear evidence on the benefits of supplementation, it is prudent to ensure that recommendations regarding vitamin and mineral intake are met either through diet or through supplementation.

Concerning the use of mineral-based supplements, it is strongly recommended that in general they be taken about 2–4 h before or after taking the drug, thus preventing changes in gastric pH and the occurrence of complexation reactions in the intestinal lumen (Berginc and Kreft 2014). As with vitamins, individuals at risk of deficiency should preferably use mono-mineral formulas to avoid major interactions.

Table 2 presents information on the major mineral–drug interactions of clinical relevance. Calcium supplementation may reduce the absorption of drugs such as biphosphonates, which are commonly used in the treatment of osteoporosis, penicillamine, which is a disease-modifying anti-rheumatic drug, and antibiotics, namely quinolones and tetracyclines. In the case of antibiotics, the decrease in plasma concentrations due to chelation phenomena that reduce drug absorption can be of particular concern, since it can lead to therapeutic failure, as well as potentiate the development of antimicrobial resistance, currently a major threat to global public health. As a general recommendation, the administration of calcium and biphosphonates should be separated at least 30 min, and with penicillamine or antibiotics at least 2 h (Karalliedde et al. 2010). Besides, the prolonged use of calcium supplements, especially when in high doses, can induce hypercalcemia, and in the case of concomitant therapy with cardiac glycosides such as digoxin, fatal arrhythmias can occur (Mouly et al. 2017). Hence, the co-administration of calcium supplements and digoxin should be avoided. Hypercalcemia is also a rare adverse effect of tamoxifen, the risk thereof can increase with calcium supplementation (Mason 2008). Healthcare professionals should be aware of this interaction and monitor their patients when calcium supplementation in patients taking tamoxifen is unavoidable. On the other hand, drugs such as antiepileptics and corticosteroids can lessen serum calcium concentrations, wherefore calcium supplements may be required in these cases.

Concerning iodine, supplementation can alter the response to thyroid treatments, requiring adjustments in dose and duration of therapy (Berginc and Kreft 2014). Close monitoring of triiodothyronine, thyroxine and thyroid-stimulating hormone (TSH) levels is strongly recommended.

Iron supplements, which are widely used by women, owing to the higher risk of anemia in this gender (Skeie et al. 2009), can reduce the absorption of drugs such as quinolones, tetracyclines (Mouly et al. 2017; Ramos et al. 2014), levothyroxine (Levy et al. 2017; Ramos et al. 2014), biphosphonates (Mouly et al. 2017) and levodopa (Mason 2008). Hence, female individuals may be particularly susceptible to the aforementioned interactions and should be advised not to supplement without the recommendation of a health professional. In general, the advice is to separate the administration of drug doses as much as possible from

Table 2. Interactions between drugs and mineral-based supplements (↗ Increase; ↘ decrease).

	Interactions			
Mineral	Effects on the drug	References	Effects on the mineral	References
Boron	**Plasma levels (↗) | Excretion (↘):** Magnesium (mineral). **Excretion (↗):** Vitamin B2.	(Koren-Michowitz et al. 2005)		(Mason 2008)
Calcium	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Quinolones, tetracyclines (antibiotics); levothyroxine (thyroid drug); bictegravir, dolutegravir, elvitegravir, raltegravir (antiretrovirals); alendronate, risedronate, etidronate (bisphosphonates); penicillamine (antirheumatic drug). The interaction mechanism is related to the formation of insoluble chelates. Estramustine (anticancer). The interaction mechanism is related to the formation of a weakly absorbable calcium phosphate complex. Magnesium, fluoride, iron, zinc (minerals). The interaction mechanism should be related to the competition for absorption. **Effectiveness (↘) | Adverse effects (↗):** Digoxin (cardiotonic and antiarrhythmic): increased risk of severe cardiac arrhythmias as a result of the occurrence of hypercalcaemia; digitalic toxicity. The levels of calcium are directly related to the action of digoxin, wherefore, elevated levels, even if transitory, can potentiate digoxin toxicity. **Adverse effects (↗):** Thiazides (diuretics): increased risk of milk-alkali syndrome. The interaction mechanism is related to the fact that thiazides decrease the excretion of calcium. Tamoxifen (anticancer): increased risk of hypercalcaemia.	(Bordes et al. 2020; Karalliedde et al. 2010; Levy et al. 2017; Mason 2008; Mouly et al. 2017; Neuhofel et al. 2002; Ramos et al. 2014; Straub 2007)	**Absorption (↗) | Plasma levels (↗):** Vitamin D: increased risk of hypercalcaemia. **Plasma levels (↗) | Excretion (↘):** Thiazides (diuretics): increased risk of hypercalcaemia. **Absorption (↘) | Plasma levels (↘):** Alendronate, risedronate (bisphosphonates); aluminum-containing antacids; fluoride (mineral). Phenytoin, fosphenytoin, pentobarbital, carbamazepine (antiepileptics): increased risk of hypocalcemia and osteomalacia. These drugs lessen calcium absorption by increasing vitamin D metabolism. Proton-pump inhibitors and histamine type-2 receptor antagonists lessen the absorption of calcium carbonate, which needs a low pH environment. Laxatives. These drugs reduce the transit time in the intestine, causing diarrhea and, consequently, an increase in the fecal loss of minerals. **Absorption (↘) | Plasma levels (↘) | Excretion (↗):** Corticosteroids. These drugs can cause important bone loss. **Plasma levels (↘) | Excretion (↗):** Loop diuretics; acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation); sodium (mineral). **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics.	(Ito and Jensen 2010; Karalliedde et al. 2010; Mason 2008; Mouly et al. 2017; Straub 2007)
Chromium	**Action (↗) | Adverse effects (↗):** Insulin and oral antidiabetics: increased risk of hypoglycemia. Chromium is a key cofactor in insulin regulation. It works by promoting the binding of insulin to receptors and increasing their number and phosphorylation, resulting in increased transport of insulin to the liver, muscle, and adipose tissue.	(Dubey, Thakur, and Chattopadhyay 2020; Ramos et al. 2014)	**Absorption (↗) | Plasma levels (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation); vitamin C. **Absorption (↘) | Plasma levels (↘):** Aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium carbonate (antacids). **Plasma levels (↘):** Iron (mineral). Chromium and iron use the same carrier, transferrin, hence, in the presence of high levels of iron, there is a competition phenomenon that can result in chromium deficiency.	(Mason 2008; Ramos et al. 2014)

(*Continued*)

Table 2. (Continued)

Mineral	Interactions			
	Effects on the drug	References	Effects on the mineral	References
Copper	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Penicillamine (antirheumatic drug); trientine (copper-chelating); iron, zinc (minerals).	(Mason 2008)	**Absorption (↘) | Plasma levels (↘):** Penicillamine (antirheumatic drug); trientine (copper-chelating); vitamin C; molybdenum, iron (minerals). Zinc (mineral). The interaction mechanism is related to the induction of metallothionein proteins in intestinal cells, which bind to copper and inhibit its absorption. Allopurinol (uricosuric). The interaction mechanism should be related to the chelation of copper by allopurinol. **Excretion (↗):** Hydralazine (antihypertensive).	(Karalliedde et al. 2010; Mason 2008; Noland and Drisko 2020)
Fluoride			**Absorption (↘) | Plasma levels (↘):** Calcium (mineral).	(Karalliedde et al. 2010)
Iodine	**Action (↗|↘):** Thyroid drugs.	(Mason 2008)		
Iron	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Quinolones, tetracyclines (antibiotics); levothyroxine (thyroid drug); alendronate, risedronate (bisphosphonates); levodopa, carbidopa (antiparkinson's drugs); penicillamine (antirheumatic drug); bictegravir, dolutegravir, elvitegravir, raltegravir (antiretrovirals). The interaction mechanism is related to the formation of insoluble chelates.	(Bordes et al. 2020; Levy et al. 2017; Mason 2008; Mouly et al. 2017; Ramos et al. 2014)	**Absorption (↘) | Plasma levels (↘):** Aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium carbonate (antacids); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); cimetidine, ranitidine (histamine type-2 receptor antagonists); tetracyclines (antibiotics); warfarin (anticoagulant); trientine (copper-chelating); calcium, copper, zinc (minerals). **Plasma levels (↘)** Antiplatelet drugs. **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics.	(Karalliedde et al. 2010; Mason 2008; Mouly et al. 2017; Noland and Drisko 2020; Ramos et al. 2014)
Manganese	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Bictegravir, dolutegravir, elvitegravir, raltegravir (antiretrovirals). The interaction mechanism is related to the formation of insoluble chelates.	(Bordes et al. 2020)	**Absorption (↘) | Plasma levels (↘):** Iron (mineral).	(Mason 2008)
Magnesium	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Quinolones, tetracyclines (antibiotics); levothyroxine (thyroid drug); bictegravir, dolutegravir, elvitegravir, raltegravir (antiretrovirals); alendronate, risedronate (bisphosphonates); penicillamine (antirheumatic drug). The interaction mechanism is related to the formation of insoluble chelates. **Plasma levels (↘):** Digoxin (cardiotonic and antiarrhythmic). **Adverse effects (↗):** Calcitriol, doxercalciferol (vitamin D analogues): increased risk of hypermagnesaemia.	(Mason 2008; Mouly et al. 2017; Ramos et al. 2014)	**Absorption (↘) | Plasma levels (↘):** Warfarin (anticoagulant); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); cimetidine, ranitidine (histamine type-2 receptor antagonists). **Excretion (↗):** Loop and thiazide diuretics; digoxin (cardiotonic and antiarrhythmic). **Action (↘):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation). Possible antagonistic effect. **Plasma levels (↘) | Body stores (↘):** Long-term administration of antibiotics. Estrogens (oral contraceptives/hormone therapy replacement). Penicillamine (antirheumatic drug).	(Karalliedde et al. 2010; Mason 2008; Mouly et al. 2017; Noland and Drisko 2020)

Molybdenum	**Plasma levels (↘):** Copper (mineral).	(Mason 2008)		
Phosphorous			**Absorption (↘) | Plasma levels (↘):** Calcium-, magnesium- and aluminum- containing drugs.	(Karalliedde et al. 2010)
Potassium	**Absorption (↘) | Plasma levels (↘):** Trientine (copper-chelating). **Absorption (↘) | Plasma levels (↘) | Excretion (↗):** Methenamine (antibiotic). Potassium citrate increases the urine pH, which leads to an increase in the excretion of this drug. **Adverse effects (↗):** Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic receptor antagonists (antihypertensives and heart failure drugs); cyclosporin, tacrolimus (immunosuppressants); potassium-sparing diuretics; ibuprofen, naproxen (nonsteroidal anti-inflammatory drugs): increased risk of hyperkalaemia. Additive effect. Loop and thiazide diuretics; acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation); cortisone, prednisone (corticosteroids): increased risk of hypokalemia.	(Karalliedde et al. 2010; Mason 2008)	**Absorption (↗) | Plasma levels (↗) | Excretion (↘):** Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic receptor antagonists (antihypertensives and heart failure drugs); cyclosporin, tacrolimus (immunosuppressants); potassium-sparing diuretics; ibuprofen, naproxen (nonsteroidal anti-inflammatory drugs). **Absorption (↘) | Plasma levels (↘)** Trientine (copper-chelating). **Plasma levels (↘)** Antiplatelet drugs. **Absorption (↘) | Plasma levels (↘) | Excretion (↗):** Laxatives. **Excretion (↗):** Loop and thiazide diuretics; acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation); cortisone, prednisone (corticosteroids).	(Karalliedde et al. 2010; Mason 2008; Noland and Drisko 2020)
Selenium		(Dodig and Čepelak 2004)	**Plasma levels (↘):** Clozapine (antipsychotic); zinc (mineral).	(Karalliedde et al. 2010)
Zinc	**Absorption (↘) | Plasma levels (↘) | Effectiveness (↘):** Quinolones, tetracyclines (antibiotics); alendronate, risedronate (bisphosphonates); penicillamine (antirheumatic drug); integrase inhibitors (antiretrovirals); calcium, selenium, iron, copper (minerals). **Plasma levels (↘)** Eltrombopag (thrombopoietin receptor agonist); baloxavir marboxil (cap-endonuclease inhibitor).	(Hadeler and Maderal 2021; Mason 2008; Mouly et al. 2017)	**Absorption (↘) | Plasma levels (↘):** Tetracyclines (antibiotics); penicillamine (antirheumatic drug); cimetidine, ranitidine (histamine type-2 receptor antagonists); omeprazole, lansoprazole, rabeprazole, esomeprazole (proton-pump inhibitors); estrogens (oral contraceptives/hormone therapy replacement); warfarin (anticoagulant). Folic acid (vitamin B9): increased risk of intrauterine growth retardation and congenital malformations. This interaction is particularly serious in pregnant women, who are recommended to use folic acid to prevent neural tube defects and other birth anomalies. Iron (mineral): increased risk of intrauterine growth retardation and congenital malformations. **Excretion (↗):** Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers (antihypertensives and heart failure drugs); hydrochlorothiazide, chlorthalidone (diuretics). **Action (↘):** Calcium (mineral).	(Hadeler and Maderal 2021; Koren-Michowitz et al. 2005; Mason 2008; Mouly et al. 2017; Noland and Drisko 2020)

the iron supplement intake and monitor effects, increasing the dose of the drug if necessary (Karalliedde et al. 2010). With regard to specifically the co-administration of iron and levothyroxine, the doses should be separated by at least 2 h and thyroid function tests should be done regularly (Karalliedde et al. 2010). Conversely, antacids and proton-pump inhibitors can reduce the absorption of iron, as well as other minerals such as calcium, magnesium and zinc, and vitamins such as B9, B12 and D (Mouly et al. 2017). In these cases, it is recommended to separate the administration of minerals and drugs by at least 2 h (Karalliedde et al. 2010).

As with calcium supplements, those with magnesium should not be taken simultaneously with quinolones, tetracyclines, bisphosphonates, levothyroxine, and penicillamine, as an eventual reduction in the bioavailability of these drugs can result in subtherapeutic doses (Ramos et al. 2014). To minimize this, the drug dose should be administrated at least 2 h apart from the magnesium supplement (Karalliedde et al. 2010). Magnesium supplements may furthermore lower plasma concentrations of digoxin (Ramos et al. 2014). In this case, simultaneous use should be avoided when possible, and when otherwise patients should be closely monitored.

Potassium supplements are often used to lower blood pressure and are associated with an increased risk of hyperkalaemia when used concomitantly with antihypertensive drugs such as angiotensin-converting-enzyme inhibitors and potassium-sparing diuretics (Karalliedde et al. 2010). Co-administration of potassium and the aforementioned drugs, if absolutely necessary, requires close monitoring of serum potassium levels, ideally daily (Karalliedde et al. 2010). Hyperkalaemia is often asymptomatic or has nonspecific symptoms but if not promptly detected and treated it can lead to fatal cardiac arrhythmias (Karalliedde et al. 2010).

As the issue of antimicrobial resistance is a pressing global challenge that requires our full attention, affecting antibiotics and also other antimicrobial agents such as antiparasitics, antifungals and antivirals, the retrospective study of James et al. (2020) is worthy of mention. This research involving 360 patients medicated with antiretrovirals, namely integrase inhibitors, 152 of which took simultaneously mineral and/or vitamin supplements, assessed the impact of polyvalent cations, e.g., calcium and iron, on the efficacy of the pharmacological therapy. Virological suppression was found to have failed in a total of 46 patients (13% of the sample), 28 of which had taken polyvalent cations (18.4% of the respective sample), and 18 of which had not (8.7% of the respective sample). Individuals who took polyvalent cations exhibited a risk of treatment failure 2 times greater than those without any type of supplementation (James et al. 2020). Antiretroviral therapy has evolved significantly, providing simpler therapeutic regimens, better safety profiles and higher efficacy, yet it often involves the use of several drugs simultaneously, which exponentially increases the risk of serious clinical interactions when associated with self-medication of food supplements (Bordes et al. 2020). Hence, patients under this type of therapy need to be regularly reminded of the risk of self-medicating with food supplements to ensure the safety and effectiveness of the treatment now and in the future.

4. Amino acid-based and fatty acids-based supplements

Currently, the growth in demand for food supplements is mainly driven by supplements based on amino acids and fatty acids (PwC Deals 2020). There is no solid evidence to support the benefits of consumption of amino acid-based supplements and, at least in some cases, such practice may pose risks (Table 3). Regarding essential fatty acid-based supplements, fish oils are the most used, and they can be of two types: (1) fish liver oils (typically from cod, halibut, hake and shark) and (2) fish body oils (from sardines, mackerel, herring and anchovies). Both contain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and vitamin E. Fish liver oils are also rich in vitamins A and D (Mason 2008). Fish oils are used in a variety of health conditions, in particular in the prevention and management of cardiovascular diseases, and there is convincing evidence that they can contribute to reducing triglycerides, blood clotting, and blood pressure (Buckley, Goff, and Knapp 2004; Mason 2008). Patients with arthritis and inflammatory bowel diseases may also use them, and there is some scientific evidence to support this use, although not as robust. For other conditions such as cancer or mental illnesses, the evidence is insufficient.

According to the study of Dickinson et al. (2011) a very large number of patients seek omega-3 supplements to improve their cardiovascular health. Actually, 80% of the surveyed cardiologists reported that their patients ask them about these supplements. In addition, over 25% of the inquired doctors in each speciality, i.e., cardiology, dermatology and orthopedics, said they had taken omega-3/fish oil supplements, which attests to the high prevalence of consumption of these supplements even among healthcare professionals. Also, 69% of cardiologists believe that individuals with a family history of cardiovascular diseases should consider taking omega-3 fatty acids supplements (Dickinson et al. 2011). In this regard, a very recent study by Ishitsuka et al. (2021) about food supplementation practices in Japanese elementary schools reports that 6.8% of the surveyed children were supplement consumers. The most common products provided were amino acids or protein-based supplements, followed by omega-3 fatty acids or fish oils, multivitamins, and multivitamin-minerals. Notably, the use of amino acids or protein-based supplements and multivitamins was significantly associated with sports practice. Supplements of omega-3 fatty acids are commonly used in youngsters to improve their cognitive and nutrition status (Ishitsuka et al. 2021). The results of the previously mentioned work are in line with those of a national survey conducted in the USA by Qato et al. (2018) during 2003–2014, which showed that an increasing number of children and adolescents use non-vitamin and non-mineral supplements, namely amino acid and protein-based supplements and omega-3 fatty acids. Altogether, these studies alert to the need to be aware of

Table 3. Interactions between drugs and amino acids- and fatty acids-based supplements (↗ Increase; ↘ decrease).

	Interactions	
Amino acids and amino acid derivatives	Effects on the drug	References
Amino acids in general	**Metabolism (↗|↘):** The administration of high doses of a specific amino acid may affect the metabolism of other amino acids. **Absorption (↘) | Transport across the blood-brain barrier (↘):** Levodopa (antiparkinson's drug).	(van Kessel and El Aidy 2019)
Creatine	**Action (↗) | Adverse effects (↗):** Creatine can potentiate kidney dysfunction. Caution in co-administration with nephrotoxic drugs (e.g. aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, anticancer drugs, or radiocontrast dye).	(Boccanegra et al. 2020)
Glutamine	**Effectiveness (↘):** Antidiabetic drugs. Glutamine is implicated in gluconeogenesis as a source of carbon skeletons through the tricarboxylic acid cycle.	(Boccanegra et al. 2020; Letellier et al. 2013)
Branched-chain amino acids (L-leucine, L-isoleucine, L-valine)	**Action (↗) | Adverse effects (↗):** Antidiabetic drugs. Possible additive hypoglycemic effect. For example, L-leucine promotes glucose uptake in skeletal muscle and increases insulin sensitivity. **Other problems:** Branched-chain amino acids may compete with aromatic amino acids (L-tryptophan, L-tyrosine, L-phenylalanine) for transport across the blood-brain barrier.	(Boccanegra et al. 2020; Mason 2008)
L-arginine and L-citrulline (its precursor)	**Action (↗):** Antihypertensives. Possible additive blood pressure lowering effects. **Action (↗) | Adverse effects (↗):** Laxatives: intensification of nausea and diarrhea. This effect should be related to the induction of nitric oxide production in the intestine, which when in excess can disturb the balance between intestinal absorption and secretion, inducing excessive loss of water and depletion of nutrients. Beta- and alpha-antagonists: increased risk of palpitations, tachycardia, and syncope. Possible synergistic effect with agents that increase potassium levels.	(Boccanegra et al. 2020)
L-carnitine or DL-carnitine	**Action (↗) | Adverse effects (↗):** Acenocoumarol (anticoagulant): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis.	(Bachmann and Hoffmann 2004; Nauffal and Gabardi 2016)
L-lysine	**Adverse effects (↗):** L-lysine can potentiate kidney dysfunction. Caution in co-administration with nephrotoxic drugs (e.g. aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, anticancer drugs, or radiocontrast dye).	(Nauffal and Gabardi 2016)
L-tryptophan	**Adverse effects (↗):** Fluvoxamine, paroxetine (antidepressants): increased risk of serotoninergic syndrome.	(Mouly et al. 2017)
Taurine	**Adverse effects (↗):** Taurine can potentiate kidney dysfunction. Caution in co-administration with nephrotoxic drugs (e.g. antibiotics, nonsteroidal anti-inflammatory drugs, anticancer drugs, or radiocontrast dye). **Metabolism (↗) | Plasma levels (↘):** Corticosteroids. The mechanism of interaction should be related to the CYP3A4 induction. **Effectiveness (↘):** Antihypertensives. Taurine administration interferes with haemodynamic.	(Boccanegra et al. 2020; Nauffal and Gabardi 2016)

(*Continued*)

Table 3. (Continued).

Amino acids and amino acid derivatives	Interactions	
	Effects on the drug	References
	Fatty acids	
Borage oil (derived from the seeds of *Borago officinalis*)	**Action (↗) | Adverse effects (↗):** Warfarin (anticoagulant): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis.	(Ulbricht et al. 2008)
Evening primrose oil (derived from the seeds of *Oenothera biennis*)	**Action (↗) | Adverse effects (↗):** Phenothiazines (antipsychotics): increased risk of seizure. Apixaban (anticoagulant): risk of severe thrombocytopenia. Evening primrose oil reduces platelet aggregation and exhibits anti-thrombotic effects. These properties should be related to the presence of quinine compounds, namely thymoquinone. Caution in co-administration with drugs that affect haemostasis.	(X. Wang, Jiang, and Batra 2020; Williamson, Driver, and Baxter 2009)
Fish oil/Omega-3 fatty acids (Potential plant sources of omega-3 are soybean and canola genetically modified to contain higher quantities of these fatty acids)	**Plasma levels (↗) | Adverse effects (↗):** Vitamins A and D: hypervitaminosis. **Action (↗) | Adverse effects (↗):** Warfarin, enoxaparin (anticoagulants), acetylsalicylic acid, clopidogrel (inhibitors of platelet aggregation): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis. Corticosteroids. Co-administration might increase the pro-atrophic effects of glucocorticoids in skeletal muscle. The interaction mechanism should be related to the increased activity of the ubiquitin-proteasome system. Omega-3 long-chain polyunsaturated fatty acids (PUFA) are metabolized and activated by at least four CYP families (CYP2C, CYP2J, CYP4, and CYP4F), wherefore pharmacokinetic interactions with drugs metabolized by these CYP enzymes may occur.	(Boccanegra et al. 2020; Buckley, Goff, and Knapp 2004; Levy et al. 2017; Spanakis et al. 2021)
Flaxseed oil (derived from the seeds of *Linum usitatissimum*)	**Action (↗) | Adverse effects (↗):** Warfarin (anticoagulant), acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis.	(Levy et al. 2017; Williamson, Driver, and Baxter 2009)
Sesame oil	**Action (↗) | Adverse effects (↗):** Glibenclamide (antidiabetic): potentiation of the hypoglycemic effect.	(Sankar et al. 2011)

the growing use of these products, especially by very young individuals, and not to overlook potential toxic effects, namely those arising from their interactions with drugs.

Table 3 lists possible interactions between the amino acids- and fatty acids-based supplements and drugs commonly used in clinical practice. With regard to amino acids, it is important to emphasize that there is growing scientific evidence, including that from clinical studies, indicating that supplementation based on these significantly interferes with the absorption of levodopa from the intestinal lumen and also with its transport across the blood-brain barrier, thus restricting the effectiveness of the treatment with this drug (van Kessel and El Aidy 2019). Therefore, it is prudent to avoid co-administration of amino acid supplements in patients taking levodopa. As for fish oils, these can increase the effects of anticoagulants and antiplatelets, so individuals taking warfarin, for example, should avoid them (Buckley, Goff, and Knapp 2004). Otherwise, patients should be monitored and alerted to be aware of any effects arising from increased anticoagulant effects such as bruising or bleeding, and doses should be adjusted as needed. The potentiating effect of these drugs should be related to the fact that omega-3-fatty acids can lessen thrombin generation and plasma concentrations of fibrinogen, prothrombin, among other coagulation factors (Spanakis et al. 2021). Other oils rich in omega-3 fatty acids, such as borage, evening primrose and flaxseed oils, might possibly have also an additive effect on anticoagulant or antiplatelet drugs. Fish oils may also contain heavy metals, dioxins and polychlorinated biphenyls (Boccanegra et al. 2020), which can potentiate harmful interactions and represent an increased risk.

It is also important to mention the study by Elliott (2019), in which supplements marketed for children consumption in Canada were studied, showing that the variation in vitamin, mineral, or fish oil dosage found among similar food supplements was huge (e.g., vitamin B12 ranging between 83% and 5557% of the AI). This considerable variation in dosage depending on the food supplement should be stressed, as supplements present essentially the same types of features and appeals on the package, which, when used together, can more easily lead to overdoses and to potentially more serious interactions with drugs.

5. Polyphenolic-based food supplements

Polyphenolic compounds, namely phenolic acids and flavonoids, are commonly found in vegetables and fruits and are an important source of antioxidants (Lopes et al. 2021). Numerous benefits have been reported to be associated with their consumption, namely in the prevention of cardiovascular and neurodegenerative diseases and tumors (Adebooye, Alashi, and Aluko 2018; Lopes et al. 2021). In view of the increasing evidence about these protective effects on human health, consumer interest in these compounds has grown dramatically. As a result, the industry is ever more focused on developing new food supplements based on polyphenols (Adebooye, Alashi, and Aluko 2018). The use of these supplements makes it possible to greatly increase the intake of polyphenolic compounds, which can be positive given the current large consumption of foods poor in these compounds. The recommended limit for the daily intake of many polyphenols remains undetermined, although high doses can cause important adverse effects, namely through a pro-oxidant effect. Hence, if on the one hand the use of polyphenol-based supplements can be beneficial given the current lifestyle, on the other hand there is growing evidence that their high intake can lead to toxicity, usually achieved via supplementation only (Martin 2010). This can be potentiated when these compounds interact with commonly prescribed drugs.

Although there are few studies evaluating the prevalence and habits of consumption of supplements containing polyphenols, it is important to bear in mind two studies that show the high prevalence of use of these products in at least some groups of individuals. Sepowitz et al. (2015) conducted a study to assess the USA Army soldiers' consumption of phytonutrient-containing supplements, namely genistein, quercetin and resveratrol. The prevalence of use found was 34%. The main reason given for taking phytonutrient supplements was weight loss, but most consumers were not sure why. Only a small minority reported consuming purified resveratrol, quercetin or genistein supplements. Most soldiers reported using supplements of complex composition containing, in addition to phytonutrients, a multitude of other compounds (Sepowitz et al. 2015). The potential for toxicity is hence unclear as it is not known whether interactions between phytonutrients and these compounds occur. This is of particular concern as several of the soldiers reported using simultaneously single-component and multi-component formulas, which leads to higher concentrations of phytonutrients and other components present, thus heightening the risk of adverse effects. Lewanda, Gallegos, and Summar (2018) assessed the patterns of use of food supplements in another target group, children with Down syndrome. It was found that nearly half of parents interviewed administer or have administered supplements to their children to improve their health and development. On average, children have received three supplements, approximately 30% of which starting supplementation before the first year of life . Surprisingly, the most popular supplements were antioxidants (25.8%), e.g. green tea extracts and curcumin. Most parents know about the supplements through parent support groups or friends, and in about 20% of the cases the child's physician was not aware of their use . This is worrying, especially considering the young age at which some children start to receive supplementation, usually between 4 and 6 months of age. Babies and very young children are unable to verbalize complaints, and even the oldest may find it difficult to do so owing to developmental delays (Lewanda, Gallegos, and Summar 2018). Moreover, some of these children may be on medication, which adds to the risk of adverse effects resulting from interactions.

Table 4 gives an overview of potential interactions of polyphenolic-based food supplements, with commonly prescribed medications.

Table 4. Interactions between drugs and polyphenolic -based supplements (↗ – Increase; ↘ – decrease).

	Interactions			
Polyphenolic compounds	Effects on the drug	References	Effects on the compound	References
Biochanin A	**Plasma levels (↗):** Digoxin (cardiotonic and antiarrhythmic drug); paclitaxel (anticancer drug). The interaction mechanism should be related to the P-gp inhibition.	(Williamson, Driver, and Baxter 2009)		
Catechins	**Metabolism (↘) | Plasma levels (↗):** Simvastatin (antihyperlipidemic); tacrolimus (immunosuppressant); sildenafil (phosphodiesterase inhibitor). The interaction mechanism should be related to the CYP3A4 inhibition. **Action (↗) | Adverse effects (↗):** Clopidogrel, acetylsalicylic acid (inhibitors of platelet aggregation): increased bleeding risk. Catechins exhibit antiplatelet aggregation action. Caution in co-administration with drugs that affect haemostasis. **Adverse effects (↗):** Catechins can potentiate liver dysfunction. Caution in co-administration with hepatotoxic drugs (e.g., acetaminophen, isoniazid, carbamazepine, methotrexate, amiodarone, or methyldopa). In addition, they may cause gastrointestinal toxicity. **Absorption (↘) | Plasma levels (↘):** Iron (mineral) and iron-containing drugs. The interaction mechanism should be related to a chelation phenomenon. Rosuvastatin (antihyperlipidemic). The interaction mechanism should be related to the inhibition of intestinal OATP1A2 or OATP2B1. Nadolol (antihypertensive). The interaction mechanism should be related to the inhibition of intestinal OATP1A2. **Plasma levels (↘):** Digoxin (cardiotonic and antiarrhythmic drug). **Effectiveness:** Warfarin (anticoagulant).	(Eagappan et al. 2014; Ge, Zhang, and Zuo 2014; Hegazy 2014; T. E. Kim et al. 2017; Misaka et al. 2014; Vischini et al. 2011; Werba et al. 2015; Williamson, Driver, and Baxter 2009; Xiao, Sarker, and Asakawa 2020)		
Curcumin	**Metabolism (↘) | Plasma levels (↗):** Midazolam (anxiolytic). The interaction mechanism should be related to the CYP3A inhibition. **Plasma levels (↘):** Talinolol (antihypertensive).	(Williamson, Driver, and Baxter 2009)		
Daidzein	**Metabolism (↘) | Plasma levels (↗):** Theophylline (bronchodilator). The interaction mechanism should be related to the CYP1A2 inhibition. **Effectiveness (↘|↗):** Contradictory results for tamoxifen (anticancer drug).	(Mouly et al. 2017; Williamson, Driver, and Baxter 2009)		
Diosmin	**Metabolism (↘) | Plasma levels (↗):** Metronidazole (antibiotic). The interaction mechanism should be related to the CYP3A4 inhibition. Diclofenac (nonsteroidal anti-inflammatory drug). The interaction mechanism should be related to the CYP2D6 inhibition. Chlorzoxazone (muscle relaxant). The interaction mechanism should be related to the CYP2E1 inhibition.	(Rajnarayana, Reddy, and Krishna 2003)		
Galangin	**Absorption (↘) | Plasma levels (↘):** Iron (mineral) and iron-containing drugs. The interaction mechanism should be related to a chelation phenomenon.	(Egert and Rimbach 2011)		

Genistein	**Plasma levels (↗):** Paclitaxel (anticancer drug). The interaction mechanism should be related to the P-gp inhibition. **Effectiveness (↘|↗):** Contradictory results for tamoxifen (anticancer drug).	(Williamson, Driver, and Baxter 2009)
Hesperidin	**Plasma levels (↗):** Verapamil, diltiazem (antihypertensives). The interaction mechanism may be related to the P-gp and CYP3A4 inhibition. **Absorption (↘) | Plasma levels (↘):** Celiprolol (antihypertensive).	(Xiao, Sarker, and Asakawa 2020)
Kaempferol	**Absorption (↗) | Plasma levels (↗):** Lovastatin (antihyperlipidemic). The interaction mechanism should be related to the fact that kaempferol may be an esterase inhibitor. At the intestine, esterases catalyze the hydrolysis of lovastatin into lovastatin acid, a compound that is poorly absorbed, wherefore the inhibition of these enzymes can increase the stability of lovastatin and, consequently, its absorption. **Absorption (↘) | Plasma levels (↘):** Iron (mineral) and iron-containing drugs. The interaction mechanism should be related to a chelation phenomenon.	(Egert and Rimbach 2011; Williamson, Driver, and Baxter 2009)
Luteolin	**Absorption (↘) | Plasma levels (↘):** Iron (mineral) and iron-containing drugs. The interaction mechanism should be related to a chelation phenomenon.	(Egert and Rimbach 2011)
Naringin	**Plasma levels (↗):** Felodipine, nimodipine (antihypertensives); cyclosporin (immunosuppressant); saquinavir (antiretroviral). **Metabolism (↘) | Plasma levels (↗):** Lovastatin, simvastatin (antihyperlipidemics). The interaction mechanism should be related to the CYP3A4 inhibition. **Plasma levels (↘):** Fexofenadine (antihistamine). The interaction mechanism should be related to the inhibition of enteric OATP1A2.	(Morris and Zhang 2006; Williamson, Driver, and Baxter 2009)
Nordihydroguaiaretic acid	**Action (↗) | Adverse effects (↗):** Acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis.	(Ulbricht et al. 2008)
Puerarin	**Adverse effects (↗):** Antianginal drugs; antihypertensives; anticoagulants; inhibitors of platelet aggregation. **Effectiveness (↘):** Benzodiazepines (anxiolytics). Puerarin is a weak benzodiazepine antagonist.	(Williamson, Driver, and Baxter 2009)

(*Continued*)

Table 4. (Continued)

	Interactions			
Polyphenolic compounds	Effects on the drug	References	Effects on the compound	References
Quercetin	**Plasma levels (↗):** Cyclosporin (immunosuppressant); pravastatin (antihyperlipidemic); fexofenadine (antihistamine); digoxin (cardiotonic and antiarrhythmic drug). **Absorption (↘) | Plasma levels (↘):** Iron (mineral) and iron-containing drugs. The interaction mechanism should be related to a chelation phenomenon. **Plasma levels (↘):** Midazolam (anxiolytic); talinolol (antihypertensive). **Adverse effects (↗):** Vinblastine, vincristine (anticancer drugs). The interaction mechanism should be related to the P-gp and CYP3A4 inhibition. Quercetin can potentiate kidney dysfunction. Caution in co-administration with nephrotoxic drugs (e.g. aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, anticancer drugs, or radiocontrast dye).	(J. S. Choi, Choi, and Choi 2004; Egert and Rimbach 2011; Karalliedde et al. 2010; K. A. Kim, Park, and Park 2009; Nguyen et al. 2014, 2015; Williamson, Driver, and Baxter 2009; Wu et al. 2012; Xiao, Sarker, and Asakawa 2020)		
Resveratrol	**Action (↗) | Adverse effects (↗):** Warfarin (anticoagulant), clopidogrel, acetylsalicylic acid (inhibitors of platelet aggregation): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis. Resveratrol may potentiate liver dysfunction. Caution in co-administration with hepatotoxic drugs (e.g., acetaminophen, isoniazid, carbamazepine, methotrexate, amiodarone, or methyldopa). Resveratrol may cause kidney damage. Caution in co-administration with nephrotoxic drugs (e.g., aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, anticancer drugs, or radiocontrast dye).	(Huang et al. 2020; Williamson, Driver, and Baxter 2009; Xiao, Sarker, and Asakawa 2020)		
Rutin	**Action (↗) | Adverse effects (↗):** Warfarin (anticoagulant): increased bleeding risk. Caution in co-administration with drugs that affect haemostasis. **Adverse effects (↘):** Docetaxel (anticancer drug): reduces fluid retention.	(Ulbricht et al. 2008)		
Silymarin	**Absorption (↗) | Plasma levels (↗):** Talinolol (antihypertensive). The interaction mechanism should be related to the P-gp inhibition. **Absorption (↗) | Metabolism (↘) | Plasma levels (↗):** Domperidone (peristaltic stimulant and anti-emetic drug). The interaction mechanism should be related to the P-gp and CYP3A4 inhibition. **Absorption (↘) | Metabolism (↗) | Plasma levels (↘) | Excretion (↗):** Metronidazole (antibiotic). The interaction mechanism should be related to the P-gp and CYP3A4 induction.	(Morris and Zhang 2006; Williamson, Driver, and Baxter 2009; Xie et al. 2019)		
Tangeretin	**Plasma levels (↗) | Effectiveness (↘):** Tamoxifen (anticancer drug). The interaction mechanism should be related to the fact that tangeretin is a suppressor of natural killer cell activity.	(Williamson, Driver, and Baxter 2009)		

The ability of polyphenols to modify the pharmacodynamics and pharmacokinetics of medicines, in particular their metabolism by CYP450, as well as their absorption, distribution and excretion by drug carriers such as P-gp, OATPs, and OCTs, has been assessed in vitro and also in some animal assays, but few data from clinical studies in humans are available. Currently, all scientific evidence indicates that there is no reason to avoid polyphenols in the diet, and there are multiple reasons for adopting a diet rich in these compounds (Lopes et al. 2021; Noad et al. 2016). When ingested in high doses, polyphenols can cause changes in the metabolism of drugs that are substrates of P-gp, OAT, or CYP1A2, CYP2D6, CYP2E1, and CYP3A4, which can lead to a change in their bioavailability and effect, as well as to potentiate their toxicity (Misaka et al. 2014; Mouly et al. 2017; Rajnarayana, Reddy, and Krishna 2003). The use of polyphenol-based supplements with conventional drugs is especially common in patients with cardiovascular diseases (Teschke and Xuan 2019). An example of polyphenol-drug interactions is provided by tea catechins. Catechins are potent antioxidants and exhibit chemoprotective and antimicrobial activities. They also reduce serum cholesterol and LDL-cholesterol oxidation (Mason 2008). Owing to these effects and others yet to be well established, such as the reduction of body weight (Mason 2008), their consumption has been widely promoted. In clinical studies, green tea catechins have shown to increase the bioavailability of simvastatin (Werba et al. 2015) (antihyperlipidemic), tacrolimus (immunosuppressant) (Vischini et al. 2011) and sildenafil (phosphodiesterase inhibitor) (Hegazy 2014), and decrease the bioavailability of digoxin (cardiotonic and antiarrhythmic drug) (Kim et al. 2018), rosuvastatin (antihyperlipidemic) (Kim et al. 2017), and nadolol (antihypertensive) (Misaka et al. 2014). Healthcare professionals should be aware of these potential interactions.

Kim et al. (2018) ascertained in clinical trials that the interaction of catechins with digoxin brings about a marked decrease in peak plasma concentrations of this drug (28%), which strongly suggests that such co-administration is not recommended. Tacrolimus is an immunosuppressant that also has a narrow therapeutic margin. Even though there is only a single case report in the literature published by Vischini et al. (2011), in this work an important increase in plasma levels of tacrolimus in a patient after drinking green tea, followed by normalization of plasma levels after discontinuing its consumption was reported. Therefore, it is cautious to avoid the simultaneous use of products rich in catechins. The interaction of catechins with warfarin (anticoagulant) is also of clinical relevance, and a decrease in the INR has been reported in several studies (Eagappan et al. 2014; Ge, Zhang, and Zuo 2014; Teschke and Xuan 2019). Besides, catechins have antiplatelet effects, which can be additive to those of antiplatelet drugs (Ge, Zhang, and Zuo 2014; Williamson, Driver, and Baxter 2009). Therefore, simultaneous use should be precautionarily avoided.

Diosmin and hesperidin are other examples of polyphenols widely used for their phlebotonic and vascular protective effects, which are marketed as Daflon and Detralex (90% diosmin + 10% hesperidin). They have been used to treat the pain and bleeding of hemorrhoids in venous disease, lymphedema, and inflammatory bowel disease (Rajnarayana, Reddy, and Krishna 2003). Patients with the latter condition are often treated with metronidazole, a drug that has antimicrobial, anti-inflammatory, and immunosuppressive properties. The administration of 500 mg/day of diosmin to healthy individuals showed to increase the plasmatic concentrations of metronidazole, attributed to the inhibitory effect of diosmin on CYP3A4 (Rajnarayana, Reddy, and Krishna 2003). The possibility of this interaction to occur and the consequent risk of potentiation of the adverse effects of metronidazole should not be overlooked.

Quercetin-based supplements are also among the most popular, and are sought after to prevent and treat cardiovascular, autoimmune, and oncological diseases. Quercetin is also used to reduce the risk of cataracts and to improve the symptoms associated with schizophrenia, even if the scientific evidence to support these uses is limited (Mason 2008). Furthermore, quercetin can interact with drugs commonly used in the management of these diseases, such as statins (Wu et al. 2012), beta-blockers (Nguyen et al. 2014), cardiac glycosides (Wang et al. 2004), calcineurin inhibitors (Choi, Choi, and Choi 2004), antitumor alkaloids (Karalliedde et al. 2010), and benzodiazepines (Nguyen et al. 2015). An increase of 36% in the bioavailability of the immunosuppressant cyclosporin, a drug with a narrow therapeutic margin, was observed after the administration of a single dose of quercetin (5 mg/kg) to healthy subjects, and of 47% after administration of multiple doses of this flavonoid (5 mg/kg twice a day) (Choi, Choi, and Choi 2004). Note that in food supplements, the typical recommended daily dose of quercetin is between 500 and 1000 mg. A 2.6-fold increase in plasma digoxin concentration was detected in experiments with pigs, as the pharmacokinetics of digoxin in these animals is akin to that in humans, and cases of animal death were reported upon administration of 20 µg/kg of the cardiac glycoside digoxin, a medicine with a narrow therapeutic index, and 50 mg/kg of quercetin (Wang et al. 2004). A 43% increase in the peak plasma concentration of digoxin was also observed after co-administration in humans of acetyldigoxin and carob seed flour rich in quercetin (Williamson, Driver, and Baxter 2009). Hence, given the available data, it is prudent not to recommend the consumption of supplements containing quercetin to patients taking cyclosporin or digoxin. Even though quercetin is one of the most studied phenolic compounds in terms of safety, there is still a need for further studies regarding its potential to interact with conventional drugs.

Resveratrol is a stilbene well-known for its anti-aging properties (Huang et al. 2020). It exhibits strong antioxidant effects, prevents cholesterol biosynthesis and LDL-cholesterol oxidation, inhibits atherosclerosis, protects endothelial tissue, promotes vasodilation and suppresses platelet aggregation, widely promoted as beneficial in the prevention and management of a multiplicity of cardiovascular diseases (Mason 2008). Resveratrol also has anti-inflammatory and estrogenic properties, and has shown to be a promising molecule in the prevention and treatment of cancer, lowering the proliferation of tumor cells (Mason 2008; Xiao, Sarker, and

Asakawa 2020). As resveratrol displays clinically relevant antiplatelet properties, it can exert an additive effect with anticoagulant and antiplatelet drugs, as well as other medicines that cause bleeding (Huang et al. 2020). Note that although there is insufficient clinical data to not recommend the use of resveratrol in patients taking these drugs, it is prudent to be aware of the potential for increased risk of bleeding. Also, patients should be instructed by healthcare professionals to be alert for any signs of bruising or bleeding and to inform them immediately, should they occur. In addition, resveratrol can potentiate the adverse effects of hepatotoxic and nephrotoxic drugs. High doses of resveratrol, ≥1000 mg/day, inhibit CYPP450 isoenzymes such as CYP2C9, CYP2D6, and CYP3A4, and can induce CYP1A2 (Huang et al. 2020; Xiao, Sarker, and Asakawa 2020). Resveratrol can also inhibit P-gp, OATP1/3, and multidrug resistance-associated protein 2 (MRP2) due to many drug interactions (Huang et al. 2020; Xiao, Sarker, and Asakawa 2020).

Other examples could be given, but the key point is that the potential of many polyphenols to interact with drugs has been clearly demonstrated, together with the risk of serious effects arising from these interactions. In this context, it is important to stress that people often take food supplements with more than one polyphenol or more than one polyphenol-based supplement simultaneously, and little or nothing is known about polyphenol-polyphenol interactions.

6. Alkaloid-based food supplements

Table 5 gives an overview of potential interactions of alkaloid-based food supplements with commonly prescribed medications. Ephedrine alkaloids are an excellent example of how natural is not necessarily safe. Ephedra plant species have been used since ancient times in the treatment of respiratory diseases such as asthma, bronchitis, and nasal congestion. The alkaloids present in their constitution, mostly ephedrine and pseudoephedrine, are the main active compounds responsible for these therapeutic properties. The use of ephedra has interest for weight loss, increased sports performance, and as a stimulant drug of abuse (European Food Safety Authority Panel on Food Additives and Nutrient Sources added to Food (EFSA-ANS Panel)), 2013). Given the serious adverse and eventually life-threatening effects associated with its use, particularly on the cardiovascular and nervous systems, the use of ephedra plant or ephedra alkaloids of the ephedrine-type in food supplements has been banned in several countries, including the EU (European Food Safety Authority Panel on Food Additives and Nutrient Sources added to Food (EFSA-ANS Panel)), 2013). However, they are still available on the internet and consumers seem to continue to ignore their dangers. Given that there are authorized medicines whose safety profile has been properly established, containing ephedrine alkaloids, there is a potential for the occurrence of additive effects resulting from the combined action of these drugs and unauthorized food supplements (European Food Safety Authority Panel on Food Additives and Nutrient Sources added to Food (EFSA-ANS Panel)), 2013). Ephedrine alkaloids interact most noteworthily with monoamine oxidase inhibitors (MAOIs), on account of their potential to cause severe hypertensive crises (Ulbricht et al. 2008). Another worrying interaction is that resulting from the joint use of ephedrine with caffeine, as this combination also increases the risk of severe hypertensive crises, psychosis and even death (Ulbricht et al. 2008).

Caffeine and melatonin are two other highlight worthy alkaloids commonly present in food supplements, both with a remarkable potential for interaction with drugs that act upon the central nervous system (CNS) or coagulation. Caffeine is a vasoconstrictor and central nervous system (CNS) stimulant, wherefore it can antagonize the effects of drugs such as antihypertensives, sedatives, and anxiolytics (Williamson, Driver, and Baxter 2009). In addition, caffeine can increase the bioavailability of antipsychotic drugs such as clozapine and, consequently, increase the risk of adverse effects (Belayneh and Molla 2020). Concerning melatonin, it can potentiate the CNS depressant effects of drugs such as zolpidem (non-benzodiazepine hypnotic), thioridazine (antipsychotic), and imipramine (antidepressant) (European Medicines Agency (EMA)), 2021). Also, melatonin may decrease the effectiveness of nifedipine (antihypertensive) (Lusardi, Piazza, and Fogari 2000) and interact with hemostatic drugs (de Boer, van Hunsel, and Bast 2015). By contrast, drugs such as fluvoxamine (antidepressant), cimetidine (anti-ulcer drug) and estrogens (oral contraceptives/hormone replacement therapy) can increase melatonin levels and its effect, i.e., drowsiness (European Medicines Agency (EMA)), 2021). In general, caution should be exercised when co-administrating melatonin with any of these drugs, but especially with those with action on CNS. The potential interaction of melatonin with fluvoxamine deserves particular attention, as a clinical study reported this drug markedly increase the levels of melatonin through the CYP1A2 and CYP2C19 inhibition, by 17-fold higher area under concentration-time curve and a 12-fold higher serum peak concentration (Härtter et al. 2000). Hence, this combination should be absolutely avoided.

The interest in the use of melatonin has recently escalated due to its sleep-inducing properties and immunomodulatory effects, promising as adjuvant to suppress the exaggerated immune response that leads to severe acute lung injury in COVID-19 patients (Boccanegra et al. 2020). To the best of our knowledge, 11 clinical trials are ongoing, registered in the Cochrane Collection Library Database (*Cochrane Library* 2021) (21 September 2021). Very different formulation types, doses, and therapeutic approaches are being evaluated. In one of these clinical trials, melatonin is assessed in the prophylaxis of COVID-19 in high-risk contacts. A dose of 2 mg/day of melatonin is given orally to healthcare professionals over a 12-week period to test whether melatonin can be a protective tool or not (García et al. 2020). In another clinical trial, the results of the use of a melatonin formulation for intravenous infusion in patients with COVID-19 admitted to an intensive care unit was evaluated to obtain a better

Table 5. Interactions between drugs and alkaloid-based supplements (↗ – Increase; ↘ – decrease).

	Interactions			
Alkaloid compounds	Effects on the drug	References	Effects on the compound	References
Berberine	**Plasma levels (↗):** Cyclosporin (immunosuppressant). The interaction mechanism should be related to the P-gp inhibition.	(Williamson, Driver, and Baxter 2009)		
Caffeine	**Absorption (↗) | Plasma levels (↗):** Felodipine (antihypertensive); acetylsalicylic acid (nonsteroidal anti-inflammatory drug/inhibitor of platelet aggregation); halofantrine (antimalarial); ergotamine (antimigraine); levodopa (antiparkinson's drug). The interaction mechanism should be related to the change in gastric pH. **Metabolism (↘) | Plasma levels (↗) | Adverse effects (↗):** Enoxacin, pefloxacin (antibiotics); amitriptyline, clomipramine, fluvoxamine, imipramine, mianserin (antidepressants); clozapine, olanzapine, haloperidol (antipsychotics); phenylpropanolamine (sympathomimetic drug); idrocilamide (skeletal muscle relaxant); psoralens (photochemotherapy agents/psoriasis and vitiligo drugs); warfarin (anticoagulant); mexiletine (antiarrhythmic); theophylline, furafylline (bronchodilators); zolpidem (hypnotic/sedative drug); lidocaine, ropivacaine (local anesthetic drugs); propranolol, verapamil (antihypertensives); triamterene (diuretic); methotrexate (anticancer/immunosuppressant). The interaction mechanism should be related to the CYP1A2 inhibition. Dextromethorphan (antitussive). The interaction mechanism should be related to the CYP2D6 inhibition. **Action (↗):** Diuretics; laxatives. **Absorption (↘) | Plasma levels (↘):** Iron (mineral) and iron-containing drugs; escitalopram (antidepressant). The interaction mechanism should be related to the formation of insoluble complexes. Midazolam (anxiolytic); phenothiazines, butyrophenone (antipsychotics). The interaction mechanism should be related to the change in gastric pH. Thyroxine (thyroid drug). The interaction mechanism should be related to a chemical sequestration phenomenon. **Metabolism (↗) | Plasma levels (↘) | Effectiveness (↘):** Acetaminophen (nonnarcotic analgesic and antipyretic drug). The interaction mechanism should be related to the CYP448 induction. **Transport across the blood-brain barrier (↘):** Donepezil, memantine (antidementia drugs). The interaction mechanism should be related to the increase in the "tightness" of the blood-brain barrier. **Excretion (↗):** Oxandrolone, epioxandrolone (anabolic steroids). **Effectiveness (↘):** Antihypertensive drugs. Caffeine is a vasopressor. Triazolam (benzodiazepine anxiolytic); zopiclone (nonbenzodiazepine anxiolytic). Caffeine is a neurostimulant. Adenosine (antiarrhythmic). Caffeine is an adenosine receptor antagonist.	(D. G. Bailey et al. 2016; Spanakis et al. 2021; Williamson, Driver, and Baxter 2009)		
Capsaicin	**Plasma levels (↗):** Phenazone (nonsteroidal anti-inflammatory drug); ciprofloxacin (antibiotic). **Action (↗) | Adverse effects (↗):** Pentobarbital (antiepileptic): prolonged drowsiness may occur.	(Williamson, Driver, and Baxter 2009)		

(*Continued*)

Table 5. (Continued)

Alkaloid compounds	Interactions			
	Effects on the drug	References	Effects on the compound	References
Ephedrine	**Adverse effects (↗):** MAOIs: increased risk of hypertensive crises due to the increased sympathomimetic activity. Furazolidone, linezolid (antibiotics): increased risk of severe hypertensive crises. Both drugs have MAO-inhibitory activity. Amitriptyline (antidepressant): increased risk of hypotension. Caution in co-administration with tricyclic antidepressants and other cholinergic agents. Theophylline (bronchodilator): additive neurologic and cardiovascular toxic effects. Caffeine. Fatalities were attributed to the concomitant use of caffeine and ephedrine. The interaction mechanism should be related to the fact that both caffeine and ephedrine can induce catecholamine release and intensify the mobilization of calcium from intracellular stores, which, consequently, leads to vasoconstriction and can cause myocardial ischemia. Bromocriptine (ergot derivative): increased risk of occurrence of severe headache, hypertension, psychosis and seizures in postpartum women. **Excretion (↗) | Effectiveness (↘):** Dexamethasone (corticosteroids). **Effectiveness (↘):** Propofol (anesthetic): accelerated regression of epidural block. Guanethidine (antihypertensive).	(Baxter 2009; Ulbricht et al. 2008; Williamson, Driver, and Baxter 2009)	**Action (↗):** Propofol (anesthetic): enhanced pressor response.	(Ulbricht et al. 2008)
Melatonin	**Action (↗) | Adverse effects (↗):** Zaleplon, zopiclone, zolpidem (non-benzodiazepine hypnotics); benzodiazepines in general: increased cognitive function impairment. Melatonin activity involves interactions akin to those of benzodiazepines at the gamma-aminobutyric acid (GABA) receptors in the brain. Thioridazine (antipsychotic); imipramine (antidepressant): increased feeling of "mental confusion." Possible additive effects. The use of melatonin in children and adolescents needs to be carefully considered. It might cause harmful effects on reproductive and endocrine systems. **Effectiveness (↘):** Valproic acid (antiepileptic). Nifedipine (antihypertensive). Melatonin affects calcium signaling by antagonizing calmodulin. **Action (↗|↘):** Contradictory results for anticoagulants and inhibitors of platelet aggregation. Caution in co-administration with drugs that affect haemostasis.	(Boccanegra et al. 2020; Caspi 2004; de Boer, van Hunsel, and Bast 2015; European Medicines Agency (EMA)), 2021; Lusardi, Piazza, and Fogari 2000)	**Metabolism (↘) | Plasma levels (↗) | Adverse effects (↗):** Fluvoxamine (antidepressant). The interaction mechanism should be related to the CYP1A2 and CYP2C19 inhibition. Psoralens (photochemotherapy agents/ psoriasis and vitiligo drugs). The interaction mechanism should be related to the CYP1A2 inhibition. Cimetidine (anti-ulcer drug). The interaction mechanism should be related to the CYP2D inhibition. Estrogens (oral contraceptives/hormone replacement therapy). The interaction mechanism should be related to the CYP1A1/2 inhibition. Quinolones (antibiotics). The interaction mechanism should be related to the CYP1A2 inhibition. Increased incidence of the adverse effects of melatonin (e.g., dry mouth, dizziness, and irritability). **Metabolism (↗) | Plasma levels (↘) | Effectiveness (↘):** Rifampicin (antibiotic); carbamazepine (antiepileptic). The interaction mechanism should be related to the CYP1A2 induction.	(European Medicines Agency (EMA)), 2021; Härtter et al. 2000)

Piperine	**Absorption (↗) | Plasma levels (↗) | Excretion (↘):** Phenytoin (antiepileptic drug). **Plasma levels (↗):** Nevirapine (antiretroviral); propranolol (antihypertensive); rifampicin (antibiotic); theophylline (bronchodilator).	(Ulbricht et al. 2008; Williamson, Driver, and Baxter 2009)
Synephrine	**Action (↗) | Adverse effects (↗):** MAOIs (antidepressants): increased risk of hypertensive crisis.	(Ulbricht et al. 2008)
Yohimbine	**Action (↗) | Adverse effects (↗):** Phenothiazines (antipsychotics): increased risk of alpha-2 adrenergic receptor antagonism. MAOIs (antidepressants): increased risk of hypertensive crisis. Naloxone (opioid antagonist): increased withdrawal symptoms. Morphine (opioid analgesic). **Effectiveness (↘):** Clonidine (antihypertensive). The interaction mechanism is related to the fact that yohimbine is an alpha-adrenergic receptor antagonist.	(Ulbricht et al. 2008)

understanding of the doses to be administered and the degree of effectiveness of melatonin in critically ill individuals, namely in the reduction of their mortality rate (Acuña-Castroviejo et al. 2020). As far as we know, no data on the results of these ongoing clinical trials have yet been published. That said, meanwhile the COVID-19 pandemic may induce a rise in the use of melatonin, which brings about an increased risk of the occurrence of interactions.

7. Strategies to avoid the occurrence of supplement-drug interactions

An important aspect to emphasize is that food supplements should be used under the recommendation of an authorized health care professional, since it is essential to carry out an attentive risk-benefit analysis of their use, which only a specialist can do. In addition, these professionals are especially trained to be alert to potential interactions and adverse effects, which is essential in managing the problem. Another point is that, as most patients "self-medicate" with food supplements and do not reveal this to healthcare professionals, one of the most relevant approaches to detect and prevent supplement-drug interactions is to build a trusting relationship that stimulates them to dialogue about the use of these products (Asher, Corbett, and Hawke 2017). Health professionals need to routinely check their patients' food supplement consumption habits and this information should be recorded in the clinical files. If an interaction is identified as causing an adverse event or is highly suspected of causing it, it should be reported to local and international pharmacovigilance and nutrivigilance programs (Levy et al. 2017; van Regnault et al. 2021). Simultaneously, patients and caregivers need to be made aware that sharing supplement use with the healthcare professional can be critical to preserving their health and avoiding potentially serious adverse events (Gouws and Hamman 2020; Werner 2014). Even though there have been scientific studies reporting potential interactions between supplements and drugs for over 40 years, the truth is that it is still a great challenge to keep updated all professionals involved and mainly to raise the awareness of the general population to this issue (Spanakis et al. 2019). Yet, this may be about to change. There is, currently, a strong focus on developing technologies that help specialists and patients to improve the well-being, prevent disease, and manage existing pathologies to achieve the best clinical outcomes. An aspect of great relevance is the development of tools that provide information on potential complications arising from the simultaneous use of drugs and food supplements (Spanakis et al. 2019). Ng, Mooghali, et al. (2020) published a review in which the existing resources for this purpose are listed, including web-based clinical decision tools, alert systems based on medical record data, mobile applications, among others. The fact is that there is already a vast number of these resources which can be of great value to health professionals, scientists, and patients, and should be taken advantage of. However, the quality and frequency of updating of these resources vary widely and a careful formal assessment thereof is of great relevance so that they can be used safely and contribute actively to the mitigation of the problem (Ng, Mooghali, et al. 2020). In this sense, in subsequent work, Ng, Munford, et al. (2020) evaluated the online available resources about supplement-drug interactions using the DISCERN tool and compiled a list of those based on appropriate scientific evidence. The resources with the highest total scores included Micromedex, Merck Manual, and Drugs.com, which are examples of tools that can be used as a source of high-quality information (Ng, Munford, et al. 2020). Hence the use of these resources introduces a new era in healthcare and can be crucial to prevent potential supplement-drug interactions.

8. Conclusion

The present review underlines the risks of an often overlooked interaction of food supplements with medicines. In a society where consuming food supplements is a routine practice, the compilation and systematization of the data available so far brings to light the need to take more seriously the safety vulnerabilities in the use of some food supplement constituents. Tighter regulations and increasing consumer awareness of the need for a benefit-risk assessment are required, and should be done on a case-by-case basis by an expert. A centralization of all adverse effects and perceived interactions should be collected in one dedicated Nutrivigilance System, linked with the pharmacovigilance systems as the one existing in Europe. Such system would support the proper causality investigation and allow a better identification of hazards related to specific substances and the performance of an appropriate risk assessment and thus enable a better risk management. Food scientists, nutritionists and healthcare professionals need to work together for the benefit of consumers and be alert in their practice to the risk and signs/symptoms of food supplement-drug interactions.

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ORCID

Maria Lopes http://orcid.org/0000-0003-0683-5685
Manuel A. Coimbra http://orcid.org/0000-0001-8898-6342
Maria do Céu Costa http://orcid.org/0000-0002-9887-0973
Fernando Ramos http://orcid.org/0000-0002-6043-819X

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