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Adverse food–drug interactions

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ABSTRACT

Food supplements and herbal products are increasingly popular amongst consumers. This leads to increased risks of interactions between prescribed drugs and these products containing bioactive ingredients. From 1991 up to 2014, 55 cases of suspected adverse drug reactions due to concomitant intake of health-enhancing products and drugs were reported to Lareb, the Netherlands Pharmacovigilance Centre. An overview of these suspected interactions is presented and their potential mechanisms of action are described. Mainly during the metabolism of xenobiotics and due to the pharmacodynamics effects interactions seem to occur, which may result in adverse drug reactions. Where legislation is seen to distinct food and medicine, legislation concerning these different bioactive products is less clear-cut. This can only be resolved by increasing the molecular knowledge on bioactive substances and their potential interactions. Thereby potential interactions can be better understood and prevented on an individual level. By considering the dietary pattern and use of bioactive substances with prescribed medication, both health professionals and consumers will be increasingly aware of interactions and these interactive adverse effects can be prevented.

1. Introduction

With a growing population in the economically instable Western world in the 20th century, the main focus of food consumption was to alleviate hunger and to provide for necessary macro- and micronutrients (Georgiou et al., 2011; Menrad, 2003). Together with the increased possibilities to chemically produce drugs, this instigated the separate study of pharmaceutics and nutrition, where both were highly connected fields traditionally with their foundation in nature (Eussen et al., 2011). Pharmaceutical products concentrated on curing diseases or alleviating symptoms of disease (Eussen et al., 2011). The potential of food (ingredients) to affect health is recognised both in science and by consumers during the last few decades. Food intake currently not only aims to relieve hunger but is also used to enhance health, thereby shifting more towards the function of pharmaceutical products (Georgiou et al., 2011). This increased interest in the health effects of foods pushes sales of products as functional foods, health foods and food supplements (Alissa, 2014; Euromonitor International, 2015, 2013). The active ingredients of these products, the components which are shown to affect human health, are called 'bioactives' (Biesalski et al., 2009). These products are considered to be foodstuffs, but consumers also seem to get more interested in products at the interface between nutrition and pharmaceuticals as foods for special groups (traditional), herbal medicinal products and cosmoceuticals (Alissa, 2014; Euromonitor International, 2013, 2011). With more health conscious consumers using products with bioactive ingredients, the risk of serious adverse reactions due to interactions between prescribed medication and potentially bioactive compounds is increasing. Various drug–food interactions (e.g. drugs interacting with the fat content of the meal), drug–nutrient interactions (e.g. with grapefruit juice or soy) and herb–drug interactions (e.g. with ginkgo biloba or St John's wort) have been described and reviewed (Boullata and Hudson, 2012; Cheng, 2006; Fugh-Berman, 2000; Pirmohamed, 2013).

The Netherlands Pharmacovigilance Centre Lareb receives reports of health professionals, consumers and the pharmaceutical industry on experienced adverse reactions to medicines and vaccines (Netherlands Pharmacovigilance Centre Lareb, 2015). Amongst these suspected adverse reactions also interactive effects of drugs ingested with xenobiotics, as food supplements and herbal products are reported to Lareb. This paper discusses the received reports on suspected adverse effects following xenobiotics intake

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collected by Lareb and describes several other potential interactions between such substances with drugs and their mechanisms of action. This study thereby gives an overview of clinically relevant interactions and can help to focus the attention of health professionals and consumers on the possibility of interactions between prescribed medication with bioactive products as consumed supplements or herbal extracts.

2. Legal perspective

The Softenon®-affair in the 1960s, where the consumption of thalidomide by pregnant women caused birth defects in children, increased public awareness of potential adverse effects of drugs. As a result, two global measures were taken: (i) medicines must meet requirements for efficacy, quality and safety; and (ii) a system was introduced to report adverse drug reactions (Netherlands Pharmacoviglance Centre Lareb, 2015a). Hereby all legislation concerning drugs was drastically changed (Lachmann, 2012). This was the start of pharmacovigilance: all activities related to monitoring, understanding and preventing medicine-related problems including the occurrence of adverse effects (World Health Organization, 2015). In the Netherlands, these adverse effects are monitored by the Netherlands Pharmacovigilance Centre Lareb. Lareb is an independent foundation and works in close collaboration with the Medicines Evaluation Board (MEB) to maintain the spontaneous reporting system and collects and assesses reports of adverse drug reactions (Netherlands Pharmacoviglance Centre Lareb, 2015b). Reports collected are from Health care professionals, consumers and Marketing Authorization Holders (Netherlands Pharmacovigilance Centre Lareb, 2015).

2.1. Pharmacovigilance

Pharmacovigilance is regulated on an EU level by means of Regulation 1235/2010[1] and Directive 2010/84/EU[2]. Directive 2010/84/EU amends Directive 2001/83/EC[3] by laying down rules for pharmacovigilance. The general provisions on pharmacovigilance are described, next to the organisation of the pharmacovigilance system in Member States, the responsibilities of the marketing authorisation holder and the tasks of the Commission (European Parliament and Council of the European Union, 2010a, 2001).

Regulation 1235/2010 amends Regulation (EC) No 726/2004[4] by including pharmacovigilance as an aspect to be taken into consideration with the authorisation and supervision of medicinal products (European Parliament and Council of the European Union, 2010b). Pharmacovigilance is therefore added to the responsibilities of the EMA's Committee for Medicinal Products for Human Use. The tasks of the marketing authorisation holder and competent authorities of Member States are also further clarified (European Parliament and Council of the European Union, 2010b, 2004a).

2.2. Food and drugs

Next to regulating pharmacovigilance, EU law also defines concepts as food and drugs. Food is defined by the General Food Law[5] as any substance or product that is intended or can be expected to be ingested by humans, directly listing various exemptions in article 2 (European Parliament and Council of the European Union, 2002a). Following the amendments made by Direction 2004/27/EC[6] to Directive 2001/83/EC, drugs can be defined as either medicinal products by presentation (substance(s) presented for treating or preventing diseases in human beings) or medicinal products by definition (substance(s) administered to human beings to make a medical diagnosis or to restore, correct or modify physiological functions) (European Parliament and Council of the European Union, 2004b, 2001). Next to Directive 2001/83/EC, Regulation (EC) No 726/2004 is one of the main EU legislation on medicinal products for human use, by establishing the EMA and describing procedures to authorise and supervise drugs (European Parliament and Council of the European Union, 2004a).

The products at the interface of food and medicine are defined by and regulated under different directives and regulations. Food supplements are defined as concentrated food ingredients aiming to supplement the normal diet (European Parliament and Council of the European Union, 2002b). Herbal medicinal products are drugs with as only active ingredients herbal substances or preparations (European Parliament and Council of the European Union, 2004c, 2001). Following amendments to Directive 2001/83/EC by the Herbal Directive[7], traditional herbal medicinal products have to fulfil specific conditions laid down in Directive 2001/83/EC (European Parliament and Council of the European Union, 2004c, 2001). This directive also defines homeopathic medicinal products due to the amendment by Directive 2004/27/EC, as medicinal products prepared from homeopathic stocks in accordance with manufacturing procedures described in either the European or a Member States' Pharmacopoeia (European Parliament and Council of the European Union, 2004b, 2001). Anthroposophic medicinal products are treated equally to homeopathic medicinal products (European Parliament and Council of the European Union, 2001). Newly developed legislation on food for special medical purposes defines this category as *'food specifically processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision'* (European Parliament and Council of the European Union, 2013). Medical devices from the last category of health-enhancing products, instruments which are used for diagnostic and/or therapeutic purposes in human beings (Council of the European Union, 1990). Although the European Commission proposed new legislation as well as recommendations on audits and assessments next to a unique identification system, currently three directives deal with medical devices: Directive 90/

[1] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation No 1394 on advanced therapy medicinal products (Consolidated version 1 January 2011).

[2] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Consolidated version 20 January 2011).

[3] Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version 16 November 2012).

[4] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version 5 June 2013).

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (Consolidated version 30 June 2014).

[6] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Consolidated version 30 April 2004).

[7] Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83 on the Community code relating to medicinal products for human use.

385/EEC[8] on active implantable medical devices; Directive 98/79/EC[9] on *in vitro* diagnostic medical devices and Directive 93/42/EEC[10] on other medical devices (Council of the European Union, 1993, 1990; European Parliament and Council of the European Union, 1998).

Where these categories are all defined in legislation, in the health and wellness category a wide variety of other terms are also used for products at the interface of food and drugs: cosmoceuticals, nutraceuticals, superfoods and functional foods. Cosmoceuticals are known as cosmetic products with bioactive ingredients which elicit positive cosmetic effects, for example on the skin (Harrison-Dunn, 2015). A nutraceutical is a bioactive food derived ingredient in a pharmaceutical formulation. Various anciently used food products to which health enhancing properties are ascribed are marketed as superfoods. Functional foods, sometimes referred to as 'health foods' are commonly defined as food products that provide health benefits beyond their normal nutritional effects, due to biologically active components (European Food Information Council, 2015; Katan, 2004). These products show that food and drugs are becoming more alike. Before legislating can be developed to deal with this shift, more knowledge upon bioactive components in nutrition and all products in this grey area is required.

3. Adverse interactions

Several interactions between bioactive components and drugs are well-known in literature and practice, as the interactive effects of grapefruit juice with various drugs. Grapefruit juice is known to affect the isoenzyme 3A4 of the enzyme cytochrome P450 (CYP3A4). This enzyme is responsible for the metabolism of various drugs to their metabolites, resulting often in the inactivation of the active substance. When grapefruit juice is consumed, this enzyme is inhibited, leading to higher blood plasma concentrations of the non-metabolised form of such drugs. This can lead to overdosing when the drug is required to be metabolised to become inactive, but when the active substance needs to be metabolised to become active too low dosages can become problematic (Pirmohamed, 2013).

3.1. Data collection

From 1991 up to 2014 Lareb received 55 reports on suspected interactive effects of food supplements or herbal (medicinal) products with prescribed drugs. These suspected interactive effects are reported by health professionals, consumers and the pharmaceutical industry based on experienced adverse reactions to medicines and vaccines (Netherlands Pharmacovigilance Centre Lareb, 2015). All reported interactions between prescribed drugs and bioactive compounds were analysed to review in which stage these interactions take place and whether these interactive effects can be explained by the properties of the specific (bio)active components.

3.2. Reported adverse interactions

The 55 reported adverse interactions are described in Table 1. The bioactive component from the health enhancing product is followed by the description of the active substance of the medicinal product. Next, the reported clinical manifestation of an interaction is described and potential phase where this interaction occurs is defined in the last column of Table 1.

Of the 55 reported interactions to Lareb, 13 reports described the concomitant use of St. John's wort. This included five reports concerning interactive effects with contraceptives. Liver enzyme inducing substances as St. John's wort (inducing cytochrome P450 3A4 and P-glycoprotein pump) are seen to lower oestrogen and progestogen levels, making the contraceptive less reliable (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015). Other reports concerned interactions with anti-depressants, which are also metabolised (at least partially) via CYP3A4, an ACE-inhibitor which requires metabolisation before being active and an insulin mimicking substance, which is metabolised to inactive metabolites via the liver and in muscles (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015). With St. John's wort affecting metabolism, some of the different drugs will be activated too fast and others will be excreted too quickly, possibly resulting in severe adverse effects. Combining anti-depressants with St. John's wort can also lead dynamic interactions due to the synergistic effects these products elicit, known as the serotonergic syndrome (Izzo and Ernst, 2009).

Ginkgo biloba intake, either as registered medicine or supplement, resulted in six reports of adverse drug reactions: four interactions with vitamin K antagonists, one with an antiviral medicine and one with anti-epileptic drugs. Vitamin K antagonists are anti-coagulants, which inhibit synthesis of coagulation factors and thereby decrease blood clotting. Where the actions of vitamin K antagonists can be inhibited by a substance as St. John's wort, it can be intensified by other substances as antibiotics and salicylates (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015). The active substances of Ginkgo biloba are known to be flavonoids and terpenoids, of which Ginkgolide B is shown to inhibit platelet aggregation (Baxter, 2008; Williamson et al., 2013). Ginkgo biloba extracts are also seen to inhibit P-glycoprotein and various P40 enzymes, including CYP2C9 and CYP3A4. Thereby Ginkgo biloba supplementation could increase the risk of bleeding (Wiegman et al., 2009; Williamson et al., 2013). The interaction with a non-nucleoside reverse transcriptase inhibitor, an anti-viral agent which is metabolised via CYP3A4 can thereby also be explained by the inhibiting effects of Ginkgo of CYP3A4 (Wiegman et al., 2009). The neurotoxic component of Ginkgo, ginkgotoxin, is believed to cause the interactive effect of Ginkgo consumption with anti-epileptic medication. This ginkgotoxin could lead to decreased GABA levels, although the metabolism via CYP3A4 of the drugs could also be inhibited by Ginkgo biloba (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015).

Eight reports concerning interactions with glucosamine supplements (containing at least 1500 mg) were received, including four interactions with vitamin K antagonists (acenocoumarol), two with oral antidiabetic drugs and two with anti-epileptic drugs. The anti-epileptic drugs in the reports are valproic acid, metabolised for 50% via glucuronidation, 30–40% via β-oxidation and the other 10% by metabolisation in the liver via CYP2C9, 2C19 and 2A6, and fenytoine, which is approximately for 90% metabolised by CYP2C9 and 2C19 in the liver (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015). A known adverse effect of glucosamine is impaired glucose tolerance, possibly due to lowering insulin secretion by β-cells of the pancreas or by affecting peripheral glucose uptake, which could explain the possible interactive effects with oral antidiabetic drugs (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015). The increased effects of vitamin K antagonists following combined intake with glucosamine is described more often in literature, although the exact mechanism

[8] Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (90/385/EEC) (Consolidated version 11 October 2007).

[9] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (Consolidated version 7 August 2009).

[10] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (Consolidated version 11 November 2007).

Table 1
Reported adverse drug reactions due to interactions with prescribed medicines and health enhancing products.

Active substance health-enhancing product	Active substance prescribed medicinal product	Clinical manifestation of interaction	Potential phase of interaction
Homeopathic product containing Antimonium sulphuratum auratum, Bryonia cretica, Drosera rotundifolia, Eucalyptus globulus and Ipecacuanha	Pantoprazole (proton pump inhibitor)	Oedema; dyspnoea; chest discomfort; angioedema	Unknown
Homeopathic product containing Arnica montana	Insuline aspart (insulin analogue)	Blood glucose increased	Unknown
Homeopathic product containing Avena sativa[a]	Paroxetine (antidepressant)	Psychomotor hyperactivity	Unknown
Cannabis Sativa	Baclofen (muscle relaxant)	Hypotension; increased heart rate; anticholinergic syndrome; gastrointestinal motility disorder; peripheral coldness; coma	Unknown
Chrome	Levothyroxine (thyroid agent)	Dizziness	Absorption
Cranberry extract	Azathioprine (immune suppressant)	Pyrexia; alopecia	Unknown
Cranberry extract	Budesonide; oxazepam (corticosteroid and anxiolytic agent)	Drug ineffective; hyperventilation	Metabolism (cranberry-oxazepam); other unknown
Diet product with cassein	Valsartan/hydrochlorothiazide (antihypertensive drug)	Hypokalaemia	Absorption
Fish oil	Lithium carbonate (lithium)	Potentiating drug interaction	Unknown
Fish oil tablets	Enalapril (antihypertensive drug)	Hypertension	Unknown
Folic acid; vitamin B6	Phenprocoumon (vitamin K antagonist, anticoagulant)	INR increased	Unknown
Ginkgo biloba	Carbamazepine; lamotrigine (antiepileptic drug)	Epilepsy	Metabolism or dynamic
	Emtricitabine; tenofovir disoproxil fumarate; efavirenz (anti-viral medicine)	Virological failure	Metabolism
	Phenprocoumon (vitamin K antagonist, anticoagulant)	Coagulation time prolonged	Metabolism
Ginkgo biloba extract 761	Acenocoumarol (vitamin K antagonist, anticoagulant)	Therapeutic response decreased	Metabolism; dynamic
	Phenprocoumon (vitamin K antagonist, anticoagulant)	Coagulation time prolonged; haematoma	Metabolism; dynamic
	Acenocoumarol (vitamin K antagonist, anticoagulant)	Haematuria	Metabolism
Glucosamine	Acenocoumarol (vitamin K antagonist, anticoagulant)	INR increased	Unknown
	Acenocoumarol (vitamin K antagonist, anticoagulant)	INR fluctuation	Unknown
	Metformine hydrochloride (oral antidiabetic agent)	Blood glucose increased	Dynamic
	Simvastatin (lipid-lowering agent)	Blood glucose increased	Dynamic
	Phenytoin (antiepileptic drug)	Drug ineffective	Unknown
Glucosamine; chondroitin	Acenocoumarol (vitamin K antagonist, anticoagulants)	INR (international normalised radio) increased	Unknown
	Acenocoumarol (vitamin K antagonist, anticoagulant)	INR increased	Unknown
Glucosamine polymer chitosan	Valproic acid (antiepileptic drug)	Epileptic seizures	Unknown
Hop	Levothyroxine natrium-X-water (thyroid agent)	Hypothyroidism	Absorption
Melatonine	Acenocoumarol (vitamin K antagonist, anticoagulant)	INR decreased	Unknown
	Dexamfetamine (amphetamine isomer)	Syncope	Unknown
	Sodium valproate (antiepileptic drug)	Convulsion; insomnia	Dynamic
Multivitamin	Acenocoumarol (vitamin K antagonist, anticoagulant)	Inhibitory drug interaction	Dynamic
	Ethinylestradiol/levonorgestrel (oral contraceptive)	Nausea	Unknown
	Levetiracetam; fluoxetine hydrochloride (antiepileptic drug and antidepressant)	Insomnia; hallucination	Unknown
Plant sterols	Acenocoumarol (vitamin K antagonist, anticoagulant)	Potentiating drug interaction	Absorption
Plantago ovata pericarp	Candesartan cilexetil (antihypertensive drug)	Allergic rhinitis	Unknown
Homeopathic product containing Rhus toxicodendron; gum[a]	Carbamazepine; oxazepam (antiepileptic drug and anxiolytic agent)	Drug level decreased	Unknown, for gum potentially absorption
Homeopathic product containing Rhus toxicodendron[a]	Digoxin (cardiac glycosides)	Palpitations	Unknown
Saw palmetto[a]	[unknown, potentially anticoagulant]	INR increased	Unknown
Homeopathic product containing St. John's wort[a]	Desogestrel/ethinylestradiol (oral contraceptive)	Metrorrhagia	Metabolism
	Desogestrel/ethinylestradiol (oral contraceptive)	Metrorrhagia	Metabolism
St. John's wort	Ethinylestradiol/gestodene (oral contraceptive)	Metrorrhagia	Metabolism
	Ethinylestradiol/levonorgestrel (oral contraceptive)	Metrorrhagia	Metabolism
	Ethinylestradiol/levonorgestrel (oral contraceptive)	Metrorrhagia	Metabolism
	Sertraline hydrochloride (antidepressant)	Mania	Metabolism
	Clozapine (antipsychotic drug)	Psychotic disorder; anti-psychotic drug levels below therapeutic; scizophrenia aggrevated	Metabolism
	Imipramine hydrochloride (antidepressant)	Anticholinergic syndrome; dehydration	Metabolism
	Enalapril/hydrochlorothiazide (antihypertensive drug)	Drug ineffective	Dynamic
	Exemestane (hormone)	Blood creatine phosphokinase increased; myalgia; joint swelling	Metabolism
	Insulin detemir (insulin analogue)	Blood glucose fluctuation	Unknown
	Metronidazole (antimicrobial medicine)	Confusional state; influenza like illness; body temperature increased	Unknown

Table 1 (*continued*)

Active substance health-enhancing product	Active substance prescribed medicinal product	Clinical manifestation of interaction	Potential phase of interaction
	Quetiapine (antipsychotic drug)	Panic attack; insomnia; dyspepsia; dizziness	Metabolism
Valerian root	Acenocoumarol (vitamin K antagonist, anticoagulant)	INR disrupted	Metabolism
	Oxazepam, diazepam (anxiolytic agents)	Agitation, tremor, tension, insomnia	Dynamic
Vitamin B complex	Clomipramine hydrochloride (antidepressant)	Panic reaction	Dynamic
Vitamin C	Nicotine	Myocardial infarction	Unknown
Weight loss coffee[b]	Lithium carbonate (lithium)	Hypomania	Dynamic

[a] Causality questioned.
[b] Potentially caused by the illegal ingredient sibutramin.

is not known (Baxter, 2008; Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015; Knudsen and Sokol, 2008). In two of the reports concerning glucosamine and vitamin K antagonists, glucosamine is combined with chondroitin. Chondroitin is associated with increased bleeding, which could explain the reported adverse effects (Baxter, 2008).

Interactions following vitamin supplements consumed with drugs were reported in six cases. Two reports concerned the intake of vitamin K antagonists, one with folic acid and vitamin B6 and one with a multivitamin tablet which contains vitamin K, although in a normally non-problematic dosage. However, this intake of vitamin K when consuming the multivitamin tablet could be inhibiting the actions of vitamin K antagonists, leading to the reported adverse drug reactions. The effects of folic acid or vitamin B6 on vitamin K antagonists cannot be explained. Other reports concerned nicotine interacting with vitamin C and an anti-epileptic and an anti-depressant drug with a multivitamin tablet, of which the interactive effect cannot be explained. The interaction between an anti-depressant with vitamin B complex intake could result from potential effects of vitamin B6 and B11 on the central nervous system, or potential interactive effects of the metabolism of the anti-depressant via CYP450 enzymes. The last report concerned the interactive effect following multivitamin supplementation during contraceptive intake, leading to nausea. Although the use of oral contraceptives can increase the need of vitamins, there is no interaction known which could explain this adverse event.

Other reported interactions concerned combined intake of various drugs with different herbal or food supplements, including valerian extract affecting benzodiazepines and a vitamin K antagonist. Valerian root is shown to inhibit CYP3A4 and possibly other isoenzymes (Williamson et al., 2013). With acenocoumarol being metabolised by mainly CYP2C9 and partially CYP1A2 and CYP2C19, valerian root could be affecting these enzymes as well which would lead to an interaction on the level of metabolism (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015). The adverse drug reactions occurring when valerian root is used concomitantly with benzodiazepines can be explained by the sedative effects of valerian extract itself. Combining it with an anti-depressant can result in a dynamic interaction of these synergistic effects (Williamson et al., 2013).

Table 1 also describes melatonin intake to interact interacting with (i) anti-epileptic drugs, (ii) amphetamines or (iii) vitamin K antagonists which currently cannot be explained by either the pharmacokinetics or pharmacodynamics of melatonin. Cranberry extract is described to result in the increased metabolism of a purine-antagonist. It is also suggested to affect corticosteroids and benzodiazepines by potentially inducing liver enzymes. An anti-epileptic drug is suggested to interact with either a homeopathic medicinal product or gum, which could increase absorption (Commissie Farmacotherapeutisch Kompas Zorginstituut Nederland, 2015).

4. Discussion

The 55 suspected reported interactions between drugs and herbal or food supplements vary in severity of adverse effects. These 55 reports are however thought to be only a very small share of the interactions occurring due to concomitant consumption of these health enhancing products with medication. Generally speaking underreporting is a reality for spontaneous reporting systems and probably the level of underreporting is even higher for herbals or food supplements because the use of these products is often unknown to a patient's healthcare professional.

As described in Table 1, of 26 of the 55 reported adverse drug reactions the stage where the interaction occurs is not known. It is inherit to the method of spontaneous reporting in pharmacovigilance that the causality is not certain for all reported reactions. Causality of the interactive effect due to the intake of both drugs and the bioactive cannot always be validated. The interactions which can be explained mostly occur in the phase of pharmacokinetics, more specifically in the metabolism stage of the active substance of the drug. Metabolism is one of the four stages of pharmacokinetics (ADME), the process describing the distribution of a pharmacological compound, in which enzymes oxidize and subsequently conjugate the active substance. Metabolism (M) is preceded by absorption (A, focussing on the concentration or amount of a substance which is absorbed into the bloodstream) and distribution (D, stage describing the transfer of the active substance to different locations), and followed by excretion (E, removing the substance out of the body). Within the absorption and metabolism phases, most interactions are known to occur, although also the distribution and excretion of drugs and its metabolites can be altered due to specific herbal or dietary compounds (Fasinu et al., 2012; Sissingh-Blok, n.d.).

4.1. Potential interactions during phase of absorption

Various examples can be given of interactions that can occur between food components or other bioactive products and drugs. Bisphosphonates and several antibiotics are known to interact with foods rich in minerals as cheese and milk. These drugs form complexes with the calcium from these foods, decreasing their absorption up to 60% (Sissingh-Blok, n.d.). Fibres can interact in the absorption phase with digoxin and levothyroxine, decreasing the absorbed amount of the active substances. This could be an explanation for the reported interaction between hop and levothyroxine described in Table 1 (Liel et al., 1996; Sissingh-Blok, n.d.). Food products are not only able to interact with drugs, drugs can also influence the absorption of dietary components. Drugs aimed to reduce fat absorption, as litramine (a dietary fibre derived from *Opuntia ficus indica*) binding fat in the gastro intestinal tract or orlisat as a reversible inhibitor of lipases in the GI tract reducing fat absorption, could lead to decreased absorption of lipophilic

components (Chong et al., 2014; Grube et al., 2013; McClendon et al., 2009). These can be vitamins A, D, E or K, but also the absorption of other lipophilic components as pharmaceutical substances could be reduced. Where these examples all stipulate the potential of reduced absorption, other products are known to be absorbed in an increased amount as nitrofurantoin combined with milk or a meal, increasing the bioavailability with 200 up to 400% (Sissingh-Blok, n.d.).

4.2. Potential interactions during phase of metabolism

When interactions occur during the metabolism phase, the metabolising enzymes (involved in biotransformation of endogenous and exogenous compounds) or transport proteins are either inhibited or induced. This seems to occur in various reported interactions (Table 1). When the enzymes are induced, their activity is increased due to increased mRNA transcription. Thereby the enzyme is metabolising the substance more quickly, leading to altered plasma concentrations of the prescribed drug (Fasinu et al., 2012). With inhibition, the most well understood is the inhibition due to competition of a bioactive with another substance to become the substrate of the CYP enzyme. This leads to concentration dependent decreased action of the enzymes, resulting in increased plasma levels of the substrate (Fasinu et al., 2012; Zhang and Wong, 2005).

As described in section 3, the interactions between grapefruit and various drugs are well-known examples of these types of interactions (Boersma and Stolk, 1999; Pirmohamed, 2013; Sissingh-Blok, n.d.). The inhibitory effects are partly attributed to the flavonoids found in grapefruits (Boersma and Stolk, 1999; Fasinu et al., 2012; Pirmohamed, 2013). Also other flavonoids are known to affect CYP enzymes, including rotenone and resveratrol (Fasinu et al., 2012). Functional changes (in phase I) are mostly followed by conjugation (phase II), which can also be affected by flavonoids (Fasinu et al., 2012). This is exemplified by curcumin, increasing the activity of glutathione S-transferase and valerian that decreases the activity of uridine diphosphoglucoronosyl transferase (Fasinu et al., 2012). By affecting these enzymes, the plasma levels of drugs might alter which potentially causes adverse effects.

The metabolism of xenobiotics is highly influenced by individual differences, as polymorphisms of certain CYP isoenzymes or lifestyle. This can lead to idiosyncratic drug reactions, rare adverse reactions which occur due to a combination of risk factors in an individual (Ulrich, 2007). These idiosyncratic reactions could explain some of the unexpected interactions between bioactive compounds and drugs. These individual differences can have considerable influences on the effects elicited by drugs. This could explain the occurrence of more clinically relevant interactions when (sudden) serious changes in the diet are made (Sissingh-Blok, n.d.).

4.3. Potential interactions during pharmacodynamics stage

Interactions do not only occur in the pharmacokinetic stage. Also the effects of the active substances can be influenced due to concomitant intake of other bioactive substances, the pharmacodynamic stage. This is exemplified by the adverse effects reported with St. John's wort combined with anti-hypertensive medication (Table 1), in which case St. John's wort could result in increased blood pressure. Other examples include the decreased effectiveness of oral contraceptives when combined with vitamin B6 or the increased efficacy of acetylsalicylic acid when it is taken together with vitamin E (Sissingh-Blok, n.d.).

4.4. The distinction is diffuse

As described in the legal perspective, legally the definitions of food and drugs are substantially separated. An increased amount of health-enhancing products however can be found on the market, which does not seem to be fully covered by the definitions of food and drugs. To deal with these products as food supplements, medical foods and even medical devices, new legislation is developed in an attempt to ensure consumer safety and truthful advertisement on their effects.

Yet, the use of these health-enhancing products is also diffuse: consumers do not only use prescribed drugs to combat diseases or symptoms of diseases, also herbal medicinal products, homeopathic medicinal products, food supplements and food items are used in an attempt to remain healthy or increase health. With the bioactive components as main reason to use these products, the artificial separation of food and drugs in law does not seem to be applicable anymore.

5. Conclusion

The growing interest of consumers in using health enhancing products as food supplements and herbal preparations gives rise to increased risks of interactions between these bioactives and prescribed drugs. Although we focussed on the adverse reactions caused by these interactions, it is known that combining these products can result in positive effects as well. Bioactive compounds can reduce the toxicity or improve the actions of drugs: epicatechin derived from cocoa was shown to prevent cortisol resistance and protect the anti-inflammatory effects of dexamethasone, which is relevant for their use in chronic inflammatory lung diseases (Erik J B Ruijters et al., 2014a; Erik J.B. Ruijters et al., 2014b). Flavonoids are also known to prevent the cardiotoxic adverse effects of the antitumor agent doxorubicin (Bast et al., 2006). With the reported suspected interactions between bioactive components and prescribed drugs we tried to outline that the combination of these products can result in serious adverse reactions. This emphasises the need for more knowledge upon bioactive substances and the effects that can result from combining these products.

Currently, legislation does not fit the landscape of health enhancing products. The wide variety of bioactive compounds is being regulated by many different rules and regulations. With a food product being clearly defined to be a food due to its intended use, a bioactive can be considered to be a drug due to its presentation. The grey area created by these definitions is already depicted by the case of food supplements: would it become a drug due to its dosage or presented from or is it a food due to its intended use? The created legal dilemma can only be resolved by defining and characterising the bioactive substance and its interactions by studying molecular nutrition, instead of developing more legislation on new product categories. By understanding the molecular mechanisms of bioactive compounds, potential interactions can be better understood and prevented. In this respect even individual differences can be taken into account. By considering the dietary pattern and use of bioactive substances with prescribed medication, both health professionals and consumers will be increasingly aware of interactions and these interactive adverse effects can be prevented.

Conflicts of interest

Prof. Dr. Aalt Bast declares that there are no conflicts of interest.
Alie de Boer declares that there are no conflicts of interest.
Dr. Florence van Hunsel declares that there are no conflicts of interest.

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