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Review

Let thy food be thy medicine….when possible

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ABSTRACT

There is no evidence that Hippocrates, although being credited for it, ever literally stated 'let thy food be thy medicine and thy medicine be thy food'. However, yet in line with Hippocrates' philosophy, we are currently witnessing a reappraisal of the complementarity of nutrition and pharmacology. Recent studies not only underline the therapeutic potential of lifestyle interventions, but are also generating valuable insights in the complex and dynamic transition from health to disease. Next to this, nutritional biology can significantly contribute to the discovery of new molecular targets. It is clear that most of the current top-selling drugs used in chronic cardio-metabolic diseases modulate relatively late-stage complications, which generally indicate already longer existing homeostatic imbalances. Pharmacologists are increasingly aware that typical multifactorial disorders require subtle, multiple target pharmacological approaches, instead of the still often dominating 'one disease - one target - one drug' paradigm. This review discusses the recent developments in the pharma-nutrition interface and shows some relevant mechanisms, including receptors and other targets, and examples from clinical practice. The latter includes inflammatory diseases and progressive loss of muscle function. The examples also illustrate the potential of targeted combinations of medicines with nutrition and (or) other life-style interventions, to increase treatment efficacy and (or) reduce adverse effects. More attention to a potentially negative outcome of drug-food combinations is also required, as shown by the example of food-drug interactions. Together, the developments at the food-pharma interface underline the demand for intensified collaboration between the disciplines, in the clinic and in science.

1. Introduction

The title of this review refers to the popular phrase 'Let thy food be thy medicine and medicine be thy food', often ascribed to Hippocrates (400 BC), and used to emphasize the importance of nutrition to prevent or cure disease. Interestingly, it is almost certainly a historical misquotation, as the saying does not appear in any of the recovered Hippocratic documents (Cardenas, 2013). Even more, scholars argue that Hippocrates and his followers would probably disagree with this principle in the literal sense (Cardenas, 2013; Touwaide and Appetiti, 2015). Notwithstanding this, nutrition has been a central element in many traditional forms of medicine (Georgiou et al., 2011), until its role in curative medicine started to decline during last century. However, following the increased awareness of the importance of lifestyle for disease prevention, we are now facing a renaissance of nutrition, or lifestyle in general, for disease management as well. In this context, disease management not only comprises lifestyle interventions to improve general health and well-being of patients, but also nutritional strategies to stabilise or even 'reverse' the disease process itself. Here, most successful examples come from chronic disorders directly associated with an unhealthy lifestyle, specifically obesity, cardio-vascular disease, diabetes type 2 and its comorbidities (Katsagoni et al., 2017; Lean et al., 2018; Li et al., 2018b; McCombie et al., 2017; Pan et al., 2018; Perez-Martinez et al., 2017; Steinberg et al., 2017; van Ommen et al., 2018; Webb and Wadden, 2017). However, the list of other diseases for which there is evidence suggesting that healthy nutrition can reduce disease burden and (or) progression is also increasing. Examples include, but are not limited to, depression (Lucas et al., 2014; Martínez-González and Sánchez-Villegas, 2016), osteoarthritis (Rayman, 2015), functional bowel diseases (Tuck and Vanner, 2017), and multiple sclerosis (Fitzgerald et al., 2017). In parallel, increasing insight in the aetiology and complexity of certain diseases, and the high failure rate in industrial drug development (Atri et al., 2018; Hwang et al., 2016; Wong et al., 2018) has taught us that most of the low hanging fruit in pharmacology will have been picked in the meantime. Ironically, pharmacological research and development have enormously benefited from the high incidence of lifestyle-associated chronic diseases as becomes already visible form the list of most-selling drugs. However, it is clear that most, if not all of these compounds only modulate relatively late-stage complications, for example hypertension,

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insulin resistance or elevated cholesterol levels, which generally indicate already longer existing homeostatic imbalance (Section 3.2). Pharmacologists and clinicians are increasingly realizing that a 'one disease- one target – on drug' paradigm is coming up against limitations where it concerns the multi-factorial diseases that are dominating our era. As will be shown (Section 3.3), research in nutrition and lifestyle physiology is instrumental in generating new insights in mechanisms and targets that are also of interest in relation to pharmacological modulation. Together, these developments demand for more interdisciplinary interaction between nutritional, or lifestyle-biology, and pharmacology, in order to increase our understanding of the earliest events taking place in the aetiology of disorders typical for our current society. This narrative review does not intend to discuss the full scope of nutrition or lifestyle as alternative to pharma. Instead, the authors aim to illustrate the ongoing developments at the interface between food and drugs by elaborating a few examples. In view of the readership of EJP some background information on the regulatory perspective and the current role of nutrition in therapy will first be provided.

2. *Food* versus *pharma* – playing field and regulatory basics

From a regulatory point of view, the gross distinction between foods and drugs follows from the primary goal of nutrition, which is to provide essential nutrients that enable normal development and functioning. This is a principal difference with pharmaceuticals, which are generally developed to treat, cure or to prevent disease. This principle also lays down the rules for product safety, as the leading principle for food is that it should be safe for the vast majority of the general population when consumed in reasonable amounts. In other words, in case of foods, risks should be minimal and 'side-effects' are basically not acceptable. However, new insights and developments, scientifically and commercially, have generated principles and products that from their purpose or use do not simply fit in either the food or drug category. Increasingly confronted with this situation, authorities and regulators are also struggling with this, which is one reason that regulations can differ in different parts of the world. It is clear that even 'normal' food can play an important role in preventing or curing disease. General nutritional measures and early recognition of malnourishment have proven to be effective in keeping persons independent, increasing their rate of recovery from disease and reducing the number of hospitalization days (Kruizenga et al., 2016). An example is the role of proteins, either from classical food products or in products labelled as medical nutrition, in sarcopenia and cachexia, which will illustrated in Section 4.2. Another example is the evolving role of food inflammatory indexes in certain disease (Section 4.1), and lower carb diets, although still debated, for diabetes type 2 (American Diabetes, 2018; Gardner et al., 2018; Huntriss et al., 2018; van Ommen et al., 2018), or even type 1 (Lennerz et al., 2018) patients. Avoiding or reducing the intake of specific dietary components in case of food allergies (Koplin et al., 2018) or metabolic disorders such as PKU (van Spronsen et al., 2017) or gout (Kuehn, 2018) has already been in place for decades. Interestingly, this principle seems to be increasingly promoted for other disorders. Although with some of these, such as low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) diet in irritable bowel syndrome (IBS) (Gibson, 2017) the evidence is accumulating that it may be effective at least in some patients, we are also facing an increasing number of popular non-proven remedies communicated via the lay press and social media. A term that emerged about three decades ago is that of *functional foods*. Although it could be argued that any food is functional, the term is used for a category of food products that claim to provide some form of health benefit. Reaching its top in popularity around 2005, the 'functional food' as a principle hasn't met its high expectations. The term itself only has a commercial meaning and no legal status. Although more descriptions exist, the following working definition is useful: "food can be regarded as functional if it is satisfactorily demonstrated to beneficially affect one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either an improved state of health and well-being, or reduction of risk of disease" (Diplock et al., 1999).

To describe the 'functionality', or health benefits of a functional food, the principles of 'health claim' and 'reduction of disease risk' claims are in use. The EU defines a health claim as 'any message or representation that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health. A 'reduction of disease risk claim' is defined as any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease' (https://ec.europa.eu/food/safety/labelling_nutrition/claims/health_claims_en).

In the latter definition, the term 'risk factor' is of importance, since medical claims, for example referring to a specific disease, are not allowed for food products (Aggett et al., 2005). In the EU, the European Food Safety Authority (EFSA; http://www.efsa.europa.eu/) is responsible for verifying that health claims made on a food label are substantiated by solid scientific evidence. EFSA advises the European Commission and Member States, which subsequently decide whether to proceed with authorizing the health claims. Basically, three main categories are being distinguished; "general function (article 13.1) claims"; "new function (article 13.5) claims" and "claims regarding disease risk reduction and child development or health" (article 14) (de Boer et al., 2014; Eussen et al., 2011; Verhagen and van Loveren, 2016). When it comes to health claims, *food supplements* should fulfil the same criteria as set for other food products. According to the EU definition (EC directive 2002/46/EC), food supplements are 'foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills etc.'. Originally, these products mainly comprised typical micronutrients (vitamins, minerals, fatty acids or amino acids etc.). However, during the years several hundreds to thousands of products have evolved containing different compounds, including botanical preparations, pre- and probiotics, enzymes, single molecules etc. Regulations require that supplements are demonstrated to be safe, both in quantity and quality. Like with any food product, food supplements should not be labelled with drug claims. Notwithstanding this, there is continuing uncertainty in the EU about the status of several food supplements, their claims and marketing status. Examples include the so-called 'botanicals', preparations made from plants, algae, fungi or lichens. These have become widely available on the EU market in the form of food supplements. Many are labelled as natural foods carrying a variety of claims being made regarding their possible health benefits. However, in many cases substantiating these claims according to solid scientific criteria has proven to be virtually impossible, leaving their regulatory status in the EU uncertain to date. One legal 'escape' that needs repair is that some obvious food supplements are still labelled as 'medical device'. Finally, some botanicals carry the status of traditional herbal medicinal plant and are used both in medicinal products and in food supplements. One of the consequences of these regulatory ambiguities is that several herbal preparations are currently sold without any formal claim on the package, but obviously marketed with claims via 'grey' channels like advertorials and social media.

Food for medical purposes comprises a category of foods intended for the exclusive or partial feeding, under medical supervision, of individuals suffering from specific disorders or other medical conditions whose nutritional requirements cannot be met by normal foods. For the EU, directive 1999/21/EC lays down essential requirements on their composition and provides guidance for the minimum and maximum levels of vitamins and minerals. Examples of this category are coming back in Section 4.2 on sarcopenia. Finally, some words about the term *nutraceutical.* Originally coined in the late 1980s by Stephen DeFelice, it refers to the whole of non-pharmaceutical compounds that may have an

impact on health and disease states, general well-being and performance. Although the term is poorly defined and has no formal status, it keeps emerging regularly in the media and literature (Andrew and Izzo, 2017).

3. Nutritional science and pharmacological concepts

3.1. Recent development in scientific domains

From its roots in pharmacognosy and experimental physiology, pharmacology evolved during the 20th century into a research discipline focussing on the ability of molecules to change organ and body functions. Rapid developments in synthetic chemistry and the discovery of receptors and other specific molecular targets enabled and stimulated research on single compounds with high selectivity and potency. For most of the 20th century, nutrition science primarily faced the challenge to provide the population safe food with enough energy, proteins and essential micronutrients and the need to prevent deficiencies (Georgiou et al., 2011; Shao et al., 2017). Even today, undernourishment is a harsh reality for millions of people world-wide. Remarkably, poor nutritional status increasingly overlaps with overfeeding, when diets are rich in calories but poor in essential nutrients (Shao et al., 2017). Even in rich countries, nutrient deficiencies are common, in particular in elderly (Schilp et al., 2012), persons using chemotherapy (Caillet et al., 2017), and (or) in persons using multiple medications (Section 4.3). In the 1980s and 1990s, and coinciding with the popularity of the 'functional food' idea, nutrition started to adopt typical pharma strategies in its search for 'magic bullets' with specific health benefits. This also led to an increased popularity of drug-like randomized controlled trials (RCTs) for nutrients and food products. In retrospect, this approach has shown to be too simplistic in many ways (Biesalski et al., 2011; Gallagher et al., 2011; Heaney, 2012; Shao et al., 2017). Unlike drugs, most nutrients do not function in isolation and act on multiple tissues and organ systems. As a consequence, and in contrast to the classical drug-receptor interaction model, which often displays a sigmoid dose-response curve, nutrients generally show U-shaped concentration-effect behaviour (Fig. 1).

Another principal difference between nutrients/diets and pharmaceuticals, is that, in majority, effects of nutrition are far more subtle and occur more slowly compared to those of drugs. Even more complicating, but outside the scope of this review, is that inter-individual differences (Zeevi et al., 2015) and matrix effects of nutrients are by no means less than those of drugs.

To grasp the subtleness and complexity of diseases with their dynamic and highly intertwined connections and interactions, so-called systems approaches are increasingly being used (Morel et al., 2004; van der Greef and McBurney, 2005; Wang et al., 2005). Next to this, both nutrition scientists and pharmacologists have become increasingly aware of the importance to integrate with other disciplines, including epidemiology, biology and physiology, and, outside the scope of this review also psychology, sociology and economics.

3.2. Blurring boundaries between health and disease

Most chronic diseases don't develop overnight, and the borders between health and disease are often not sharp. This holds particularly true for those diseases associated with lifestyle and ageing, typical fields of interest of both nutrition and pharma. In line with this, it is difficult, if not fundamentally impossible, to establish 'perfect health' of individuals (Gallagher et al., 2011). In order to grasp the dynamic, multidimensional and time-dependent changes occurring during the transition from the 'healthy' to the 'diseased' state, practical concepts and 'indicators of health status' as opposed to 'disease markers' are needed. These models have in common that they go back to the physiological principle of homeostasis, quantifying health in terms of resilience, or the ability to continuously adapt to internal and external situations. An example is 'the ability to adapt and self-manage in the face of social, physical, and emotional challenges' (Huber et al., 2011). Within this context, the (often gradual) onset of disease starts when adaptive processes begin to deteriorate (van Ommen et al., 2014). Nutrition, together with other lifestyle factors plays an important role in maintaining or even strengthening a proper physiological bandwidth or flexibility (resilience). This is often referred to as phenotypic flexibility, being the resultant of the individual's genotype, his/her physiological and psychological state at a particular point it time, his/her microbiota etc. (van Ommen et al., 2014; Vis et al., 2014). As schematically depicted in Fig. 2, different regulatory mechanisms are fluctuating within a certain homeostatic range. Individuals maintain homeostasis for as long as possible by adaptive changes in his/her metabolic and other pathway dynamics. Chronic disease develops when an organism (individual) is no longer able to maintain homeostatic processes within a certain limit and may require intervention. A disease process can either further deteriorate or stabilise at a new homeostatic state. To measure these dynamic processes, a 'systems-approach' is highly useful, meaning that multiple biomarkers, preferably of different integration levels (e.g. gene, protein, metabolite, but also a physiological response, images etc.) are analysed at different time points and integrated into models (Gallagher et al., 2011; Morel et al., 2004; van der Greef and McBurney, 2005; Wang et al., 2005). Such combinations of health biomarkers are often different from the classical disease biomarkers. Furthermore, 'stress' or'challenge' tests are used to measure the flexibility and resilience of health. These tests measure the response to metabolic, physical, psychological or immunological stressors (Biesalski et al., 2011; Shao et al., 2017; Wopereis et al., 2015, 2013). Different biochemical, physiological or psychological protocols and endpoints are in use, indicative for specific processes (Stroeve et al., 2015). For example, a metabolic challenge test measures the response to a standardized meal or shake that provides a carbohydrate or fat "load' (Stroeve et al.,

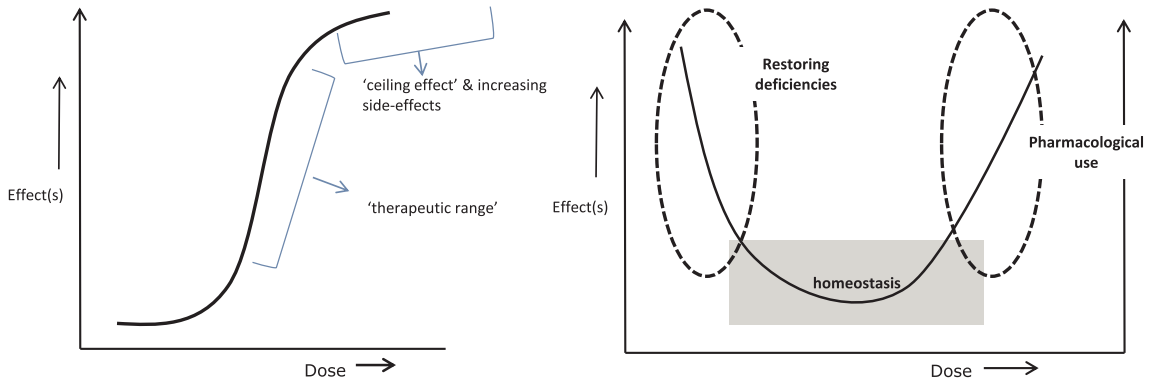

Fig. 1. Typical pharma (sigmoid) and nutrient (U-shaped) dose-reponse curves.

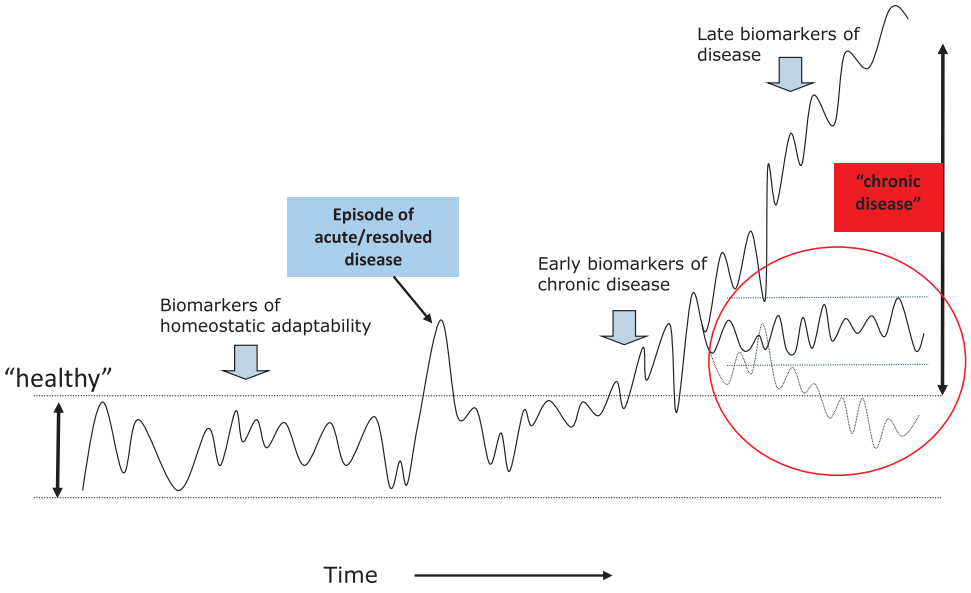

Fig. 2. Biomarker patterns in relation to homeostatic adaptability. Schematic depiction of the concept of physiological balance and the significance of biomarker patterns for various stages of development in time from normality (homeostasis), via dysfunction, to chronic disease. An organism maintains homeostasis for as long as possible by changes in its metabolic pathway dynamics. Nutrition aims to support this homeostasis. Chronic disease develops when an organism (individual) is no longer able to maintain homeostatic processes within a certain limit and may require intervention. A disease process can either further deteriorate or stabilise at a new homeostatic state.

2015). Our laboratory also applies physical challenge tests (Janssen Duijghuijsen et al., 2016). Here, a strenuous exercise protocol on a bicycle ergometer is applied to generate effects on immune function and intestinal permeability, which in turn can be used to investigate potentially positive effects of dietary interventions, probiotics etc. Other challenge tests apply vaccination, experimental infection (Ten Bruggencate et al., 2016) or psychological stress (McCrea et al., 2015; Schrieks et al., 2016).

3.3. Common molecular targets and strategies in pharmacology and nutrition

Molecular pathways and targets of drugs and nutrients are highly intertwined, since many drugs act on physiological mechanisms which are also playing crucial roles in, for example nutrient metabolism or eating behaviour. Next to this, our food has always contained compounds, mostly produced by micro-organisms or higher plants that are able to produce biological effects that go far beyond nutrition. As a matter of fact, many classical drugs are originally derived from natural compounds. To deal with these non-nutritional compounds, organisms have developed biotransformation enzymes and transporter systems allowing their elimination or to reduce their uptake. During the heydays of the functional foods, many companies were actively engaged in looking for specific targets and ingredients in order to develop products with specific health properties. Examples include cholesterol lowering, reduction of blood pressure, modulation of glucose levels, or mood improvement (Diana et al., 2014; Eussen et al., 2011; Gomez-Pinilla and Nguyen, 2012; Hulsken et al., 2013; Hunter and Hegele, 2017; Köhler et al., 2017; Rutherfurd-Markwick and Moughan, 2005). However, the number of real breakthroughs has remained limited thus far, and several companies have meanwhile abandoned such strategy, realizing the limitations of this reductionist, pharma-like approaches for foods. At the same time, pharmacology has been able to benefit from the discoveries and developments in nutritional biology, general physiology and metabolism which have contributed to the availability of new molecular targets and principles. Understandably, most intense overlap can be found in those fields with a direct link to food and health, including eating behaviour, gastro-intestinal physiology, metabolism, the immune system, microbiota etc. Within the scope of this review only a few of these mechanisms and targets will be elaborated in the next sections. Some examples of clinical implications will be described in more detail in Section 4.

3.3.1. 'Nutrient' receptors as pharmacological targets

Metabolism, nutrient intake, absorption and disposition are tightly monitored via specific receptors, transporters and, indirectly through their conversion into a variety of signalling molecules. Chemosensing of nutrients and bacterial metabolites occurs via receptors present all along the gastrointestinal tract, including the oro-nasal cavity, in various other tissues, and, for some receptors also in brain. Remarkably, the function of an increasing number of receptors has been found to go beyond direct chemosensing of ingested nutrients. An interesting example is represented by the bitter receptors. Clearly, only in the oral cavity these receptors detect 'bitterness' as we experience this. However, they are now known to be functionally expressed in many different tissues and may be used as therapeutic targets as well (Devillier et al., 2015; Dupre et al., 2017; Jaggupilli et al., 2016; Shaik et al., 2016). Similar principles apply to several other receptors, for example those that recognize fatty acids and derivatives (Witkamp, 2018), transient receptor potential channels (TRP) (Basso and Altier, 2017), bile acid receptors (Copple and Li, 2016) and receptors for satiety hormones (Witkamp, 2011). Table 1 provides an illustrative, non-exhaustive overview of receptors that link nutrition and pharma in this respect.

3.3.2. Food components, transporters and metabolizing enzymes as drug targets

Our diet contains numerous nutritional and non-nutritional compounds that directly or via their metabolite(s) can interact with pharmacological relevant receptors. For example, tomatoes and potatoes contain GABA in pharmacological active amounts (Diana et al., 2014) and the amino acids tryptophan and tyrosine can become rate-limiting as precursors in the formation and activity of serotonin (Strasser et al., 2016) and dopamine (Steenbergen et al., 2015), respectively. Another example is that several food proteins can digest into bio-active peptides interfering with opioid receptors (Garg et al., 2016; Nongonierma and FitzGerald, 2017; Park and Nam, 2015), not only locally in the GI tract, but possibly also systemically. Fatty acids represent another important class of nutrients. Next to their role as energy source and components of cell membranes, several members of this highly diverse class serve as precursors for pivotal signalling molecules and their dietary ratio co-determines the pro-/anti-inflammatory balance (Meijerink et al., 2013; Witkamp, 2018). This includes the short chain fatty acids released by the intestinal microbiota. A last example is nitrate as present in for example beetroot and green leafy vegetables. Nitrate is reduced to nitric oxide (NO) through an entero-salivary nitrate-nitrite-NO pathway that

Table 1
Illustrative overview of receptors with a nutritional/metabolic role with their (potential) pharmacological possibilities.

Receptor(s)	Nutritional / Physiological ligands (s)	Suggested pharmacological target / potential indication	References
Bitter taste receptors - T2Rs, at least 25 subtypes in humans	Different food compounds	(Airway-) inflammation, Cancer (?), GI motility, tocolytics (pre-term labour)	(Deloose et al., 2018; Devillier et al., 2015; Dupre et al., 2017; Jaggupilli et al., 2016; Shaik et al., 2016; Singh et al., 2014a; Zheng et al., 2017)
Cannabinoid receptors CB_1 / CB_2	Different plant compounds, fatty acid precursors	Appetite, inflammation, metabolic disease, pain, convulsions, anxiety	(Jager and Witkamp, 2014, 2016, 2018; Ligresti et al., 2016; Witkamp, 2014, 2016, 2018; Witkamp and Meijerink, 2014)
Free fatty acids (FFA 1 – 4)	Different short- to long chain fatty acids	Appetite regulation (FFA1, GPR40), diabetes (FFA4, GPR120) & inflammation (FFA2,GPR43 and FFA3, GPR41)	(Witkamp, 2016, 2018)
GPR109A	Nicotinic acid, butyrate, some amino acids	Gut homeostasis Inflammation, colon cancer (?)	(Gambhir, 2012; Singh et al., 2014b; Tan et al., 2017b; Thangaraju, 2009)
GPR119	N- oleoylethanolamide (OEA) and N-oleoyldopamine (OLDA); 2-oleoylglycerol, 2-palmitoylglycerol and 2-linoleoylglycerol	Diabetes, appetite regulation	(Hansen et al., 2012; Hansen and Vana, 2018; Hassing et al., 2016; Witkamp, 2011, 2018)
GLP-1	GLP − 1 and other peptides	Diabetes, appetite regulation	(Andersen et al., 2018; Drucker, 2018)
Hydroxycarboxylic acid receptors (HCA1–3)	Ketone bodies, e.g. beta-hydroxybutyrate (β-OHB)	Inflammation	(Graff et al., 2016; Offermanns and Schwaninger, 2015)
PPARS (PPARα PPARß/δ and PPARγ)	Various fatty acids and derivatives, including OEA	Cardio-metabolic diseases, lipid metabolism, inflammation	(Gross et al., 2017; Marion-Letellier et al., 2016; Wang et al., 2016)
Bile acids receptor TGR5 / GPBA	Bile acids, betulinic acid, oleanolic acid	Inflammation, pruritus	(Copple and Li, 2016; Kuhre et al., 2018; Perino and Schoonjans, 2015)
Transient receptor potential (TRP) cation channels, different families/forms (TRPV1-4, TRPA1 etc.)	Capsaicin, different fatty acid conjugates (vanilloids), cannabinoids	Pain, inflammation, IBS	(Ahern, 2013; Beckers et al., 2017; Marwaha et al., 2016; Nilius and Szallasi, 2014; Romano et al., 2013)

involves the oral microbiome (Blekkenhorst et al., 2018). Nitric oxide plays an important role in vascular tone and integrity and is a vital molecule for cardiovascular health. Increasing nitrate intake through the diet or via specific food products like beetroot juice is a potential strategy to increase NO bioavailability. Compared to nutrients, the number of bioactive non-nutritional components in foods, in particular from plants, is a multiple. As previously mentioned, several modern times drugs have evolved from these natural molecules.

Similar to receptors as presented in the previous section, pharmacology is applying numerous typical nutrient metabolizing enzymes and transporters as drug targets. Recent examples include inhibitors of dipeptidyl peptidase 4 (DPP-4) and the sodium-glucose cotransporter 2 (SGLT2) in diabetes (Tahrani et al., 2016), and various solute carrier transporters in cancer chemotherapy (Nakanishi and Tamai, 2011). A pivotal eukaryotic signalling network modulated by nutrients and of interest to pharma is mechanistic target of rapamycin (mTOR). Deregulated mTOR signalling is implicated in the progression of cancer and diabetes, as well in aging. For recent review see (Saxton and Sabatini, 2017). Signalling via mTOR is also connected to regulation via sirtuins (silent information regulator 2 (Sir2) enzymes) (Hong et al., 2014; Igarashi and Guarente, 2016). Sirtuins have emerged as central players in the regulation of critical metabolic pathways such as insulin secretion and lipid metabolism. They regulate their targets by modulating the activity of their partner proteins through reversible deacetylation (Dang, 2014; Hubbard and Sinclair, 2014; Igarashi and Guarente, 2016). The most studied sirtuin is SIRT1, which has been implicated in longevity, cell proliferation, apoptosis and the beneficial effects of caloric restriction. The natural compound resveratrol has been proposed as a natural SIRT1 activator, in addition to having other activities. Following the discovery of SIRT1 and its role in metabolism, several small-molecule SIRT1 activators have been synthesized with structures different from that of resveratrol but with considerably higher potency (Witkamp, 2011). To date, the high expectations regarding SIRT1 as drug targets apparently have not been met. In 2013, GlaxoSmithKline shut down Sirtris Pharmaceuticals, less than 10 years after its acquisition. In the meantime, clinical development of SRT2104 as selective small molecule SIRT 1activator has been terminated. A remarkable pharmacological development that evolved from lifestyle-mediated health benefits are the so-called 'exercise mimetics' (Fan and Evans, 2017), acting on the AMPK- PPARδ pathway (Dial et al., 2018; Narkar et al., 2008).

Outside the scope of this review, but obviously of increasing interest also for the food-pharma interface are the interactions with the intestinal microbiota. Several studies show that metabolism, both formation and breakdown, of active compounds in the GI tract can be significant. For reviews see for example (Kayshap and Quigley, 2018; Sharon et al., 2014; Swanson, 2015).

4. Some food-pharma examples from a clinical perspective

4.1. Targeting inflammation as underlying mechanism of chronic disease

Research as convincingly shown that a chronically elevated systemic 'low grade' state of inflammation is at the basis of many diseases associated with our current 'Western" lifestyle. Overweight and obesity are considered primary determinants of the typical cardio-metabolic disorders that are often referred to as metabolic syndrome. These typically include diabetes type II, atherosclerosis and hypertension, heart failure and non-alcoholic fatty liver disease. Other investigators argue that overweight in itself may already be a symptom of deteriorating neuro- immune- and metabolic homeostasis. Indeed, increasing evidence suggests that a network of interacting factors including stress, lethargy, physical inactivity, lack of sleep and overeating is at the root of the problem (Hackett and Steptoe, 2017; Lucas et al., 2014; Reutrakul and Van Cauter, 2018; van Ommen et al., 2018). This phenomenon is also often referred to as 'metaflammation' (Egger and Dixon, 2009; Hotamisligil, 2017). Increasing evidence suggests that its involvement goes well beyond metabolic syndrome, as an elevated inflammatory state is also associated with increased risks for depression, cognitive decline, cancer and chronic inflammatory diseases like osteoarthritis, COPD and IBD (Lee et al., 2018; Netea et al., 2017). As shown in Section 4.2, this also includes cachexia and disease-related anorexia. Presumably, an impaired barrier function of the GI tract (Martin and Devkota, 2018) is playing a central role by increasing the

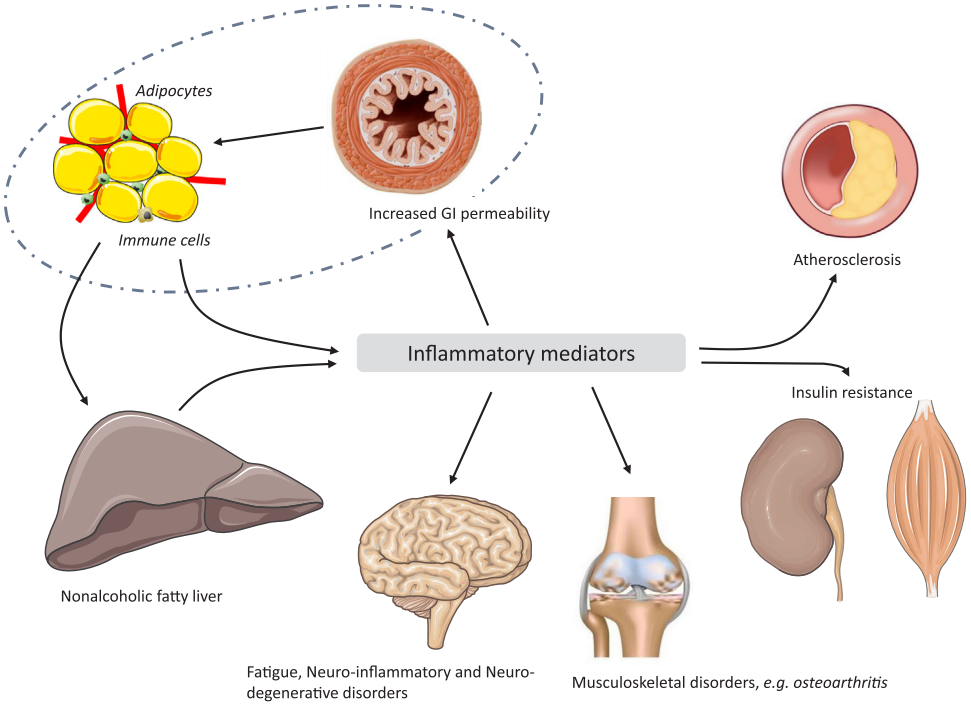

Fig. 3. Gut-adipose tissue vicious cycle acting as a driver of low-grade inflammation.

uptake of bacteria and their breakdown products and other (macro-) molecules. This generates a continuing state of activation of the immune-system, thus closing a vicious cycle (Fig. 3).

Remarkably, 140 years ago it was already shown that salicylates can attenuate diabetic symptoms. In 1876, the Berlin doctor Wilhelm Ebstein described successful treatment of two middle-aged patients with salicylic acid natron (Kaiser and Oetjen, 2014). Later reports confirmed this effect, also with acetylsalicylic acid, although very high doses, up to 7 g/day, were needed, which will obviously have led to serious side-effects. It has been shown that this action of acetylsalicylic acid cannot be explained from COX inhibition alone. Interestingly, a comparable result has been reported with the IL-1 receptor antagonist anakinra in an RCT with diabetes type 2 patients (Larsen et al., 2007). The idea that anti-inflammatory drugs can play a role in diabetes management remains of interest. However, this is probably more complicated than originally assumed, and should amongst others be part of an individualized and multi-component approach (Baye et al., 2017; Donath, 2014; Goldfine and Shoelson, 2017; Kaiser and Oetjen, 2014). In line with these observations, anti-inflammatory approaches, including the use of cytokine receptor blockers and monoclonal antibodies are also receiving considerable interest in relation to atherosclerotic disease (Ridker et al., 2017; Ridker and Lüscher, 2014; Welsh et al., 2017). Another line of evidence supporting the relevance of the metaflammation paradigm comes from the observation that statins, originally and primarily designed as inhibitors of cholesterol synthesis were found to be 'promiscuous' compounds with amongst others anti-inflammatory effects, which may explain part of their success (Oesterle et al., 2017; Ulivieri and Baldari, 2014).

Conceivably, the metaflammation paradigm is also receiving considerable attention in relation to nutrition and other life-style factors. An increasing number of studies point at the balance between pro-inflammatory, unhealthy diets ('fast food fever') (Myles, 2014) versus more anti-inflammatory food patterns. Suggested pro-inflammatory components of the diet include industrially produced trans fatty acids, a high n-6/n-3 fatty acid ratio, a low status of vitamins D and K, potassium and magnesium, a high-fat low-fiber diet, consumption of carbohydrates with a high glycemic index, a high glycemic load, a low intake of fruit and vegetables etc.. In line with this, an increasing number of systems to classify diets on their pro-/anti-inflammatory index and their links with health outcomes are being proposed. Examples include: (Adjibade et al., 2017; Assmann et al., 2018; Bodén et al., 2017; Harmon et al., 2017; Li et al., 2018a; Tabung et al., 2018; Whalen et al., 2017; Winkvist et al., 2018). Interestingly, other important lifestyle factors including physical exercise, sleep and stress reduction have also been demonstrate to contribute to an attenuated inflammatory status (Fernandez-Mendoza et al., 2017; Gleeson et al., 2011; Irwin et al., 2016; Pedersen, 2017; van Ommen et al., 2018).

4.2. Involuntary loss of muscle mass and appetite during chronic disease

Loss of muscle mass and function (sarcopenia) are commonly occurring during aging and the progression of various chronic diseases, including cancer, COPD, HIV and metabolic syndrome. When the decline in functional muscle mass becomes substantial, it is to be considered a serious medical condition as it contributes to increased morbidity and mortality (Evans et al., 2008; Levine and Crimmins, 2012; Morley et al., 2010; Springer et al., 2017). In many patients this also reduces treatment efficacy and quality of life. Both age- and disease-associated sarcopenia have a complex and multi-factorial aetiology. This might explain why pharmacological options have thus far demonstrated only limited efficacy. Sarcopenia therefore also represents a typical example of the limitations of the 'one disease- one target – on drug' paradigm as introduced in Section 1. Therefore, multiple-target approaches, including personalised combinations of medicines, diet and exercise are receiving increasing attention. Disease complexity and number of factors involved increase from moderate muscle wasting during healthy aging, via serious age-induced muscle wasting, to disease-induced muscle wasting (cachexia). Primary sarcopenia, loss of muscle mass and function with aging, affects about 5–13% of persons aged 60–70 y, further increasing to 11–50% in those over 80. This is associated with increased dependency in daily life activities, disability, institutionalization, and increased risk of falls and fractures (Sayer et al., 2006; Wickham et al., 1989). Secondary sarcopenia is accelerated muscle loss during disease (cancer, COPD, chronic heart failure, HIV, and chronic kidney disease) and part of the cachexia syndrome (Evans et al., 2008). Up to 50% of cancer patients suffer from a progressive

atrophy of skeletal muscle protein reserves. Moreover, secondary sarcopenia is estimated to be responsible for approximately 20% of deaths in cancer (Dimitriu et al., 2005; McMillan, 2009) and it may impair response to chemotherapy (Bossola et al., 2008). Muscle is a highly active tissue, with a turnover rate of about 2% of whole body skeletal muscle per day, and damaged tissue also needs to be replaced quickly. Two factors are essential for this: adequate protein availability and physical activity (Gorissen et al., 2015). Muscle protein synthesis is stimulated when plasma levels of essential amino acids are above a certain threshold (Gorissen et al., 2015). This anabolic threshold becomes lower after exercise. Interestingly, it is also lower at younger age compared to older age. Moreover, about 21% of older adults suffer from age-associated anorexia, which makes reaching this threshold more difficult (Tieland et al., 2017). Next to this, other factors play a role, including the amount of protein, its composition (e.g. the amount of essential amino acids), essential amino acid composition (e.g. % of leucine), digestibility (e.g. the fast-digested whey protein vs the slow digested casein protein) and the time of protein consumption (all at once or spread during the day). According to the ESPEN expert group, the diet of older individuals should provide 1.2–1.5 g protein/kg body weight/day (Deutz et al., 2014)., which is well above levels of between 0.8 and 1.1 g/kg/bw/day our colleagues found in older people living in different situations (Tieland et al., 2012a). Moreover, elderly should be encouraged to exercise (both resistance and aerobic) to effectively slow down sarcopenia, as protein supplementation alone only moderately reduces the loss of muscle mass. An intriguing question is whether older people would need less protein if they had consumed less protein when young. We found that mice that had been on a low macronutrient diet throughout their entire life- receiving 70 E% of all macronutrients including protein compared to the diet of the control mice - showed clear differences in body weight while lean mass was very well conserved (Rusli et al., 2017; van Norren et al., 2015). Disease represents a clear aggravating factor for muscle loss, even more at old age. Two interrelated factors are playing a major role here: immobility and inflammation. In older people the disuse-induced muscle loss accumulates over the years (Wall et al., 2013). Systemic inflammation is currently regarded the most important driver of disease-induced muscle wasting, including the life-threatening cachexia syndrome (Argilés et al., 2015; Dwarkasing et al., 2015; Molfino et al., 2015; van Norren et al., 2017). Cachexia syndrome represents a complex situation as there is no single dominating pathway responsible for the effects found and many different organs and tissues being involved (Argilés et al., 2014), A related condition is intensive care unit-acquired weakness (ICUAW) causing fatigue, impaired pulmonary function, muscle weakness and reduced ability to perform vigorous exercise that lasts for year after ICU discharge (Bloch et al., 2012). In a rat model, it was shown that inflammation and immobility (leg casting) independently contributed to muscle atrophy and that the two factors were additive (Fink et al., 2008). Another example of this complex inflammation-induced muscle loss is cancer-induced cachexia. In cancer-induced cachexia, hypothalamic inflammation might play an important role (van Norren et al., 2017). In mice studies, we identified serotonergic metabolic and signalling pathways as upstream regulators of the hypothalamic orexigenic and anorexigenic neuropeptide systems controlling appetite (Dwarkasing et al., 2015, 2016a, 2016b). Probably comparable to the situation in metabolic syndrome (Section 4.1), a reduced physical activity is among the consequences of this inflammatory process (van Norren et al., 2015). Other studies suggest that hypothalamic inflammation directly contributes to muscle wasting. The HPA-axis is suggested to be a key-regulatory system in this process (Braun et al., 2013, 2011; Braun and Marks, 2015; Burfeind et al., 2016). Again in line with the metainflammation paradigm (Section 4.1) the intestinal tract may be critically involved here as well (Argilés et al., 2014). This phenomenon has also been described for HIV (Hummelen et al., 2010) and also for other diseases with muscle wasting like IBD and cancer (Crawford, 2016; Jiang et al., 2014; Klein et al., 2013). Fig. 4 describes our current hypothesis on how the gut might accelerate the influence hypothalamic inflammation on cancer- or more in general disease-induced muscle wasting.

To reduce age-induced sarcopenia both on muscle mass and function, good results have been obtained with combinations of high protein diets and exercise (Tieland et al., 2012b). In COPD patients, muscle wasting can be reduced when the nutritional supplementation is combined with exercise and tailored to the reduced appetite of these patients, i.e. provided in between meals, in small amounts and with a fast emptying stomach (Anker et al., 2006; Schols, 2015).

For cancer cachexia and ICU patients, no treatment protocol has of yet shown to effectively reduce muscle wasting. For cancer cachexia high protein seems mandatory, and this should whenever possible be combined with exercise, although this is a challenge given the fatigue that is frequently present. Next to that, intervention should be aimed to reduce an elevated inflammatory status. This could include nutritional compounds like fish oil rich in n-3 fatty acids (Faber et al., 2008; Fearon et al., 2006; Murphy et al., 2012; van Norren et al., 2009), anti-inflammatory drugs like NSAIDs (Solheim et al., 2013), or a combination of both. Another interesting drug to combine with a nutrition and exercise could be anamorelin (Anker et al., 2015). This Ghrelin analogue showed in a meta-analysis an improvement on muscle mass, but not on muscle strength and survival. For ICU patients the situation can be complicated. These patients cannot exercise and next to that is providing enough high quality protein to these patients a challenge. They often receive tube-feeding, which when possible is to be preferred over parenteral feeding. Our studies have shown that type of protein and the position of the feeding tube is an important determinant of therapeutic outcome (Luttikhold et al., 2016). For example the ‘slow’ protein casein provides lower peaks than the ‘fast’ protein whey, when fed on the gut. This is comparable to normal oral intake. When fed on the intestine (jejunum) however, casein becomes a ‘fast’ protein (Luttikhold et al., 2015). The reason for this is probably that casein no longer coagulates in the stomach and is immediately available (Luttikhold et al., 2014). Levels of the gut hormones GLP-1 and GLP-2 in volunteers fed on the intestine were higher compared to stomach-feeding, indicating that insulin sensitivity and intestinal integrity might be improved when feeding on the jejunum (Luttikhold et al., 2013, 2016).

4.3. Food – drug and herb-drug interactions

Food-drug interactions present an example of (generally) unintentional and potentially adverse interferences between nutrition and pharma. In theory, these interactions are very common, since nutrients and drugs (in particular with oral medication) share the same passage, absorption, transport and biotransformation processes, while often overlapping in molecular targets. Fortunately, this does often not lead to clinically relevant situations. At the same time, food-drug interactions can have serious consequences. Furthermore, a major difficulty lies in the fact that interactions between drugs and diet, food products, or nutrient status are often unexpected, unpredictable and (particular for drug effects on nutrition) not always timely recognized. Food-drug interactions can be bi-directional. The vast majority of studies and case reports deal with food effects on drug outcomes. By contrast, much less has been published on effects of drugs on food- and nutrient uptake, storage, effects or elimination. A specific, though important category are interactions between herbal food supplements and drugs. As many plant-based health products fall within the food supplements category (Section 2), they will receive attention in this section as well. Based on their underlying mechanisms, food-drug interactions (foods including herbal supplements) are described in different sections:

1) Effects of nutritional/metabolic status (for example obesity, malnutrition) on drug Action (Section 4.3.1)
2) Effects of nutrition, specific nutrients or dietary supplements on drug action (Section 4.3.1)

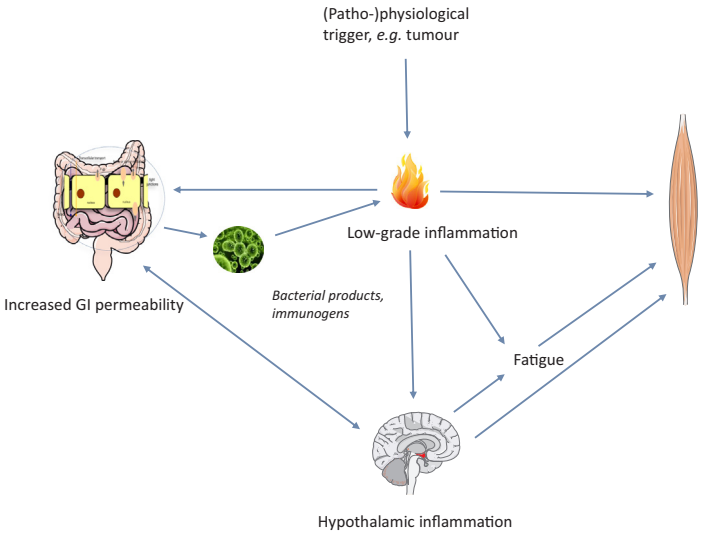

Fig. 4. Model of the role of the GI tract in hypothalamic-inflammation-mediated muscle breakdown. A pathophysiological trigger like a tumour induces inflammation. This is sensed and amplified by the hypothalamus resulting in a local low-grade inflammatory response. In parallel, the elevated systemic inflammatory status induces an increase of intestinal permeability. This in turn allows more bacterial compounds like LPS to enter the body. These trigger inflammation and are sensed by the hypothalamus, which further stimulates the response of the body to the tumour-induced elevated inflammatory tone.

3) Effects of drugs on nutrition and nutrient status (Section 4.3.2)

It is of interest to note that, in addition to unfavourable interactions, combinations of medicines and nutrition intervention are increasingly applied to achieve better results. Several examples have been given in previous sections. Another goal could be to reduce drug side-effects. An example is administering probiotics to reduce side-effects of antibacterial treatment and to prevent Clostridium difficile-associated diarrhoea (Goldenberg et al., 2017). However, this topic will not be further discussed in this review.

4.3.1. Effects of food, diet, nutrients or nutritional status on drug outcomes

This type of food-drug interactions presents a rapidly expanding field, and a topic of many recent reviews, for example (Deng et al., 2017; Mouly et al., 2017; Peter et al., 2017; Van Orten-Luiten, 2017). In the context of this article, only some general principles and examples will be addressed, as summarized in Fig. 5. Interactions can already start with in-appropriate mixing or combining drugs with food, including with enteral nutrition, before administration is taking place. A common practice for patients with swallowing difficulties is to crush tablets or open capsules in order to mix them with food. Apart from pharmaceutical problems, including disruption of sustained-release properties etc. this may also lead to interactions. Therefore, this practice should be limited to those situations in which certainty exists about safety and lack of potential interactions (Fodil et al., 2017; Gwladys et al., 2015). Regarding effects of diet and specific food components, the vast majority of food-drug interactions are those taking place within the GI tract, prior to absorption, and pharmacokinetic (PK) interactions. Pharmacokinetic interactions for example involve competition for drug transporters in the intestinal wall and effects on drug biotransformation in the intestinal epithelium, the liver or, to a lesser extent, other tissues. Although this might suggest that interactions are mainly occurring with oral drugs, interactions taking place further upstream, for example biotransformation in the liver, can also include parenterally administered drugs. A consequence of the fact that most interactions are PK- or physico-chemically determined, they often not follow therapeutic categories, which may present a complication in clinical practice. Compared to physico- chemical and PK interactions, the number of pharmacodynamics interactions is smaller. Next to more or less acute effects from specific diets or food products, more general and long term effects of food can also be relevant. Examples include effects of body composition on chemotherapy (Plas, 2018), effects of obesity on drug disposition (Smit et al., 2018) and effects of fasting for religious (Aadil et al., 2004) or other reasons, malnourishment etc. Although fasting and malnourishment may have important physiological consequences, including on processes involved in drug disposition, literature data are very scarce. As most herbal preparations fall within the food supplement category (Section 2), some words here as well on *herb-drug interactions.* For reviews see for example (de Boer et al., 2015; Eussen et al., 2011; Posadzki et al., 2012). Undoubtedly the best known is *Hypericum perforatum*, St John's Wort, a known inducer of CYP4503A4, but also interacting with some drug transporters and giving rise to pharmacodynamics interactions via serotonin. Other potentially dangerous interactions may occur with *Viscum album*, *Ginkgo biloba*, *Panax ginseng*, *Piper methysticum*, *Serenoa repens* and *Camellia sinensis* (Posadzki et al., 2012). It is clear that there are existing knowledge gaps in this field. Clinical relevance of predicted (from *in silico data*) or in vitro interactions is often not clear. Furthermore, the high, increasing number of preparations on the market, their diversity in terms of strength and quality and, in parallel inter-individual differences, polymorphisms etc. demands for attention for unexpected interactions in the clinic.

4.3.2. Effects of drugs on nutrients and nutrition status

Although drug-induced nutrient deficiencies are increasingly reported, there may be much more under the water line (Peter et al., 2017; Van Orten-Luiten, 2017). One of the explanations is that these interactions are easily overlooked, as they generally develop slowly and may go together with other social, nutritional, clinical and other changes. It seems conceivable that drug-induced nutrient deficiencies are relatively more frequent in elderly than in younger patients. Elderly persons may have specific nutritional requirements and nutrient deficiencies are already quite common in this group. This, together with the high incidence of polypharmacy, age-related physiological changes, and a potentially increasing vulnerability, underlines the importance of paying more attention to this topic. As with the previous category, mechanisms of drug effects can be sub-divided based on mechanisms and in this case to a large extent also sequence of event occurring with food intake (Fig. 6). In brief, drug effects in the oral cavity such as xerostomia, dry mouth (Scully and Bagan, 2004; Tan et al., 2017a), changes in taste and (or) smell perception (Doty and Bromley, 2004; Naik et al., 2010; Tsuruoka et al., 2005), dental or gingival disorders (Brown and Arany, 2015; Carty et al., 2015; Tredwin et al., 2005)can be relevant in particular in those already at risk for malnutrition, such as older persons. These side-effects may be easily overlooked. Further down, drugs may affect gastric emptying rate or GI motility, causing either constipation or diarrhoea, which may affect eating behaviour and (or) the absorption of certain vitamins and minerals.

Drug-induced changes of appetite and satiety can also result from central mechanisms with anti-depressants or anti-psychotics (Fava,

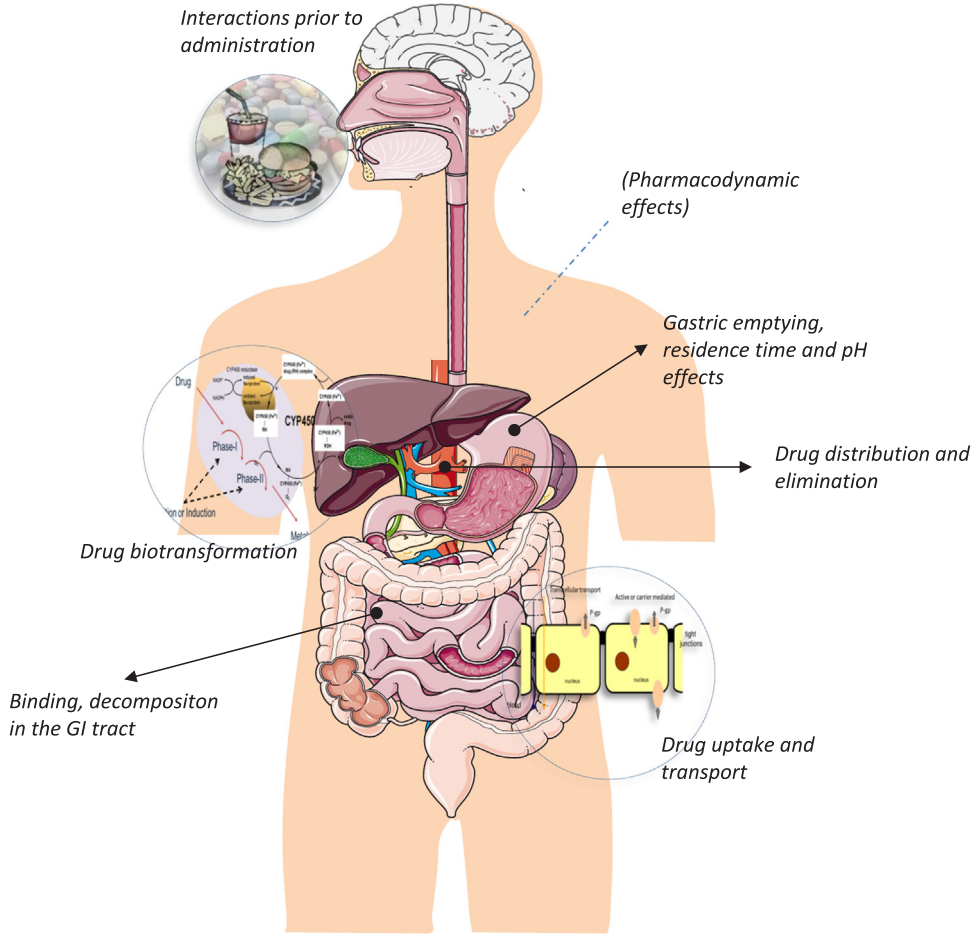

Fig. 5. Schematic representation of potential drug-food interactions.

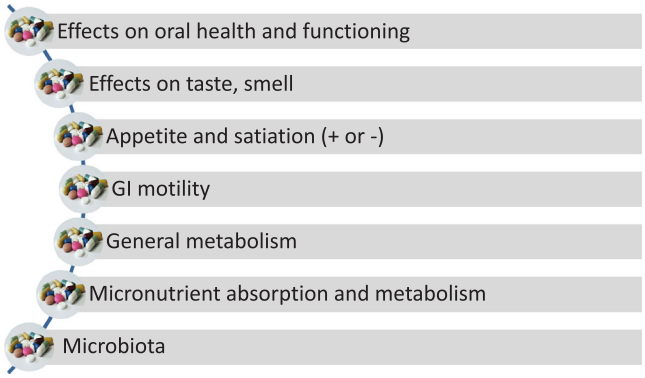

Fig. 6. Effects of drugs on nutrient intake.

2000; Gafoor et al., 2018; Himmerich et al., 2015). Again, effects may not always be timely recognized by care-takers, for example when a person has already a low dietary intake or when social or emotional problems are involved. Chronic nausea, for example during chemotherapy (Caillet et al., 2017) or with anti-cholinergics in dementia (Kavirajan and Schneider, 2007) may be another factor contributing to malnutrition. Medication can also alter vitamin absorption, storage and metabolism. Examples include vitamin B12 and vitamin D, which are often lowered in patients using metformin, proton pump-inhibitors or multiple drugs in general (van Orten-Luiten et al., 2014, 2016; Van Orten-Luiten, 2017). However, it should be noted that associations between drug use and vitamin deficiencies can also be due to the underlying disease. Last but not least, chronic drug use, for example diuretics, may lead to depletion of minerals and water. Again, elderly are specifically at risk (Van Orten-Luiten, 2017).

5. Conclusions

The prevailing viewpoint of Hippocrates' times that food should not be confused with medicine (Cardenas, 2013) is still standing, despite the fact that food is closely linked to health and disease. However, nutrients not only behave differently from medicinal compounds, but they are also taken from complex and changing mixtures as part of our total diet. Therefore, acute effects or "quick wins" are far less obvious than with pharmaceuticals. At the same time, increasing evidence shows that, in particularly during the early stages of disease, sustained lifestyle changes are by no means inferior to drug treatment, and often even more efficacious in stabilizing or even reversing the disorder. Next to this, targeted combinations of diet and medicines to improve treatment efficacy and reduce side-effects merit more attention. Therefore, clinicians should become aware again of the potential of nutritional intervention, in particular with lifestyle-associated diseases.

From a scientific perspective, pharma will benefit from nutritional biology and a physiological approach that starts from health instead of disease. This will generate more insight in the transition between health, homeostatic resilience, and chronic disease, which will assist us in finding better and more tailored treatment options. The examples of receptors and other molecular mechanisms presented in this review, even those typically known to generate sensations of taste, show that their actions sometimes go far beyond typical nutrition, also offering fascinating ways for pharmacological intervention. Last but not least, more attention is needed for nutritional status as adverse effect of drug

treatment, in particular with chronic polypharmacy in elderly and other vulnerable patients.

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