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Food-drug interactions and their impact on the pharmacotherapy

DIPLOMA THESIS

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ABSTRACT

Over the past few years, the occurrence of interactions between drugs and certain foods or nutrients has been an intriguing topic for the scientific community. The present diploma thesis aims to provide as much information as possible about food-drug interactions and to exemplify in which ways these interactions can or may have an impact on the effectiveness of each time pharmacotherapy. The relevant information upon food-drug interactions were recovered from literature, as described from various authors that have dealt with this subject.

Foods which are commonly consumed (such as dietary proteins, carbohydrates, fats and fibres, fruits and vegetables, citrus fruit juices, beverages, vitamin and mineral supplements, herbal supplements and tyramine-based foods) are described in detail with reference to the effects that they induce in drugs' kinetics. On the other hand, the changes in overall nutritional status of a patient (such as alterations in body weight, alterations in oral cavity, taste and smell, drug-induced effects on the GI tract, alterations in macronutrient metabolism and depletion in essential nutrients) which are induced by commonly prescribed and over-the-counter drugs used for the treatment of various diseases, are also described. Clinical significance of food-drug interactions and dietary recommendations for drugs with regard to food intake are also discussed.

Food-drug interactions in the mechanistic manner may be actions at membrane transporters or metabolizing enzymes (i.e. pharmacokinetics), or antagonistic, additive/synergistic on physiological function (i.e. pharmacodynamics) or physicochemical reactions (i.e. pharmaceutics). These interactions can have profound influence on pharmacotherapy. By a negative aspect, food-drug interactions can lead to serious side effects, toxicities or therapeutic failure. Generally, the effects of food on drugs result in an alteration in drug bioavailability; however, food can also alter drug clearance, while the effect of drug on food intake can affect the nutritional status of a patient either as a result of the drug's mechanism of action or by its adverse effect profile. The most important interactions are those reflecting a high risk of treatment failure owing to a significantly reduced drug bioavailability in the fed state. By a positive aspect, food-drug interactions may result in increased drug efficacy or diminished potential side effects.

The extent and clinical significance of food-drug interactions can display considerable variation, whereas clinical significance can be highly dependent on the individual patient. Furthermore, food-drug interactions involving drugs with narrow therapeutic indices and drugs where dosage and blood levels require careful control are expected to be the most clinically significant. The interactions that significantly reduce the bioavailability of some drug are often caused by chelation with dairy products and/or other food components, or by other direct interactions between drugs and food, or poor acid lability. The interactions that increase drug bioavailability are often caused by a food-induced increase in drug solubility or by the secretion of gastric acid or bile secretion (often enhanced with fat intake for lipophilic drugs). For most drugs, such an increase results in a desired increase in drug effect, but in others it may result in serious toxicity. Food intake may also affect drug bioavailability or serious side effects can occur due to other ways of interaction (e.g. direct antagonism, physical binding, inhibited deamination of dietary pressor amines, etc).

Grapefruit juice-drug interactions and St John's wort-drug interactions are perhaps the best known food-drug interaction, as grapefruit juice and St John's wort can each significantly affect the bioavailability of various drugs, along with MAOIs-tyramine food interactions which can lead to severe hypertensive crisis. Other well-described interactions include warfarin-vitamin K interactions, certain antidiabetic drugs-induced hypoglycemia and certain psychotropic drugs-induced weight gain. Disulfiram-like reactions are also among the best known interactions of drugs with alcohol.

Although food-drug interactions are not as common as drug-drug interactions, they are no less important in their ability to influence patient outcome. The knowledge of interactions between drugs and foods can enhance the work of medical scientists in the clinical setting.

KEY WORDS

Food, nutrient, drug, interaction, nutritional status, bioavailability, pharmacokinetic, pharmacodynamic, side effect, efficacy

PERSONAL STATEMENT

I declare that I carried out this diploma thesis independently and only with the cited sources, literature and other professional sources.

Author's Signature

Ioanna A. Angelakou

Brno, 2014

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1. INTRODUCTION

Over the past few years, the scientific community has expressed an increasing interest in the interactions that take place between drugs and certain foods or nutrients *[1, 2]*. The growing relevance of drug-nutrient interactions in daily practice comes along with the widespread use of medication *[3]*.

In general, the term *drug interaction* refers to a situation in which a substance (usually another drug) affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own *[4]*, while the term *food-drug interaction* refers to a situation in which a drug affects the nutritional status of an individual. Food-drug interaction is a broader term and it is often used interchangeably with the term *drug–nutrients interaction.* Actually, drug–nutrients interactions are some of the many possible food-drug interactions and also include the specific changes to the pharmacokinetics of a drug caused by a nutrient or changes to the kinetics of a nutrient caused by a drug *[5]*. For the purposes of the present diploma thesis, the term food-drug interaction will be used, comprising the interaction between drugs and nutrients.

Food-drug interactions can roughly be divided into two basic categories: a. the effect of nutrition on the drugs and b. the effect of the drugs on the dietary status of a patient *[2]*. On one hand, food, beverages and mineral or vitamin supplements can affect the effectiveness of drugs by altering absorption, bioavailability, distribution, metabolism and excretion. Nutritional status may also influence drug response. On the other hand, drugs can affect nutritional status by altering nutrient absorption, metabolism, utilization or excretion. The effect of these interactions may result in altered nutritional status *[1, 2]*. The effects of food-drug interactions can differ according to the type of medication, the form of drug (i.e. pill, liquid, etc.), the dosage, the site of absorption (mouth, stomach, intestine) or the route of administration (i.e. oral, intravenous, etc.) *[6]*.

Although drug-nutrient interactions are not as common as drug-drug interactions, however the knowledge of nutrition’s influence on drugs is of great importance since it can affect a therapeutic outcome. Knowledge of possible interactions between prescription drugs and foods and nutrients can also enhance the work of physicians, dieticians and pharmacists in the clinical practice *[1, 2]*.

2. THEORETICAL PART

2.1 What is a food-drug interaction?

According to a broader definition, a food-drug interaction can be defined as: *an event that results from a physical, chemical, physiological, or pathophysiological relationship between a drug and nutrient, multiple nutrients, nutritional status, or food in general,* which is clinically significant if drug response is altered or nutritional status is compromised *[3, 7- 9]*.

Drugs and foods have the common feature of being chemical substances that – within a proscribed concentration range – produce a beneficial physiological effect. They also share several common sites of transport within the body, each of which represents a potential site of food-drug interaction *[10]*. However, food-drug interactions can significantly decrease the effectiveness of pharmacotherapy (and prolong hospitalization in patients treated in primary health care), thus increasing its costs *[11]*.

2.2 Principals of interactions

In order for the food-drug interactions to be understood, they must be viewed in terms of pharmaceutics, pharmacokinetics and pharmacodynamics (*Figure 2.2.1*). More specifically, food-drug interactions are in fact alterations of pharmacokinetics or pharmacodynamics of a drug or nutritional element or a compromise in nutritional status as a result of the addition of a drug. Pharmacodynamics refers to the physiologic or clinical effects of a drug, while pharmacokinetics refers to the quantitative description of drug disposition, which embrace absorption, distribution, metabolism, and excretion *[12, 13]*. The basic principles of pharmacokinetics and pharmacodynamics provide a basis for understanding the occurrence and treatment of food-drug interactions *[10]*.

Pharmaceutical interactions involve physicochemical reactions that take place in a delivery device (e.g. enteral feeding tube) or within the gastrointestinal lumen. These can influence the biological availability of a drug or nutrient *[3]*.

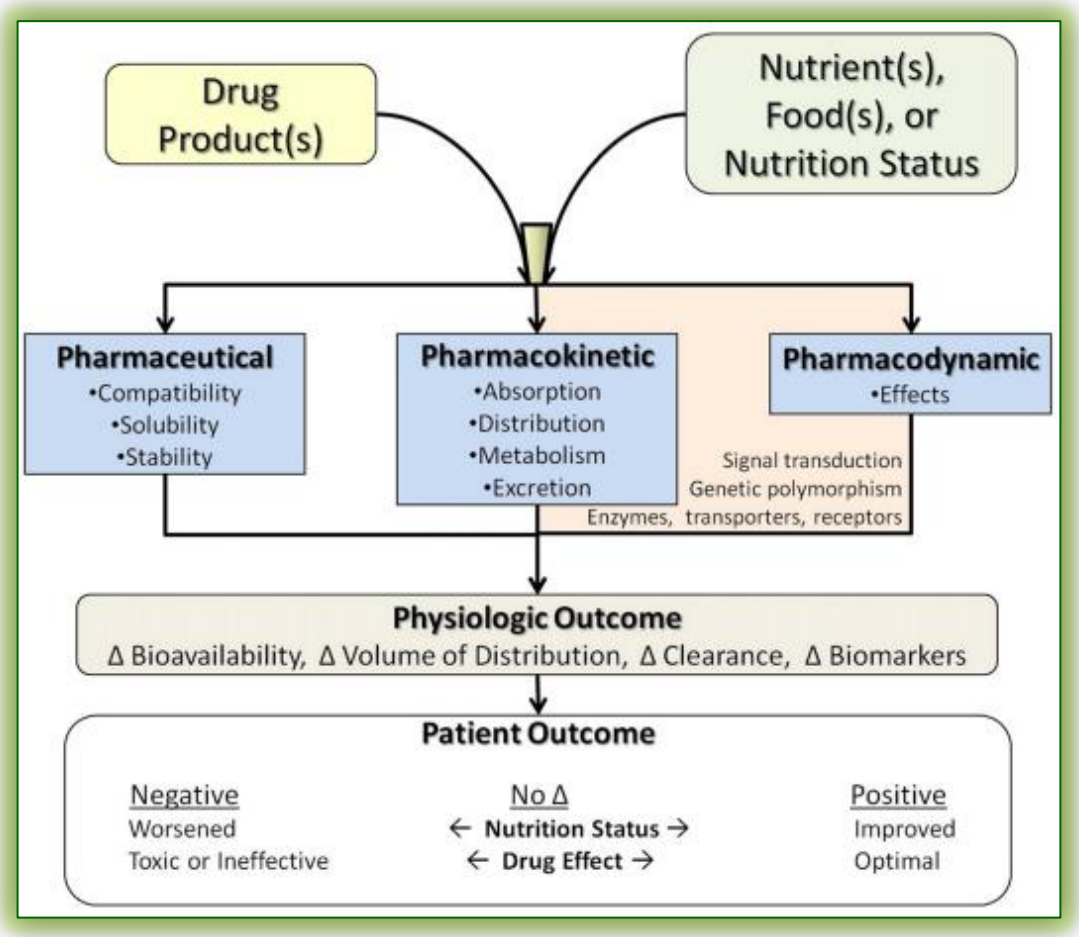

***Figure 2.2.1** **The working model of food-drug interactions** [3].*

2.2.1 Mechanism of drug interactions (pharmacodynamics)

Pharmacodynamics is the study of the biochemical and physiological effects of a drug *[5]*. In other words, it can be described as the study of how drugs affect the body. The detailed mechanism of action by which drugs produce a physiological response begins with the binding of the drug molecule to a receptor, enzyme or ion channel, continues through a signal transduction pathway where the receptor activates second messenger molecules and ends with the ultimate description of intracellular processes altered by the impact of the drug *[14]*. Eventually, this response may be enhanced or weakened by the addition of other substances with similar or opposing actions *[5]*. The pharmacodynamic interaction may be additive, synergistic, or antagonistic effects of a drug *[4]*.

The place where a drug causes a pharmacological effect is called the site of action. Broadly speaking, there are four major mechanism by which drugs can cause an effect:

they can either kill invading organisms, kill aberrant cells, neutralize acids or modify physiological processes. More specifically *[10, 15]*:

- **Cytotoxicity** is the mechanism of action of drugs that are directed either against invading organisms (i.e. bacteria, viruses, worms etc) or against aberrant cells (i.e. neoplasms). For example antibiotics and antivirals can modify biochemical processes of invading organisms, by acting on enzymatic pathways involved in the synthesis of endogenous substances or by inhibiting viral replication. In many cancer chemotherapies, antineoplastic agents such as antimetabolite drugs compete with critical precursors of RNA and DNA synthesis, thereby inhibiting cell proliferation. In both cases, the drugs exhibit selectivity for biochemical processes essential to the invading organism, but not essential to humans.
- **Neutralization of acids** is the mechanism of most common antacids. These are weak bases that convert gastric (hydrochloric) acid to water and a salt and they are used to reduce excess gastric acidity.
- **Chelation** is the mechanism of action of drugs that is used to treat poisoning with various metals or toxins. Chelating agents containing a metal ion attached by coordinate bonds to at least two nonmetal ions, forming inner ring structure and in this way inactivate or neutralize the effects of metals or toxins.
- **Modulation** is the mechanism that interferes with the normal physiological functions of cells, by targeting on enzymes or receptors, DNA, and a variety of other molecules involved in the synthesis, storage, metabolism, or elimination of endogenous substances.

Most drugs initiate a chain of events that leads to the drug's effect, by interacting with specific macromolecular components of a cell, which are called receptors. Receptors are proteins embedded: in the cell's plasma membrane, in the cytoplasm, or in the cell's nucleus. A molecule that binds to a receptor is called a ligand and apart from being a pharmaceutical drug can be another small molecule (e.g. neurotransmitter, hormone, toxin) or can be a peptide *[16]*. Receptors can be any of the following types (see *Figure 2.2.1.1*) *[15-17]*:

- **Peripheral membrane receptors** that adhere only temporarily to the biological membrane with which they are associated and they are relatively rare compared to the next type of receptors.
- **Transmembrane receptors** that cross the cell membrane, going from one side of a membrane through to the other side of the membrane. Examples of this type are:

- *ligand-gated ion channel receptors*, which consist of segments of transmembrane proteins that form pores of specific shape and size, allowing the passage of certain ions. Examples of this family ion channels are the nicotinic, cholinergic, $GABA_A$, glutamate and glycine receptors).
- *G-protein-coupled receptors* (also known as seven-transmembrane domain receptors), which are a large protein family of receptors that sense molecules outside the cell, pass through the cell membrane seven times and activate inside cell signal transduction pathways. The ligands that bind and activate these receptors include: light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, varying in size (small molecules, peptides, large proteins). They are involved in the therapy of many diseases such as cancer, cardiac dysfunction, diabetes, central nervous system disorders, obesity, inflammation and pain; 40% of all prescription pharmaceuticals on the market take their affect through this type of receptors *[18]*.
- *Tyrosine kinases receptors* or *enzyme-linked receptors*, which span the membrane and have an intracellular catalytic domain that has enzymatic activity. They include receptors for certain growth factors and insulin.

❖ **Intracellular receptors** that are located inside the cell. One example is *nuclear receptors*, which bind directly to DNA and act as transcription factors that regulate the gene expression. Moreover, they are responsible for sensing steroid hormones, thyroid hormones and certain other molecules and for influencing protein production and regulation.

Generally speaking, the interaction between receptors and drugs is usually reversible and it is compared to a "lock and key" fit, creating this way a drug-receptor complex. Each cell in the body has receptors ("locks") that require a specific "key" to produce an effect. Specific drugs are developed to "unlock" certain receptors in the body, producing the desired effect. Receptors are activated when drug molecules form weak chemical bonds with them, such as hydrogen, ionic or hydrophobic bonds *[10, 14]*. The magnitude of such a drug's effect is related to the number of receptors that are ''occupied'' *[19]*.

Not all chemical substances (drugs) fit a binding site on any receptor, but some have the tendency to do so. This tendency is called **affinity** and it is a measure of the strength of the drug-receptor complex. Only a subset of substances that bind to receptors are capable of evoking an effect through the receptor. The ability of a drug to initiate a cellular effect under specified conditions is called **intrinsic activity** or **efficacy**. Efficacy is not directly

related to receptor affinity and differs among various drugs that bind to a receptor and start the signal transduction pathway *[10, 14]*.

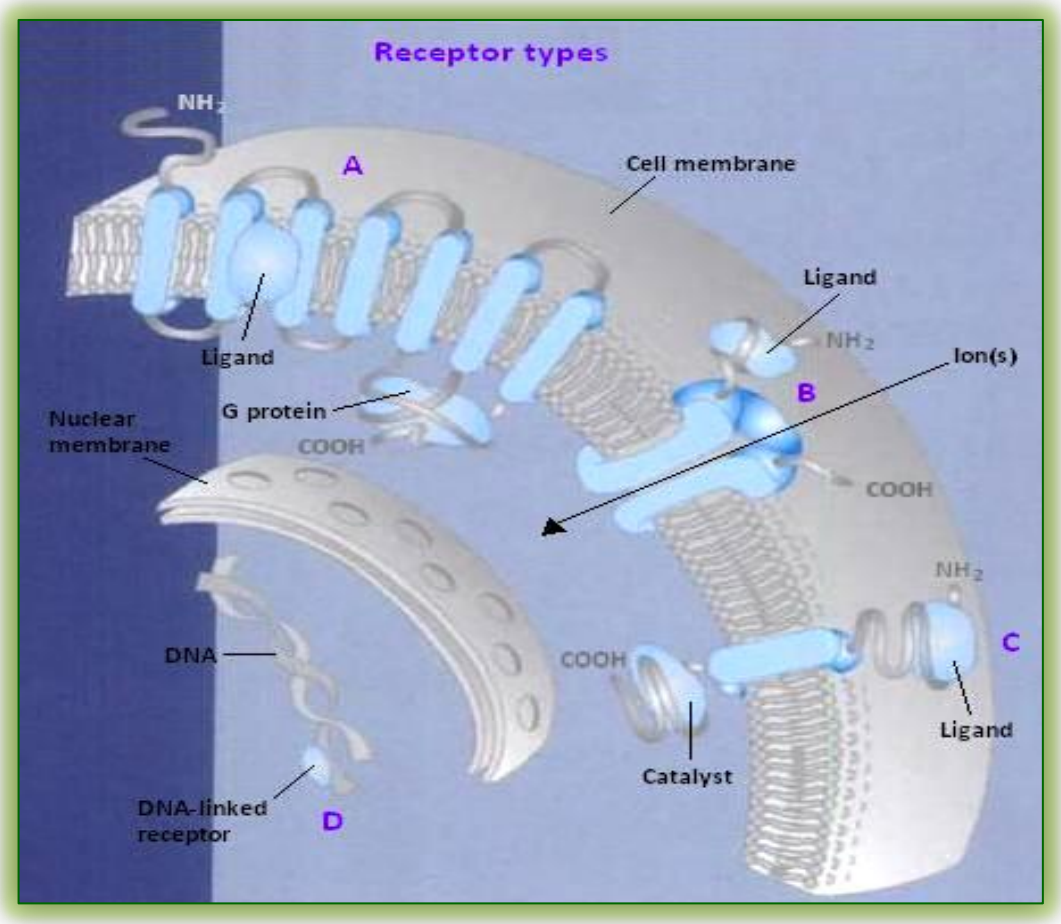

Figure 2.2.1.1* Different types of receptors.** ***A *stands for G-protein-coupled receptor,* ***B*** *stands for ligand-gated ion channel receptor,* ***C*** *stands for receptor that is an enzyme (tyrosine kinases receptor) and* ***D*** *stands for DNA-linked receptor (nuclear receptor) [15, with modifications].*

Drugs that have both receptor affinity and efficacy are called agonists, whereas drugs that have receptor affinity but lack efficacy are called antagonists. Agonists can be divided into three types *[14, 16]*:

- **Full agonists**, which are able to activate the receptor and result in a maximal biological response. They have affinity and maximal efficacy.
- **Partial agonists**, which do not activate receptors thoroughly, causing responses which are partial compared to those of full agonists. They have affinity and less than maximal efficacy.

❖ **Inverse agonists**, which reduce the activity of receptors by inhibiting their constitutive activity (negative efficacy).

With a full agonist being present, a partial agonist will act like an antagonist, preventing the full agonist from binding the receptor and exerting a maximal response. Antagonists can inhibit the access of agonists and inverse agonists to their receptors. They can be divided into two types *[14]*:

❖ **Competitive antagonists**, which are reversibly bound to the same site as the agonist on the receptor, without activating the receptor.

❖ **Noncompetitive antagonists**, which irreversibly block the agonist site usually by forming a covalent bond.

Signal transduction is linked to the postreceptor chain of events that lead to an agonist's effect. Transduction mechanisms can be ionotropic (the activation of receptor leads directly to influx of ions) or metabotropic (the activation of the receptor triggers a series of biochemical second messengers that mediate the response) *[10, 17]*. Second messengers are the substances which enter the cytoplasm and act within the cell to trigger a response. They essentially serve as chemical relays from the plasma membrane to the cytoplasm, thus carrying out intracellular signal transduction *[20]*.

Potency is a characteristic of drug action that refers to the amount of substance that is required to produce a specified level of effect and it is usually expressed in terms of median effective dose –ED50 (the dose that produces 50% of the maximal response). Potency and efficacy are independent characteristics *[10, 14]*.

The pharmacological effect of a drug is related to the concentration of the drug at the site of action. The relationship between the concentration of a drug at the site of action and the intensity of pharmacological effect caused is quantified and evaluated by the "dose-response curve". Graphic data can be used to analyze individual drug activity or be compared with other graphs (e.g. to assess potency or maximal efficacy). Precise pharmacodynamic analysis in early phase studies is usually succeeded by identifying and monitoring biomarkers. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of a normal physiological process, pathogenic process or pharmacological response to a therapeutic intervention e.g. blood glucose for anti- diabetic drugs, coagulation for new anticoagulants *[21]*.

2.2.2 Stages of drug interactions (pharmacokinetics)

Pharmacokinetics is a science that deals with the progressive movement and alteration of chemical substances within the body *[22]*. When receiving medication, there are four stages of pharmacological action taken, so as the drug to have an effect in the body or more specifically in a target organ or a tissue. These stages correspond to the pharmacokinetic arenas of absorption, distribution, metabolism, and excretion (*Figure 2.2.2.1*) and they are often referred to with the acronym **ADME**. So, in order for a pharmacological effect to be produced the next stages are followed *[5, 6, 14, 22]*:

- **Stage 1 - Absorption:** The drug needs to be dissolved into a useable form and move from the site of administration into the bloodstream.
- **Stage 2 - Distribution:** The drug needs to leave the bloodstream and be transported to a receptor (the site of action). The drug may then exert its pharmacological effect.
- **Stage 3 - Metabolism:** The drug may be metabolized, primarily in the liver.
- **Stage 4 - Excretion:** The drug is eventually eliminated from the body, primarily by the kidneys.

However, a food-drug interaction can alter the above courses of action at any point.

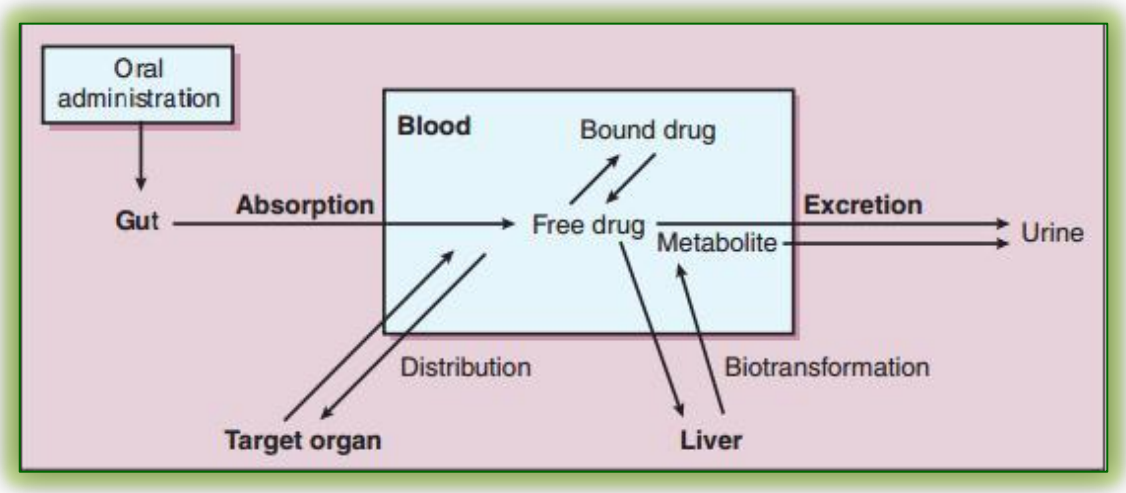

Figure 2.2.2.1 The relationship between the processes of absorption, distribution, metabolism and excretion of a typical drug, after its oral administration *[14]*.

As mentioned above, **absorption** is the process in which drug molecules move from the site of administration into the bloodstream (circulation). The process of drug absorption

applies to all routes of administration, apart from intravenous administration (drug being already in the circulation) and the topical route (drugs applied directly on the target tissue) *[14]*.

Most drugs are absorbed by passive diffusion across cells membranes while a few others are absorbed by active transport or by facilitated diffusion *[14]*. In passive diffusion, drugs diffuse across a cell membrane from a region of high concentration to one of low concentration. This process is facilitated in two ways: the drugs may be dissolved in the lipid components of the cell membranes (lipid diffusion) so lipid-soluble drugs diffuse most rapidly, or the drugs (especially the ones with small molecules) may pass through aqueous pores in cell membranes (aqueous diffusion) *[23]*. Active transport requires a carrier molecule and it is energy-dependent, driven by the hydrolysis of the terminal high-energy phosphate bond of ATP. It is capable of moving drugs against a concentration gradient. Facilitated diffusion also requires a carrier molecule, but no energy expenditure is needed and transport against a concentration gradient cannot occur *[14, 23]*.

Drugs are weak organic acids or bases, existing in unionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid-soluble, thus diffuses readily across cell membranes, while the ionized form has high water solubility (but low lipid solubility) and high electrical resistance, thus cannot penetrate cell membranes easily *[23]*. Drugs are usually absorbed in an unionized form. The weakly acidic drugs are generally absorbed in the stomach, whereas weakly basic drugs (as most drugs) are absorbed in the small intestine. Binding to other chemicals in the gastrointestinal tract may interfere with absorption. Especially when a drug is taken orally, food, food components and nutritional supplements can interfere with absorption *[22]*.

Many factors can affect absorption, the main of which are *[5, 22]*:

- The route of administration.
- The chemical nature of the drug and its ability to cross membranes.
- The quality of the product formulation and the dosage form.
- The local environment at the site of absorption, that is pH, blood flow, physiological changes of tissue, etc.
- The rate of gastric emptying (for oral drugs) and gastrointestinal movement.

Distribution is the process when the drug leaves the systemic circulation and moves to various parts of the body. Depending on its chemical nature and its ability to cross biological membranes, the drug may preferentially concentrate in a particular body area.

Drugs in the bloodstream are often bound to plasma proteins such as albumin, though only unbound drugs can leave the blood and affect target organs *[5, 22]*.

Multiple factors affect the distribution of substances in the body. Some are related to the substance itself, such as its physical and chemical characteristics, while others are related to the state of the physiological system, such as concentration of plasma proteins, lipid content of barrier or target tissues, cardiac output, etc. Many of these factors are a function of age, disease, or other influences *[10]*.

When a drug enters the body**,** it is eliminated from the blood either as one or more altered in chemistry substances from the original compound (parent drug), through the processes of **metabolism** (biotransformation) or as an unchanged drug through the processes of **excretion**.

Metabolism generally changes fat soluble compounds to water soluble compounds so that can be handled easier by the kidneys and excreted in the urine. By this way the body decreases toxicity and enhances the elimination of foreign chemicals. The end products of metabolism are referred to as metabolites. Biotransformation can happen in a specific organ or in the peripheral tissue of the body. The liver is the major organ involved in this process, though other sites, for example the intestinal membrane, contribute to variable degrees *[5, 22]*.

The drugs that are absorbed from the gut, before entering the systemic circulation, reach the liver via the hepatic portal vein (*Figure 2.2.2.2*). Many drugs after oral administration (e.g. antihypertensive agent felodipine) are biotransformed by enzymes into inactive metabolites during their first pass through the gut wall and liver and subsequently have low bioavailability. This phenomenon is called the first-pass effect or **first-pass biotransformation** *[14]* and it has been shown to have clinically relevant influences on the potency and efficacy of drugs *[12]*. On the other hand, the drugs that are administered by the sublingual or rectal route undergo less first-pass metabolism and have a higher degree of bioavailability *[14]*.

Drug metabolism can be divided into two phases, each carried out by unique sets of metabolic enzymes. Phase I includes oxidative, hydrolytic and reductive reactions and Phase II involves conjugation reactions with an endogenous substance such as glucuronic acid, sulfate or glycine *[14, 24, 22]*. One group of liver enzymes responsible for all or part of metabolic activity and synthesis of a number of endogenous compounds (for instance steroid hormones, prostaglandins) is the cytochrome P-450 enzyme system. This is the most important enzyme system of Phase I metabolism, involved in the oxidation of many

drugs and other chemicals *[25]*. Foods or dietary supplements that increase or inhibit this enzyme system can change the rate or extent of drug metabolism *[5]*. Changes in liver function or age alone, in the absence of liver pathology, may also affect drug metabolism *[22]*.

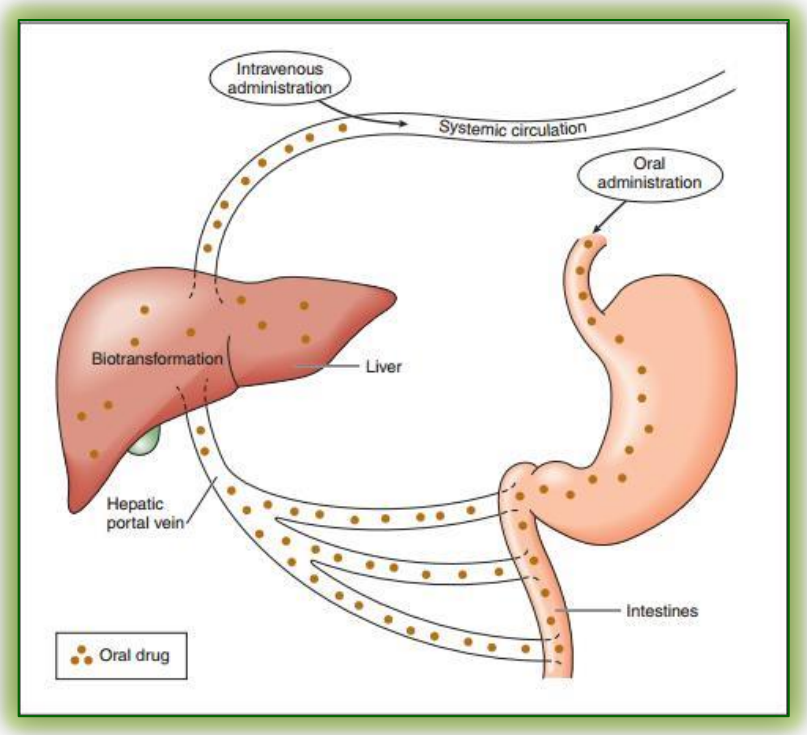

Figure 2.2.2.2 First-pass biotransformation of orally administrated drug. *The drugs that are absorbed from the gut, before reaching the systemic circulation, can be biotransformed by enzymes in the gut wall and liver. This process lowers their degree of bioavailability [14].*

Several organs are involved in eliminating drugs from the body, with the kidneys being the most important ones for this activity *[22]*. Most drugs are excreted in the urine, either as the parent compound or as a drug metabolite. To a lesser extent, other routes of excretion can be in: bile, sweat, saliva, tears, feces, breast milk and exhaled air *[14]*.

In the kidney, three major processes control the excretion of drugs, all which occur in the nephron (the functional unit of the kidney), namely glomerular filtration, active tubular secretion and tubular reabsorption. The net result of these processes is defined as the renal clearance *[26]*. In glomerular filtration, which is a low clearance process, most drug molecules enter the renal tubule as a dissolved solute in the plasma filtrate, while the passage of protein-bound drugs is restricted. Large drugs or those bound to plasma-protein cannot be filtered and are poorly excreted by glomerular filtration *[14, 27, 28]*. Active

tubular secretion is an efficient mechanism for extracting substances from the circulation and secreting them into the tubular lumen. It is not affected by plasma protein binding and it involves two carrier systems – basic carriers which transport basic drugs and acidic carriers for acidic drugs *[14, 27]*. In tubular reabsorption there is a flow of drug back into the blood stream, because the water that initially enters the nephron is reabsorbed back into the blood as a means of conserving body fluid. As this movement occurs, some drugs are transported along with it *[27]*. As mentioned above, renal clearance is the result of all three processes and can be described by the following equation: the amount of drug excreted is the sum of the amounts filtered and secreted minus the amount reabsorbed *[26]*.

Factors affecting renal excretion of drugs include: kidney function, protein binding, urine pH and urine flow *[26]*. Age can also be a factor, since renal function declines as a function of normal aging. The process of excretion can be enhanced or inhibited by the presence of other substances in the urine or the blood. Drugs altering urine production, such as diuretics, may also affect the urinary excretion of drug and its metabolites, thus resulting in interactions *[22]*.

The processes of absorption and elimination of substances generally follows either first-order kinetics (i.e., exponential decay) in which a constant fraction is absorbed or eliminated per unit time or zero-order kinetics (linear) in which a constant amount is absorbed or eliminated per unit time. Most currently used drugs follow first-order kinetics *[10]*.

2.2.3 Types of food-drug interactions

Drugs can interact with food components in several ways, given the fact that they share several characteristics which include: similar pharmacodynamic mechanisms (e.g. enzymes and receptors), similar sites of absorption in the intestine, the ability to alter physiological processes and the capacity to cause toxicity in high doses *[29, 30]*.

The various phases in which food may interact with a co-administered drug are: before and during gastrointestinal absorption, during distribution, during metabolism and during elimination. Absorption and metabolism are the phases where food has most effect *[31]*.

The food-drug interactions, based on their nature and mechanisms, can be categorized into four types *[12, 32-35]*:

❖ **Type I - ex vivo bioinactivations:** They refer to the interactions between drug molecules and nutritional constituents through biochemical or physical reactions, such as hydrolysis, oxidation, neutralization, precipitation or complexation. They usually occur in the delivery device.

❖ **Type II - interactions affecting absorption:** Absorption interactions can occur with drugs and nutrients that are only taken orally or through enteral feeding delivery systems. These interactions cause either an increase or decrease in the oral bioavailability of a drug. Absorption interactions can be sub-classified into the following three types: 1)presystemic metabolism, 2)presystemic transport and 3)presystemic binding/complexation *[36-38]*. The precipitant agents may modify the function of enzymes or transport mechanisms that are responsible for biotransformation. Complexation, binding, and/or other deactivating processes occur in the gastrointestinal tract and reduce absorption.

❖ **Type III - interactions affecting the systemic or physiologic disposition**: They occur after the drug or the nutritional constituents has been absorbed from the gastrointestinal tract and entered the systemic circulation. Changes of the cellular or tissue distribution, systemic metabolism or penetration into specific organs or tissues can occur.

❖ **Type IV - interactions affecting elimination or clearance of drugs or nutrients:** This kind of interactions influences either hepatic metabolism or renal elimination of the object agents via the involvement of precipitant agents. A number of pathways may be involved, for example antagonism, decrease or modulation of renal and/or enterohepatic elimination.

Drug-metabolizing enzymes and drug transporters play a key role in modulating drug absorption, distribution, metabolism, and elimination. Acting together or alone, they can influence the pharmacodynamics and pharmacokinetics of a drug *[33]*.

2.3 Bioavailability, half-life and side effects concepts

At this point, it is essential for the concepts of bioavailability, half-life and side effects to be mentioned:

Bioavailability is an important pharmacokinetic parameter which is correlated with the clinical effect of most drugs *[4]*. It is a term applicable to the absorptive aspects of bioactive compounds and their ability to gain access to the circulatory system *[39]*. Due to the multiple barriers to absorption, the amount of a drug that enters the systemic circulation

is less than the amount administered. The proportion (expressed either as fraction or percent) of an administered drug dose that reaches the systemic circulation is referred to as the drug's bioavailability *[10]*.

Drugs can possibly influence the bioavailability of nutrients through effects on appetite, absorption, gastrointestinal motility, hepatic metabolism and urinary excretion, whereas drug absorption and metabolism can sometimes be influenced by food supplements and nutrients *[29, 40]*.

Half-life is a term used in pharmacokinetics to describe the amount of time it takes for the body to reduce the amount of a drug in the systematic circulation by 50% *[41]*. The half-life can be expressed in terms of clearance (the volume of fluid completely cleared of drug per unit time) and volume of distribution of a drug (the apparent volume into which the drug has distributed to produce the measured concentration), indicating that the drug's half-life will change when either of these factors is altered. Disease, age, and other physiologic variables can alter drug clearance or volume of distribution and thereby change the elimination half-life (the time taken for 50% of the drug to be eliminated and to reach steady state) *[14, 42]*. Knowledge of distribution volume can be used to calculate a loading dose so as to achieve a target concentration quickly, while knowledge of clearance can be used to calculate the dose rate required to maintain a target concentration *[42]*.

Side effects are adverse effects or undesirable reactions which may accompany the desired effects of drugs. Side effects are often an extension of the desired effects, for instance bacterial overgrowth as a result of antibiotic usage *[5]* or alteration in absorption by fatty, high protein and fiber diets as major side-effects of food on drugs *[4, 43]*.

Food-drug interactions can have as an outcome two main clinical effects: either a decreased bioavailability of a drug, which predisposes to treatment failure, or an increased bioavailability, which increases the risk of adverse events and may even precipitate toxicities *[12]*.

2.4 Risk factors that lead to food-drug interactions

Regarding food-drug interactions, it is known that some foods and drugs, when taken simultaneously, can alter the ability of the body to make the most of a particular food or drug, or can cause serious side effects *[4]*. The factors that can increase the potential for interactions include *[1, 5-7]*:

- Body composition (e.g. the increased proportion of adipose tissue in obese or older patients).
- Long-term drug administration.
- Dose size and polypharmacy.
- Genetics.
- Nutritional status (e.g. poor dietary intake, special diets).
- Usage of nutritional supplements and herbal products.
- Medical history (i.e. underlying illnesses or pre-existing disease states, especially gastrointestinal disease or allergies/ intolerances).
- Increased nutritional needs due to recent surgery, infection or tube feeding.
- Alcohol intake and drugs of abuse.
- Excipients in drugs or food.
- The patient's age (very young or very old) and gender.

The development of food-drug interactions may also depend on the size and the composition of a meal as well as the exact timing of drug intake in relation to a meal *[31, 44]*. For instance, the absorption of drugs from the gastrointestinal tract can be considerably affected by simultaneous intake of meals, particularly meals with a high fat content *[45]*.

According to the above, it is obvious that there is a high need for individual assessment of a patient, regarding the effects of foods on drug action and the effects of drugs on nutritional status.

2.5 Patient populations

The clinical significance of a pharmacokinetic or a pharmacodynamic food-drug interaction can be highly dependent on the individual patient (i.e. patient’s age, general health, nutritional status, etc) *[10]*.

2.5.1 Which patients are at higher risk?

The effect of food-drug interactions differs from one patient to another with some groups of patients being at particular risk *[29, 30]*. Patient populations who have increased risks associated with food-drug interactions are *[7, 12, 29, 46]*:

- Elderly patients.
- Patients with chronic diseases (e.g. diabetes) who use multiple drugs, particularly those with a narrow therapeutic range, are at particular risk for interactions.
- Patients with cancer or acquired immunodeficiency syndrome (HIV/AIDS)
- Malnourished patient.
- Fetus, infants and children
- Pregnant women
- Transplant recipients.
- Patients receiving enteral nutrition or having gastrointestinal tract dysfunctions.
- Patients on multiple or long-term therapy.
- Patients using prescription and over-the-counter medications together.
- Patients not following medication directions.
- Patients who drink alcohol or smoke excessively.

Elderly patients are particularly at risk because more than 30% of all the prescription drugs are taken by this population *[12, 32]*. Chronic diseases, polypharmacy, nutritional inadequacies, changes in the appetite, pathological changes associated with aging etc, are some of the causes that can affect the pharmacokinetics of a drug and thus increase the risk for adverse effects and clinically important outcome of the food-drug interactions in the elderly. While several different food-drug interactions are important in the elderly, those affecting the cardiovascular system justify special attention *[47]*.

Patients with cancer or HIV are at special risk because of the high dominance of malnutrition and reduced intakes. Chemotherapy and radiation may also create greater potential for food-drug interactions due to: intense nutritional disturbances, since cytotoxic agents can cause nausea, vomiting, mouth sores, diarrhea, anorexia and reduced food intake, malabsorption caused by intestinal damage, or affected drug disposition by alterations in the gastrointestinal tract *[5]*.

Fetuses, infants and pregnant women are groups of population facing high risk for food-drug interactions. Infants and children are at particular risk because of the relative

inefficiency of the gastrointestinal and hepatic drug metabolizing enzymes and poorly developed renal function *[29]*. Fetus or an infant may unnecessarily be exposed to potentially harmful drugs. It is difficult to assess the risk of negative drug effects, including food-drug interactions, since not many drugs have been tested on these groups *[5]*.

2.5.2 Special group of patients with variant genotype (pharmacogenetics-pharmacogenomics)

In a large patient population, a drug that is proven to be effective for many patients, often fails to work for some other patients *[48]*. The factors that influence how individuals respond to medication are their external and internal environments and overall health, as well as their genetic make-up *[49]*. Genetic make-up of a patient importantly influences inherent pharmacokinetics, ultimately giving rise to interpatient variation in drug absorption, distribution, biotransformation, and elimination *[50]*.

The assessment of how a person's genetic make up (genotype) influences the way they respond to a drug (their phenotype in this regard) and the role genetic differences play in interindividual variability of response to drugs, is called **pharmacogenetics** *[10]*. The study of genetic variations causing variable drug response includes the study of genetic polymorphism of drug transporters, drug metabolizing enzymes and drug receptors. **Pharmacogenomics** is the research area at the genome level which aims at identifying disease genes and new drug response markers (allele polymorphisms) *[51]*.

Food-drug interaction implications are seen in genetic polymorphisms of cytochrome P-450 enzymes (e.g. CYP2D6 and CYP2C19), glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency, slow inactivation of isoniazid or phenelzine and warfarin resistance *[5, 48]*.

The knowledge of a person's phenotype can facilitate better choice of therapeutic approach and the design of more optimal drug regimens, particularly in patients who may not be achieving the expected effect of a drug *[10]*. The ability to predict response to specific drugs determines more effective treatments for cardiac conditions, respiratory conditions, breast and other cancers, psychiatric conditions, dementia and pain management. Genotyping will help reduce adverse drug reactions, including food-drug interactions *[5, 49]*.

3. AIM OF WORK

The occurrence of food-drug interaction has been intriguing for years. Even though drug-drug interactions are a more frequent problem in medical practice, food-drug interactions are less taken into consideration when prescribing medications. Since food components and drugs appear to be sharing several characteristics and common sites of transport within the body, an improper management of food-drug interactions may lead to therapeutic failure or cause serious adverse effects to the patients.

The aim of the present diploma thesis is to provide as much information as possible about the interactions between foods and drugs and to exemplify in which ways these interactions can or may have an impact on the effectiveness of each time pharmacotherapy.

4. METHODS

Relevant sources upon food-drug interaction were recovered by scanning the literature for available scientific data, including *in vivo* and *in vitro* experiments, reviews and clinical studies, as described from various authors that have dealt with this subject. The research was facilitated by using a combination of keywords relevant to the thesis' subjects or authors, in the online search engine Google Scholar and the Ezproxy server library. Most e-books, journal articles and abstracts were retrieved from online citation databases, such as ScienceDirect & Scopus (Elsevier B.V.), PubMed, SpringerLink, EBSCOhost and Web of Knowledge. The classification of drugs was facilitated by Lexicomp Online database and Galinos Drug Guide (Greek online information service for human use medications).

In literature there is a voluminous amount of information concerning food-drug interactions topic. For the purposes of the present diploma thesis, the information gathered were categorized into two basic parts: the theoretical part which includes the basic concepts and principals of food-drug interactions and the clinical part which consists of four basic chapters: the first in relation to specific foods which are commonly consumed and the effects that they induce in drugs' kinetics; the second in relation to the changes in overall nutritional status of patients induced by commonly used drugs for the treatment of various diseases; the third and fourth chapter in relation to the clinical significance of food-drug interactions and to dietary recommendations for commonly used drugs, respectively. The listings of foods and drugs were of course not all-inclusive, while drugs listed in the text mainly concerned orally administrated drugs, used with their generic names only.

The assessment of the impact on pharmacotherapy was interpreted as being consistent with the clinical significance aspect of food-drug interactions, while food-induced changes in the bioavailability and clearance of drugs were found to be important indications of the risk for treatment failure or serious side-effect. Drug-induced changes in nutritional status were ascribed to drug's mechanism of action or adverse effect profile. Grapefruit juice and St John's wort were most discussed in literature to interact with various drugs, ranking them as perhaps the best known food-drug interactions. Frequently other interactions were also discussed (e.g. warfarin-vitamin K, MAOIs-tyramine foods, etc). Finally, food-drug interactions involving drugs with narrow therapeutic indices and drugs with dosage and blood levels requiring careful control were given credit for the likelihood of being the most clinically significant.

5. CLINICAL PART

5.1 Food/ nutrients effects on drugs

The consideration of the effects that the meals can have on drugs, allows health professionals to advise patients on how taking their medicines (with or without food). Even though the effect of food and nutrients is not clinically important for many drugs, some drugs have strict guidelines about when they should be taken in relation to meals, since there are food-drug interactions which may have adverse results on pharmacotherapy. So as for these interactions to be avoided, patients should be advised to take their medicines consistently at the same time with respect to meals *[52]*.

It is vital to take into account the interactions between meals and medications, for the reason that the pharmacokinetics of a drug may be affected when it is co-administered with food *[31, 33, 53]*. Among the stages of pharmacological action taken when receiving medication, absorption and metabolism are the stages where food has most effect *[31]*. The mechanisms which are related to food effects on drug absorption have been described under 5 categories: those causing decreased, delayed, increased or accelerated absorption *[31, 54]*. The rate and magnitude of absorption or both can be changed. Meal intake stimulates gastric and intestinal secretions, which usually improve the dissolution of drugs and facilitate absorption *[12]*; however the co-administration of drugs with food generally delays drug absorption *[52]*.

The variables that interface between effects of food and postprandial bioavailability are *[31, 44, 45, 52]*:

- Meal timing in relation to time of drug administration.
- Size and composition of meals (especially fat, protein and fibre).
- The physicochemical characteristics and composition of the drug.
- Dose size.

Nevertheless, the influence of food is largely a matter of the design of the pharmaceutical formulation, given that a drug may be differently affected by food when it is administered in different formulations *[31, 52, 54]*.

5.1.1 Specific foods regarding interactions

This chapter provides an overview of the effects that specific foods and nutrients induce in drug kinetics, as they have been reported in literature.

5.1.1.1 Dietary proteins, carbohydrates, fibre and fat

The variety of macronutrients found in foods (e.g. proteins, carbohydrates and lipids) can have major consequences on the metabolism and effects of some drugs *[55]*. It is notable that the rate of gastric emptying is mainly determined by the energy content of food and is inversely proportional to the energy density of a meal *[31, 56]*. Therefore, fat delays gastric emptying to a larger degree than protein or carbohydrate do. Isocaloric concentrations of fat, protein and carbohydrate will leave the stomach at similar rates. In addition, meals that have the same energy content but vary in fat content show similar patterns of gastric emptying. However, such meals are not expected to have similar effects on drug bioavailability *[31]*.

The impact of **carbohydrates** on drug metabolism is conflicting. On one hand, high-carbohydrate diets may induce the expression of several glycolytic and lipogenic hepatic enzymes, but on the other hand it is suggested that carbohydrates have little impact on drug metabolism *[57-59]*. However, it is noted that antipyrine and theophylline metabolism decrease in carbohydrate-supplemented diets but increase in the protein-enriched diet, suggesting that carbohydrates and protein have opposite effects on oxidative drug metabolism *[57, 60]*.

Dietary fibre can influence drug absorption, as well as can have important outcomes on the effect of other components present in a diet, particularly on lipid and carbohydrate metabolism and mineral absorption *[31, 61-63]*. Dietary fibres consist mainly of plant cell wall polysaccharides (i.e. cellulose, hemicellulose, pectins and lignins) that are resistant to hydrolysis by the enzymes of the small intestine *[31, 64]*. Fibres can influence the absorption of a drug in the small intestine, depending on their macromolecular and structural properties. The most plausible mechanism for decreasing drug absorption appears to be complex formation within the intestinal lumen *[31, 65]*.

The ingestion of fiber-rich meals (e.g. oat bran, oatmeal and soluble-fibre cereal) can decrease the absorption of lovastatin, whereas an increased intake of wheat bran decreases

the bioavailability of thyroxine (in patients with hypothyroidism). Similar effects have been reported with lithium salts *[31, 57, 66, 67]* and penicillins (i.e. phenoxymethylpenicillin and amoxicillin) *[44]*. Plus fiber-rich meals can significantly reduce the bioavailability of digoxin *[57, 68]*. Yet, in patients with Parkinson's disease having also severe constipation, it was found that a high-fibre diet caused a 71% increase in levodopa bioavailability via an increase in gastrointestinal motility *[44, 69]*.

The increased bioavailability of drugs in the presence of a **high-fat meal** has been documented, for example, it was found that the bioavailability of ketoconazole had a tendency to be increased by intake of a high-fat meal, but to be reduced by intake of a high-carbohydrate meal *[44, 70]*. Generally, the mechanism for such a facilitated absorption is unknown, but is thought to result from the increased secretion of bile salts, pancreatic juice, digestive enzymes and gastric hormones which occurs following high-fat meals *[31, 71]*.

The effect of dietary fat on drug absorption strongly depends on the route of drug absorption, either portal or lymphatic. For the drugs absorbed via the portal route, dietary fat enhances the absorption of poorly bioavailable lipophilic drugs by improving their dissolution, while for the drugs absorbed via the lymphatic route, dietary fat enhances the absorption of the presumably dissolved drug *[31, 72]*. Therefore the bioavailability of lipophilic drugs is often increased by a high fat content, either because of increased drug solubility (e.g. albendazole and isotretinoin) or stimulation of bile secretion (e.g. griseofulvin and halofantrine) *[44]*. Conversely, lipophilic medications that have good bioavailability will less likely to be impacted by a high-fat meal *[57]*.

Moreover, the absorption of hydrophilic drugs is not significantly affected when these drugs are co-administered with fatty meals *[31, 57, 72]*. In contrast, the bioavailability of pravastatin (a hydrophilic hypolipidaemic agent) was found to significantly decrease (by 31%) when it was taken with a high-fat meal *[31, 73]*.

Zidovudine (an antiviral agent) is also impacted by dietary fat. When the drug is orally administered and taken with a high-fat meal, its absorption is reduced in comparison with when taken in the fasted state. So, it is recommended that zidovudine be taken on an empty stomach to achieve peak serum concentrations *[57, 74]*.

The binding of a drug to **dietary proteins** may trigger changes in bioavailability that occur after a protein meal. For example protein in the diet can enhance or interfere with the absorption of some drugs like gabapentin, whose absorption is enhanced *[31]*, or theophylline whose absorption has been reported to be faster after a high-protein meal than

after a high-carbohydrate or high-fat meal *[55, 75]*. The buffering capacity of protein is greater than for carbohydrate and fat. Therefore, a high-protein diet may enhance the bioavailability of acid-labile drugs to a greater extent than a lower protein diet. However, it has been reported that a low-protein diet can benefit patients with Parkinson's disease during treatment with levodopa, by reducing unpredictable fluctuations in response (the "on–off" phenomenon) *[55, 76, 77]*.

Dietary protein can also modify the disposition of drugs that are cleared primarily by the kidneys, by influencing renal plasma flow, creatinine clearance, and renal tubular transport *[55, 78, 79]*. For example, high-protein meals have been reported to enhance the bioavailability of propranolol, metoprolol and lidocaine (medications that undergo extensive first-pass effect) owing to enhanced hepatic blood flow *[57]*. Renal tubular transport of basic drugs or drug metabolites may be especially reduced, for instance, the decrease in renal clearance of oxypurinol (the major metabolite of allopurinol) which is excreted largely unchanged in the urine, during a low-protein diet. This practically means that, in patients treated with allopurinol the dietary restriction may enhance the retention of oxypurinol and increase the likelihood of adverse effects *[55, 80]*. In humans, protein content of the diet appears to be more important for regulating oxidative drug metabolism than carbohydrate or fat. The exact mechanism whereby dietary protein accelerates drug oxidation in humans is not established *[55]*.

5.1.1.2 Vegetables and fruits

Common foods such as vegetables and fruits are well-known to be significant constituents in a healthy diet, given that they have low energy density and are rich sources of micronutrients, fiber, and other components with functional properties, known as phytochemicals *[81-84]*. Phytochemicals are in fact secondary metabolites, many of which have been associated with health benefits *[33, 82- 85]*. There are five major families of phytochemicals: alkaloids, phenolics (including flavonoids, coumarins, tannins), carotenoids (eg, beta carotene, lycopene), nitrogen compounds and sulfur compounds (e.g. isothiocyanates, allylic sulfur) *[57]*.

Phytochemicals also possess anticarcinogenic and other beneficial properties, so are referred to as chemopreventers. One of the predominant mechanisms of their protective action is due to their antioxidant activity and the capacity to scavenge free radicals *[82,*

83]. The majority of chemopreventers is found in fruits, vegetables, grains, and tea, whereas various naturally occurring chemicals in garlic, soybeans, tea, and red wine appear to have beneficial effects on several chronic diseases. Some vitamins, plant polyphenols, flavonoids, catechins and some components in spices are among the most investigated chemopreventers (see also *Figure 5.1.1.2.1*) *[83]*.

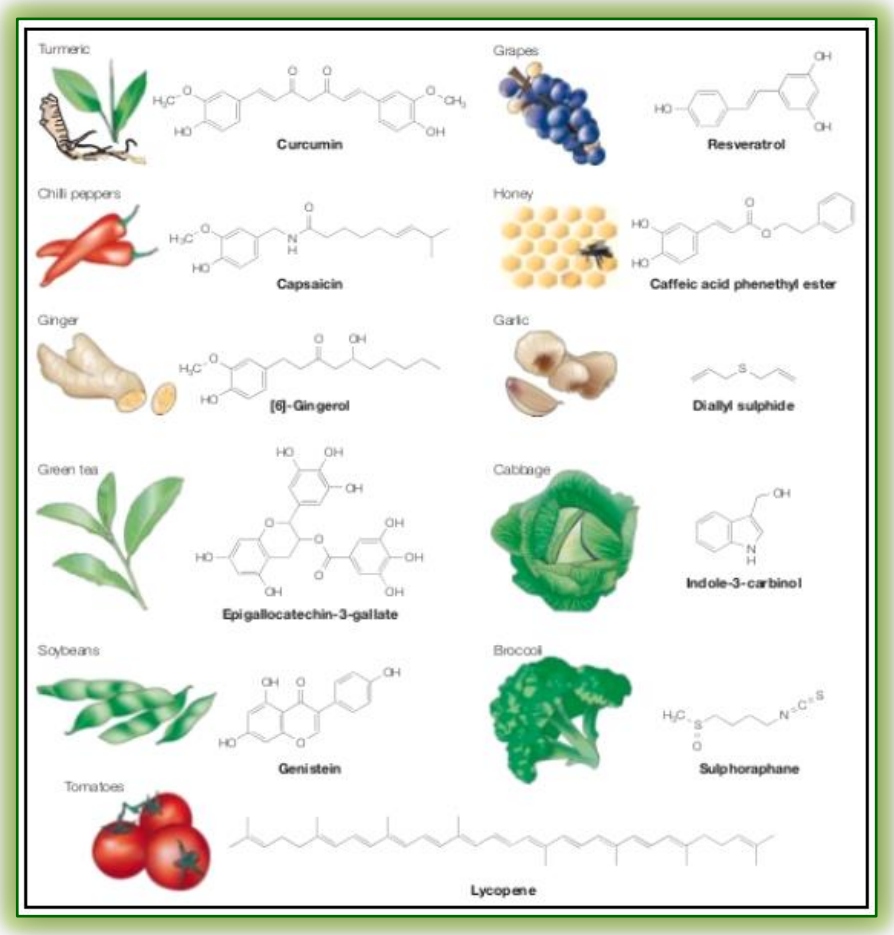

Figure 5.1.1.2.1 ***Representative chemopreventive phytochemicals and their dietary sources.*** *[86]*.

Figure 5.1.1.2.1 illustrates the chemical structures of representative dietary phytochemicals which are known to have chemopreventive potentials, as well as their dietary sources. These include: *Curcumin*-a yellow pigment found in the rhizome of turmeric and related species, *Capsaicin*-a pungent component of hot chilli peppers, *[6]-Gingerol*-a phenolic substance responsible for the spicy taste of ginger, *Epigallocatechin-3-gallate (EGCG)*-an antioxidant and chemopreventive polyphenol found in green tea, *Genistein*-a soy-derived isoflavone, *Lycopene*-the most important carotenoid present in tomatoes and tomato products, *Resveratrol*-a phytoalexin present in grapes and a key

antioxidant ingredient of red wine, *Caffeic acid phenethylester (CAPE)* in honey, *Diallyl sulphide* in garlic, *Indole-3-carbinol* in cabbage and *Sulphoraphane* in broccoli *[86]*.

Consumption of a diet high in fruits and vegetables increases antioxidant concentration in blood and body tissues and potentially protects against oxidative damage to cells and tissues *[82]*. Increased fruit and vegetable consumption can also help displace food high in saturated fats, sugar, or salt. However potential problems occur when patients taking medicines regularly also consume certain fruits or vegetables *[81]*.

Many phytochemicals have been shown to have pharmacokinetic interactions with drugs. More specifically, phytochemicals can modify absorption characteristics of drugs, through interactions with drug transporters as well as drug-metabolizing enzyme systems, thus they can affect the pharmacological activity of drugs. Such effects are more likely to occur in the intestine and liver, where high concentrations of phytochemicals may occur (see *Figure 5.1.1.2.2*) *[33, 81]*.

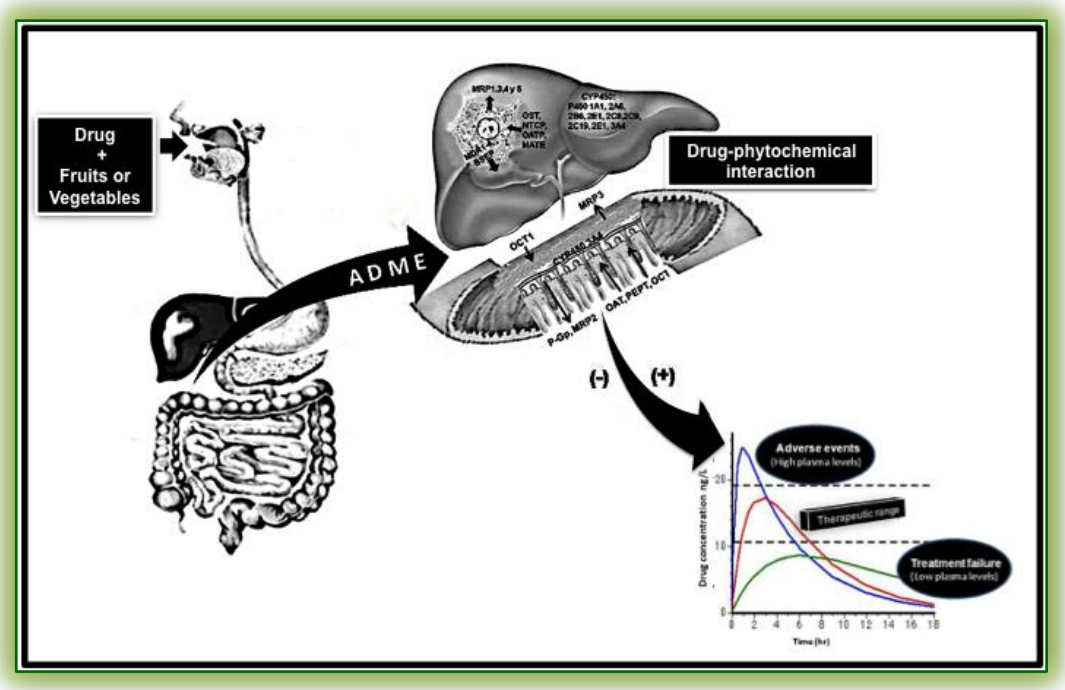

***Figure 5.1.1.2.2* Drug–fruit/vegetable interaction and effects on bioavailability of drugs.** *During the consumption of drugs with fruits or vegetables, the ADME properties of drug (absorption, distribution, metabolism, and excretion) can be modified by drug–phytochemical interaction. As a result of this interaction, plasma concentrations of a drug can be increased or decreased that can lead to the presence of adverse events or treatment failure. [33, 81]*

Recent research and literature reports have focused on how fruits and vegetables can influence a variety of enzymatic pathways *[33, 57, 81]*. So, some of the most commonly

consumed fruits and vegetables that can lead to important food–drug interactions are discussed below:

❖ Leaf vegetables such as spinach and especially those of the family Brassicaceae- also called Cruciferae *[87]* (**cruciferous vegetables**) such as Brussels sprouts, cabbage, cauliflower, broccoli, watercress, kale and turnips, contain a large variety of phytochemicals. More specific, cruciferous vegetables contain indoles that can significantly enhance the oxidative metabolism of antipyrine and phenacetin and the conjugation of acetaminophen *[55, 57, 88, 89]*. Cabbage and Brussels sprouts, which are particularly rich in indoles, have effects on the metabolism of environmental carcinogens such as aflatoxin B_1 and binding of their metabolites to DNA *[55, 90-92]*.

Broccoli and cauliflower have high levels of the aliphatics glucosinolate and glucoraphanin. Upon hydrolysis, glucoraphanin produces several products that include the bioactive isothiocyanate sulforaphane. The glucosinolate hydrolysis products have been shown to induce phase I and phase II drug-metabolizing enzymes in intact liver cells *[33, 81, 93]*. Watercress is also an excellent source for glucosinolates and beta-phenylethyl isothiocyanate *[33, 81, 94, 95]*. Watercress can impair CYP2E1 activity and the metabolism of drugs such as chlorzoxazone *[55, 96]*, plus it is a bifunctional agent with the ability to induce both phase I (CYP450) and II enzymes *[33, 81]*.

Large amounts of broccoli, spinach (an important antioxidant vegetable rich in flavonoids and isothiocyanates *[33,81]*) and other green leafy vegetables high in vitamin K (that promotes the formation of blood clots) can counteract the effects of heparin, warfarin and other drugs given to prevent clotting *[97,98]*.

❖ The **vegetable fruit** tomato contains numerous phytochemicals, such as: carotenoids (e.g. phytofluene, phytoene, neurosporene, γ-carotene, ζ-carotene and lycopene being the most important one), flavonols (e.g. quercetin and kaempferol), phytosterols and phenylpropanoids, which may influence health *[33, 81, 99-101]*. Lycopene appears to inhibit bioactivation enzymes and induce detoxifying enzymes, while it has been suggested that might have a potential advantage over other phytochemicals by facilitating the elimination of genotoxic chemicals and their metabolites *[33, 81, 102]*.

Red peppers, apart from being fruit stimulants and rubefacient in traditional medicine, they are also used in the treatment of some diseases (i.e. putrid sore throat, hoarseness, dyspepsia, yellow fever, piles and snakebite). Their pungency derives from a group of compounds called capsaicinoids (e.g. dihydrocapsaicin, capsaicin), which possess biological properties and provide a spicy flavor *[81, 103]*. Capsaicin, which is a

fundamental component, has antioxidant properties, thus it is associated with potent antimutagenic and anticarcinogenic activities *[81, 104]*. It has also been reported to inhibit the constitutive enzymes CYP 2A2, 3A1, 2C11, 2B1, 2B2 and 2C6, while being a substrate of CYP1A2 *[105, 106]*. When capsaicin is taken along with some medicines that are CYP450 substrates, potential interaction may occur. Also, a likely result of the gastrointestinal effect of capsaicin can be the reduction of oral salicylate bioavailability after pepper ingestion *[81,107]*. On the other hand, capsaicinoid-induced changes of glucose can possibly happen, therefore patients consuming red pepper and taking antidiabetic therapy could suffer potential drug-food interaction *[81, 108]*.

Carrots, which are widely consumed as food and include beta-carotene and panaxynol as active components, have been reported to induce phenolsulfotransferase activity and decrease CYP1A2 activity *[81, 109, 110]*. Another fruit vegetable, avocado, is a good source of bioactive compounds such as monounsaturated fatty acids and sterols *[111]* and has been reported to inhibit the effect of warfarin *[33, 81, 112, 113]*.

❖ **Other vegetables** such as potatoes and eggplants contain solanaceous glycoalkaloids (natural insecticide compounds) that even in small amounts may greatly slow the metabolism of muscle relaxants and anesthetic agents such as suxamethonium, mivacurium and cocaine. Cooking does not reduce them and they may remain in the body for several days after ingestion *[57, 114]*.

It has been reported that a diet supplemented with apiaceous vegetables (e.g. dill weed, celery, parsley, parsnip) can result in a 13-15% decrease in CYP1A2 activity *[81, 109]*. Celery and parsley, as well as onion, are known to have a high content of polyphenols, which can potentially affect phase I (either by direct inhibition of phase I enzymes or by regulating the expression of enzyme levels) and modulate phase II metabolism. Polyphenols have also been shown to interact with ABC drug transporters involved in drug resistance and drug absorption, distribution and excretion *[33, 81, 115, 116]*.

❖ Among **fruits**, grapes have been well recognized worldwide as one of the most valued conventional fruits, since they are a source of unique natural products for various medicines against diseases, but also for manufacturing various industrial products. The main biologically active and well-characterized constituent from the grape is resveratrol, a natural phytoalexin abundantly found in grapes and red wine, which has potent antioxidant, anticarcinogenic as well as antineoplastic properties *[117]*. Resveratrol has been reported to be irreversible (probably mechanism-based) inhibitor for CYP3A4 and non competitive reversible inhibitor for CYP2E, while resveratrol might be responsible for the red wine

effect on CYP3A4 substrates such as cyclosporine, causing wine to significant decrease drug exposure *[118-120]*.

Apple and its products contain high amounts of polyphenols, showing diverse biological activities and possibly contributing to beneficial health effects *[81]*. It has been found that apple juice extract inhibits CYP1A1 at levels of CYP1A1 mRNA, protein, and enzymatic activity. It has also been reported that apple juice and its constituents can interact with members of the OATP transporter family by reducing their activities and resulting in a significant reduction in the oral bioavailability of fexofenadine in human plasma levels *[121, 122]*.

Mango, in which there have been identified a series of polyphenols, including phenolic acids, flavonoids (e.g. quercetin) and glycosylated xanthones (e.g. mangiferin), is a fruit known for its beneficial health effects *[81, 123]*. It has been suggested that mango and the polyphenols derived may inhibit the major human P450 enzymes involved in drug metabolism and affect the activity of multidrug transporter P-gp ABCB1, accordingly the potential for drug interactions with mango fruit should be considered *[123,124]*.

Edible berries (i.e. raspberries, black raspberries, black mulberry), which are a potential source of natural antioxidants, have demonstrated a broad spectrum of biomedical functions, including cardiovascular disorders, inflammatory responses, advancing age-induced oxidative stress and diverse degenerative diseases *[125]*. They contain vitamin C and are also a rich source of phytochemicals, in particular anthocyanins (a flavonoid). They also contain phenolic acids (ellagic acid, gallic acid) other flavonoids (quercetin, cyanidins, pelargonidins, kaempferol) and catechins *[33, 81, 126]*. More specifically, black raspberries have been called the “king of berries” for their superior health benefits, while black mulberries are most commonly used for their antioxidants properties and for their high bioactive content of phenolics, anthocyanins and gallic acid. It has been suggested that black raspberry and black mulberry may increase the plasma concentration levels of concomitantly ingested CYP3A substrate drugs or decrease the plasma concentrations of concomitantly ingested OATP-B substrate drugs *[33, 81]*. For example, it has been shown that black raspberry and black mulberry are able to inhibit the human CYP3A-catalyzed midazolam 1-hydroxylation activity in liver microsomes *[127]*. *In vivo* studies, concerning the interactions between black raspberry and black mulberry with CYP3A substrates, are needed to determine whether inhibition of CYP3A activity by fruit juices is clinically relevant *[33, 81]*.

5.1.1.3 Grapefruit and other citrus fruit juices

Among all fruit juices, **grapefruit** juice possesses high interaction with almost all types of drugs *[4]*. The interaction of grapefruit with certain drugs was unintentionally discovered in 1989 when grapefruit juice was used in a study of the effects of alcohol on felodipine metabolism. The finding was that grapefruit juice could markedly increase oral drug bioavailability *[55, 128]*. This discovery has led to the publication of numerous articles regarding the interaction between grapefruit juice and various drugs, focusing on different aspects: interaction mechanisms, grapefruit juice constituents that are responsible for the interaction, drugs exhibiting the interaction and the clinical relevance *[129]*.

There have been many reports on the effects of grapefruit and its components on CYP450 drug oxidation and transportation *[81, 130, 131]*. Several results showed that grapefruit juice has a major effect on the intestinal CYP system with a minor effect at the hepatic level *[81, 132]*. For this interaction, the predominant mechanism is the inhibition of CYP3A4 in the small intestine, which results in a significant reduction of drug presystemic metabolism *[81]*. Owing to a lack in decrease of CYP3A4 mRNA following grapefruit juice intake *[129, 133]*, it appears that the mechanism for CYP3A4 inhibition by grapefruit juice is post transcriptional, possibly through facilitated degradation of the enzyme *[36, 129]*. Accordingly, drugs that are substantially metabolized by CYP3A, during absorption from the intestinal lumen, are most notably affected by grapefruit juice. Parenterally administered drugs are not expected to be affected. Inhibition is both reversible and irreversible. Anyhow, the effect of grapefruit juice on metabolism of drugs that are metabolized by CYP3A4 has become perhaps the best known food–drug interaction *[55]*.

An additional mechanism for grapefruit juice-drug interactions, may be the inhibition of P-glycoprotein (P-gp) transporters activity, which reduce the fraction of drug absorbed by carrying the drug from the enterocyte back to the intestinal lumen *[129, 134]*. It has also been reported that the major constituents of grapefruit significantly inhibit the organic anion-transporting polypeptide B (OATP-B) function *in vitro* (e.g the inhibition of the OATP-B-mediated uptake of glibenclamide) *[131, 135]*.

A number of constituents have been proposed to be involved in the interactions between grapefruit juice and drugs *[129]*. That is, flavonoids (the major components in grapefruit) such as naringin, naringenin, quercetin, and kaempferol, which are responsible

for drug interaction. Another group of components that have been detected in grapefruit juice are the furanocoumarins, which are known to be mechanism-based inactivators of CYP450. The major furanocoumarin present in grapefruit is bergamottin. Colored grapefruit juice and white grapefruit juice are equally effective in producing drug interactions. What it is more interesting about grapefruit-drugs interactions is that grapefruit juice and medication do not need to be taken simultaneously in order for the interaction to be produced. Grapefruit juice has been reported to double drugs' bioavailability, even when taken 12 h after ingestion *[81]*.

Grapefruit has been shown to interact with more than 50 medications, some of which are essential for treatment of serious medical conditions, by causing reduction in the normal extent of first-pass metabolism *[136]*. Furanocoumarins, have been shown to increase the oral bioavailability of drugs that are CYP 3A4 substrates, like felodipine, midazolam, cyclosporine and raise their concentrations above toxic levels *[4, 96, 137,138]*. Overall, kaempferol and naringenin present in grapefruit juice are shown to mediate pharmacokinetic drug interaction with most of the calcium channel antagonist and the statin groups of drugs, such as enalapril and lovastatin, due to their capability of esterase inhibition *[4, 139]*. Furanocoumarines and active flavonoids are also inhibitors of OATP and when ingested concomitantly, can reduce the oral bioavailability of the OATP substrate, fexofenadine *[4, 122, 137]*. I*n vitro* data suggest that compounds present in grapefruit juice are able to inhibit the P-gp activity modifying the disposition of drugs that are P-gp substrates such as talinolol *[4, 140]*. Other drugs affected by grapefruit or its components include: nisoldipine and verapamil (calcium-channel blockers), diazepam, triazolam, carbamazepine, buspirone and sertraline (central nervous system modulators), simvastatin and atorvastatin (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors), saquinavir (an antiviral), sildenafil (a phosphodiesterases-5inhibitor), terfenadine (an antihistamine), amiodarone (antiarrhythmic) and erythromycin (antibacterial) *[81, 136]*. The above and more are drugs with increased oral bioavailability with grapefruit juice from inhibition of intestinal CYP3A4. Some drugs (e.g. amlodipine, diltiazem, alprazolam, pravastatin) show no change in oral bioavailability with grapefruit juice, while others have a potential for increased oral bioavailability (e.g. sirolimus) *[136]*.

The search for other fruit juices which would create drug interactions, by inhibition of CYP3A4, plausibly required determination of the active ingredient or ingredients in grapefruit juice. **Citrus fruits**, such as grapefruit, Seville orange, tangerine, lime, pummelo, pomegranate and cranberries, contain a number of flavonoids, furanocoumarins,

liminoids and other polyphenolic compounds. *In vitro* it was found that grapefruit furanocoumarins might be primarily responsible for the effects on cytochrome P450 activity in humans *[136, 141]*.

The juice made from **Seville oranges**, in contrast with most types of orange juice, appears to be somewhat similar to grapefruit juice and can affect the pharmacokinetics of CYP3A4 substrates. For instance, Seville orange juice increases felodipine exposure, comparable to what is observed after grapefruit juice consumption. Most probably, the mechanism of this effect is similar to that of grapefruit juice-mediated interactions, because Seville orange contains significant concentrations of bergamottin and 6',7'-dihydroxybergamottin, two of the major furanocoumarins in grapefruit *[81, 136, 142]*. Compounds present in orange juice (such as 3,3′,4′,5,6,7,8-heptamethoxyflavon, tangeretin and nobiletin) have also shown to might exert inhibitory effects on P-glycoprotein (P-gp)-mediated drug efflux, which could enhance the bioavailability of drugs and thus lead to an increase in the risk of adverse events *[33, 81, 143]*.

Additionally, orange juice and its constituents (naringin in particular) have shown to interact with members of the OATP transporter family by reducing their activities *[144]*. For example, the significant reduce in oral bioavailability of fexofenadine, possibly by preferential direct inhibition of intestinal OATP activity *[122]*. It has also been reported that orange juice might reduce the intestinal absorption of anionic drugs, such as glibenclamide, via the inhibition of OATP-B [135], as well as other OATP-B substrates (e.g., digoxin, benzylpenicillin, and hormone conjugates), resulting in a decrease in concentration in the blood *[33,81]*.

Other reports have indicated that orange juice slightly reduces the absorption of ciprofloxacin and levofloxacin *[33, 81]*, moderately reduces the bioavailability of atenolol *[145]* and substantially reduces the bioavailability of celiprolol *[146]*. A study of an interaction between orange juice and pravastatin showed an increase in area under curve (AUC) *[33, 81]*.

In **tangerine** juice, tangeretin (a flavonoid found in high levels) can stimulate the *in vitro* catalytic activity of CYP3A4) *[136]*, while diosmin (which is one of the main components of citrus fruits such as tangerine) may increase the absorption or bioavailability of co-administered drugs able to serve as P-gp substrates. As a result, some caution may be required with its clinical use *[33, 81, 147]*. It has also been reported that tangerine juice might have some impact on the absorption process of midazolam (an anxiolytic/sedative drug) *[148]*.

The consumption of **lime juice**, which was found to contain high bergamottin content, has been reported to inhibit the CYP3A4 enzymes activity, plus having an impact on the bioavailability of felodipine. Thus, lime juice and bergamottin seem to have clinical activity *[29, 136, 149]*.

Pummelo (or pomelo) is a citrus fruit closely related to grapefruit. Fruit juice of the pummelo was found to have substantial furanocoumarin content and to cause inhibition of CYP3A4-mediated testosterone 6b-hydroxylation by human liver microsomes *[136, 150]*. It has been reported that pummelo juice increases the oral bioavailability of felodipine and cyclosporine (possibly for the latter by inhibiting CYP3A or P-gp activity or both in the gut wall) while increases the blood concentrations of tacrolimus (immunosuppressive agent widely used in patients after transplantation to prevent allograft rejection) by inhibiting CYP 3A4, P-gp or both *[136, 150-152]*.

Pomegranates, which are cultivated and eaten around the world, have a high antioxidant capacity and have been shown to exert significant antiatherogenic, antihypertensive, and anti-inflammatory effects, plus having potential cardioprotective benefits *[153]*. Pomegranate is rich in several chemicals such as pectin, tannins, flavonoids, and anthocyanins *[33, 81]*. It has been reported that the inhibition potency of pomegranate juice is similar to that of grapefruit juice, whilst pomegranate juice component(s) inhibits the human CYP3A-mediated metabolism of carbamazepine *[154]*. Furthermore, it has been suggested that some constituents of pomegranate juice, most probably punicalagin, may impair the enteric functions of sulfoconjugation and therefore might have effects upon the bioavailability of drugs *[155]*.

Cranberries are being used in the prevention of urinary tract infections as well as many diseases and infections, including cardiovascular diseases, various cancers and infections involving the urinary tract, the dental health and Helicobacter pylori-induced stomach ulcers and cancers *[156]*. Cranberry juice is rich in flavonol glycosides, anthocyanins, proanthocyanidins and organic & phenolic acids which might be responsible for the cranberries-drugs interactions *[33, 81, 156]*. It has been reported that cranberry juice potentially interacts with warfarin and might increase its anticoagulant effect. The mechanism behind this interaction might be the inhibition of CYP3A4 and/or CYP2C9 enzymes, which are responsible for warfarin metabolism, by cranberry flavonoids. Though, cranberry juice-mediated pharmacokinetic or pharmacodynamic interaction with warfarin seems questionable *[136, 157]*. Furthermore, other findings suggest that cranberry juice inhibits the CYP3A-mediated metabolism of nifedipine in humans *[33, 81, 158]*.

5.1.1.4 Beverages

The term beverage refers to any drinkable liquid other than plain water. They are typically classified as **caffeinated** (coffee, tea, colas and other sodas), **alcoholic** (beer, distilled spirits and wines), **milk and milk-based beverages**, **fruit/vegetables juices** and **mineral waters**. Depending on the beverage type taken with a medication, drug absorption may be affected due to changes in gastric pH *[31, 57]*. Some examples of beverage effects on drugs are the following *[31, 57]*:

❖ Caffeine, which is a methylxanthine with central nervous system stimulatory properties *[5, 55]* and a major component of caffeinated beverages, is speculated to delay or decrease the drug absorption when co-ingested with a drug. More specific, the absorption of caffeine is delayed because of slower gastric emptying, which could be further slowed if the beverage is sweetened with sugar *[159]*, while the absorption rate of caffeine appears to increase with its dose *[160]*. In addition, when it is ingested regularly can also accumulate and influence drug metabolism, by means of saturation and inhibition or induction of hepatic enzymes (CYP enzymes) that metabolize methylxanthines, drugs and chemicals *[55]*. However, it has been reported that caffeine had no general influence on the extent of paracetamol absorption (it was only observed a slightly positive influence of caffeine on the absorption rate of paracetamol although this effect was not responsible for the established enhancement of paracetamol analgesia by caffeine *[161]*), whereas it was found a faster and more extensive metabolism of theophylline when caffeine was eliminated from diet *[162]*. Furthermore, it has been found that changes in the habitual caffeine intake can alter the metabolism of clozapine in schizophrenic patients [163]. Yet, caffeine increases the adverse effects of stimulant drugs (e.g. amphetamines, methylphenidate, theophylline) causing nervousness, tremor and insomnia, though opposes or counteracts the antianxiety effect of tranquilizers (e.g. lorazepam) [5].

❖ The tannins which are found in teas may impair iron absorption, probably by forming non-absorbable complexes with the iron within the intestinal lumen. That may be of great importance among heavy tea drinkers who are on low iron diets *[164]*.

❖ The soft drinks, such as colas, may decrease the rate of drug absorption for varied reasons. The phosphoric acid and sugar in these drinks can slow the gastric emptying rate, plus the trend to serve them chilled may also reduce the rate of blood flow within the intestines *[159, 165, 166]*. Furthermore, the carbonation may increase mixing and possibly

motility *[167]*. Interestingly, in recent studies it is suggested that the co-administration of acidic beverages with the drugs ketoconazole and itraconazole, in patients who are hypochlorhydric or achlorhydric (especially patients with AIDS), may improve drug bioavailability *[168, 169]*.

❖ Generally speaking, ethanol combined with certain medications can produce additive toxicity, affecting various body organs and systems, plus it can affect the physical characteristics of a medication. For example, if morphine sulfate is taken with alcoholic beverages, the extended-release beads of morphine can dissolve rapidly, delivering a potentially fatal dose of morphine. Moreover, if ethanol is combined with central nervous system (CNS) depressant drugs such as benzodiazepine (e.g. diazepam) or barbiturate (e.g. phenobarbital) may cause excessive drowsiness, incoordination and other signs of CNS depression *[5]*. Alcoholic beverages can also reduce the absorption of folic acid, vitamin B_{12} and magnesium *[170]*.

❖ The dairy products (i.e. milk) even in a small volume may decrease the absorption and reduce the bioavailability of tetracyclines, due to the formation of insoluble chelates between the calcium present in the beverage and the drug *[171]*. Other drugs whose bioavailability may be decreases by milk and dairy products are suprofen, norfloxacin, ciprofloxacin, fluoride and estramustine phosphate *[172-176]*.

❖ As far as the interaction between mineral waters and drugs is concerned, it has been suggested that the absorption of the drug alendronate (an oral bisphosphonate effectively used in the treatment of osteoporosis) decreases based on the calcium concentration of mineral water, so mineral water containing high levels of calcium is not recommended when alendronate is taken *[177]*.

❖ The effects of fruit/vegetables juices on drug disposition are extensively discussed in chapters 5.1.1.2 and 5.1.1.3.

5.1.1.5 Dietary supplements (herbs, vitamins and minerals)

Dietary supplements are products (other than tobacco) intended to supplement a normal diet and contain one or more dietary ingredients or their constituents. These include: **vitamins**, **minerals**, **herbs** or other **botanicals**, **amino acids** and other substances *[97, 178]*. Supplements may interact with over-the-counter or prescription drugs, while some dietary components can increase the risk of side effects *[97]*.

Observations in patient populations suggest that ingestion of vitamins to correct vitamin deficiencies may alter drug metabolism. The effects of vitamin C have been most studied in humans. Large doses of this vitamin may have effects on nonoxidative pathways of drug metabolism, for example, vitamin C may reduce sulfate conjugation of salicylamide and acetaminophen by competing for available sulfate *[55, 179, 180]*. Moreover, vitamin C may diminish antibiotic activity *[181]*, while in high doses may reduce steady-state indinavir plasma concentrations *[55, 182]*. Another example of a vitamin interacting with drugs is vitamin B_6, which induces metabolism of anticonvulsant medication (phenytoin) up to 50%, affecting the efficacy of the drug. Since patients who are on phenytoin may become deficient in folic acid and vitamin B_6, supplementation of these substances is problematic *[181, 183]*. Vitamin B_6 can also reduce or abolish the effects of levodopa, unless levodopa is prescribed in its combination form (e.g. co-beneldopa or co-careldopa) *[29]*.

Supplements containing minerals bind several drugs in the gastrointestinal tract with a consequent reduction in the absorption of both the drug and the mineral, for example Fe and Zn which form insoluble complexes with several antibiotics such as tetracyclines and some of the 4-quinolones (e.g. ciprofloxacin, norfloxacin and ofloxacin) *[184-186]*. Fe has also been shown to reduce the absorption of penicillamine (a drug used to chelate excess Cu in the treatment of Wilson's disease), while chelation of levodopa by Fe can potentially lead to reduced control of Parkinson's disease *[29, 187-189]*. Given that drug absorption is often reduced by more than one mineral, it is suggested to separate doses of the drug and mineral preparation by at least 2 h *[29]*. Nonetheless, in most instances, mineral deficiencies (i.e., zinc, iron, copper, iodine, magnesium and potassium) have been associated with a decrease in drug oxidation and drug clearance *[57, 190]*.

Several herbal dietary supplements are known or suspected of interacting with conventional medications. Some of the most widely sold include: St. John's wort (*Hypericum perforatum*), valerian (*Valeriana officinalis*), ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*), liquorice (*Glycyrrhiza glabra*), echinacea (*Echinacea spp.*), garlic (*Allium sativum*) and green tea (*Camellia sinensis*) *[191]*.

Pharmacokinetic herb–drug interactions can be caused by phytochemical-mediated alterations in the activity of xenobiotic metabolizing enzymes (CYPs, transferases) or transport proteins/polypeptides (e.g., P-gp, OCTP, OATP). Together, these proteins are principal determinants in the absorption, distribution, and elimination of many chemicals including drugs. Thus, herbal dietary supplements that modulate drug metabolizing

enzyme activity and/or transporter function can adversely affect the bioavailability or clearance for drugs that are substrates for the affected proteins. The outcome may be either diminished drug efficacy or enhanced toxicity. On the other hand, pharmacodynamic interactions appear to result from phytochemicals whose pharmacological action either diminishes or exacerbates the effects of conventional medications by mechanisms unrelated to altered metabolism or transport *[137]*.

St John's wort is better known for its capacity to interact with drugs than for its effective anti-depressive and anti-inflammatory properties *[191, 193, 194]*. Its scientific name is *Hypericum perforatum* and the name St John's wort exists because the bloom time of this plant coincides with the time of the feast of St. John the Baptist in June *[192]*. The extracts of *H. perforatum* contain numerous phytochemicals, including: hypericins, hyperforin, adhyperforin, catechins, flavonoids, derivatives of phenolic acid and volatile oil, but the most active pharmacological compound seems to be hyperforin (a prenylated phloroglucinol), which has many beneficial for health activities *[137, 191]*. *H. perforatum* extracts alter the concentrations of concomitantly administered drugs through two major mechanisms: firstly they have the ability to induce intestinal transporter (e.g., P-gp) activity and secondly they can increase the activity of CYP3A4 through pregnane X receptor (PXR) activation *[192, 195-197]*. It has been reported that hyperforin is a potent ligand of PXR, thus herbal medicinal products containing *H. perforatum* extract can significantly affect the absorption and metabolism of various drugs and consequently their bioavailability and efficacy *[191, 197]*. A number of *in vitro* and *in vivo* studies have pointed out the effects of St John's wort on drugs. More specific, it has been demonstrated that St John's wort reduces the efficacy of conventional medications that are CYP3A4 and/or P-gp substrates, including indinavir, imatinib, cyclosporine, tacrolimus, warfarin, digoxin, carbamazepine, theophylline, simvastatin and methadone, while increases the clearance of the oral contraceptive, norethindrone, producing breakthrough bleeding after prolonged use *[137, 191, 192, 195, 198]*. St John's wort may also interact with a number of medications based on pharmacodynamic properties, such as antidepressants which include selective serotonin reuptake inhibitors (SSRIs) (e.g. paroxetine, sertraline) and other agents (e.g. trazodone, nefazodone) that can cause symptoms consistent with that of excess serotonin or serotonin syndrome *[137, 192, 199, 200]*. Patients who are currently being on prescription medications, as well as on SSRIs or other antidepressants that increase the concentrations of serotonin, should be warned of the potential risks associated with this herbal product *[192]*. The fact that there is considerable evidence of *H.*

perforatum reducing drug bioavailability, led the US FDA to issue a public health advisory in 2000 concerning the risk of interactions between herbs and drugs *[191, 201]*.

Valerian root medicine (*Valeriana officinalis*) is popular and widely sold for the treatment of insomnia, anxiety and stress *[191]*. Current knowledge suggests that the potential for valerian causing pharmacokinetic interactions with CYP substrates appears fairly low. However, valerian may cause pharmacodynamic interaction with other drugs that depress cognitive function, since it has been suggested that valerian extracts affect g-aminobutyric acid-type A (GABAA) receptors, with potential additional action on inducing the release of the inhibitory neurotransmitter GABA in the brain *[192, 202-204]*. Valerian may also synergize the sedative effect of other drugs, for instance, valerian has been shown to prolong thiopental- and pentobarbital-induced sleep. Consequently, it may be wise to avoid concurrent use of sedative agents and antiepileptic agents with valerian *[192]*.

Ginkgo, which is a popular herb that is derived from the dried leaves of *Ginkgo biloba* or maidenhair (a native tree in China), is used for a variety of purposes including cognition, memory, cerebral vascular disease, peripheral vascular disease, and multiple sclerosis. The pharmacologically active constituents of *Ginkgo biloba* are extracted from the leaves, which contain flavonol glycosides and terpene lactones (ginkgolides A, B, C, and bilobalides) *[192, 205, 206]*. The findings regarding the potential for *Ginkgo biloba* to alter drug absorption due to CYP and P-gp inhibition are contradictory and further studies are needed *[191]*. It is possible that the disparity among ginkgo products with regard to phytochemical composition, dissolution rate and bioavailability, could explain some of the inconsistencies among studies *[137, 192, 207]*. Yet, in a number of case reports ginkgo has been attributed to an increased risk of serious bleeding events in concomitant use with other anticoagulant agents. It may be possible that this interaction is ascribed to inhibition of platelet activating factor by various ginkgolides *[137, 192, 208, 209]*. Thus, in patients receiving antithrombotic therapy, especially antiplatelet agents, or prior to any scheduled surgery, caution should be exercised when ginkgo is used *[192]*.

The dried roots of *Panax ginseng* (ginseng) are used in traditional medicine for their ability to improve cognitive performance and resistance to physical stress *[191]*. Compounds known as the ginsenosides are thought to be responsible for the therapeutic activity of ginseng. However, due to the complex activity of these compounds, as well as the activity of non-ginsenoside compounds found in the herb, the overall pharmacology of ginseng is very complex *[192, 210]*. Like *Ginkgo biloba*, *Panax ginseng* appears to have

little or no effect on CYP-mediated drug metabolism and is probably less prone to cause pharmacokinetic interaction *[137]*. In addition, among commercial ginseng preparations there has been reported significant variability in ginsenoside content, so clinically significant effects on CYP and other drug metabolizing enzymes could be brand specific *[137, 211]*. However, ginseng has been reported to induce headaches, tremulousness and manic episodes in patients taking antidepressants, such as phenelzine sulfate, while it is suggested not to be used with estrogens or corticosteroids because of possible additive effects *[55, 181, 212, 213]*. Moreover, it has been found that ginseng may alter bleeding time and thus should not be used concomitantly with warfarin sodium, whereas given that ginseng may affect blood glucose levels, it should not be used in patients with diabetes mellitus. Ginseng may also interfere with either digoxin pharmacodynamically or with digoxin monitoring *[213]*. No studies have yet been carried out on possible interactions of ginseng with P-gp *[191]*.

Licorice (*Glycyrrhiza glabra*) extract is a common ingredient in many multicomponent dietary supplements *[137]*. The roots and rhizomes of licorice species have long been used worldwide as a herbal medicine and natural sweetener. In traditional medicine is used mainly for the treatment of peptic ulcer, hepatitis C, pulmonary and skin diseases, but a number of studies have suggested that licorice has also antiviral, antimicrobial, anti-inflammatory, antioxidative and other properties. The main phytochemicals found in licorice are: triterpenoid saponins (e.g. glycyrrhizin, liquiritic acid, glycyrretol, glabrolide), flavonoids, chalcones, isoflavones, coumarins, stilbenoids, fatty acids, phenols and sterols *[191, 214]*. Chronic ingestion of licorice extract may interfere with various medications, including anti-hypertensives and anti-arrhythmic agents *[137]*. Licorice also reacts with oral contraceptives resulting in adverse effects *[181]* and may also potentiate oral and topical corticosteroids *[215]*. More specific, licorice increases plasma concentrations of prednisolone and potentiates hydrocortisone activity *[181]*. Furthermore, consumption of licorice is contraindicated during pregnancy and for patients with liver disorders and hypokalemia, like those who are taking cardiac glycosides *[214]*. Licorice (like ginseng) may interfere with either digoxin pharmacodynamically or with digoxin monitoring and can also offset the pharmacological effect of spironolactone *[213]*.

Echinacea (*Echinacea spp.*) extract products, which are widely used in traditional Western medicine to treat common colds and upper respiratory infections, consist mainly of lipophilic constituent alkamides with immunomodulatory properties. A number of *in vitro* experiments have revealed potential CYP and OATP-B inhibition, with findings in

humans to be contradictory, so further research is needed to clarify the Echinacea effects on drug bioavailability and identify the risk factors that predict a possible interaction with drugs *[191]*. However, it has been suggested that *Echinacea spp.* (which is an immuno-stimulant) should not be given with medications with immuno-suppressive properties (e.g. corticosteroids and cyclosporine) as it could offset or minimize their effects, and with hepatoxic drugs (anabolic steroids, amiodarone, methotrexate, and ketoconazole) as it could cause hepatotoxicity. Still, the magnitude of *Echinacea* hepatoxicity has been questioned since it lacks the 1, 2 unsaturated necrine ring system associated with hepatoxicity of pyrrolizidine alkaloids *[181, 213]*.

Over the centuries, garlic (*Allium sativum*) has been used as a flavoring ingredient in food and has acquired a reputation in the folklore of many cultures as a formidable prophylactic and therapeutic medicinal agent *[192, 216]*. In modern medicine garlic is used to prevent hypercholesterolemia and subsequent vascular disease and its major bioactive phytochemicals are the sulphur compounds aliin, allicin, diallyl disulphide, diallyl sulphide, S-allyll-cysteine, and saponins *[191]*. Garlic supplements are commercially available as garlic oil, as dehydrated garlic powder and as aged garlic extract, each with their own unique composition of purported bioactive components *[137, 216]*. Garlic–drug interactions are product specific and may reflect differences in the type, quantity and bioavailability of garlic phytochemicals, as well as the duration of use *[137]*. It has been found that garlic can interact with antithrombotic drugs through pharmacodynamic mechanisms, given it inhibits platelet aggregation and may increase the risk of bleeding in patients taking ticlopidine, clopidogrel, and warfarin *[192]*. Garlic oil was also found to inhibit the activity of CYP2E1 (enzyme responsible for the metabolism of many inhalation anesthetic agents), so it is possible that in patients who use garlic oil on a chronic basis, the dosing requirement of anesthetic agents for surgery may be decreased. Garlic may also interact with saquinavir (an anti-HIV protease inhibitor and P-gp/CYP3A4 substrate) by decreasing the systemic exposure and maximum concentrations of saquinavir *[191, 192, 217]*. However, the occurrence and severity of CYP/P-gp-mediated garlic–drug interactions is difficult to predict, but patients taking drugs that are P-gp, CYP2E1 and CYP3A4 substrates should be monitored when there is concomitant use of garlic *[191]*.

Green tea is made with dehydrated *Camellia sinensis* leaves (which have been used to make tea for almost 50 centuries, mainly in Asian countries) guaranteeing minimal polyphenol oxidation and ensuring that the beverage and extract have high flavonoid content. Catechins, which represent 30–45% of solid green tea extract, seem to be

responsible for the health effects of the tea, having also many beneficial health properties (e.g. anti-cancer, anti-metastatic, anti-inflammatory, anti-anthrax lethal factor, and vasculoprotective properties) *[191, 218-220]*. Green tea has been found to inhibit OATP *in vitro* and folic acid transport in human, plus it is suggested that consumption of green tea and green tea extract should be monitored in patients receiving drugs metabolized by CYP3A4 *[191, 221]*. Still, green tea can be a significant source of vitamin K, thus antagonize the anticoagulant effect of warfarin and reduce a patient's degree of anticoagulation. However, the mechanism in these cases does not involve the CYP450 system, but rather involves the role of vitamin K in activating coagulation factors *[181, 222, 223]*.

Most reports on herb–drug interactions need more critical evaluation. Many interactions between herbs and drugs do not necessarily indicate interaction problems but rather pharmacologic activities of the herbs themselves *[181]*.

5.1.1.6 Tyramine based foods

Among the various biogenic amines found in food, tyramine was the first of interest to healthcare professionals. This interest was initiated by the discovery of the relationship between the hypertensive crisis, involving severe headaches and even deaths, of some English patients undergoing treatment with anti-depressants (e.g. phenelzine, pargyline, tranylcypromine and isocarboxazide) known as MAOIs *[55, 224, 225]*. Cheese was also the food initially associated with such hypertensive disturbances *[226]*. Therefore, these hypertensive crisis are termed as the “tyramine reactions’’ or ‘‘cheese reactions’’ and they are among the best-known drug–food interactions *[55, 225, 226]*. Physiological effects of tyramine include peripheral vasoconstriction, increased cardiac output, increased respiration, elevated blood sugar, and the release of norepinephrine. Tyramine has also been implicated as cause of migraine and cluster headaches *[224, 226]*.

Tyramine is a vasoactive pressor amine that is mildly toxic and is formed from tyrosine due to the actions of bacterial and fungal tyrosine decarboxylase *[55, 224]*. A healthy gut normally detoxifies tyramine in food by the enzyme monoamine oxidase (MAO). Two primary isoforms of monoamine oxidase selectively deaminate neurotransmitters and one isoform will predominate in various body tissues. MAO-A isoform deaminates serotonin in the central nervous system and dietary monoamines in the

gastrointestinal system, while MAO-B isoform is found predominantly in liver and muscle and deaminates dopamine and phenylethylamine. Both isoforms deaminate tyramine. Inhibition of one of the isoforms therefore produces different effects *[224,227]*. However, if the MAO enzyme is inhibited by a drug, severe and potentially fatal rises in blood pressure can occur when tyramine-rich foods are ingested *[57]*.

Any food containing protein is capable of causing a reaction if contaminated by certain strains of bacteria and stored under conditions favorable to bacterial growth *[224]*. Generally, foods that are spoiled or not refrigerated, handled, or stored properly and aged, pickled, fermented, or smoked foods may contain tyramine. For example, aged cheeses (e.g. blue cheese) and highly flavored cheeses (e.g. cheddar) are most commonly associated with tyramine-drug interaction. Other high-protein foods that have started to ferment and may also contain large amounts of tyramine include: pickled herring, yeast preparations, broad beans (e.g. fava beans), dry sausages, beef or chicken liver, certain wines (e.g., Chianti) and beers (e.g. tap lager beer). Tyramine can also be found in soy products (e.g. tofu and soya sauce), sauerkraut products, ripped bananas, raspberry products, fish and shrimp sauces and in excessive amounts of chocolate *[55, 226-229]*.

Apart from MAOIs, other drugs that have weak MAO-inhibiting properties and have been implicated in tyramine reactions include furazolidone (an antibacterial and antiprotozoal drug), meperidine (an opioid analgesic) and isoniazid (an antituberculosis drug) in combination with tricyclic antidepressants. Concurrent sympathomimetic drugs may also exacerbate tyramine reactions. Moreover, the antimicrobial linezolid (oxazolidinone antibiotic) is a reversible and nonselective MAO inhibitor with potential interaction, so patients should avoid ingesting large amounts of tyramine while being treated with this drug. Procarbazine (a drug for Hodgkin's disease) has also been reported to cause hypertension in patients consuming foods containing tyramine while taking this drug *[55, 230-232]*. In any case, dietary restrictions and development of new pharmaceutical products have been comprised in strategies to avoid tyramine reactions in patients taking MAO inhibitors *[55, 233]*.

Except for tyramine, other pressor agents which are considered to be the most important biogenic amines occurring in foods and beverages include: histamine, putrescine, cadaverine, tryptamine, β-phenylethylamine, spermine, and spermidine. These biogenic amines are important from a hygienic point of view as they have been implicated as the causative agents in a number of food poisoning episodes and they are able to initiate various pharmacological reactions [224, 226].

5.2 Drug effects on nutrition

Prescription and over-the-counter medications are daily used to treat acute and chronic diseases. Drugs are grouped into classes based on illnesses or conditions for which they are prescribed, or based on their chemical make-up or actions in the body. Different foods can interact with more than one class of drugs *[6]*. Some classes of drugs and their purpose of use include *[4, 6]*: **Analgesics** (e.g. acetaminophen), **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)** (e.g. naproxen, ibuprofen, ketoprofen, etc) as well as **salicylate NSAIDs** (e.g. aspirin) are used to relieve pain and for a number of other problems such as chronic joint pain, inflammation, headaches, fever and arthritis. **Antacids and Acid Blockers** (e.g. ranitidine, cimetidine, famotidine, nizatidine)-antacids neutralize stomach acids, while acid blockers reduce stomach acid production, thus are used to relieve stomach upsets and ulcers. **Antibiotics/antibacterials** (e.g. amoxicillin, penicillin, tetracycline, erythromycin, azithromycin, etc) exist in many different types and are used to treat bacterial infections. **Anticoagulants** (e.g. warfarin) slow the process of blood clotting, thus are able to decrease risk of strokes in patients whose blood tends to clot too easily. **Anticonvulsants** (e.g. phenytoin, phenobarbital, primidone) are used in the control of epileptic seizures. **Antidiabetics** (e.g. glimepiride) are used to treat patients with diabetes mellitus by stabilizing and controlling glucose levels in the blood. **Antihistamines** (e.g. chlorpheniramine, diphenhydramine) are used to treat allergies. **Antihyperlipemics** (e.g. lovastatin, cholestyramine, colestipol) are used to reduce high blood cholesterol levels. **Antihypertensives** (e.g. felodipine, nifedipine) are used to control high blood pressure. **Antineoplastics** (e.g. methotrexate, mercaptopurine, tamoxifen) are agents used to treat different forms of cancer. **Bronchodilators** (e.g. theophylline, albuterol) are used for the treatment of breathing difficulties. They are most useful in obstructive lung diseases, in conditions such as asthma and chronic obstructive pulmonary disease. **Diuretics** (e.g. furosemide, spironolactone) cause the body to excrete more urine, so as to help with water retention and are often used to treat high blood pressure and fluid buildup. **Laxatives** (e.g. polycarbophil) speed up the movement of materials through the digestive tract, thus helping with constipation. **Psychotherapeutics/psychotropics** (e.g. MAOIs: tranylcypromine, phenelzine, isocarboxazid) are used to treat depression, anxiety and other mental health conditions.

Drugs interfering with food intake, therefore affect a patient's nutritional status, either as a result of the drug's mechanism of action or by its adverse effect profile. These drug-related changes to nutritional status may be considered a subclass of adverse drug effects *[234, 235]*. The changes in a patient's nutritional status might concern: alterations in body weight and growth, alterations in taste perception (thereby decreasing intake), decrease or prevention of nutrient absorption, alterations in macronutrient metabolism or depletion in essential vitamins and minerals. Nevertheless, changes to overall nutritional status or to nutrient-specific status can be multifactorial *[3, 7, 12, 234, 235]*.

5.2.1 Specific drugs regarding interactions

This chapter provides an overview of the effects that specific drugs or classes of drugs induce in the nutritional status, as they have been reported in literature.

5.2.1.1 Drug- induced weight gain

Several drugs, or classes of drugs, which are used in the treatment of chronic disease, are consistently associated with weight gain as a side effect and considered "obesogenic" *[236]*. The most commonly reported drugs related to large weight gain are the **psychotropic medications**, which include *[234,236, 237]*:

- Antipsychotic drugs, such as conventional neuroleptics (e.g. chlorpromazine, thioridazine) and atypical antipsychotic drugs (e.g. clozapine, olanzapine, risperidone, ziprasidone and quetiapine-the latter two are associated with the smallest weight gains, while risperidone has been associated with minimal to moderate weight gain. Each of the antipsychotic agents differs with reference to the timing and severity of potential weight gain. The mechanism of weight gaining while on neuroleptics is related to blockage of sites which are related to appetite stimulation (i.e. anticholinergic, serotonergic and histaminergic sites) *[237]*. With regard to atypical antipsychotics, potential mechanisms of weight gain include effects on neurotransmitters, principally serotonin (5-hydroxytryptamine, 5-HT), dopamine and norepinephrine, antihistaminergic effects, effects on leptin and changes in insulin resistance *[238]*.
- Mood stabilizers, such as lithium (which is used for bipolar disorders and weight gain is a frequent side effect of long-term maintenance therapy), valproate-related products (i.e.

valproic acid and its derivatives which apart from epilepsy treatment they are also used in the treatment of manic episodes associated with bipolar disorder) and carbamazepine which is used for bipolar disorders and is less commonly associated with weight gain, however, information about appetite stimulation is controversial and it is possible that weight gain while on carbamazepine is related more to improvement in mood than to a direct effect of the drug. Valproate is associated with significant weight gain which may be explained by increased food intake, decreased energy expenditure, reduction of thermogenesis and greater availability of long-chain fatty acids as a result of competitive binding to serum albumin. On the other hand, the mechanism for lithium-induced weight gain without hypothyroidism is not known. It has been proposed either that lithium often increases thirst and may promote consumption of fluids rich in calories or lithium-induced edema may also contribute to weight gain, controversially it has been suggested that lithium increases storage of carbohydrates and lipids. It is possible that lithium-induced hypothyroidism could also explain weight accumulations *[237]*.

❖ Antidepressant drugs**,** such as tricyclic antidepressants (e.g. amitriptyline, imipramine) and other antidepressants (e.g. mirtazapine). Most antidepressants are associated with increased weight, since they can enhance appetite and induce a craving for carbohydrates. Their tendency to cause weight gain may be linked to improved appetite and more joyful eating patterns as symptoms of depression diminish. Tricyclic antidepressants cause weight gain more often than MAOIs do and a possible mechanism for weight gain while on tricyclics has been considered to be anticholinergic activity, for the reason that it causes dry mouth, so can lead to excessive consumption of high-calorie beverages or sweets *[237]*.

The weight gain induced by long-term therapy with psychotropic medications does not regress easily and can result in increased risk for diabetes, coronary artery disease and other health-related problems, while negative self-image from the weight gain can further complicate the patient's success with psychotropic therapy. The extent of weight change depends on the specific drug, the dosage, and the duration of treatment and sometimes weight gain during pharmacotherapy may be a reflection of improvement in the patient's mental status *[234,237, 239, 240]*.

Antidiabetics (e.g. insulin, sulfonylureas, thiazolidinediones) are drugs also related to the adverse effect of weight gain. Weight increases from 0,8 to 6,6 kg have been reported after the start of these medications, while most weight gain reached a plateau effect by 6–

12 months. In addition, the higher dosages were associated with greater weight gain *[234, 236]*.

Some other drugs known to favor weight gain include: **steroid hormones** like testosterone and estrogens, **anabolic/androgenic steroids** like testosterone derivatives-e.g. oxandrolone, **oral contraceptives**, **corticosteroids** (e.g. prednisone) which are used for treating inflammatory diseases, **β-blockers** (e.g. propranolol) used for the management of hypertension and coronary heart disease and **cyproheptadine**, an antihistamine used for allergies and hay fever *[234, 236]*. Testosterone and selective estrogen receptor modulators have been used intentionally to facilitate weight gain in malnourished patient, while oxandrolone has been used to promote weight gain in patients who have lost weight as a result of chronic infection, surgery or severe trauma *[234, 241]*. Testosterone therapy also increases lean body mass in HIV-positive patients with low testosterone levels and abdominal obesity *[242]*. Anabolic steroids, along with other drugs, have been successfully used for the promotion of weight gain in anorexia–cachexia syndromes (HIV/AIDS and cancer) *[234,241]*.

5.2.1.2 Drug- induced weight loss

Treatment with medication for therapeutic purposes may result in an adverse effect of weight loss. Drugs associated with weight loss as an unwanted adverse effect predominantly are drug **stimulants**. These central nervous system stimulants (e.g. methylphenidate, dextroamphetamine) have been used in children with Attention Deficit Hyperactivity Disorder (ADHD) and apart from improving the main symptoms of ADHD they may also have minor growth suppression (accompanying weight loss) and possibly some suppression of stature, but these effects are not long-lasting and seem to have little effect on adult height or weigh *[243]*. Stimulants have also been used in obese patients for weight loss, due to their anorexic properties. Other common drug stimulants or drugs with stimulant properties include: amphetamine, methamphetamine, lisdexamfetamine, armodafinil, modafinil, doxapram, caffeine and theophylline *[234]*.

Serotonergic drugs (both selective serotonin reuptake inhibitors (SSRI) and serotonin receptor agonists (SRA)), have also been reported to cause weight loss in non-obese and obese individuals. The effect is strongly associated with hypophagia and is probably mediated by the hypothalamic melanocortin system *[234,244]*. Among serotonergic drugs,

fluoxetine and sertraline as well as other **psychotropic medications** such as molindone, isocarboxazid, nefazodone, bupropion, loxapine and trazodone, cause or may cause loss of appetite and of weight. The latter two have also been associated with weight gain *[237]*.

Other medications that may exhibit an anorexic adverse effect include: the **antiepileptic agents** topiramate, lamotrigine and zonisamide, the **antiparkinsonian drug** benztropine, the **antineoplastic agents** dacarbazine, epirubicin and etoposide, **nicotine** and sibutramine which is a drug used in the **management of obesity** *[234, 237]*.

In general, medications can cause weight loss indirectly by causing dysphagia, gastrointestinal side effects, delayed gastric emptying, early satiety, altered taste or smell, sedative effects leading to lack of desire to eat or napping and missed meals, or they may cause depression *[245]*.

5.2.1.3 Drugs altering oral cavity, taste and smell

Medications can lead to altered food choices. Many drugs have been reported to directly affect the perception of taste and smell, as well as some drugs themselves have an unpleasant taste that might interfere with food intake *[12, 246]*. The mechanisms by which medications alter the chemical senses are not well understood *[5]*. Generally, the mechanisms underlying drug-induced taste and/or smell alterations can be classified into two groups *[247]*:

- Primary mechanisms, due to a direct action of a drug (e.g. drug-receptor interaction, alteration of the neurotransmitter function, disturbance of action potential propagation in cell membranes of afferent and efferent neurons and changes in interplays between neural networks in brain regions associated with sensory coding and modulation).
- Secondary mechanisms in which the altered perception is due to collateral effects of the drug. Secondary mechanisms include the limited access of chemicals to sensing receptors (i.e. drying the mucosa, closing off taste pores, increasing nasal engorgement) and changing the chemical or ionic milieu in the environment of sensing receptors (i.e. altering the constituents of mucous or saliva).

In any case, sensory disturbances may include deposition of silver sulfate in nerves after use of topical agents containing silver, altered influx of calcium and other ions, chelation or depletion of tissue-bound zinc, disturbed bradykinin catabolism and second messenger synthesis, catabolism and altered prostaglandin systems *[248]*.

The alterations in taste sensation can result in symptoms of ageusia (loss of taste), dysgeusia (distortion of taste), hypogeusia (decreased sense of taste) and phantogeusia (gustatory hallucination) *[234, 248, 249]*. For example, drugs that cause dysgeusia include **phenytoin** (anticonvulsant), **cisplatin** (antineoplastic) and **captopril** (antihypertensive drug) which may also cause a metallic or salty taste and the loss of taste perception. An unpleasant metallic taste has also been reported by patients (up to 34%) taking the sleep aid **eszopiclone**, while the antibiotic **clarithromycin** has been reported to have a bitter taste that stays in the mouth as long as the drug is present in the body *[5]*. Disturbances in olfaction can cause anosmia (inability to detect odors) or hyposmia (decreased ability to detect odors). Total anosmia is a relatively common clinical problem *[248, 249]*.

Xerostomia (dry mouth), which results from the suppression of saliva production, is also associated with altering taste perception or loss of taste sensation. Long-term dry mouth can cause problems in the oral cavity (e.g. dental caries, loss of teeth, gum disease, stomatitis and glositis) as well as nutritional imbalance and undesired weight loss *[5, 234]*. Many drugs are associated with xerostomia, especially those medications with **anticholinergic** properties, for example amitriptyline (tricyclic antidepressant), diphenhydramine (antihistamine) and oxybutynin (antispasmodic bladder control agent) *[5]*. Other drugs that cause xerostomia are the **antihistamines**: brompheniramine, cetirizine, cyproheptadine, loratadine, terfenadine and trimethobenzamide (sedating antihistamine used as an antiemetic), the **antivirals**: rimantadine and didanosine (also antiretroviral), the **cardiovascular** drugs: flecainide and procainamide (antiarrhythmics), pentoxifylline (vasodilator) and bumetanide (loop diuretic), the **gastrointestinal** drugs: granisetron and ondansetron (antiemetics), mesalamine (anti-inflammatory), nizatidine (H_2-antagonists) and propantheline (antispasmodic/ synthetic anticholinergic), the **antibacterial** drug isoniazid (antituberculous), the **antiparkinsonian** drugs orphenadrine (also an anticholinergic agent) and selegiline, the **ophthalmological** drug cyclopentolate (antiglaucoma and also anticholinergic), the **antipsychotics**: flunitrazepam (also hypnotic), molindone (neuroleptic), olanzapine (atypical) and the **antidepressants**: imipramine (anticholinergic effects) and nortriptyline (tricyclics), sertraline (SSRI), trazodone (an serotonin antagonist receptor and reuptake inhibitor (SARI)) *[234, 249]*.

Antineoplastic drugs used in cancer chemotherapy except for affecting cells that reproduce rapidly, also affect the mucous membranes. Inflammation of mucous membranes (mucositis) manifests either as stomatitis, glossitis or cheilitis and can be extremely painful for the patients, to a point that they are not able to eat or drink.

Antineoplastics that cause severe mucositis are for example aldesleukin, paclitaxel and carboplatin *[5]*.

5.2.1.4 Drugs affecting the gastrointestinal (GI) tract

One of the main functions of the gastrointestinal tract is to provide the body with a constant supply of water, electrolytes and other nutrients. The GI tract innervations are supported by the enteric nervous system, which controls most of the GI functions under the direction of the autonomic nervous system. The degree of activity of the enteric nervous system is strongly affected by the parasympathetic and sympathetic nervous signals from the brain to the GI tract, with acetylcholine and norepinephrine being the primary neurotransmitters for the parasympathetic and sympathetic system, respectively. Additional GI neurotransmitter receptors include cholinergic, histaminic, dopaminergic, opiate, serotonergic, and benzodiazepine receptors. Any drug affecting these neurotransmitters (either centrally or locally) can affect GI tract function of absorbing nutrients and ultimately affecting nutritional status *[234, 250, 251]*.

Drugs can affect the GI tract function of absorbing nutrients either by inducing nausea and emesis (vomiting) or motility disturbances. Nutritional complications become a concern when emesis is prolonged or severe, for example in cytotoxic chemotherapy, which may be highly emetogenic. The **chemotherapy agents** being associated with the most nausea and/or emetogenic potential include: aldesleukin, altretamine, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, lomustine, mechlorethamine, mitoxantrone, pentostatin, and streptozocin (an antibiotic antineoplastic) *[234, 250]*.

The motility of the GI tract can be either increased or decreased by medications. The medications that increase the motility of the GI tract or cause GI intolerance may result in abdominal pain, cramping or diarrhea. As in vomiting, if these adverse effects are severe or prolonged, then the outcome might be altered nutrient absorption. Moreover, patients with drug-induced abdominal pain and cramping may decrease nutrient intake simply due to decreased appetite. Attributable to prolonged or severe diarrhea, nutrient losses occur owing to the increased oral–cecal transit or decreased GI absorption time. Drugs that are associated with increasing motility and diarrhea include **metoclopramide** and **cisapride** (gastrointestinal drugs), **erythromycin** and **other antibacterials**, like: 3rd generation

cephalosporins (e.g. cefdinir), clindamycin, ampicillin, tetracycline hydrochloride, etc (broad-spectrum antibiotics which their prolonged therapy use alters the normal bowel flora, predisposing to the overgrowth of *Clostridium difficile* and the production of its toxins) and **orlistat** (a lipase inhibitor for weight loss-antiobesity drug) *[5, 234, 252]*.

Aspirin, other NSAIDs and iron are notorious for causing GI irritation. **Acetylsalicylic acid (aspirin)** or **nonsteroidal anti-inflammatory agents** (e.g. ibuprofen, ketoprofen) apart from stomach irritation can also cause dyspepsia, gastritis, ulceration and sudden serious gastric bleeding, thus sometimes leading to fatalities. Other drugs involving GI bleeding and/or ulceration include: **bisphosphonates** (e.g. the antiosteoporosis drug alendronate that can cause oesophagitis), **antineoplastics** (e.g. erlotinib hydrochloride, vinblastine sulfate), **corticosteroids** (e.g. prednisone) and **SSRIs** (e.g. fluoxetine, sertraline) especially when given with NSAIDs, the antiparkinsonian drugs **levodopa**, the antifungal antibiotic **amphotericin B**, etc. **Ethanol** in the GI tract also acts as a stomach mucosal irritant and produces the same effects as aspirin or other NSAIDs, so it may increase the risk of GI ulceration and bleeding. Due to its hepatotoxic potential, ethanol should not be combined with drugs that also show a risk of hepatotoxicity, such as acetaminophen (an analgesic/antipyretic & synonym of paracetamol), methotrexate (an antimetabolite antineoplastic drug) and amiodarone (a cardiovascular/antiarrhythmic drug) *[5]*.

Decreased GI motility, which may also result in constipation and inadequate delivery of nutrients, is associated with opioids and anticholinergic medication or those with anticholinergic effects. The opioids increase the resting tone of smooth muscles in the GI tract resulting in delayed gastric emptying and decreased peristaltic movement *[251]*, whilst anticholinergic agents decrease GI motility by blocking the action of acetylcholine at the parasympathetic receptor sites *[234]*. **Opioid drugs** that can cause constipation include the analgesic/narcotics codeine and morphine, while **drugs that have anticholinergic effects** and cause constipation include: the atypical antipsychotics clozapine and olanzapine, the tricyclic antidepressant amitriptyline, the sedating antihistamine drug diphenhydramine and the bronchodilator/anti-asthma drug ipratropium (anticholinergic agent) *[5]*. Other **anticholinergic medications** commonly used include: the cardiovascular drug atropine, the antiparkinsonian drugs benztropine and trihexyphenidyl, the gastrointestinal drugs hyoscyamine, isopropamide and scopolamine (synonym for hyoscine), belladonna herb and the urological drug oxybutynin. Also, drugs with anticholinergic effects commonly prescribed include: the atypical antipsychotic

zotepine, the tricyclic antidepressants imipramine and the cardiovascular/ antiarrhythmics drug procainamide. In patients with severe constipation or bowel obstruction, these medications should be discontinued and alternative therapy should be instituted *[5, 234]*.

5.2.1.5 Drugs inducing metabolic effects

Medications can alter the metabolic function or macronutrient status of a patient, while acute metabolic changes may range from transient to life threatening for the patient. Drug-induced metabolic effects have been reported with several medications concerning alterations in glucose and lipid metabolism, as well as osteoporosis and pancreatitis may be chronic consequences of exposure to some medication *[234]*.

Many drugs affect the **metabolism of glucose**, causing hypoglycemia or hyperglycemia and in some cases franc diabetes. The mechanisms of these effects can vary from drug to drug and from patient to patient. Medications may impair glucose uptake or stimulate glucose production, plus they may inhibit insulin secretion, decrease insulin sensitivity or increase insulin clearance *[5]*.

As far as hypoglycemia is concerned, falling plasma glucose concentrations cause an array of symptoms that can be manifestations of the autonomic nervous system response (neurogenic symptoms such as tremulousness, palpitations, anxiety/arousal, sweating, hunger and paresthesias) as well as the brain's response to being deprived of glucose (neuroglycopenic symptoms such as sensations of warmth, weakness and fatigue, confusion, difficulty thinking, behavioral changes-irritability is often noted- and emotional lability). Episodes of hypoglycemia may be severe, characterized by loss of consciousness and/or seizures and, in instances of sustained hypoglycemia, may result in brain damage or death *[253, 254]*. The most highly documented drug-induced hypoglycemia occurs with medications used to treat hyperglycemia *[253]*. **Antidiabetic drugs** especially insulin, sulfonylureas (i.e. long-acting sulfonylureas such as chlorpropamide and glibenclamide, which have been associated with severe, prolonged and sometimes fatal hypoglycaemia) and thiazolidinediones (e.g. rosiglitazone mostly when is given with a sulfonylurea or insulin) are the most common causes of hypoglycemia encountered in clinical practice *[234, 255, 256]*. Other drugs that include risk factors and frequency of hypoglycemic events are: **fluoroquinolones** (especially the antibacterial gatifloxacin), **NSAIDs** (e.g. indomethacin) including **salicylates**, **quinine** (an antimalarial drug), **pentamidine** (an

antiprotozoal drug), **disopyramide** (an antiarrhythmic drug), **beta-blockers** (especially propranolol) which may also mask the symptoms of hypoglycemia and **angiotensin converting enzyme (ACE) inhibitors** (especially captopril)–both used for hypertension and cardiovascular diseases *[253, 257]*. **Alcoholic hypoglycemia** is also a well-known alteration of carbohydrate metabolism induced by alcohol, although excessive alcohol intake induces glucose intolerance, probably due to an inhibition of glucose-stimulated insulin secretion *[258]*. **Additional medications** associated with hypoglycemia include anabolic steroids, calcium channel blockers (e.g the cardiovascular/antiarrhythmic drug verapamil), insulin-like growth factor 1 (IGF-1), tetracycline and warfarin *[234, 259, 260]*. Moreover, SSRIs agents can cause hypoglycemia in rare cases, with diabetic patients having a higher risk of experiencing SSRI-induced hypoglycemia, while non-diabetic patients can also experience this side effect *[261]*. Serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine and the anxiolytic oxazepam (which is also used for the control of symptoms associated with alcohol withdrawal) have been reported to induce severe hypoglycemia resulted from self-intoxication with these drugs *[234, 262]*.

It is well recognized that certain medications can also cause clinically significant elevations in glucose concentrations. Drug-induced episodes of hyperglycemia may worsen glucose control in the diabetic patient as well as increase patient risk for developing hyperglycemia and subsequent diabetes *[234]*. Often signs and symptoms of hyperglycemia include the classical symptoms of polyphagia, polydipsia and polyuria. In patients with Type 1 diabetes, untreated hyperglycemia is commonly accompanied with excretion of ketones in urine (diabetic ketoacidosis-DKA) and it is a medical emergency which can result in fatigue, weakness, fruity odor of the breath, confusion, lack of concentration, shortness of breath, nausea and vomiting, dry skin, and flushing of the skin. Patients with Type 2 diabetes are more likely to develop hyperosmolar hyperglycemic state (HHS), formerly known as hyperosmolar hyperglycemic nonketotic coma *[263]*. Common drugs associated with hyperglycemia and/or new-onset diabetes include: **thiazide and thiazide-like diuretics** (e.g. hydrochlorothiazide and metolazone respectively), **corticosteroids** (mainly those with glucocorticoid actions), **β-blockers,** such as propranolol (which has also been implicated in inducing hypoglycemia), metoprolol and atenolol (carvedilol and nebivolol are not associated with the development of hyperglycemia or new-onset diabetes), **fluoroquinolones** which are the only class of antibacterials consistently associated with the development of hyperglycemia, with the most weakly implicated being levofloxacin, whereas gatifloxacin is the most commonly

implicated and has been also associated with the development of hypoglycemia, thus avoidance of its use has been proposed for patients with diabetes, **calcineurin inhibitors (CNIs)** such as cyclosporine, sirolimus and tacrolimus, which are immunosuppressant agents often used to avoid allograft rejection in transplantation therapy, have also been implicated in post-transplantation diabetes, **protease inhibitors** (e.g. ritonavir) that have antiviral activity and they are used in the treatment of HIV infection and AIDS, may induce hyperglycemia in treated people with or without diabetes *[234, 263]*, as well as **atypical antipsychotics** or second-generation antipsychotic drugs, especially olanzapine, clozapine and risperidone. The latter three may increase the risk of hyperglycemia and most likely increase the risk of Type 2 diabetes when used in people with schizophrenia or schizoaffective disorder, in comparison with the classical antipsychotics (e.g. haloperidol) *[263, 264]*. **Other drugs** commonly reported to implicate in the induction of hyperglycemia include: alcohol, caffeine, estrogens, oral contraceptives, growth hormone, morphine, nicotine, phenytoin, sympathomimetic amines, theophylline, and thyroid products *[234, 260]*.

Many medications (besides lipid-lowering drugs) can affect serum lipid levels in either a potentially harmful or beneficial way, thus might increase or decrease the risk of cardiovascular disease, while medications can also induce protein effects. Drugs that may adversely affect the lipid profile of a patient (concerning increases of total cholesterol, low density lipoprotein cholesterol and triglycerides by up to 40, 50 and 300%, respectively and decrease of high density lipoprotein cholesterol by a maximum of 50%) include: **cardiovascular drugs** such as diuretics (e.g. thiazide & loop diuretics) and beta-blockers, **sex hormones and their modulators** such as danazol, progestogens and combined oral contraceptives containing 2nd generation progestogens, **immunosuppressive agents** (e.g. sirolimus, cyclosporine), **HIV-protease inhibitors** (e.g. ritonavir, indinavir) which are associated with the lipodystrophy syndrome (characterized by peripheral fat wasting, central adiposity and the so called “buffalo hump”, hyperlipidaemia and insulin resistance) and **enzyme-inducing anticonvulsants** (e.g. carbamazepine, phenytoin, phenobarbital) *[234, 265, 266]*. Some drugs, for example retinoid dermatological drugs (e.g. isotretinoin, acitretin) and antipsychotics (e.g. clozapine) mainly elevate triglyceride levels, while in some cases (e.g. in protease inhibitor therapy and clozapine therapy) pancreatitis attributable to drug-induced hypertriglyceridaemia has been reported *[265, 267]*. On the other hand drugs that induce protein effects include: drugs with anabolic properties such as **growth hormone**, **IGF**-1 (insulin-like growth factor-1) and **anabolic steroids** which

among others they respectively increase protein synthesis, stimulate glucose and amino acids transport into muscles and improve nitrogen retention and restore muscle mass *[234, 268]*, while **corticosteroids** (including inhaled corticosteroids) in high-dose and long-term treatment have been associated with a decreased rate of growth in children, since they decrease the secretion of growth hormone and the tissue's sensitivity to its effect *[234, 269]*. **Alcohol** intake can also induce protein loss by inhibiting intestinal protein absorption and increasing urinary nitrogen excretion, as well as leading to negative nitrogen balance (in spite of adequate protein intake) whilst chronic excessive alcohol intake (especially the abstinence period which is homologous to an acute stress situation) increases protein catabolism given that alcohol possibly acts as a direct toxin on muscle proteins generating a muscle damage that is observed in up to 50% of alcoholics *[258]*.

5.2.1.6 Drugs inducing nutrient depletions

The changes in the nutrient status of a patient may not necessarily be directly owing to a medication but may instead be owing to a nutrient deficiency resulting from the medication. Multiple drugs (including also alcohol and illicit drugs) have been reported to cause electrolyte, mineral and vitamin deficiencies. Some examples of drug-induced nutrient depletions include *[234]*:

- Hypocalcemia (low serum calcium levels in the blood), hypomagnesemia (low level of magnesium in the blood), hypophosphatemia (low level of phosphate in the blood) and hypokalemia (low level of potassium in the blood).
- Zinc, iron, copper and selenium deficiencies.
- Folic acid, vitamin A (Retinol), vitamin B_1 (Thiamin), vitamin B_2 (Riboflavin), vitamin B_3 (Niacin), vitamin B_6 (Pyridoxine), vitamin B_{12} (Cyanocobalamin), vitamin C, vitamin D, vitamin E and vitamin K deficiencies.

Commonly prescribed drugs that cause nutrient depletions involve: **cardiovascular drugs** mostly including weak diuretics (e.g., triamterene, amiloride), loop diuretics (e.g. bumetanide, ethacrynic acid, torsemide, furosemide) or thiazide diuretics (e.g. hydrochlorothiazide, chlorothiazide), cardiac glycosides (e.g. digoxin), antihyperlipidemics (e.g. cholestyramine, colestipol) and beta blockers (e.g. the antiarrhythmic sotalol), **oral contraceptives** and **estrogen replacement therapy** medications, **antibacterials** including tetracyclines (e.g. demeclocycline), aminoglycosides (e.g. gentamicin, tobramycin,

neomycin), cephalosporins (e.g. cefotetan, cefoperazone), fluoroquinolones, sulfonamides, penicillins (e.g. nafcillin, oxacillin, piperacillin, ticarcillin, carbenicillin, mezlocillin, penicillin G-synonym for benzylpenicillin), the antituberculous ethambutol & isoniazid and Polymyxin B**, antidiabetics** (e.g. chlorpropamide, insulin, metformin), **analgesics/ anti-inflammatories** including salicylate NSAIDs (e.g. aspirin), other NSAIDs (e.g. celecoxib, indometacin- synonym for indomethacin) and opioid analgesics (e.g. codeine), **anticonvulsants** (e.g. phenytoin, carbamazepine, valproic acid, phenobarbital, primidone and felbamate), **gastrointestinal drugs** mostly including antacids and histamine H_2-antagonists (e.g. cimetidine, famotidine, nizatidine, ranitidine) for treatment and prophylaxis of peptic ulcer disease, laxatives (e.g. docusate, bisacodyl, saline laxatives, phosphates), alvimopan (an opioid μ-receptor antagonist for the treatment of postoperative ileus) and antiemetics (e.g. ondansetron), as well as **sedatives/hypnotics** (e.g. pentobarbital, barbiturates), **antipsychotics** (e.g. risperidone, clozapine, phenothiazines) and **antidepressants** (e.g. fluoxetine, lithium) *[234, 270]*. In *Table 5.2.1.6.1* the above drugs and more are summarized, according to their therapeutic use, stating the nutrient depletions that they induce (see also Appendix *Compilation Table B*).

Table 5.2.1.6.1 The most common drug-induced mineral depletions

Drug therapeutic use	Induced nutrient depletions
Analgesics Anti-inflammatory Drugs & Antipyretics	Hypocalcemia, hypokalemia, iron, folic acid, vitamin C, vitamin E
Antibacterials	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, zinc, iron, copper, vitamin A, vitamin B_1, vitamin B_2, vitamin B_3, vitamin B_6, vitamin B_{12}, vitamin K
Antidepressants	Hypokalemia
Antidiabetics	Hypokalemia, vitamin B_{12}
Antiepileptics	Hypocalcemia, hypophosphatemia, zinc, selenium, folic acid, vitamin B_1, vitamin B_3, vitamin B_{12}, vitamin K
Antifungals	Hypocalcemia, hypomagnesemia, hypokalemia
Antigout Drugs	Hypokalemia, vitamin B_{12}
Antineoplastics	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, folic acid
Antiobesity drugs	vitamin A, vitamin D, vitamin E, vitamin K
Antiparkinsonians	Hypokalemia
Antiprotozoals	Hypocalcemia, hypomagnesemia

***Table 5.2.1.6.1* (Continued)**

Drug therapeutic use	Induced nutrient depletions
Antivirals	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, zinc, copper, vitamin B_{12}
Anxiolytic Sedatives Hypnotics & Antipsychotics	Hypocalcemia, hypokalemia, selenium, vitamin B_2, vitamin K
Blood Products Plasma Expanders & Haemostatics	Hypocalcemia, hypomagnesemia, hypokalemia, iron
Bone Modulating Drugs	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia
Bronchodilators & Anti-asthma Drugs	Hypocalcemia, hypomagnesemia, hypokalemia, vitamin B_6
Cardiovascular Drugs	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, zinc, iron, folic acid, vitamin A, vitamin B_1, vitamin B_3, vitamin B_6, vitamin B_{12}, vitamin E, vitamin K
Chelators Antidotes & Antagonists	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, zinc, iron
Corticosteroids	Hypocalcemia, hypomagnesemia, hypokalemia, zinc, folic acid, vitamin E
Disinfectants and Preservatives	Hypomagnesemia, hypophosphatemia, iron, vitamin A, vitamin B_1, vitamin B_3, vitamin B_6, vitamin B_{12}
Electrolytes	Hypocalcemia, hypophosphatemia, hypokalemia, iron,
Gastrointestinal Drugs	Hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, copper, folic acid, vitamin B_{12}
General Anaesthetics	Hypokalemia
Immunosuppressants	Hypomagnesemia, hypophosphatemia, hypokalemia
Miotics Mydriatics & Antiglaucoma Drugs	Hypokalemia
Nutritional Agents & Vitamins	Hypocalcemia, hypophosphatemia, hypokalemia, zinc, folic acid
Pharmaceutical Excipients	Hypocalcemia, vitamin A, vitamin D, vitamin K
Productive Cough Suppressants	Hypokalemia
Sex Hormones and their Modulators	Hypocalcemia, hypomagnesemia, hypokalemia, zinc, folic acid, vitamin B_2, vitamin B_6, vitamin B_{12}, vitamin E
Thyroid and Antithyroid Drugs	Hypocalcemia

Source: [234, 270]

5.3 Clinical significance of food-drug interactions

The potential for interactions between food and drugs is almost infinite, but it is unclear what proportion of the total has been indentified, but more importantly how many of the indentified food-drug interactions are clinically significant *[7, 29]*. Food-drugs interactions are considered to be clinically significant if therapeutic drug response is altered (reduced or enhanced) or nutrition status is compromised resulting in some degree of malnutrition *[3, 29]*. Though, the extent and clinical significance of food-drug interactions can display considerable variation. For several drugs the interaction with food is not accompanied by any significant change in clinical effects, but for other drugs the food-induced changes in the bioavailability of the drug are considered to be clinically significant. The most important interactions are those reflecting a high risk of treatment failure owing to a significantly reduced drug bioavailability in the fed state. For some other drugs, concurrent food intake may increase drug bioavailability and thereby drug effect, which is usually desirable, but may also lead to serious toxicity *[44]*.

In clinically significant food–drug interactions the precipitating factor produces significant change in the object of the interaction, based on some measureable physiologic criteria. In some cases, the drug can be the object of the interaction (i.e. changes in drug disposition or effect resulting from a nutrient, food, or nutritional status); while in others the drug can be the precipitating factor (i.e. causing changes to nutritional status). The magnitude of change in a given pharmacokinetic or pharmacodynamic parameter reflects the severity or clinical significance of an interaction after taking into consideration patient (e.g. age, organ function) and drug (e.g. therapeutic index) factors *[3, 7, 9]*.

The majority of clinically significant food-drug interactions are caused by food-induced changes in the bioavailability of the drug, which is an important pharmacokinetic effect parameter, since the bioavailability and clinical effect of most drugs are correlated. In order to evaluate the clinical significance of a food-drug interaction, the impact of food intake on the pharmacological effect of the drug has to be quantified. The quantity of change in bioavailability determines how clinically significant the difference is between the fed and fasted states *[3, 44]*. In the present diploma thesis the clinical significance of food-drug interactions is based upon information and estimations as described in literature.

Food-drug interactions involving drugs with a narrow therapeutic index (e.g. lithium, phenytoin, theophylline) and drugs where dosage and blood levels require careful control

(e.g. warfarin) are expected to be the most clinically significant *[29, 40]*. The reason is that in medications with narrow therapeutic indices the difference between blood levels needed to achieve efficacy and toxicity is small. So, even moderate food-drug interactions (especially in susceptible patients) may result in treatment failure requiring dosage adjustment. Therefore, vigilant monitoring of patients on these medications is the standard of care *[44, 245]*.

It must also be underlined that individual variability generally has a larger impact on drugs that have a narrow therapeutic index *[48]* and that the physiologic manifestations of food-drug interactions may differ based on genetic polymorphism. Patient genetics may affect drug bioavailability and pharmacological response to a drug at its receptor site, while variations in drug disposition alter the concentration of a toxic drug or metabolite in the target tissue to cause variable toxicity. So, the genetic polymorphisms of receptors involved in drug pharmacodynamics and of the metabolizing enzymes and transporters involved in drug pharmacokinetics are likely to be the most important sources of individual variability in drug efficacy *[9, 48, 271]*. Pharmacogenetic knowledge is important for the interpretation and prediction of drug interaction-induced adverse events, since efficacy and safety disparity of drugs vary according to races and genetic variants *[5, 271]*.

5.4 Food-drug interactions with regard to dietary recommendations

Several authors have discussed the topic of food-drug interactions providing also dietary recommendations *[1, 6, 52, 44, 229]*. When drugs are used, food intake may lead to clinically important interactions, thus patients taking certain drugs may need special dietary recommendations in order to know what can do to prevent them *[229]*. So, for achieving quality use of medicines it is important to take into consideration the possible clinical implications when taking drugs with or without a meal *[52]*. With some medicines it is vital to avoid co-administration of food and drugs because food can make the drug less effective, while for other drugs it is prudent to take them with food to prevent GI irritation *[6]*. Taking a medicine with a meal implies taking the dose within 30 minutes of a meal, whereas taking a medicine on an empty stomach implies taking the dose one hour before or two hours after a meal *[52]*.

In the text that follows, dietary recommendations are presented for a variety of drugs commonly used for the treatment of various diseases, as they have been provided in

literature. Such drugs when interacting with food may result in a high risk of treatment failure or serious side-effects or changes in the patient nutritional status may occur.

To begin with, in the case of **analgesic drugs, NSAIDs** and **salicylate NSAIDs** long-term use may lead to gastrointestinal adverse effects (i.e. stomach irritation and eventually ulcers). A full stomach lowers the risk for stomach irritation, so these drugs should be taken with food or milk, while alcohol should be avoided (mainly while on narcotic analgesics such as codeine, morphine, methadone and meperidine) since co-administration can produce excessive gastritis, liver damage, hepatotoxicity, gastrointestinal bleeding, comma or even death, especially when these drugs are taken on an empty stomach *[1, 5, 6, 52, 229]*. Concomitant food intake will delay but not significantly reduce the absorption or the effect of most NSAIDs *[44, 272]*. Moreover in some cases tyramine-containing foods should be avoided due to risk of tyramine reactions (e.g. while on meperidine) *[55]*, or the use of St John's wort should be avoided because it may reduce the efficacy of the drug (e.g. while on methadone) *[191,195]*. Theoretically, the use of methadone with grapefruit juice may increase drug serum concentrations and the risk of adverse effects, but the clinical significance of this interaction is unknown *[273]*. In some other cases, the use of high dose of vitamin C supplements may have effects on the nonoxidative pathways of drug metabolism (e.g. while on acetaminophen or salicylamide) *[55, 179, 180]*. Some of the drugs of this class can cause nutrient depletions that involve hypocalcemia, hypokalemia, iron, folic acid, vitamin C and vitamin E deficiencies (e.g. aspirin) *[234, 270]*, while anti-inflammatory agents, including salicylates, are thought to increase risk of hypoglycemia, with indomethacin having the greatest evidence *[253]* (see Appendix, *Compilation Tables A* and *B*).

As far as the different types of antibacterials are concerned, prolonged use of broad-spectrum **antibiotics** leads to the destruction of intestinal flora (that synthesizes vitamin K) predisposing to the overgrowth of *Clostridium difficile* and thus to events of increased GI motility and diarrhea *[1, 5, 252]*. The intake of food can reduce the bioavailability of most antibiotics as well as dairy products and/or dietary supplements (iron, zinc, calcium, magnesium and aluminium) do. These antibiotics should be taken on an empty stomach, one hour before or two hours after a meal, with a full glass of water, while dairy products and supplements should be avoided for two to three hours after taking the drug (e.g. in the case of tetracycline). The reason is that the co-administration of calcium rich foods and mineral supplements results in chelation and reduced drug absorption (e.g. in the cases of tetracycline, norfloxacin, ciprofloxacin), while in response to food intake the exposure of

the drug to acid and prolonged gastric residence leads to chemical degradation and reduced bioavailability (e.g. penicillin, phenoxymethylpenicillin) with a risk of therapeutic failure (e.g. in the cases of azithromycin, erythromycin, ampicillin) *[1, 6, 44, 52, 229]*. The cation content (i.e. iron, magnesium and zinc) of certain enteral feeds may also cause chelation with some antibiotics (e.g. ciprofloxacin, ofloxacin) by significantly reducing their absorption and thus their bioavailability (especially ciprofloxacin) *[44, 274]*. Specifically for erythromycin, the effect of food on its pharmacokinetics depends on the drug formulation and is very complex, so giving a general recommendation for this drug is difficult. However, the risk of treatment failure is limited with standard dosages of the drug. Some patients prefer taking erythromycin with meals because it alleviates adverse gastrointestinal effects. As for further food-drug interactions, it is mentionable that erythromycin is affected by ingestion of grapefruit juice, which increases the bioavailability of the drug by inhibition of first-pass metabolism *[44, 81, 136]*. On the other hand, the bioavailability of some antibiotics is unaffected by ingestion of regular food (e.g. in the case of norfloxacin, ciprofloxacin) and the ingestion of regular food and/or milk (e.g. in the cases of amoxicillin, ofloxacin) but it is reduced by a high-fibre diet (e.g. in the case of amoxicillin which can be taken with water, fruit juice, milk or carbonated beverages) *[1, 44]*. In some cases, tyramine-restricted diet should be followed (e.g. while on linezolid) *[55, 231, 229]*. Generally, antibiotic activity may be diminished by vitamin C *[181]*. Furthermore, a tyramine-restricted diet is also recommended in the case of the **antimycobacterial** agent isoniazid, while it should be taken without food given that food intake decreases its bioavailability and the risk of treatment failure due to acid lability is possible *[44, 55, 229, 230]*. Caution is needed when isoniazid is administrated because this drug demonstrates slow acetylation (slow inactivation) and patients might belong to one of the two distinct phenotypes of acetylation: “slow acetylators” or “rapid acetylators”. Slow acetylators metabolize drugs more slowly than average (because of inherited lower levels of the hepatic enzyme acetyltransferase) so unacetylated drug levels remain higher for longer periods in these patients than in others who are rapid acetylators. Consequently, a dose of the drug prescribed normally for rapid acetylators can be toxic for slow acetylators. High blood levels of the drug in slow acetylators increase the possibility for food-drug interactions (slow inactivation of isoniazid increases the risk of pyridoxine deficiency and peripheral neuropathy) *[5, 48]*. Alcohol intake should be avoided in all cases, but particularly in patients treated with certain cephalosporin antibiotics (e.g. cefotetan, cefoperazone) because adverse reactions such as flushing, headache, nausea, vomiting,

weakness, vertigo, hypotension, blurred vision and seizures develop soon after alcohol is consumed. This is called disulfiram-like reaction and it is one of the best known interactions of drugs with alcohol *[1, 5, 55]*. In general, antibacterials apart from affecting the GI tract, they further implicate with the nutritional status of a patient by causing nutrient depletions and other effects such as xerostomia, alteration in taste, hypoglycemic or hyperglycemic events (see Appendix, *Compilation Table B*).

On the contrary, for other anti-infective agents, concomitant food intake can increase drug bioavailability and thereby drug effect, as in the case of **antifungals** (e.g. griseofulvin, itraconazole capsules, ketoconazole). Increased drug bioavailability in response to food intake occurs either because of the secretion of gastric acid, since reliable absorption depends on acid environment (itraconazole capsules, ketoconazole) or because bile acid enhances drug dissolution (griseofulvin). These drugs should be taken with meals or at a consistent time with respect to meals *[44, 52]*. Moreover, griseofulvin and ketoconazole work better when taken with fatty food so it is recommended to be taken with a high-fat meal *[6, 44, 70, 229]*, while it is found that acidic beverages intake (e.g. cola drinks) may improve drug bioavailability of itraconazole and ketoconazole *[168, 169]*. Alcohol intake should be avoided while on griseofulvin and ketoconazole as it can or may cause disulfiram-like reactions *[1, 55]*. In addition, the use of itraconazole with grapefruit may lead to decreased oral bioavailability, resulting in an increased risk of antifungal failure. The clinical significance of this interaction is unknown, therefore monitoring of patients for altered response is essential *[273]*. As far as **antivirals** are concerned, concomitant food intake can also increase drug bioavailability and thereby drug effect of saquinavir. The drug should be taken with meals or at a consistent time with respect to meals (because food increases drug dissolution) whereas administration in the fasted state is associated with high risk of treatment failure. In fact, the extent of absorption is more than doubled by taking saquinavir after a full cooked breakfast *[44, 52]*. Grapefruit juice may also increase the oral bioavailability of saquinavir but the clinical significance of this interaction is unknown as there is a high inter-individual variability in the bioavailability of saquinavir, thus monitoring patients for altered response may be wise *[81, 136, 273]*, while garlic can decrease systemic exposure and maximum concentrations of the drug *[191, 192, 217]*. In contrast food intake can reduce the bioavailability of indinavir (by causing precipitation) which is reflecting a high risk of treatment failure *[44]*. Supplements such as St John's wort can reduce the efficacy of the drug *[137, 191, 195, 198]*, while vitamin C in high doses may reduce steady-state indinavir plasma concentrations *[55, 182]*. Didanosine,

as in the case of indinavir, should also be administrated without food since food intake can reduce the bioavailability of the drug (due to chelation or acid lability) with a risk of treatment failure only in adults (in children didanosine bioavailability is unaffected by food intake) *[44]*. In patients taking zidovudine, a high-fat meal can delay and prolong the absorption of the drug, so in order for maximal serum concentrations to be achieved this drug should be administrated on an empty stomach *[57, 74]*.

In relation to antiparasitic agents, food intake (with high-fat content) very significantly increases the bioavailability of the **antimalarial** drug halofantrine (because of the secretion of bile in response to food intake) which may lead to toxic drug concentrations with a high risk of cardiotoxicity (e.g. arrhythmias and even cardiac arrest). Consequently, halofantrine should never be taken with food and should be used cautiously *[44]*. The bioavailability of the **anthelmintic** drug albendazole is also increased when taken with food with especially a high-fat content (due to increased drug solubility) which enhances its chemosterilant properties against systemic parasitic infections *[44, 275, 276]*. The administration of albendazole in the fasted state though may be preferable or appropriate for the treatment of intraluminal intestinal parasites where a systemic effect is not required *[44, 276]*.

The drugs used in cancer treatment (**antineoplastics)** can affect the nutritional status of a patient in various ways. These drugs can irritate the cells lining the mouth, stomach and intestines by inducing alterations in oral cavity and taste sensation or inflammations of mucous membranes (e.g. cisplatin, aldesleukin, carboplatin, paclitaxel), by inducing ulcers and/or bleeding, nausea, vomiting and/or diarrhea (e.g. aldesleukin, carboplatin, carmustine, dacarbazine, dactinomycin, lomustine, etc) or they can cause lost of appetite and weight loss (e.g. dacarbazine, epirubicin, etoposide), plus nutrient depletions (for more detail see Appendix, *Compilation Table B*). In some cases, as for example when a patient is on procarbazine, tyramine-containing food should be avoided in order to avoid hypertension events in patients treaded for Hodgkin's disease *[1, 6, 55, 232]*, while alcohol intake should also be avoided as it can cause disulfiram-like reactions *[5, 55]*. Besides this, drugs that show a risk of hepatotoxicity should not be combined with ethanol or *Echinacea spp. [5, 213]*, as in the case of methotrexate. As for food intake while on this drug, in children patients methotrexate bioavailability is reduced when it is administered with food but drug bioavailability is unaffected by food in adult patients. Thus there is a risk of treatment failure only in children and the drug is recommended to be taken without food. Methotrexate acts as folic acid antagonist, thus risk of folic acid deficiency is possible for people taking this drug or for people already having depleted folate stores.

Therefore supplementation of folic acid may be recommended for people taking this drug *[1, 6, 234, 270]*. Another drug that is also recommended to be taken without food is mercaptopurine. In adults, the bioavailability of this drug is reduced when it is administered with food (because food can cause oxidation into inactive metabolites) with consequent risk of treatment failure. In contrast, mercaptopurine bioavailability in children is reduced or unaffected by food *[44]*. Moreover, it is stated that concurrent intake of cow's milk (which contains a high level of xanthine oxidase) and mercaptopurine (which is inactivated by xanthine oxidase) may potentially reduce drug bioavailability. This interaction may be clinically significant, thus patients should try to separate the timing of taking mercaptopurine and drinking milk *[4, 277]*.

As for **immunosuppressants** agents with regard to meal intake, in the case of tacrolimus (drug with a narrow therapeutic index) the influence of food on the oral absorption of tacrolimus appears to be dependent on its fat content and relative time of administration *[278, 279]*. Patients on this drug should take tacrolimus with a consistent relationship to meals so as to avoid adverse fluctuations in drug concentrations *[44, 279]*. Moreover co-ingestion of tacrolimus with grapefruit juice should be avoided as can lead to significantly increased plasma concentrations and increased risk of toxicity, making this interaction possibly clinically significant *[273]*. In the case of cyclosporine, as it is discussed in literature, the impact of food on cyclosporine absorption is controversial. The effects of food intake on cyclosporine may exhibit considerable inter- and intrapatient variability (e.g. drug bioavailability may be increased or unchanged in conventional formulation) or the bioavailability due to food intake may be unaffected or marginally reduced (e.g. in microemulsion formulation) *[44, 57]*. Still, intake of cyclosporine with grapefruit juice should be avoided, since grapefruit increases the oral bioavailability of the drug and raises its concentration above toxic levels, thus this interaction has high clinical significance (e.g. may cause renal dysfunction, cholestasis, paraesthesia) *[4, 96, 137, 138, 273]*. St John's wort supplementation should also be avoid in both cases as it can reduce the efficacy of these drugs *[137, 191,192,195]*, while *Echinacea spp.* has been found to offset/minimize the effects of cyclosporine *[181, 213]*. Moreover, administration of red wine with cyclosporine causes a significant decrease in drug exposure and given that cyclosporine is a drug with narrow therapeutic index, caution may be necessary with concomitant intake of red wine and cyclosporine *[118-120]*. Pummelo juice has been reported to increase the oral bioavailability of cyclosporine and blood concentrations of tacrolimus *[136, 151, 152]*. Both drugs are associated with hyperglycemia and post-

transplantation diabetes *[234, 263]*, whereas immunosuppressive agents in general can adversely affect the lipid profile of a patient *[234, 265]* and can cause nutrient depletions such as hypomagnesemia and/or hypophosphatemia *[234, 270]*.

In the case of **anticoagulant drugs**, much has been made about the interactions between specific food or nutrients and warfarin. Warfarin is an oral, widely used anticoagulant with a narrow therapeutic index that works by interfering with the vitamin K cycle. Prothrombin time and international normalized ratio are used to closely monitor patients receiving this drug *[3]*. Several authors have reviewed the warfarin-food/nutrient interactions *[3, 44, 280, 281]*. More specific, it is found that the intake of a regular meal does not affect the bioavailability of warfarin *[44, 282]* but sudden variations in dietary intake of vitamin K can have a profound effect on clotting control in patients on anticoagulant therapy *[44, 280, 281]* while supplements with the fat-solube vitamins A, D, E (especially vitamins A & E) increase the risk for abnormal bleeding events *[280]*. The pharmacodynamic effect of warfarin may directly be antagonized by the ingestion of food rich in vitamin K such as broccoli, spinach and other green leafy vegetables *[97, 98]*, liver *[6, 44]* and avocado (despite being low in vitamin K) *[33, 81, 112, 113]*. Cranberry juice potentially interacts with warfarin and might increase its anticoagulant effect, however cranberry juice-mediated pharmacokinetic or pharmacodynamic interaction with warfarin seems questionable *[136, 157]*. Certain herbal supplements have also been found to interact or potentially interact with warfarin. For example, St John's wort can reduce the efficacy of warfarin *[191,195]*, while garlic can decrease platelet aggregation which might theoretically increase warfarin's bleeding risk but no cases have been reported in literature *[3, 192]*. Ginseng may alter bleeding time in concomitant use with warfarin *[213]* and ginkgo has been attributed to an increased risk of serious bleeding events in concomitant use with anticoagulant agents as well *[137, 192, 208, 209]*. Green tea antagonizes the anticoagulant effect of warfarin and reduces a patient's degree of anticoagulation because of being a significant source of vitamin K *[181, 222, 223]*. As for implications in the nutritional status of a patient, warfarin has been associated with hypoglycemia *[234]*. Patients on warfarin can take the drug on a full or empty stomach, but they should avoid fad diets or high consumption of vitamin K foods and should limit alcohol and caffeine. Recommendations about alcohol intake should be based on knowledge of the patient's drinking habits. Complete avoidance of alcohol would be a safe advice though *[229, 280]*. As always, close monitoring of patients is vital *[1, 6, 229]*. The genetic polymorphism of several enzymes involved in warfarin drug action and pharmacokinetics have been shown

to affect individual variability of warfarin therapy to various extents. For instance, due to the polymorphisms of genes that influence warfarin anticoagulation, some patients may display warfarin resistance, needing high doses of warfarin to reach a desired international normalized ratio value instead of others that might need half a daily dose. Warfarin resistance affects individual requirements for and response to drug given that patients receiving an insufficient warfarin dose are at risk of failing to control blood clotting, whereas patients given too high a dose can experience excessive and uncontrolled bleeding *[5, 48]*.

With regard to food intake and other agents affecting the cardiovascular system, such as digoxin (a **glycoside** with narrow therapeutic index) the ingestion of a regular meal does not affect digoxin bioavailability, but a high-fibre diet reduces drug bioavailability which may result in treatment failure requiring dosage adjustment *[44, 57, 68]*. It is recommended that patients should take the drug with water one hour before or two hours after meal (at consistent time with respect to meals), while concurrent ingestion with fibre should be avoided (they can take digoxin at least two hours before or two hours after eating foods high in fiber, such as bran) *[1, 52, 229]*. Certain herbal supplements should also be avoided as they may reduce the efficacy of the drug (e.g. St John's wort) or may either interfere with digoxin pharmacodynamically or with digoxin monitoring (e.g. ginseng, licorice) *[137, 191,195, 213]*. When taking digoxin, potassium supplementation is often required to prevent hypokalemia and digitalis toxicity *[1]*. Except for hypokalemia, digoxin can cause and other nutrient depletions, such as hypocalcemia, hypomagnesemia, hypophosphatemia and vitamin B_1 deficiency *[234, 270]*. In the case of **diuretics**, some increase urine loss of minerals, while others limit mineral loss. For instance, loop and thiazide diuretics increase urinary excretion of sodium, potassium and magnesium. Loop diuretics also increase urinary excretion of calcium, whereas thiazide diuretics actually decrease it *[1, 6]*. Patients can take diuretics with food which can decrease GI irritation *[6, 229]*, apart perhaps from the case of furosemide which its bioavailability is reduced when taken with food and this may lead to a reduction in diuretic response. Generally, the food interaction with furosemide is not considered to be of major clinical significance *[44]*. However, when potassium-sparing diuretics are used, a high intake of potassium-rich foods (e.g. bananas, spinach) may result in hyperkalaemia (e.g. severe hyperkalaemia with serious cardiac arrhythmia has been developed after excessive use of potassium-containing salt substitutes in patients treated with spironolactone) *[44, 283]*. Consumption of potassium-rich foods, potassium supplements and potassium salt substitutes must also be

avoided for the same reasons when the weak diuretic triamterene is being used (patients can take this drug with or after breakfast) *[1, 229]*. On the other hand, potassium-rich foods or potassium supplements can be consumed when the thiazide diuretic hydrochlorothiazide is used. Patients can take this drug with breakfast or high-potassium food and food low in sodium, while natural licorice use should be avoided and alcohol should be limited. High-carbohydrate meals can decrease gastric emptying time, leading to increased absorption of hydrochlorothiazide *[1]*. Apart from the induction of nutrient depletions, some diuretics may adversely affect the lipid profile of patients and/or may promote hyperglycemia and/or new-onset diabetes (see Appendix, *Compilation Table B*).

Patients on antihypertensive therapy with **ACE inhibitors** have as frequent complication the induction of hyperkalaemia, which can be aggravated by intake of potassium-rich foods or salt substitutions. For instance, in the case of captopril therapy the patient should take the drug one hour before meal, avoiding potassium salt substitutes *[1, 229]*. Although food intake decreases the bioavailability of captopril, this interaction has limited clinical relevance because the haemodynamic and humoral effects of the drug are not significantly affected by food *[44]*. On the therapy with **beta-blockers** such as metoprolol and propranolol, patients should take these drugs with food, following a low sodium and low calcium diet. Propranolol and metoprolol are extensively metabolized during first-pass hepatic extraction. Food can increase absorption of these drugs by decreasing first-pass metabolism. Especially high-protein meals have been reported to enhance the bioavailability of these drugs owing to enhanced hepatic blood flow *[1, 57]*. On **calcium-channel blockers** therapy, for example in the case of nifedipine, the effect of food on drug absorption depends on the drug formulation. Nifedipine capsules or tablets should be taken with a meal to avoid rapid drug absorption resulting in high peak drug concentrations and so to reduce the risk of developing adverse effects such as hypotension, flushing and headache (the bioavailability and desired clinical effect are maintained). In contrast, food increases the bioavailability of nifedipine sustained-release preparations, which is reflected in a significantly increased hypotensive effect, thus the drug should be taken with a consistent relationship to meals *[44, 284-286]*. Co-administration of nifedipine with grapefruit juice can increase oral drug bioavailability leading to a risk of unwanted effects, which may be of concern in patients with severe hypertension or stable angina *[52, 273]*, while co-administration with cranberry juice can inhibit CYP3A-mediated metabolism of the drug *[33, 81, 158]*. Grapefruit has also effects on felodipine when there is concomitant use. In fact grapefruit juice markedly increases oral

bioavailability and raises drug concentrations above toxic levels (e.g. there is an increased risk of severe hypotension and myocardial ischaemia), thus this is a clinically significance interaction and grapefruit juice use should be avoided in patients on felodipine therapy *[4, 96, 137, 138, 273]*. Other citrus fruit juices that may/can interact with felodipine are Seville orange, pummel and lime (see Appendix, *Compilation Table A*). In patients on diltiazem the co-ingestion of grapefruit juice may be acceptable with appropriate monitoring and awareness (patients are recommended to take this medicine one hour before or two hours after meals and limit alcohol) *[1, 52, 136]*. In the case of verapamil (which patients should take on an empty stomach and limit alcohol) the references with regard to concurrent grapefruit juice intake are ambiguous. Some authors have stated that grapefruit increases drug oral availability and that co-ingestion of grapefruit juice with verapamil should be avoided due to risk of unwanted effect, whereas some other authors have stated that a single administration of GJ with verapamil has no significant effect on drug pharmacokinetics *[31, 52, 136, 287]*. Given that, it can be concluded that patients taking verapamil should use grapefruit juice with caution. Generally speaking, ACE inhibitors, beta-blockers and calcium-channel blocker have been associated with hypoglycemic events *[234, 253, 257, 259, 260]* but beta-blockers have also been associated with the induction of hyperglycemia and/or new-onset diabetes *[234, 263]*, as well as that they can adversely affect the lipid profile of a patient *[234, 265]* (see Appendix, *Compilation Table B*). Moreover, weight gain and fluid retention are common adverse effects of several antihypertensive agents (e.g. propranolol, nifedipine). The use of diuretics in the management of hypertension can help in reducing fluid retention. Patients should be encouraged to exercise, reduce their weight and follow a low-salt diet while taking antihypertensive medications *[1, 234, 236]*.

Patients on lipid-lowering drugs (**antihyperlipemics**) can take most statins on a full or empty stomach. Some statins work better if they are taken with an evening meal, as in the case of lovastatin, since food increases drug bioavailability (due to increased solubility), reflected in an increased drug effect *[1, 44, 229]*. Patients however should follow an appropriate diet low in fible, given that high-fibre diets reduce the absorption of the drug and increase the risk of treatment failure *[31, 44, 57, 66]*, whereas they should avoid excessive ingestion of grapefruit juice because it increases the bioavailability of lovastatin, leading to drug accumulation and to possible development of adverse effects *[4, 44, 139]*. Co-ingestion of grapefruit juice should also be avoided, due to risk of possible adverse effects, with simvastatin and atorvastatin (for the latter bioavailability and lipid-lowering

efficacy are unaffected by food). The interaction of these drugs with grapefruit may be clinically significant given that the increased bioavailiability of atorvastatin and the increased serum concentrations of simvastatin may result in increased risk of myopathy or rhabdomyolysis. Pravastatin on the other hand is no subject to grapefruit juice-drug interaction. Food intake reduces the bioavailability of pravastatin but its lipid-lowering efficacy is unchanged, thus this food-drug interaction is not clinically significant *[44, 81, 136, 273]*. Moreover, the bioavailability of pravastatin has been found to significantly decrease when taken with a high-fat meal *[31, 73]*. Simvastatin has also been found to interact with St John's wort, which reduces the efficacy of the drug *[137, 191, 195]*. The bile-acid binding resins cholestyramine and colestipol have been associated with decreased absorption of nutrients such as calcium, iron, folic acid, vitamin B_{12} and fat-soluble vitamins (A, D, E, K) thus for patients on long-term therapy, use of multivitamins and calcium or other supplements is recommended *[1, 6, 234, 270]*(see Appendix, *Compilation Table B*). As it is discussed in literature, statins demonstrate large and dose-dependent individual variations in drug efficacy and drug safety, with recent studies suggesting that the genetic polymorphisms of HMGCoA reductase and drug transporters to contribute to the variability in the efficacy and side effects of the lipid-lowering drugs *[48]*.

Regarding **antidiabetic** therapy, patients using for instance the oral hypoglycemic agent sulfonylureas (for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise) should take their drugs before a meal to avoid the risk of significant hypoglycemia *[52]*. For example, in the case of glimepiride, patients should take this drug with breakfast or the first main meal of the day. Glimepiride has absolute bioavailability and the absence of food interaction guarantee highly reproducible pharmacokinetics *[4, 288]*. Patients receiving antidiabetic drugs should avoid alcohol because acute alcohol ingestion can alter carbohydrate metabolism, leading to hypoglycemia. On the other hand, chronic alcohol use can cause increased hepatic metabolism of sulfonylureas, leading to hyperglycemia *[1]*. Sulfonylureas have also been associated with disulfiram-like reactions *[55]*. Moreover, patients consuming red pepper and receiving antidiabetic therapy could suffer potential drug-food interaction, because capsaicinoid-induced changes of glucose could possibly happen *[81, 108]*. Sulfonylureas as well as other antidiabetic agents (i.e. insulin, thiazolidinediones) have also been associated with weight gain and they are the most common causes of hypoglycemia encountered in clinical practice *[234, 236, 255, 256]*.

In relation to antiepileptic therapy, the **anticonvulsants** phenytoin and carbamazepine are both drugs with a narrow therapeutic index *[29, 44]*. Patients on phenytoin are recommended to take the drug with food or after meals to reduce gastric irritation and if vitamin B_6 or folic acid supplementation is needed should be administrated cautiously so as to avoid decreased anticonvulsant efficacy *[1, 181, 183]*. However, when enteral feeding is instituted in patients receiving phenytoin there is a high risk of treatment failure (due to chelation with divalent cations or binding to protein components in the enteral formulas) but also risk of sudden toxicity when the enteral feeding is discontinued without phenytoin dosage reduction *[44, 289]*. Patients on carbamazepine (tablets) are recommended to take the drug with meals or at a consistent time with respect to meals (absorption is favoured by bile secretion) so as to avoid adverse fluctuations in drug concentration, not to mention that co-ingestion of grapefruit juice should also be avoided due to risk of adverse effects (since grapefruit juice increases carbamazepine oral bioavailability and this interaction may be clinically significant) *[44, 52, 136, 273]*. In addition patients should also avoid co-ingestion of St John's wort because it reduces the efficacy of carbamazepine *[191,195]*. Pomegranate juice is also found to interact with carbamazepine by inhibiting the CYP3A-mediated metabolism of the drug *[154]* In the case of phenobarbital, since food decreases its absorption, patients are recommended to take the drug on an empty stomach (i.e. one hour before or two hours after a meal) *[1]*. Generally, anticonvulsant drugs (e.g. phenytoin, phenobarbital, primidone) increase the use of vitamin D in the body, so less vitamin D is available for important functions (e.g. calcium absorption). Thus vitamin D supplements may be needed in patients taking these drugs *[1, 6]*. Some anticonvulsants may also cause diarrhea and a decrease in appetite, favoring this way loss of weight (e.g. lamotrigine, topiramate, zonisamide *[234, 237]*) which may lead to decreased availability of many nutrients. Apart from that, some anticonvulsants favor weight gain (e.g. carbamazepine, valproic acid *[234, 236, 237]*), while others can cause alterations in taste sensation (e.g. phenytoin *[5]*). Some anticolvusants can also adversely affect the lipid profile of a patient (e.g phenytoin, phenobarbital, carbamazepine *[234, 265]*) or they are implicated in the induction of hyperglycemia (e.g phenytoin *[234, 260]*). Alcohol should be avoided while taking anticolvusants as it can add to the side effects caused by these medicines, such as drowsiness in the case of phenobarbital *[1, 5, 229]*. Osteomalacia and rickets may occur in epileptic patients who are taking anticonvulsants such as phenytoin, phenobarbital and primidone *[1]*.

In the case of **antiparkinsonian** therapy, food intake can not affect or can marginally decrease the bioavailability of levodopa (as there is competition with food components) leading to a risk of insufficient drug response, thus it is recommended to take levodopa without food *[44]*. However, protein content of a meal does not appear to influence levodopa bioavailability *[44, 290]* but a high protein meal can reduce the cerebral uptake (not bioavailability) of levodopa and potentially reduce its clinical efficacy *[52]*. On the other hand, a low-protein diet can benefit patients with Parkinson's disease during treatment with levodopa by reducing unpredictable fluctuations in response (the "on–off" phenomenon) *[55, 76, 77]*. Moreover, a high-fibre diet is found to increase levodopa bioavailability in patients with Parkinson's disease and severe constipation via an increase in gastrointestinal motility *[44, 69]*. Patients on levodopa therapy should avoid or restrict vitamin B_6 supplementation as it can reduce or abolish the effects of levodopa, as well as Fe supplements because chelation of levodopa by Fe can potentially lead to reduced control of Parkinson's disease *[29, 189]*. Levodopa therapy has been associated with adverse GI effects such as ulceration and/or bleeding *[5]* and nutrient depletions such as hypokalemia *[234, 270]*.

As far as other agents affecting the nervous system are concerned (i.e. **sedatives, hypnotics, anxiolytics, mood stabilizers, antidepressanst** and **antipsychotics**), alcohol must be avoided while using these medicines since alcohol can add to the side effects caused by these drugs (e.g. alcohol can intensify drowsiness), while caffeine should also be avoided or limited as caffeine can increase drug blood concentration and cause side effects (e.g. in the case of clozapine) or can increase anxiety and reduce drug's effectiveness (e.g. in the cases of lorazepam, benzodiazepines) *[1, 5, 6, 97, 229]*. In reference to food intake, patients can take these medicines on a full or empty stomach, or patients can take these drugs immediately after meal or with food/milk, as in the case of lithium (drug with narrow therapeutic index *[29, 40]*) so as to avoid stomach upset. High-fibre diets can decrease the bioavailability of lithium salts while lithium itself can cause sodium loss. However a low-salt diet increases the risk of lithium toxicity while excessive salt reduces the efficacy of the drug. So patients while on this medicine should maintain a normal diet, including salt and should drink plenty of fluids (eight to twelve glasses a day) *[57, 97, 229]*. On the other hand, in the case of sedatives and hypnotics patients should take these medicines at bedtime and not with a meal or right after a meal so as to get to sleep faster, for example when taking triazolam *[1, 229]*. Moreover in the case of MAOIs, patients taking these agents should follow a tyramine-restricted diet in order to avoid risk of hypertensive crisis

[55, 224, 225, 226] as for example in the case of phenelzine which its slow inactivation increases the risk of hypertensive crisis if high-tyramine foods are consumed *[5]*. Alcoholic drinks, caffeine and chocolate can act like tyramine and should be avoided or consumed only in moderation while on MAOIs *[1, 229]*. In the case of ziprasidone, although data suggest an increase in systemic exposure when this drug is taken after fatty foods (possibly due to improved drug dissolution), there is not any dietary recommendation since the clinical significance of this food–drug interaction has not been determined *[44, 291]*. In some cases though co-ingestion of grapefruit juice perhaps should be avoided as can increase oral drug bioavailability and may cause adverse effects (e.g. in the cases of diazepam, triazolam, alprazolam, buspirone, sertraline *[81, 136]*) or even can raise drug concentrations above toxic levels, as in the case of midazolam *[4, 96, 137,138]*. Moreover with some of these drugs co-ingestion of herb supplements, like St John's wort, ginseng and valerian, should also be avoided due to risk of unwanted effects. For example, in the cases of paroxetine, sertraline, trazodone and nefazodone concurrent use of St John's wort can cause symptoms of excess serotonin or serotonin syndrome *[199, 200]*, in the case of phenelzine sulfate co-ingestion of ginseng can induce headaches, tremulousness and manic episodes in treated patients *[55, 181, 212, 213]*, while in the case of pentobarbital concurrent use of valerian prolongs drug-induced sleep *[192]*. Some of these drugs increase appetite while others decrease it and either effect can impact weight in a significant way. Some drugs as well, have effects on nutritional status by inducing alterations in oral cavity and taste, by inducing GI irritation and motility, by inducing severe hypoglycemia or elevating triglyceride levels (see Appendix, *Compilation Table B*).

In relation to agents used in the treatment of gastrointestinal disorders, long term use of **antacids** and **acid blockers** may lead to certain nutrient deficiencies such as malabsorption of vitamin B_{12}, reduced bioavailability of riboflavin, folic acid, copper and iron (all depending on a low pH), decreased absorption of vitamin A (from aluminum-containing antacids), hypocalcemia, hypophosphatemia and hypomagnesemia (see Appendix, *Compilation Table B*). This can happen due to the fact that stomach acid is important in the digestion and/or absorption of nutrients *[1, 6, 57]*. As far as food intake is concerned, these medications should be taken one hour after eating, for maximum benefit. For other gastrointestinal drugs, for example, cimetidine food generally delays, but does not ultimately decrease the absorption of the drug. Cimetidine should be given with food to assist the maintenance of a therapeutic blood concentration, whereas patients should limit caffeine and avoid high protein foods and alcohol use or other items that increase stomach

acidity. Similar dietary recommendations are also given for famotidine *[1, 4, 97]*. Excessive use of **laxatives** can also deplete vitamins and minerals needed for normal body function. They reduce the time for nutrient absorption by speeding up the movement of materials through the digestive tract. For example prolonged use of bisacodyl increases the rate of transit and reduces the absorption of glucose, protein, sodium, potassium and some vitamins. Laxatives also increase fluid losses which may lead to dehydration *[1, 6]*.

In the case of agents for the respiratory system, **bronchodilators** such as theophylline have different effects with food. The effect of food on different forms of theophylline (drug with a narrow therapeutic index) can vary widely *[4, 29, 40, 229]*. As it is discussed in literature, first generation drugs of theophylline ultraslow release products (older preparations) should be taken without food since food intake increases the bioavailability of theophylline and may cause "dose-dumping" (sudden delivery of a substantial part of the dose) of theophylline, resulting in increased theophylline concentrations and possible toxicity. Moreover, newer once daily theophylline preparations may be taken without regard to food, while non-retarded and sustained release formulations of theophylline are largely unaffected by concomitant food intake *[44]*. Generally, high-fat meals may increase the amount of theophylline in the body, while high-carbohydrate/low-protein diets may decrease the metabolism of theophylline. On the other hand, low-carbohydrate/high-protein diets may increase the levels of metabolizing enzymes, which increases the length of time it takes to achieve therapeutic levels of most drugs. Charcoal-broiled meats should be avoided as may accelerate drug metabolism, reducing the half-life of theophylline (by 20% as it has been reported in literature) *[1, 4, 55, 57, 60, 75, 97]*. Patients should avoid eating or drinking large amounts of foods and beverages that contain caffeine (e.g. chocolate, colas, coffee, and tea); hence the consumption of large amounts of these substances while taking theophylline increases the risk of drug toxicity. The reason is that caffeine has some bronchodilatory effects and thus can have additive effects on theophylline. Patients may complain of nervousness, tremor or insomnia. For those patients who consume excessive quantities of coffee (more than 6 cups daily), a lower dosage of theophylline may be necessary. Alcohol should also be avoided because it can increase the risk of side effects such as nausea, vomiting, headache and irritability *[4, 5, 97]*. When taking theophylline the co-ingestion of grapefruit juice increases drug bioavailability. This may be acceptable with appropriate monitoring and awareness *[52]*. In addition patients may be advised not to use St John's wort when taking theophylline because it reduces the efficacy of the drug *[191, 195]*. Theophylline has been associated with weight loss due to

its anorexic properties, implicated as well in the induction of hyperglycemia and nutrient depletions such as hypokalemia and vitamin B_6 deficiency *[234, 260, 270]*.

As for **antihistamines**, such as fexofenadine, loratadine, cetirizine, it is best to take these drugs on an empty stomach to increase their effectiveness; terfenadine though it is recommended to be taken with food to reduce GI irritation and possible nausea *[4, 97]*. Many of these drugs often cause drowsiness and xerostomia, while they may also increase appetite leading to weight gain (e.g. cyproheptadine). Still, increased physical activity can help reduce weight gain *[6, 234, 249]*. Alcohol and alcoholic beverages should be avoided when using antihistamines as they may increase the central nervous system depressant effects of these drugs (e.g. cause an even greater increase in drowsiness) *[6, 97]*. Grapefruit juice when ingested concomitantly with fexofenadine can reduce oral bioavailability of the drug (as apple juice and Seville orange juice also do) *[4, 121, 122, 137]*, but when grapefruit juice is ingested concomitantly with terfenadine increases the drug oral bioavailability *[81, 136]*. Terfenadine was voluntarily removed from the USA market (though with a different motivation) when it was implicated in a death event ascribed to a drug-grapefruit interaction, but remains available in several other countries *[44, 292]*.

Regarding **sex hormones** and food intake, estrogens for example should be taken with or after food to reduce GI irritation and minimize nausea, while a sodium-restricted diet should be followed, as in the case of oral contraceptives as well, because salty foods increase fluid retention. Furthermore, sex hormones reduce the absorption of certain nutrients (e.g. folate, vitamin B6, etc), thus patients may be advised to increase intake of foods high in these nutrients to avoid deficiencies *[1, 97]*. Patients taking sex hormones should carefully use certain herbal supplements because co-ingestion can lead to serious adverse effects (e.g. St John's wort may increase the clearance of norethindrone, producing breakthrough bleeding after prolonged use *[137, 191,195]*, concurrent use of anabolic steroids with *Echinacea spp*. may cause hepatotoxicity *[213*], ginseng in concurrent use with estrogens may cause additive effects *[213]*, co-ingestion of licorice with oral contraceptives can result in adverse effects *[181]* etc). Weight gain is a common adverse effect of sex hormone medications *[234, 236]*. Some sex hormones are also associated with hyperglycemia (e.g. anabolic steroids, estrogens, oral contraceptives) while some induce protein effects (e.g. anabolic steroids) or adversely affect the lipid profile of a patient (e.g. danazol, progestogens) *[234, 259, 260, 265, 268]*. In literature it is stated that orally administered estrogens and anabolic steroids can cause profound, dose-related

effects on lipoprotein metabolism, while oral estrogens are known to increase serum triglyceride levels. Oral contraceptives (e.g. newer low-dose triphasic oral contraceptives) do not have any appreciable alterations in lipid profiles, but combined oral contraceptives containing 2nd generation progestogens can adversely affect the lipid profile of a patient *[57, 234, 265]*.

Sodium and water retention are common side effects of **corticosteroid**s too, thus patients should take these drugs under similar dietary recommendations (i.e. with food and a sodium-restricted diet). Except for fluid and electrolyte imbalances from corticosteroids use, the use of glucocorticoids (e.g. prednisolone, prednisone) can result in a negative nitrogen balance, so increased dietary protein intake is important to help maintain a positive balance of nitrogen. Alcohol use with corticosteroids should be avoided because it can produce excessive GI bleeding or gastritis, especially when these drugs are taken on an empty stomach. Given that corticosteroids reduce the absorption of certain nutrients (e.g. calcium, vitamin K, potassium, etc) patients may be advised to increase intake of foods high in these nutrients to avoid deficiencies *[1, 97]*. Patients taking corticosteroids should carefully use certain herbal supplements because their co-ingestion can interfere with the drug effects or can lead to serious adverse effects; for example concurrent use of corticosteroids with *Echinacea spp.* could offset or minimize drug's effects *[181, 213]*, while ginseng in concurrent use with corticosteroids may cause additive effects *[213]*. Moreover, weight gain is a known adverse effect of corticosteroid medications, whereas corticosteroid therapy (mainly with glucocorticoids) has been associated with hyperglycemia and/or new-onset diabetes and the induction of protein effects after high-dose/long-term treatment (including use of inhaled corticosteroids) *[234, 236, 263, 269]*.

As far as preparations for thyroid dysfunctions are concerned, patients should generally take **thyroid drugs** (e.g. levothyroxine-a drug with a narrow therapeutic index) once a day in the morning and at the same time every day, on an empty stomach (at least one-half hour to one hour before eating any food) because food intake may decrease drug absorption. Iron supplements and soy products taken at the same time as thyroid hormone replacement therapy may also interfere with the absorption of thyroid drugs *[1, 229, 293, 294]*. Moreover, high-fiber diets (e.g. wheat bran) have been found to decrease levothyroxin bioavailability in patients with hypothyroidism, through a mechanism involving nonspecific adsorption of the drug to dietary fibres. In such cases hypothyroid patients may therefore need larger than expected doses of thyroxine *[31, 67]*. Grapefruit juice in the case of levothyroxine may slightly delay drug absorption, but it seems to

have only a minor effect on its bioavailability. Therefore, the clinical relevance of the grapefruit juice-levothyroxine interaction is likely to be small *[4, 295]*. Thyroid products may also cause changes in the nutritional status of a patient by inducing metabolic effects; they have been implicated in the induction of hyperglycemia *[234, 260]* On the other hand**, antithyroid drugs** have been reported to cause calcium depletions (hypocalcemia), whereas iodine-foods should be ingested cautiously because even a slight increase in dietary iodine can result in a decreased efficacy of antithyroid treatment (e.g. in patients with Graves-Basedow disease-induced hyperthyroidism) *[234, 270, 296]*.

With regard to the **osteoporosis drugs** bisphosphonates and food intake, their interaction is considered to be of high clinical significance, since bisphosphonates have an exceptionally high affinity for chelation with components in food, with a consequent reduction in their bioavailability and a high risk of treatment failure. For example, the absorption of alendronate is impaired by food, calcium and almost everything including orange juice and coffee. Therefore it is recommended to be taken first thing in the morning with plain water to prevent the formation of chelates which significantly reduce drug bioavailability. The patients must be sitting or standing up when taking alendronate but do not lie down for at least 30 minutes after taking the drug. They must also not consume any food for at least 30 minutes after taking the drug and must not lie down until they eat the first food of the day *[52, 97, 229]*. Concurrent use of this drug with mineral water containing high levels of metal cations (in particular calcium) must be avoided *[177]*. Alendronate may cause severe GI bleeding and/or ulceration and oesophagitis *[5]* and nutrient depletions such as hypocalcemia, and hypophosphatemia *[234, 270]*.

Finally, in reference to **dermatological agents**, isotretinoin for instance is a drug which its bioavailability is increased when taken with food (due to its increased solubility), especially with a high fat content given that it is a lipophilic drug. Patients though, should take this drug with a consistent relationship to meals because isotretinoin dosage is titrated according to drug effect and the appearance of adverse effects *[44, 52]*. Moreover, isotretinoin it is found to elevate triglyceride levels and to compete with vitamin A, thus vitamin A supplements should be avoided when taking this drug *[1, 57, 265]*.

Much more can be said about the effects of food-drug interactions and the dietary recommendations for patients to follow when taking specific drugs, in order to avoid serious adverse effects and/or treatment failure. However, the present diploma thesis can only be a reference for basic information upon food-drug interactions and their impact on pharmacotherapy.

6. DISCUSSION

Over the past few years, the occurrence of food-drug interactions has been an intriguing topic for the scientific community *[1, 2]*. The widespread use of medicines in combination with the extensive variability in dietary habits, food composition, use of dietary supplements and nutritional status of a patient, create the conditions in which food-drug interactions are likely to happen. These interactions are related to alterations in the disposition and effect of the drug or food/nutrient *[3]*. The theoretic potential for interactions between food and drugs is almost innumerous, but it is unclear how many are clinically significant *[29]*.

Many decades ago, reference works in literature hardly mentioned the potential for interaction between drug therapy and nutrition *[3, 297]*. This began to change with publication of isolated reports which are now considered classic findings *[3, 8, 9]* such as: the influence of vitamin C deficiency on barbiturate action *[298]*, the influence of isoniazid on vitamin B_6 metabolism *[299]* and the influence of iron on tetracycline absorption *[300]*. Classic reviews also followed on the effect of food on drug absorption *[301]*, the impact of malnutrition on drug metabolism *[302]* and the influence of drugs on nutrient disposition *[303]*. By that time, the most clinically recognized interactions were the more obvious intraluminal interactions between drugs and food *[300, 301]*, while the updates that followed often repeated the same lists of examples without always putting them into clinical or mechanistic perspective *[3]*. In contemporary literature, the topic of food-drug interactions has been reframed, providing a more systematic approach to identifying and evaluating them *[3, 7, 9, 13, 29]*. Despite the some progress that has been made in recognizing and understanding several mechanisms of food-drug interactions, data on how best to prevent or manage individual interactions still remain inadequate at this time *[3, 9]*.

The present diploma thesis, since it is not intended to be a systematic review of all the available literature, it re-introduces the topic of interactions between drugs and foods, including examples of specific foods and food components that induce effects on specific drugs, as well as examples of specific drugs or classes of drugs that induce effects on nutritional status. More specific, food choices including: specific vegetables and fruits (e.g. green leafy vegetables and cruciferous vegetables, red peppers, avocado, potatoes, eggplants, grapes, apples, black raspberries & mulberries), citrus fruit juices (e.g. grapefruit, Seville orange, tangerine, lime, pummelo, pomegranate and cranberry juices),

beverages (e.g. caffeinated, milk & milk-based, alcoholic, mineral waters), vitamin and mineral supplements (e.g. vitamin C, vitamin B_6, Fe, Zn, K), herbal supplements (e.g. *Hypericum perforatum, Valeriana officinalis, Ginkgo biloba, Panax ginseng, Glycyrrhiza glabra, Echinacea spp., Allium sativum, Camellia sinensis*), tyramine-based foods and dietary proteins, carbohydrates, fibre and fat, may affect the pharmacokinetics of drugs and have a unique influence on drug disposition. On the other hand the changes in overall nutritional status of a patient due to food-drug interactions can be multifactorial and may concern: alterations in body weight and growth, alterations in oral cavity and taste perception (e.g. xerostomia or unpleasant drug taste can lead to altered food choices or decreased food intake), decrease or prevention of nutrient absorption (i.e. due to nausea, emesis or GI motility disturbances), alterations in macronutrient metabolism (e.g. glucose or lipid metabolism) or depletion in essential micronutrients (e.g. electrolytes, vitamins and minerals).

In a mechanistic manner food-drug interactions: can involve changes in relevant parameters (e.g. bioavailability, volume of distribution, clearance); in these interactions the activity of transporters and enzymes is important for the drug or nutrient absorption, distribution, metabolism and excretion (i.e. pharmacokinetics), can involve the clinical effect of a drug or the physiologic effect of a nutrient (i.e. pharmacodynamics) and these interactions can be antagonistic (e.g. warfarin with vitamin K intake has impact on the anticoagulant effects of drug) or additive in effect (e.g. valerian prolongs pentobarbital-induced sleep), or may involve physicochemical reactions in a delivery device or within GI lumen (i.e. pharmaceutics); these interactions can influence drug or nutrient bioavailability (e.g. the significantly reduced bioavailability of ciprofloxacin due to chelation in enteral feeding formulas) *[3, 8, 44, 192, 274,280, 281]*.

Given that food and drugs share several pharmacokinetic and pharmacodynamic characteristics and can interact in a variety of mechanisms, food-drug interactions can impact the effectiveness of pharmacotherapy (by either reducing or enhancing the therapeutic response) and thus result in partial or total failure of drug therapy (although the latter is quite rare) or cause adverse drug events or may even precipitate toxicities *[12*, 29]. Among the phases in which food may interact with a drug, absorption and metabolism are the stages where food has most effect *[31]*.

The influence of food intake in drug kinetics is principally a matter of the design of the pharmaceutical formulation *[31, 52, 54]*. However, various other factors that can modify drug bioavailability include: meal timing in relation to time of drug administration (e.g.

administration in the fasted or fed state can differently affect drug disposition), size of meals (i.e. it may affect the time taken for gastric emptying), the composition of meals (i.e. carbohydrates, fats, proteins and fibres), the physicochemical properties of the drug (e.g. lipophilicity or hydrophilicity of the drug) and dose size *[31, 44, 45, 52]*.

The cytochrome P-450 enzyme system is very important for many food–drug interactions, while effects on transporters (e.g. P-glycoprotein (P-gp), OATP transporter family) are also important for some drugs and dietary components. Both drugs and food components can alter the activity of these enzymes and so they can greatly influence the bioavailability and clearance of food components and drugs respectively *[1, 2, 10]*. In particular, the pharmacokinetic effects of fruit/vegetable/herb interactions with drugs are mediated by phytochemicals, which can inhibit or induce the activity of one or more of the CYP enzymes and/or the function of transporter proteins (that are principal determinants in the absorption, distribution, and elimination of the drugs), thus having effects on the drugs that are substrates for the affected proteins (e.g. drugs which are CYP and/or P-gp substrates). Pharmacodynamic interactions also result from phytochemicals whose pharmacological action either diminishes or exacerbates drug effects by mechanisms unrelated to altered metabolism or transport *[137]*.

Interactions are considered clinically significant if they alter therapeutic drug response and/or compromise nutritional status, while they are no less important than drug-drug interactions in their ability to influence patient outcome *[8]*. Food-drug interactions involving drugs with narrow therapeutic indices (e.g. tacrolimus, cyclosporine, digoxin, phenytoin, carbamazepine, lithium, theophylline, levothyroxine) and drugs where dosage and blood levels require careful control (e.g. warfarin) are expected to be the most clinically significant *[29, 40]*.

The clinical significance of a pharmacokinetic or a pharmacodynamic food-drug interaction can be highly dependent on the individual patient *[10]*. Patients particularly at risk are elderly patients, patients with chronic diseases or cancer HIV/AIDS, fetuses, infants and pregnant women, etc *[7, 12, 29, 46]*, while the risk for experiencing significant interactions may depend on several factors (e.g. age, gender, medical history, polypharmacy, nutritional status, etc) *[1, 5-7]*. Moreover, physiologic occurrence of a food-drug interaction may differ based on genetic polymorphisms of proteins involved in drug pharmacodynamics and pharmacokinetics (e.g. the cases of warfarin resistance and slow inactivation of isoniazid or phenelzine) which are likely to be the most important sources of individual variability in drug efficacy *[5, 9, 48, 271]*.

The extent and clinical significance of food-drug interactions can display considerable variation. For several drugs the interaction with food is not accompanied by any significant change in clinical effects (e.g. furosemide, pravastatin). However, for other drugs the food-induced changes in the bioavailability of the drug are considered to be clinically significant. The most important interactions are those reflecting a high risk of treatment failure owing to a significantly reduced drug bioavailability (e.g. indinavir and bisphosphonates which must be taken without food because drug administration in the fed state is associated with high risk of treatment failure). For some other drugs, concurrent food intake may increase drug bioavailability and thereby drug effect (e.g. saquinavir, which must be taken with meals or at a consistent time with respect to meals because food increases drug dissolution) *[44]*.

The interactions that significantly reduce the bioavailability of some drug are often caused by chelation with dairy products (e.g. tetracycline, norfloxacin, ciprofloxacin) or chelation with other components in food (e.g. tetracycline, norfloxacin, ciprofloxacin, didanosine, alendronate,) or by other direct interactions between the drug and certain food components (e.g. indinavir, mercaptopurine, levodopa) *[1, 6, 44, 52,97, 229]*. Additionally, for some drugs the poor acid lability in response to food intake, due to exposure to acid and prolonged gastric residence, leads to chemical degradation and reduced bioavailability with risk of therapeutic failure (e.g. azithromycin, erythromycin, ampicillin, isoniazid, didanosine). On the other hand, the interactions that increase drug bioavailability are often caused by a food-induced increase in drug solubility (e.g. saquinavir, lovastatin, albendazole, isotretinoin) or by the secretion of gastric acid, since reliable absorption depends on acid environment (e.g. itraconazole capsules, ketoconazole) or bile acid which enhance drug dissolution (e.g. griseofulvin, halofantrine) in response to food intake. The bioavailability of lipophilic drugs is often increased by a high fat intake (e.g. albendazole, griseofulvin, halofantrine). For most drugs, such an increase results in a desired increase in drug effect, but in others it may result in serious toxicity (e.g. halofantrine) *[44, 52]*.

Moreover, in some food-drug interactions, food intake can affect the bioavailability of the drug or serious side effects can occur either by direct antagonism (e.g. warfarin with vitamin K) *[1, 44, 97, 98, 280, 281]* or by physical binding/adsorption (e.g. digoxin bioavailability is reduced because of binding to fibre and levothyroxin bioavailability is decreased due to nonspecific adsorption of the drug to dietary fibres) *[31, 44, 52, 57, 67]* or by inhibited deamination of dietary pressor amines (e.g. MAOIs antidepressants with tyramine foods can result in hypertensive crisis) *[52, 55, 224, 225, 226]* or by sudden

delivery of a substantial part of the dose (e.g. in theophylline older preparations food intake increases drug bioavailability resulting in increased theophylline concentrations and possible toxicity) *[31, 44, 97]* or by pharmacodynamic interactions (e.g. severe hyperkalemia due to the concomitant use of ACE inhibitors or potassium-sparing diuretics with potassium-rich foods) *[1, 44, 52, 229, 283]*.

Alcohol affects body processes and interacts with almost every medication, thus it should be avoided while on pharmacotherapy, especially with all psychotropic medications sedatives and hypnotics as well as other drugs such as narcotic analgesics, anticolvusants, antihistamines, corticosteroids and theophylline, as it can result in serious side effects and toxicities (e.g. disulfiram-like reactions associated with concurrent use of some cephalosporin antibiotics, griseofulvin, ketoconazole, procarbazine and sulfonylureas) *[1, 4-6, 52, 55, 97, 229]*. The use of caffeine on the other hand must be avoided or limited in many cases of drugs, but especially with theophylline or agents affecting the nervous system *[4, 5, 57, 97, 229]*.

Several herbal supplements are known or suspected of interacting with medicines; while some can increase the risk of serious side effects (e.g. use of hepatoxic drugs such as amiodarone, methotrexate and ketoconazole with *Echinacea spp*. could cause hepatotoxicity or the concomitant use of anticoagulant & antiplatelet agents with *Ginkgo biloba* can increase the risk of serious bleeding events) *[137, 192, 208, 209, 213]*. St John's wort (*Hypericum perforatum*) is the better known for its capacity to interact with drugs, given that can significantly affect the absorption or metabolism of various drugs that are CYP3A4 and/or P-gp substrates (e.g. indinavir, cyclosporine, tacrolimus, warfarin, digoxin, carbamazepine, theophylline, simvastatin, methadone) consequently affecting their bioavailability and efficacy or affecting their clearance and producing serious side-effects (e.g. norethindrone), or can interact based on the drugs' pharmacodynamic properties (e.g. paroxetine, sertraline, trazodone, nefazodone) causing symptoms consistent with that of excess serotonin or serotonin syndrome *[137, 191, 192, 195, 198-200]*.

Among citrus fruit juices, grapefruit juice has become perhaps the best known food-drug interaction as it possess high interaction with almost all types of drugs *[4]*. Grapefruit primarily affects the metabolism of numerous drugs that are metabolized by intestinal CYP3A4, thus increasing their oral bioavailability *[55, 81,136]*. Apart from CYP3A4 inhibition grapefruit components may also affect drugs that are P-gp or OATP substrates *[4, 122, 137, 140]*. Specifically, its active components furanocoumarins have been shown to increase the oral bioavailability of drugs like felodipine, midazolam, cyclosporine (that

are CYP3A4 substrates) and raise their concentrations above toxic levels, with cyclosporine-grapefruit interaction having the highest clinical significance *[4, 96, 137,138, 273]*. Other interactions which may be clinically significant occur with atorvastatin, simvastatin, carbamazepine and possibly tacrolimus *[273]*. Grapefruit effects are long-lasting so it is not needed to be taken simultaneously with drugs in order for an interaction to be produced *[81]*.

It is vital taking into consideration the possible clinical implications when using drugs with or without a meal *[52]*. Thus, dietary recommendations are needed for drugs because food-drug interactions may adversely affect pharmacotherapy. With some medicines it is prudent to take them with food or at a consistent time with respect to meals so as to prevent GI irritation or adverse fluctuations in drug concentrations while for other drugs it is vital to avoid co-administration of food and drug because food can make the drug less effective or can lead to serious side-effects and toxicities *[1, 6, 44, 52, 229]*.

The knowledge of the possible interactions between prescription /over-the-counter drugs and foods/nutrients is of great importance, since it enhances the everyday practice of the medical doctors, the dieticians and the pharmacists in the clinical setting *[2]*. Pharmacists in particular, it is essential to be alerted to monitor and to keep up-to-date on potential food-drug interactions of medications, especially today's new drugs, so that they can give proper counseling to the patients and advise them which foods, beverages or dietary supplements to avoid when taking certain medications. The role of pharmacists to discuss potential side effects and give instructions on how to take a medication is a valuable task, since it is very important to provide information to patients on when to take their medications in relation to food intake so as they receive full therapeutic benefit from their drugs and avoid experiencing adverse side effects or toxicity *[97]*. However, interdisciplinary collaboration among medical scientists (i.e. doctors, dietetic experts, herbalists, pharmacists) needs to be improved and encouraged, because the knowledge of how dietary factors can improve or decrease drug efficacy can help to design an optimal differentiated and individualized treatment *[181]*. Moreover, a systematic understanding of the gene systems that modulate response to medications may change the way medications are prescribed, since checking the genetic background of a patient can ensure that the prescribed medications are effective and free from side effects *[51]*. Finally, the awareness of all the factors involved can help to design drugs, nutrition diets, and herbal therapies for individual patients, avoiding adverse reactions and promoting healing and health *[181]*.

7. CONCLUSION

In the present diploma thesis, the information obtained from literature indicated that several foods which are commonly consumed can interact in a variety of mechanisms with prescription or over-the-counter medicines, given that foods and drugs share several pharmacokinetic and pharmacodynamic characteristics. Specific foods which can affect drug pharmacokinetics and thus drug disposition, as well as drugs which can affect the nutritional status of a patient, were described in detail.

Interactions between foods and drugs may have an impact on each pharmacotherapy, as they may inadvertently reduce or increase the effect of a drug. By a negative aspect, food-drug interactions can lead to serious side effects, toxicities or therapeutic failure. Generally, the effects of food on drugs result in an alteration in drug bioavailability, but food can alter drug clearance too. In addition, the effect of drug on food intake can affect the nutritional status of a patient either as a result of the drug's mechanism of action or by its adverse effect profile. By a positive aspect, food-drug interactions can lead to enhanced therapeutic drug effects or diminished potential side effects.

Grapefruit juice-drug interactions and St John's wort-drug interactions are perhaps the best known food-drug interaction, as grapefruit juice and St John's wort can each significantly affect the bioavailability of various drugs, along with MAOIs-tyramine food interactions which can lead to severe hypertensive crisis. Other well-described interactions include warfarin-vitamin K interactions, certain antidiabetic drugs-induced hypoglycemia and certain psychotropic drugs-induced weight gain. Disulfiram-like reactions are also among the best known interactions of drugs with alcohol.

The most important food-drug interactions are those reflecting a high risk of treatment failure owing to a significantly reduced drug bioavailability in the fed state, while food-drug interactions involving drugs with narrow therapeutic indices and drugs where dosage and blood levels require careful control are expected to be the most clinically significant.

The knowledge of confirmed or possible interactions between drugs and foods or nutrients can enhance the work of medical scientists in the clinical setting. Dietary recommendations should be provided to patient using drugs, because the awareness of the possible clinical implications when taking drugs with or without a meal is important in order for patients to receive full therapeutic benefit from their drugs and avoid adverse implications in pharmacotherapy.

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APPENDIX

Compilation Table A. ***Examples of specific foods and their effects on drugs***

DRUGS (GENERIC NAMES)	FOOD THAT INTERACTS	EFFECT OF FOOD ON DRUGS
ANALGESICS, ANTI-INFLAMMATORIES & ANTIPYRETICS		
acetaminophen (paracetamol synonym)	-cruciferous vegetables -caffeine -vitamin C supplements -ethanol	-significantly enhance conjugation [89] -slightly positive influence on the absorption rate of the drug [161] -in high dose may reduce sulfate conjugation by competing for available sulfate[55, 179, 180] -risk of severe side effects (hepatotoxicity)[5]
antipyrine (phenazone synonym)	-carbohydrate diets -protein-enriched diets -cruciferous vegetables	-decreased metabolism [57, 60] -increased metabolism [57, 60] -significantly enhance oxidative metabolism [55,88]
meperidine	-tyramine-containing food	-tyramine reactions [55]
methadone	-St John's wort -grapefruit juice	-reduces the efficacy of the drug [191,195] - may increase drug serum concentrations and the risk of adverse effects[273]
morphine sulfate	-ethanol/ alcoholic beverages	-the drug can dissolve rapidly, delivering a potentially fatal dose of morphine [5]
narcotic analgesics in general	-ethanol/ alcoholic beverages	-can produce severe or fatal side effects [1, 5, 6, 229]
oral salicylate	-red peppers	-reduction of drug bioavailability[81,107]
phenacetin	-cruciferous vegetables	-significantly enhance oxidative metabolism [55,88]
salicylamide	-vitamin C supplements	-in high dose may reduce sulfate conjugation by competing for available sulfate[55, 179, 180]
suprofen	-milk/dairy products	-may decrease drug bioavailability [172]
ANTHELMINTICS		
albendazole (lipophilic)	-high-fat content	-increased drug solubility & increased bioavailability which enhances its chemo-sterilant properties against systemic parasitic infections [44, 275, 276]
ANTIBACTERIALS		
amoxicillin	-high-fibre diets	-reduced bioavailability[44]
antibiotics in general	-vitamin C supplements	-may diminish antibiotic activity [181]
benzylpenicillin	-Seville orange juice	-inhibition of OATP-B & decreased blood concentrations [33,81]

certain cephalosporins (e.g. cefotetan, cefoperazone)	- ethanol/ alcoholic beverages	-can cause disulfiram-like reactions [1 ,5, 55]
ciprofloxacin	-Seville orange juice -milk/dairy products -mineral supplements (Fe & Zn)	-slightly reduces drug absorption [33, 81] -may decrease drug bioavailability [174] -form insoluble complexes with drug & significantly impair drug absorption [185, 186]
erythromycin	-grapefruit juice	-increased oral bioavailability [81, 136]
isoniazid	-tyramine-containing food	-potential reaction when isoniazid is combinated with tricyclic antidepressants[55, 230]
levofloxacin	-Seville orange juice	-slightly reduces drug absorption [33, 81]
linezolid	-tyramine-containing food	-potential interactions [55, 231]
norfloxacin	-milk/dairy products -mineral supplements (Fe)	-may decrease drug bioavailability [173] -form insoluble complexes with drug & reduce drug absorption [185]
ofloxacin	-mineral supplements (Fe)	-form insoluble complexes with drug & reduce drug absorption [185]
phenoxymethylpenicillin	-fibre	-reduced bioavailability[44]
tetracycline	-mineral supplements(Zn) -milk/dairy products	-may reduce absorption of the drug [184] -may decrease the absorption & reduce the bioavailability of the drug [171]
ANTIDEPRESSANTS		
antidepressants in general	-ethanol/ alcoholic beverages	-concurrent use of ethanol can add to the side effects caused by these drugs[1, 5, 6, 97, 229]
lithium	-salt	- a low-salt diet increases the risk of lithium toxicity while excessive salt reduces the efficacy of the drug [57, 97, 229]
lithium salts	-high-fibre diets	-decreased bioavailability [57]
MAOIs in general	-tyramine-containing food -ethanol/alcoholic drinks, caffeine & chocolate	- high risk of hypertensive crisis (tyramine reactions) [55 ,224, 225, 226] - can act like tyramine and should be avoided or consumed in moderation [1, 229]
nefazodone	-St John's wort	-excess serotonin/serotonin syndrome[199, 200]
paroxetine	-St John's wort	-excess serotonin/serotonin syndrome[199, 200]
phenelzine sulfate	- *Panax ginseng* - high-tyramine foods	-induce headaches, tremulousness and manic episodes in treated patients [55, 181, 212, 213] - phenelzine slow inactivation increases the risk of hypertensive crisis if high-tyramine foods are consumed [5]
sertraline	-St John's wort -grapefruit juice	-excess serotonin/serotonin syndrome[199, 200] -increased oral bioavailability [81, 136]
trazodone	-St John's wort	-excess serotonin/serotonin syndrome[199, 200]

ANTIDIABETICS		
antidiabetic therapy in general	-red peppers -ethanol	-capsaicinoid-induced glucose changes, potential interactions[81, 108] - acute ethanol ingestion can alter carbohydrate metabolism & cause hypoglycemia[1]
glibenclamide	-Seville orange juice	-inhibition of OATP-B & reduction of intestinal absorption [135]
sulfonylureas	-ethanol	-can cause disulfiram-like reactions [55] while chronic ethanol use can cause increased hepatic drug metabolism & hyperglycemia[1]
ANTIEPILEPTICS		
anticolvusants in general	-ethanol	it can add to the side effects caused by these medicines, thus should be avoided[1, 5, 229]
carbamazepine	-St John's wort -grapefruit juice -pomegranate juice	-reduces the efficacy of the drug [191,195] -increases oral bioavailability which can lead to risk of adverse effects [81, 136, 273] -inhibits the CYP3A-mediated metabolism of the drug[154]
gabapentin	-protein	-enhanced absorption [31]
phenobarbital	-ethanol/ alcoholic beverages	-may cause excessive drowsiness, incoordination and other signs of CNS depression [5]
phenytoin	-vitamin B_6 supplements -folic acid supplements -enteral feeding	-induces metabolism up to 50%, affecting the efficacy of the drug [181, 183] -can cause decreased anticonvulsant efficacy if not administrated cautiously [1] - high risk of treatment failure & sudden toxicity when enteral feeding is discontinued without drug dosage reduction [44, 289]
ANTIFUNGALS		
griseofulvin (lipophilic)	-high-fat content	-stimulation of bile secretion & increased bioavailability[44]
itraconazole	-grapefruit juice -acidic beverages (cola drink)	- may lead to decreased oral bioavailability, thus in an increased risk of drug failure[273] -co-administration in patients especially those with AIDS, may improve drug bioavailability [169]
ketoconazole	-high-fat meals -high-carbohydrate meals -*Echinacea spp.* -acidic beverages (cola drink)	-increased bioavailability [44, 70] -reduced bioavailability[44, 70] -could cause hepatotoxicity[213] -co-administration in patients may improve drug bioavailability [168]
ANTIGOUT DRUGS		
allopurinol & its major metabolite oxypurinol	-low-protein diets	-reduced renal tubular transport, decreased renal clearance & increased likelihood of adverse effects [55, 80]

ANTIHISTAMINES		
antihistamines in general	- ethanol/ alcoholic beverages	- concurrent use may increase the central nervous system depressant effects of these drugs[6, 97]
fexofenadine	-grapefruit juice & its components -apple juice -Seville orange juice	-when ingested concomitantly can reduce oral bioavailability of the drug [4, 122, 137] -reduction of OATP transporters activities & significant reduction in oral drug bioavailability[121, 122] -preferential direct inhibition of OATP activity & significant reduction in oral bioavailability[122]
terfenadine	-grapefruit juice	-increased oral bioavailability [81, 136] -has been voluntarily removed from the USA market but remains available in several other countries [44, 292] -a death event has been ascribed to this drug-grapefruit interaction[44, 292]
ANTIMALARIALS		
halofantrine (lipophilic)	-high-fat content	stimulation of bile secretion & very significantly increased bioavailability, probably leading to cardiotoxicity[44]
ANTINEOPLASTICS		
estramustine phosphate	-milk/dairy products	-may decrease drug bioavailability [176]
imatinib	-St John's wort	-reduces the efficacy of the drug [191,195]
mercaptopurine	- cow's milk	-concurrent intake may potentially reduce drug bioavailability [4, 277]
methotrexate	-*Echinacea spp.* -ethanol	-could cause hepatotoxicity[213] -risk of hepatotoxicity[5]
procarbazine	-tyramine-containing food -ethanol	-interaction that causes hypertension in patients treaded for Hodgkin's disease [55,232] -can cause disulfiram-like reactions [5, 55]
ANTIPARKINSONIANS		
levodopa	-high-fibre diets -low protein diet -high protein meal -vitamin B_6 -mineral supplements (Fe)	-increase bioavailability in patients with Parkinson's disease & severe constipation [44, 69] -in Parkinson's disease reduces unpredictable fluctuations in drug response [55, 76, 77] -can reduce the cerebral uptake of drug and potentially reduce its clinical efficacy [52] -can reduce or abolish drug effects[29] -cause chelation of drug & can potentially lead to reduced control of Parkinson's disease [29, 189]

ANTIPROTOZOALS		
furazolidone	-tyramine-containing food	-tyramine reactions [55]
ANTIVIRALS		
indinavir	-St John's wort -vitamin C supplements	-reduces the efficacy of the drug[137,191, 195,198] -in high doses may reduce steady-state indinavir plasma concentrations [55, 182]
saquinavir	-grapefruit juice -garlic	-increased oral bioavailability [81, 136, 273] -decreases systemic exposure & maximum concentrations of the drug [191, 192, 217]
zidovudine	-high-fat meals	-decreased absorption whentaken orally[57, 74]
ANXIOLYTIC SEDATIVES HYPNOTICS & ANTIPSYCHOTICS		
alprazolam	-grapefruit juice	- no change in oral bioavailability[136]
anxiolytic, sedatives hypnotics & antipsychotics in general	-ethanol -caffeine	-concurrent use of ethanol can add to the side effects caused by these drugs[1, 5, 6, 97, 229] - caffeine can increase drug blood concentration & cause side effects or can increase anxiety and reduce drug's effectiveness[1, 5, 6, 97, 229]
benzodiazepines in general	-ethanol -caffeine	- use of ethanol should be avoided (can add to the side effects caused by drugs[97, 229] - caffeine increases anxiety and reduce drug's effectiveness[97]
buspirone	-grapefruit juice	-increased oral bioavailability [81, 136]
clozapine	-caffeine	-changes in the habitual caffeine intake can alter the metabolism of drug in schizophrenic patients [163]
diazepam	-ethanol/ alcoholic beverages -grapefruit juice	-may cause excessive drowsiness, incoordination and other signs of CNS depression [5] -increased oral bioavailability [81, 136]
lorazepam	-caffeine	-opposes /counteracts the antianxiety effect of the drug [5]
midazolam	-tangerine juice -grapefruit juice & its components -black raspberry & black mulberry	-may impact drug absorption[148] -increases oral bioavailability & raises drug concentrations above toxic levels[4, 96, 137,138] -inhibit CYP3A -catalyzed midazolam 1-hydroxylation activity in liver microsomes[127]
pentobarbital	- *Valeriana officinalis*	-prolongs pentobarbital- induced sleep [192]
triazolam	-grapefruit juice	-increased oral bioavailability [81, 136]
ziprasidone	-fatty foods	- increased systemic exposure when this drug is taken after fatty foods [44, 291]

BONE MODULATING DRUGS		
alendronate (a bisphosphonate)	-food, calcium, orange juice & coffee	-interacts with almost everything, resulting in reduced bioavailability &high risk of treatment failure [97, 229]
	-mineral water with high levels of calcium	-drug absorption is decreased [177]
BRONCHODILATORS & ANTI-ASTHMA DRUGS		
theophylline	- food intake in general	-with older drug preparations food can increase drug bioavailability & may cause "dose-dumping", resulting in increased drug concentrations & possible toxicity [44]
	-carbohydrate diets	-decreased metabolism [57, 60]
	-protein-enriched diets	-faster absorption [55, 75] & increased metabolism [57, 60]
	- high-fat meals	- may increase drug amount in the body [4]
	- charcoal-broiled meats	- may accelerate drug metabolism, reducing the half-lives of theophylline [1, 57,60]
	-St John's wort	-reduces the efficacy of the drug [191,195]
	-ethanol	-can increase the risk of side effects [4, 5, 97]
	-caffeine/ caffeinated foods and beverages	-faster & more extensive metabolism of the drug in the absence of caffeine [162]
		-eating or drinking large amounts of these while taking theophylline increases the risk of drug toxicity [4, 97]
		-increase the adverse effects of the drug & causes nervousness, tremor & insomnia [5,97]
	- grapefruit juice	-co-ingestion increases drug bioavailability, which may be acceptable with appropriate monitoring and awareness [52]
CARDIOVASCULARS		
amiodarone	-grapefruit juice	-increased oral bioavailability [81, 136]
	-*Echinacea spp.*	-could cause hepatotoxicity [213]
	-ethanol	- risk of severe side effects [5]
amlodipine	-grapefruit juice	- no change in oral bioavailability [136]
anticoagulant & antiplatelet agents in general	- *Ginkgo biloba*	- increased risk of serious bleeding events in concomitant use [137, 192, 208, 209]
atenolol	- Seville orange juice	- moderately reduces drug bioavailability [145]
atorvastatin	- grapefruit juice	-increased oral bioavailability resulting in increased risk of side effects [81, 136, 273]
captopril	- potassium-rich foods or salt substitutions	- drug-induced hyperkalaemia can be aggravated by intake of such foods [1, 229]
celiprolol	- Seville orange juices	-substantially reduce drug bioavailability [146]
clopidogrel	- garlic	- may increase the risk of bleeding [192]

digoxin	- fiber-rich meals	- significantly reduce drug bioavailability which may result in treatment failure [44,57,68]
	-St John's wort	-reduces the efficacy of the drug [137, 191,195]
	-Seville orange juice	-inhibition of OATP-B & decreased blood concentrations [33, 81]
	- *Panax ginseng*	-may interfere with digoxin monitoring or with digoxin pharmacodynamically [213]
	- *Glycyrrhiza glabra*	-may interfere with digoxin monitoring or with digoxin pharmacodynamically [213]
diltiazem	-grapefruit juice	-no change in oral bioavailability[136]
enalapril	-grapefruit juice & its components	- mediate pharmacokinetic drug interactions due to their capability of esterase inhibition[4, 139]
felodipine	-Seville orange juice	- markedly increases drug exposure[81, 142]
	-pummelo juice	-inhibiting CYP3A and/ or P-gp activity & increases oral bioavailability [136, 150]
	-lime juice	-inhibition of CYP3A4 enzymes activity & impact on drug bioavailability[29, 136, 149]
	-grapefruit juice & its components	-increase oral bioavailability & raise drug concentration above toxic level[4, 96, 137,138, 273]
heparin	-broccoli, spinach, other green leafy vegetables	- high in vitamin K, counteract drug effectiveness [97,98]
hydrochlorothiazide	-high-carbohydrate meals	- can decrease gastric emptying time, leading to increased drug absorption [1]
	- *Glycyrrhiza glabra*	- natural licorice use should be avoided [1]
	-sodium in foods	- patients should eat foods low in sodium [1]
lovastatin	-fiber-rich meals	- decrease absorption and increase the risk of treatment failure [31, 44, 57, 66]
	-grapefruit juice & its components	-mediate pharmacokinetic drug interactions due to the capability of esterase inhibition[4, 139] while excessive juice ingestion can increase drug bioavailability leading to drug accumulation & adverse effects [4, 44, 139]
metoprolol	-high-protein meals	- enhanced hepatic blood flow & drug bioavailability[57]
	-sodium and/or calcium in foods	- a low sodium and low calcium diet should be followed[1]
nifedipine	-grapefruit juice	- can increase oral drug bioavailability leading to a risk of unwanted effects [52, 273]
	-cranberry juice	- inhibits CYP3A-mediated metabolism of the drug [33, 81, 158]
nisoldipine	-grapefruit juice	- increased oral bioavailability [81, 136]
potassium-sparing diuretics in general	- potassium-rich foods (e.g. bananas, spinach)	- concurrent high intake of these foods may result in hyperkalaemia[44, 283]
pravastatin (hydrophilic)	- high-fat meals	- significantly decrease bioavailability [31,73]
	-Seville orange juice	-increase in area under curve (AUC) [33, 81]

pravastatin (continued)	-grapefruit juice	- no change in oral bioavailability[136]
propranolol	-high-protein meals -sodium and/or calcium in foods	- enhanced hepatic blood flow & drug bioavailability[57] -a low sodium and low calcium diet should be followed[1]
simvastatin	-St John's wort -grapefruit juice	-reduces the efficacy of the drug [137, 191,195] -increased oral bioavailability resulting in increased risk of side effects [81, 136, 273]
spironolactone	- *Glycyrrhiza glabra* - potassium-containing salt substitutes	- can offset the pharmacological effect of the drug [213] - excessive use can lead to severe hyper-kalemia & serious cardiac arrhythmia[44,283]
sympathomimetics	-tyramine-containing food	- may exacerbate tyramine reactions [55]
talinolol	- grapefruit juice & its components	- inhibit the P-gp activity modifying the disposition of the drug[4, 140]
ticlopidine	- garlic	- may increase the risk of bleeding [192]
triamterene	-potassium-rich foods, supplements &salt substitutes	- can lead to severe hyperkalemia & serious cardiac side effects [1, 229]
verapamil	-grapefruit juice	- ambiguous; may increase oral bioavailability so result in unwanted effects, or may not affect drug pharmacokinetics[31, 52, 81, 136, 287]
warfarin	- vitamin K foods -broccoli, spinach, other green leafy vegetables - liver -avocado -St John's wort -garlic -green tea -cranberry juice -vitamin A, D, E supplements	- sudden dietary variations can have profound effect on clotting control[44, 280, 281] -high in vitamin K, counteract drug effectiveness [97,98] - pharmacodynamic effects of warfarin may directly be antagonized by liver intake [6, 44] -inhibits the drug effects[33, 81, 112, 113] -reduces the efficacy of the drug [191,195] -may increase the risk of bleeding [192] -source of vitamin K, thus antagonizes the anticoagulant effect of the drug[181, 222, 223] -might inhibite CYP3A4 and/or CYP2C9 enzymes activity & might increase its anticoagulant effect[136, 157] - increase the risk for abnormal bleeding events [280]
warfarin sodium	- *Panax ginseng*	- may alter bleeding time in concomitant use[213]
CHELATORS ANTIDOTES & ANTAGONISTS		
penicillamine	-mineral supplements (Fe)	-reduce the absorption of the drug[187, 188]
CORTICOSTEROIDS		
corticosteroids in general	- *Panax ginseng* -*Echinacea spp.*	-possible additive effects [213] -could offset/minimize drug's effects[181, 213]

corticosteroids in general (continued)	-*Glycyrrhiza glabra* -ethanol	-may potentiate oral & topical corticosteroids [215] - it can produce excessive GI bleeding or gastritis [1]
prednisolone	- *Glycyrrhiza glabra*	-potentiates hydrocortisone activity [181]
DERMATOLOGICALS		
isotretinoin (lipophilic)	-high-fat content -vitamin A supplements	-increased drug solubility & increased bioavailability[44] -drug competes with vitamin A, thus vitamin A supplements should be avoided when taking this drug [1, 57]
GASTROINTESTINALS		
cimetidine, famotidine	-high protein foods, alcohol, caffeine	- patients should limit caffeine and avoid high protein foods and alcohol use, as they can increase stomach acidity [1, 4, 97]
GENERAL ANAESTHETICS		
anesthetic agents for surgery	-garlic oil	-inhibits CYP2E1 activity & on chronic basis use, dosing requirement of the drug may be decreased[191, 192]
thiopental	- *Valeriana officinalis*	-prolongs thiopental- induced sleep [192]
IMMUNOSUPPRESSANTS		
cyclosporine	-red wine -St John's wort -*Echinacea spp.* -pummelo juice -grapefruit juice & its components	-effect on CYP3A4 activity & significantly decrease drug exposure [118-120] -reduces the efficacy of the drug [137,191,192,195] -could offset/minimize drug's effects[181, 213] -inhibiting CYP3A and/ or P-gp activity & increases oral bioavailability [136, 151] -increase oral bioavailability & raise drug concentration above toxic level [4,96,137,138,273]
sirolimus	-grapefruit juice & its components	-potential for increased oral bioavailability[136]
tacrolimus	- grapefruit juice -St John's wort -pummelo juice	- significantly increased plasma concentrations & increased risk of toxicity[273] -reduces the efficacy of the drug [191,192,195] -inhibiting CYP3A and/ or P-gp activity & increases drug blood concentrations [136, 152]
LOCAL ANAESTHETICS		
cocaine	-potatoes, eggplants	-greatly slow drug metabolism [57, 114]
lidocaine	-high-protein meals	-enhanced hepatic blood flow & drug bioavailability[57]
MINERALS, ORALS,TOPICALS		
fluoride	-milk/dairy products	-may decrease drug bioavailability [175]

MUSCLE RELAXANTS		
chlorzoxazone	-watercress	-impairs CYP2E1 activity & drug metabolism[55, 96]
NEUROMUSCULAR BLOCKERS		
mivacurium, suxamethonium	-potatoes, eggplants	-greatly slow drug metabolism [57, 114]
SEX HORMONES & THEIR MODULATORS		
anabolic steroids	-*Echinacea spp.*	-could cause hepatotoxicity[213]
estrogens	- *Panax ginseng* -sodium in foods	-possible additive effects [213] - a sodium-restricted diet should be followed as salty foods increase fluid retention [1, 97]
norethindrone	-St John's wort	-increases the clearance of the drug, producing bleeding after prolonged use [137, 191,195]
oral contraceptives	-*Glycyrrhiza glabra* - sodium in foods	-reaction resulting in adverse effects [181] - a sodium-restricted diet should be followed as salty foods increase fluid retention[97]
STIMULANTS & ANORECTICS		
amphetamine, methylphenidate	-caffeine	-increases the adverse effects of the drug & causes nervousness, tremor & insomnia [5]
THYROIDS & ANTITHYROIDS		
antithyroid drugs in general	- iodine in foods	-even a slight increase in dietary iodine can result in a decreased efficacy of antithyroid drugs [296]
thyroid drugs in general	-iron supplements & soy products	may interfere with the absorption of these drugs [229, 293, 294]
thyroxine/ levothyroxin	-increased wheat bran intake - grapefruit juice	-decreased bioavailability [31, 67] -may slightly delay drug absorption [4, 295]
UROLOGICALS		
sildenafil	-grapefruit juice	-increased oral bioavailability [81, 136]

Compilation Table B. ***Examples of specific drugs and their effects on nutritional status***

DRUGS (GENERIC NAMES)	EFFECT OF DRUG ON NUTRITIONAL STATUS
ANALGESICS, ANTI-INFLAMMATORIES & ANTIPYRETICS	
acetaminophen (paracetamol synonym)	-risk of GI ulceration, bleeding & hepatotoxicity in combination with ethanol[5]
aspirin	-causes severe GI irritation (bleeding, gastritis, ulceration)[5] -causes nutrient depletions (hypokalemia, iron-folic acid-vitamin C- vitamin E deficiencies)[234, 270]
celecoxib	- causes nutrient depletions (folic acid deficiency)[234, 270]
codeine	-can cause decreased GI motility (constipation)[5] -causes nutrient depletions (hypocalcemia)[234, 270]
ibuprofen	-causes severe GI irritation (bleeding, gastritis, ulceration)[5]
indomethacin	-increased risk of hypoglycemic events[253, 257] -causes nutrient depletions (folic acid-iron deficiencies)[234, 270]
ketoprofen	-causes severe GI irritation (bleeding, gastritis, ulceration)[5]
morphine	-can cause decreased GI motility (constipation)[5] -implicated in the induction of hyperglycemia[234, 260]
NSAIDs in general	-severe GI irritation (bleeding, gastritis, ulceration) [5] -induce hypoglycemic events[253, 257] -cause nutrient depletions (folic acid deficiency)[234, 270]
salicylates in general	- induce hypoglycemic events[253, 257]
ANTIBACTERIALS	
aminoglycosides	-cause nutrient depletions (vitamin B_1- vitamin B_2-vitamin B_3- vitamin B_6- vitamin B_{12}- vitamin K deficiencies)[234, 270]
ampicillin	-associated with increased GI motility & diarrhea[5]
broad-spectrum antibiotics in general	-associated with increased GI motility & diarrhea, prolonged use leads to overgrowth of *Clostridium difficile* & production of its toxins[5,252]
cephalosporins	-cause nutrient depletions (vitamin B_1- vitamin B_2-vitamin B_3- vitamin B_6- vitamin B_{12}- vitamin K deficiencies)[234, 270]
cefoperazone	-causes nutrient depletions (vitamin K deficiency)[234, 270]
clarithromycin	-alteration in taste sensation (bitter taste)[5]
clindamycin	-associated with increased GI motility & diarrhea[5]
cefdinir	-associated with increased GI motility & diarrhea[5]
cefotetan	-causes nutrient depletions (hypophosphatemia, vitamin K deficiency)[234, 270]
demeclocycline	-causes nutrient depletions (hypophosphatemia)[234, 270]

ethambutol	-causes nutrient depletions (zinc & copper deficiencies)[234, 270]
erythromycin	- associated with increased GI motility & diarrhea[234]
fluoroquinolones in general	-induce hypoglycemic events [253, 257] -among antibacterials they are consistently associated with the development of hyperglycemia [234, 263] -cause nutrient depletions (vitamin B_1- vitamin B_2-vitamin B_3- vitamin B_6- vitamin B_{12}- vitamin K deficiencies)[234, 270]
gatifloxacin	-induces hypoglycemic events[253, 257] -among fluoroquinolones is the most commonly implicated with hyperglycemia [234, 263]
gentamicin	-causes nutrient depletions (hypocalcemia, hypomagnesemia, hypokalemia)[234, 270]
isoniazid	- associated with xerostomia[234, 249] -causes nutrient depletions (hypocalcemia, vitamin B_3- vitamin B_6 deficiencies)[234, 270]
levofloxacin	- among fluoroquinolones is the most weakly implicated with hyperglycemia [234, 263]
penicillins (carbenicillin , mezlocillin, nafcillin, oxacillin, penicillin G, piperacillin, ticarcillin)	- cause nutrient depletions (hypokalemia)[234, 270]
neomycin	-causes nutrient depletions (iron- vitamin A- vitamin B_{12} deficiencies)[234, 270]
Polymyxin B	-causes nutrient depletions (hypocalcemia,hypokalemia)[234, 270]
sulfonamides in general	- cause nutrient depletions (hypocalcemia, hypomagnesemia, iron- vitamin B_1- vitamin B_2-vitamin B_3- vitamin B_6- vitamin B_{12}- vitamin K deficiencies)[234, 270]
tetracyclines in general	-associated with hypoglycemia[234, 259, 260] -cause nutrient depletions (hypocalcemia, iron- vitamin B_1- vitamin B_2-vitamin B_3- vitamin B_6- vitamin B_{12}- vitamin K deficiencies)[234, 270]
tetracycline hydrochloride	- associated with increased GI motility & diarrhea[5]
tobramycin	- causes nutrient depletions (hypocalcemia, hypomagnesemia, hypokalemia)[234, 270]
ANTIDEPRESSANTS	
amitriptyline	-large weight gain[234,236, 237] -causes xerostomia[5] -can cause decreased GI motility (constipation)[5]
bupropion	-causes/may cause loss of appetite & weight[237]
fluoxetine	-causes/may cause loss of appetite & weight[237] -associated with GI irritation (bleeding and/or ulceration)[5] -causes nutrient depletions (hypokalemia)[234, 270]

imipramine	-large weight gain[234, 237] -associated with xerostomia[234, 249] -can cause decreased GI motility (constipation)[5, 234]
isocarboxazid	cause/may cause loss of appetite & weight[237]
lithium	-large weight gain[234,236, 237] -causes nutrient depletions (hypokalemia)[234, 270] -can cause sodium loss[229]
MAOIs in general	-small weight gain [237]
mirtazapine	-large weight gain[234,236, 237]
nefazodone	-cause/may cause loss of weight[237]
nortriptyline	-associated with xerostomia[234, 249]
SSRIs in general	-can cause hypoglycemia in rare cases (diabetic patients at higher risk than non-diabetics) [261]
sertraline	-causes/may cause loss of appetite & weight[237] -associated with xerostomia[234, 249] -associated with GI irritation (bleeding and/or ulceration)[5]
trazodone	-associated with both weight gain & loss[237] -associated with xerostomia[234, 249]
venlafaxine	-induces severe hypoglycemia from self-intoxication [234, 262]
ANTIDIABETICS	
chlorpropamide	-induce severe hypoglycemia[234, 255, 256] -causes nutrient depletions (hypokalemia)[234, 270]
glibenclamide	-induces severe hypoglycemia[234, 255, 256]
insulin	-favors weight gain[234,236] -common cause of hypoglycemia[234, 255, 256] -causes nutrient depletions (hypokalemia)[234, 270]
metformin	-causes nutrient depletions (vitamin B_{12} deficiency)[234, 270]
rosiglitazone	-induces severe hypoglycemia[234, 255, 256]
sulfonylureas	-favor weight gain[234,236] -common causes of hypoglycemia[234, 255, 256]
thiazolidinediones	-favor weight gain[234,236] -common causes of hypoglycemia [234, 255, 256]
ANTIEPILEPTICS	
carbamazepine	-favors weight gain[237] -adversely affect the lipid profile of a patient[234, 265] -causes nutrient depletions (folic acid deficiency)[234, 270]
felbamate	-causes nutrient depletions (hypophosphatemia)[234, 270]
lamotrigine	-can cause diarrhea & a decrease in appetite, thus induce weight loss and decreased availability of many nutrients [234, 237]
phenobarbital	-adversely affect the lipid profile of a patient[234, 265] -causes nutrient depletions (hypocalcemia)[234, 270]

phenobarbital (continued)	-increases use of vitamin D in the body, so less vitamin D is available for important functions (supplements may be needed)[1, 6] -osteomalacia & rickets may occur in epileptic patients who are taking this drug [1]
phenytoin	-causes alteration in taste sensation (dysgeusia) [5] -implicated in the induction of hyperglycemia[234, 260] -adversely affect the lipid profile of a patient[234, 265] -causes nutrient depletions (hypocalcemia, folic acid- vitamin B_1- vitamin B_{12}- vitamin K deficiencies)[234, 270] -increases use of vitamin D in the body, so less vitamin D is available for important functions (supplements may be needed)[1, 6] -osteomalacia & rickets may occur in epileptic patients who are taking this drug [1]
primidone	-causes nutrient depletions (folic acid deficiency)[234, 270] -increases use of vitamin D in the body, so less vitamin D is available for important functions (supplements may be needed)[1, 6] -osteomalacia & rickets may occur in epileptic patients who are taking this drug [1]
topiramate	-can cause diarrhea & a decrease in appetite, thus induce weight loss and decreased availability of many nutrients [234, 237]
valproate-related products (e.g. valproic acid)	-significant weight gain[234,236, 237] causes nutrient depletions (zinc- selenium - folic acid- vitamin B_3 deficiencies)[234, 270]
zonisamide	-can cause diarrhea & a decrease in appetite, thus induce weight loss and decreased availability of many nutrients [234, 237]
ANTIFUNGALS	
amphotericin B	-associated with GI irritation (bleeding and/or ulceration)[5] -causes nutrient depletions (hypocalcemia, hypokalemia hypomagnesemia)[234, 270]
ANTIHISTAMINES	
brompheniramine	-associated with xerostomia[234, 249]
cetirizine	-associated with xerostomia[234, 249]
cyproheptadine	-known to favour weight gain[234,236] -causes xerostomia[234, 249]
diphenhydramine	-causes xerostomia[5] -can cause decreased GI motility (constipation)[5]
loratadine	-associated with xerostomia[234, 249]
terfenadine	-associated with xerostomia[234, 249]
trimethobenzamide	-associated with xerostomia[234, 249]
ANTIMALARIALS	
quinine	- induce hypoglycemic events[253, 257]

ANTINEOPLASTICS	
aldesleukin	-causes severe mucositis[5] -induces severe nausea and emesis[234, 250]
altretamine	- induces severe nausea and emesis[234, 250]
carboplatin	-causes severe mucositis[5] -induces severe nausea and emesis[234, 250] -causes nutrient depletions (hypocalcemia, hypomagnesemia, hypokalemia)[234, 270]
carmustine	- induces severe nausea and emesis[234, 250] -causes nutrient depletions (hypokalemia)[234, 270]
cisplatin	- causes alteration in taste sensation (dysgeusia) [5] -induces severe nausea and emesis[234, 250] -causes nutrient depletions (hypocalcemia, hypomagnesemia, hypokalemia, hypophosphatemia)[234, 270]
cyclophosphamide	- induces severe nausea and emesis[234, 250]
dacarbazine	- anorexic adverse effect, thus weight loss[234] -induces severe nausea and emesis[234, 250]
dactinomycin	- induces severe nausea and emesis[234, 250]
daunorubicin	- induces severe nausea and emesis[234, 250] -causes nutrient depletions (hypocalcemia)[234, 270]
doxorubicin	- induces severe nausea and emesis[234, 250] -causes nutrient depletions (hypocalcemia,hypokalemia)[234, 270]
epirubicin	- anorexic adverse effect, thus weight loss [234] - induces severe nausea and emesis[234, 250]
erlotinib hydrochloride	- associated with GI irritation (bleeding and/or ulceration)[5]
etoposide	- anorexic adverse effect, thus weight loss [234]
idarubicin	-induces severe nausea and emesis[234, 250]
ifosfamide	-induces severe nausea and emesis[234, 250] -causes nutrient depletions (hypophosphatemia)[234, 270]
irinotecan	-induces severe nausea and emesis[234, 250]
lomustine	-induces severe nausea and emesis[234, 250]
mechlorethamine	-induces severe nausea and emesis[234, 250]
methotrexate	- risk of GI ulceration, bleeding & hepatotoxicity in combination with ethanol[5] -causes nutrient depletions (folic acid deficiency)[1, 6, 234, 270]
mitoxantrone	- induces severe nausea and emesis[234, 250]
paclitaxel	- causes severe mucositis[5]
pentostatin	- induces severe nausea and emesis[234, 250]
streptozocin	- induces severe nausea and emesis[234, 250]

vinblastine sulfate	- associated with GI irritation (bleeding and/or ulceration)[5]
ANTIPARKINSONIANS	
benztropine	- may cause loss of appetite & weight[234,237] - can cause decreased GI motility (constipation)[5, 234]
levodopa	- associated with GI irritation (bleeding and/or ulceration)[5] - causes nutrient depletions (hypokalemia)[234, 270]
orphenadrine	- associated with xerostomia[234, 249]
selegiline	- associated with xerostomia[234, 249]
trihexyphenidyl	-can cause decreased GI motility (constipation)[5, 234]
ANTIPROTOZOALS	
pentamidine	-induce hypoglycemic events[253, 257] -causes nutrient depletions (hypocalcemia, hypomagnesemia)[234, 270]
ANTIVIRALS	
antivirals in general	-can cause nutrient depletions (hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, zinc-copper-vitamin B_{12} deficiencies)[234, 270]
didanosine	-associated with xerostomia[234, 249] -causes nutrient depletions (hypocalcemia, hypokalemia, hypomagnesemia)[234, 270]
indinavir	- adversely affect the lipid profile of a patient[234, 265, 266]
protease inhibitors in general	-may induce hyperglycemia in treated people with or without diabetes [234, 263] -HIV-protease inhibitors adversely affect the lipid profile of a patient[234, 265, 266] -can cause pancreatitis attributable to drug-induced hypertriglyceridaemia [265]
rimantadine	-associated with xerostomia[234, 249]
ritonavir	- may induce hyperglycemia in treated people with or without diabetes [234, 263] - adversely affect the lipid profile of a patient[234, 265, 266]
ANXIOLYTIC SEDATIVES HYPNOTICS & ANTIPSYCHOTICS	
antipsychotics in general	-can elevate triglyceride levels [265]
barbiturates in general	-cause nutrient depletions (vitamin K deficiency)[234, 270]
chlorpromazine	-large weight gain [234,236, 237]
clozapine	-large weight gain [234,236, 237] -can cause decreased GI motility (constipation)[5] -increases the risk of hyperglycemia & Type 2 diabetes when used in people with schizophrenia or schizoaffective disorder[263, 264] -elevates triglyceride levels & can cause pancreatitis attributable to drug-induced hypertriglyceridaemia [265, 267] -causes nutrient depletions (selenium deficiency)[234, 270]

eszopiclone	-alteration in taste sensation (unpleasant metallic taste)[5]
flunitrazepam	-associated with xerostomia[234, 249]
loxapine	-associated with both weight gain & loss[237]
molindone	-causes/may cause loss of appetite & weight[237] -associated with xerostomia[234, 249]
olanzapine	-large weight gain [234,236, 237] -associated with xerostomia[234, 249] -can cause decreased GI motility (constipation)[5] -increase the risk of hyperglycemia & Type 2 diabetes when used in people with schizophrenia or schizoaffective disorder[263, 264]
pentobarbital	-causes nutrient depletions (hypocalcemia)[234, 270]
phenothiazines in general	-cause nutrient depletions (vitamin B_2 deficiency)[234, 270]
oxazepam	-induces severe hypoglycemia from self-intoxication [234, 262]
quetiapine	-small weight gain [237]
risperidone	-minimal to moderate weight gain [237] -increases the risk of hyperglycemia & Type 2 diabetes when used in people with schizophrenia or schizoaffective disorder[263, 264] -causes nutrient depletions (hypokalemia)[234, 270]
thioridazine	-large weight gain [237]
ziprasidone	-small weight gain [234,236, 237]
zotepine	-can cause decreased GI motility (constipation)[5, 234]
BONE MODULATING DRUGS	
alendronate	-cause severe GI irritation (bleeding and/or ulceration) and/or oesophagitis[5] -causes nutrient depletions (hypocalcemia, hypophosphatemia)[234, 270]
BRONCHODILATORS & ANTI-ASTHMA DRUGS	
caffeine	-anorexic properties, associated with weight loss[234] -implicated in the induction of hyperglycemia[234, 260]
ipratropium	-can cause decreased GI motility (constipation)[5]
theophylline	-anorexic properties, associated with weight loss[234] -implicated in the induction of hyperglycemia[234, 260] -causes nutrient depletions (hypokalemia, vitamin B_6 deficiency)[234, 270]
CARDIOVASCULARS	
ACE inhibitors in general	-induce hypoglycemic events[253, 257]
amiloride	-causes nutrient depletions (hypokalemia)[234, 270]
amiodarone	-risk of GI ulceration, bleeding & hepatotoxicity in combination with ethanol[5]

atenolol	-promotes hyperglycemia [234, 263]
atropine	-can cause decreased GI motility (constipation)[5, 234]
Beta-blockers in general	-induce hypoglycemic events[253, 257] -can promote hyperglycemia and/or new-onset diabetes[234, 263] -adversely affect the lipid profile of a patient[234, 265]
bumetanide	-associated with xerostomia[234, 249] -causes nutrient depletions (hypocalcemia, hypokalemia, hypomagnesemia)[234, 270]
calcium channel blockers in general	-associated with hypoglycemia[234, 259, 260]
captopril	-causes dysgeusia (metallic or salty taste) & the loss of taste perception[5] -induce hypoglycemic events[253, 257]
chlorothiazide	-causes nutrient depletions (hypomagnesemia, hypokalemia)[234, 270]
cholestyramine	-causes nutrient depletions (hypocalcemia, hypomagnesemia, hypophosphatemia, iron-folic acid-vitamin A- vitamin B_3- vitamin B_{12}- vitamin D-vitamin E & vitamin K deficiencies)[1, 6, 234, 270]
colestipol	-causes nutrient depletions (iron-folic acid-vitamin A -vitamin B_3-vitamin D-vitamin E & vitamin K deficiencies)[1, 6, 234, 270]
digoxin	-causes nutrient depletions (hypocalcemia, hypomagnesemia, hypophosphatemia,hypokalemia,vitamin B_1 deficiency)[234, 270] - potassium supplementation is often required to prevent hypokalemia and digitalis toxicity [1]
disopyramide	-induces hypoglycemic events[253, 257]
ethacrynic acid	-causes nutrient depletions (hypocalcemia, hypokalemia, hypomagnesemia)[234, 270]
flecainide	-associated with xerostomia[234, 249]
furosemide	-causes nutrient depletions (hypocalcemia, hypokalemia, hypomagnesemia)[234, 270]
hydrochlorothiazide	-promotes hyperglycemia and/or new-onset diabetes[234, 263] -causes nutrient depletions (hypomagnesemia, hypokalemia, zinc deficiency)[234, 270]
loop diuretics in general	-adversely affect the lipid profile of a patient[234, 265] -cause nutrient depletions (vitamin B_1- vitamin B_6-vitamin E deficiencies)[234, 270] - increase urinary excretion of calcium, sodium, potassium and magnesium[1, 6]
metolazone	-promotes hyperglycemia and/or new-onset diabetes[234, 263]
metoprolol	-promotes hyperglycemia [234, 263]
nifedipine	-favors weight gain and fluid retention [1]
pentoxifylline	-associated with xerostomia[234, 249]
potassium-sparing diuretics in general	-cause nutrient depletions (zinc, folic acid)[234, 270]

procainamide	-associated with xerostomia[234, 249] -can cause decreased GI motility (constipation)[5, 234]
propranolol	-favors weight gain[234,236] and fluid retention [1] -induces hypoglycemic events[253, 257] -associated with hyperglycemia and/or new-onset diabetes[234, 263]
sotalol	-causes nutrient depletions (hypokalemia)[234, 270]
sympathomimetic amines	-implicated in the induction of hyperglycemia[234, 260]
thiazide diuretics in general	-promote hyperglycemia and/or new-onset diabetes[234, 263] -adversely affect the lipid profile of a patient[234, 265] - increase urinary excretion of sodium, potassium and magnesium, but decrease urinary excretion of calcium, [1, 6]
thiazide-like diuretics in general	-promote hyperglycemia and/or new-onset diabetes[234, 263]
triamterene	-causes nutrient depletions (hypocalcemia)[234, 270] -can cause hyperkalemia, accompanied by serious side effects [229]
torsemide	-cause nutrient depletions (hypocalcemia, hypokalemia)[234, 270]
verapamil	-associated with hypoglycemia[234, 259, 260]
warfarin	-associated with hypoglycemia[234, 259, 260]
CORTICOSTEROIDS	
corticosteroids in general	-associated with weight gain[234,236] -promote hyperglycemia and/or new-onset diabetes (mainly those with glucocorticoid actions) [234, 263] -induce protein effects after high-dose/long-term treatment [234, 269] -cause nutrient depletions (hypocalcemia, hypomagnesemia, hypokalemia, zinc, folic acid, vitamin E & vitamin K)[97, 234, 270] - sodium, water retention and electrolyte imbalances are common side effects[1]
glucocorticoids in general	- can result in a negative nitrogen balance, so increased dietary protein intake is important to help maintain a positive balance of nitrogen [1] - promote hyperglycemia and/or new-onset diabetes[234, 263]
prednisone	-favors weight gain[234,236] -associated with GI irritation (bleeding and/or ulceration)[5] -can result in a negative nitrogen balance[1]
DERMATOLOGICALS	
acitretin, isotretinoin	-elevate triglyceride levels[265]
GASTROINTESTINALS	
alvimopan	-causes nutrient depletions (hypocalcemia)[234, 270]
antacids & acid blockers in general	- can cause malabsorption of vitamin B_{12}, reduced bioavailability of vitamin B_2, decreased absorption of vitamin A (from aluminum-containing antacids) and other nutrient depletions (hypocalcemia, hypophosphatemia, hypomagnesemia, folic acid, copper & iron deficiency) [1, 6, 57, 234, 270]

bisacodyl	-causes nutrient depletions (hypokalemia)[234, 270] - increases the rate of transit & reduces the absorption of glucose, protein, sodium, potassium and some vitamins [1]
cimetidine	-causes nutrient depletions (hypocalcemia)[234, 270]
cisapride	-associated with increased GI motility & diarrhea[234]
docusate	-causes nutrient depletions (hypomagnesemia)[234, 270]
famotidine	-causes nutrient depletions (hypocalcemia)[234, 270]
granisetron	-associated with xerostomia[234, 249]
hyoscyamine	-can cause decreased GI motility (constipation)[5, 234]
isopropamide	-can cause decreased GI motility (constipation)[5, 234]
laxatives in general	- excessive use can deplete vitamins and minerals needed for normal body function [6] - they increase fluid losses which may lead to dehydration [6]
mesalamine	-associated with xerostomia[234, 249]
metoclopramide	-associated with increased GI motility & diarrhea[234]
nizatidine	-associated with xerostomia[234, 249] -causes nutrient depletions (hypocalcemia)[234, 270]
ondansetron	-associated with xerostomia[234, 249] -causes nutrient depletions (hypokalemia)[234, 270]
phosphates	-cause nutrient depletions (hypocalcemia, hypomagnesemia, hypokalemia)[234, 270]
propantheline	-associated with xerostomia[234, 249]
ranitidine	-causes nutrient depletions (hypocalcemia)[234, 270]
saline laxatives in general	-causes nutrient depletions (hypocalcemia, hypokalemia)[234, 270]
scopolamine	-can cause decreased GI motility (constipation)[5, 234]
GROWTH HORMONE AND ITS MODULATORS	
IGF-1	-associated with hypoglycemia[234, 259, 260] -induces protein effects[234, 268]
growth hormone	-implicated in the induction of hyperglycemia[234, 260] -induces protein effects[234, 268]
IMMUNOSUPPRESSANTS	
cyclosporine	-associated with hyperglycemia & post-transplantation diabetes[234, 263] -adversely affect the lipid profile of a patient[234, 265] -causes nutrient depletions (hypomagnesemia)[234, 270]
immunosuppressive agents in general	-adversely affect the lipid profile of a patient[234, 265]

sirolimus	-associated with hyperglycemia & post-transplantation diabetes[234, 263] -adversely affect the lipid profile of a patient[234, 265] -cause nutrient depletions (hypophosphatemia, hypokalemia)[234, 270]
tacrolimus	-associated with hyperglycemia & post-transplantation diabetes[234, 263] -cause nutrient depletions (hypophosphatemia, hypomagnesemia)[234, 270]
MIOTICS MYDRIATICS & ANTIGLAUCOMA DRUGS	
cyclopentolate	-associated with xerostomia[234, 249]
SEX HORMONES & THEIR MODULATORS	
anabolic steroids in general	-favor weight gain[234,236] -associated with hypoglycemia[234, 259, 260] -induce protein effects[234, 268] -can cause profound, dose-related effects on lipoprotein metabolism [57]
danazol	-adversely affect the lipid profile of a patient[234, 265]
estrogens	-favor weight gain[234,236] -implicated in the induction of hyperglycemia[234, 260] -cause nutrient depletions (hypocalcemia, hypomagnesemia, zinc-vitamin B_6 deficiencies)[234, 270] -can cause profound, dose-related effects on lipoprotein metabolism [57] - are known to increase serum triglyceride levels [57]
oral contraceptives	-favor weight gain[234,236] -implicated in the induction of hyperglycemia[234, 260] -combined oral contraceptives with 2nd generation progestogens adversely affect the lipid profile of a patient[234, 265] -cause nutrient depletions (hypomagnesemia, zinc- folic acid-vitamin B_2-vitamin B_6-vitamin B_{12}-vitamin E deficiencies)[234, 270]
oxandrolone (testosterone derivative)	-favors weight gain[234,236]
progestogens	-adversely affect the lipid profile of a patient[234, 265]
sex hormones in general	-reduce the absorption of certain nutrients (folate, vitamin B_6) [97] - sodium and water retention are common side effects [1]
testosterone	-favors weight gain[234,236] -cause nutrient depletions (hypokalemia)[234, 270]
STIMULANTS & ANORECTICS	
amphetamine , armodafinil, dextroamphetamine, doxapram, methamphetamine, methylphenidate, modafinil, lisdexamfetamine, sibutramine	-have anorexic properties, associated with weight loss[234]

THYROIDS & ANTITHYROIDS	
thyroid products	-implicated in the induction of hyperglycemia[234, 260]
antithyroid drugs in general	-can cause nutrient depletions (hypocalcemia)[234, 270]
UROLOGICALS	
oxybutynin	-causes xerostomia[5] -can cause decreased GI motility (constipation)[5, 234]