Chapter 8

Clinical Relevance of Medicinal Plants and Foods of Vegetal Origin on the Activity of Cytochrome P450

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Abstract

Drug metabolism is a pharmacokinetic process whose main objective is to modify the chemical structure of drugs to easily excretable compounds. This process is carried out through phase I and phase II reactions. The enzymes of cytochrome P450 (CYP450) participate in phase I reactions, and their activity can be inhibited or induced by xenobiotics. The aim of this chapter is to study the clinical relevance of the induction and inhibition of CYP450, by describing the effect that some bioactive compounds present in medicinal plants or foods can modify, either increasing or decreasing the activity of CYP450 enzymes and with it modify the bioavailability and depuration of drugs. Examples will be described on the interaction of medicinal plants and foods of vegetal origin that when combined with some drugs can generate toxicity or therapeutic failure; this will allow gathering relevant information on the adequate pharmacological management in different clinical situations.

Keywords: cytochrome P450, drug metabolism, medicinal plants, foods of vegetal origin toxicity, therapeutic failure

1. Introduction

When a patient is in pharmacological treatment, and at some point a pharmacological response different from the expected one is observed, it is possible to think that a pharmacological interaction occurred. This occurs when a drug is administered or consumed in combination

with other drugs, foods, or medicinal plants. In this context, changes in responses to drugs can be positive or negative for the patient. However, it is of particular interest to study the negative changes in pharmacological responses such as intoxication or therapeutic failure.

In this chapter, we focus on describing the effect of the interaction between drugs, medicinal plants, and foods of vegetable origin on the activity of cytochrome P450. Due to the natural products may modify the plasmatic concentrations of the drugs, either by inhibition or induction enzymatic, respectively.

In clinical practice, it is very important to know this topic to identify which medicinal plants and foods of vegetable origin should not be consumed when the patient is in pharmacological treatment and to avoid suffering a change in the response to medications that they consume by prescription and that could put their lives at risk.

2. General aspect of pharmacokinetics

To understand the effect of the chemical compounds, present in some medicinal plants and foods of vegetable origin on the activity of cytochrome P450 (CYP450), we will start with a brief description of the pharmacokinetics because the CYP450 participates in the phase I reactions of drug metabolism.

Pharmacokinetics is the branch of pharmacology that is responsible for studying and explaining the processes by which drugs are absorbed, distributed, metabolized, and eliminated from organism [1, 2]. It is important to know these pharmacokinetics processes and how they influence the bioavailability of drugs [2].

Bioavailability refers to the amount of drug found in the bloodstream and is available to exert its pharmacological effect [3]. However, if the plasma quantity of a drug is modified, the pharmacological response will be modified [1–3]. The four pharmacokinetic processes influence the bioavailability of the drugs. In the process of metabolism, the plasma concentrations of the drugs can be modified, either by inhibition or by induction of different CYP isoenzymes, as shown in **Figure 1**.

The following example makes it easier to understand the importance of adherence to treatment to avoid fluctuations in plasmatic concentration. When patients are in pharmacological treatment, it is important that dosage regimen be complied. For example, if the prescription is 500 mg of acetaminophen every 8 h, this patient should be taken exactly three tablets of 500 mg of acetaminophen per day.

In order for patient has an adequate pharmacological response to acetaminophen, and a lower probability of presenting adverse effects or therapeutic failure, the amount of drug and the time of administration indicated in each shot must be respected. If, patient modifies any of these two variables, the plasma concentration of the drug changes and with it its response also changes [4].

When a single dose of drug is administered orally, after a certain time, the plasma concentrations of the drug are enlarged until reaching a maximum level. This maximum point is known as maximum plasma concentration (C_{max}), and it is reached in a determined maximum

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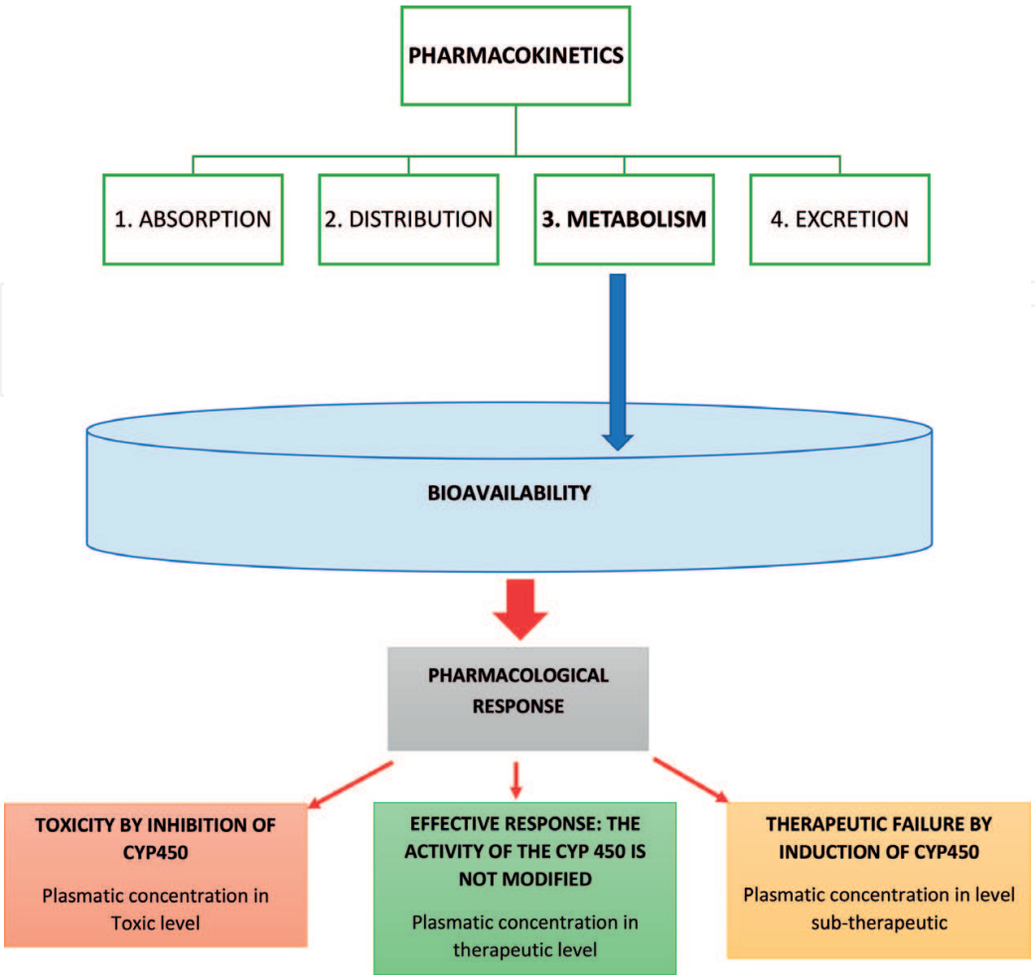

Figure 1. Effect of drug metabolism on the pharmacological response.

time (t_{max}). These parameters are specific for each drug [6]. The C_{max} of a drug is within the therapeutic range [4].

On the other hand, after several administrations of a drug, the final concentration begins to increase due to the remainder of the previous dose, until reaching a constant concentration called the equilibrium state [1]. Steady state is usually achieved after four to five half-lives [1, 2]. The half-life ($t_{1/2}$) is defined as the time required by a drug to decrease its initial concentration by half [1].

In the equilibrium state, the drug plasmatic concentrations are within the range of therapeutic effect. If the patient suspends the administration of the drug, the plasma levels fall to concentrations below the therapeutic level causing therapeutic failure. Generally, the elimination of a drug is carried out after four to five half-lives [1–3].

When the patient does not remember if took the dose of the drug and decides to take the dose thinks was needed, the concentration of that drug will accumulate, then the plasma concentration reaches levels above the therapeutic concentration, and additionally, some signs of toxicity begin to appear [5].

In this chapter, we will focus on describing the effect that some compounds present in medicinal plants and some foods of vegetable origin can have on the activity of cytochrome P450 enzymes. The World Health Organization (WHO) estimates that more than 80% of

the population of developed and underdeveloped countries use medicinal plants as a first resource for their health care and, on the other hand, there is a context cultural acceptance of the traditional practice with herbs, which makes its use popular and that in many cases patients combine their pharmacological treatment with herbal treatment [6–10].

On the other hand, the consumption of certain foods of vegetable origin with nutraceutical properties has increased considerably in recent years, especially to treat and prevent conditions such as cancer, diabetes, hypertension, hypercholesterolemia, obesity, among others. Therefore, by combining these foods with the pharmacological treatment indicated in the abovementioned conditions, they can significantly modify the plasma levels of some drugs and put the patient's life at risk, either due to therapeutic failure (decrease in plasma concentration) or toxicity (increased plasma concentration) [11–15].

2.1. Pharmacokinetic process of drug metabolism

The drugs are defined chemically as acids or weak bases, and during the absorption process, the nonionized fraction of a drug is the one that crosses the biological membranes, due to its lipid solubility. Until the condition of lipid solubility is not lost, the drug will continue remaining in the body, by means of processes of reabsorption at the renal level or the enterohepatic circuit and redistribution from drug deposits in adipose tissue [16–19].

If this lipid solubility condition is not lost, the drug will not be able to be eliminated [2, 18]. Fortunately, the pharmacokinetic process of the metabolism helps to modify the chemical structure of drugs into structures more polar, so that these can be more easily excreted [2, 18, 19].

The main organ that participates in the metabolism of drugs and other xenobiotics is the liver. However, other tissues also have metabolic capacity such as the gastrointestinal tract, lungs, skin, kidneys, and brain [20–23].

The functional unit of this organ is the hepatocyte, and it contains different enzymes that are in the mitochondria, smooth and rough reticulum membrane, cytosol, etc. [23].

During this process of drug metabolism, the following may occur:

1. Transform to a more active molecule [1–3].
2. Transform to give biological activity (prodrug) [1–3].
3. Transform to an inactive molecule [1–3].
4. Transform to a toxic molecule [1–3].

It is important to mention that there are drugs that do not transform. Their chemical structure is not modified, and they are eliminated unaltered [2].

2.1.1. Effect of metabolism of the first step

When drugs are administered orally, they suffer a phenomenon of elimination prior to the process *per se* of the metabolism. This effect is known as first-pass metabolism and occurs in the epithelial cells of the gastrointestinal tract mainly in the small intestine [24]. Subsequently,

the amount of drug that was not biotransformed enters the liver through the portal circulation, and there in the hepatocytes the metabolism process *per se* is carried out [24]. The amount of drug remaining after liver extraction is bioavailable to give an adequate pharmacological response. It is important not to modify this bioavailability because the effective doses of the drugs used in the clinical ready are considered as the effect of metabolism of the first step. Above all, caution should be exercised in drugs with a narrow safety margin, such as barbiturates [1, 2].

2.1.2. Enterohepatic circuit

When drugs are biotransformed by phase I reactions, and the molecule obtained is not polar enough to be eliminated, their biotransformation continues through phase II reactions. In this phase, the metabolites are generally conjugated with glucuronide acid, giving a polar molecule with a higher molecular weight [1, 2]. These conjugates are secreted from the hepatocyte into the bile and stored there in the form of a drug-glucuronide complex; when the bile is secreted in the intestine by some stimulus, the drug-bile complex is eliminated through the feces [25]. However, intestinal microorganisms produce various enzymes, such as beta-glucuronidases, which break the bond between the drug and glucuronide acid, leaving the drug free again, where it can be reabsorbed through the small intestine and enter the general circulation. In this case, the half-life of the drugs is increased [25].

2.1.3. Factors that affect the metabolism of drugs

2.1.3.1. Physiological factors: age and pregnancy

In children and older adults, the metabolic rate is decreased compared to the metabolic rate of a young adult [1]. In the child, the microsomal enzymes are not yet fully induced [26]. In elderly people, the number of hepatocytes and blood flow that reaches this organ is reduced [27]. So, there are fewer cytochrome P450 enzymes available to metabolize drugs. In pregnancy, there is greater hepatic flow and greater activity of cytochrome P450, which increases the metabolic rate [28].

2.1.3.2. Pathological factors: liver disease

The number of hepatocytes decreases, and the metabolic rate also decreases. In addition, there is an increase in the plasmatic concentrations and half-life of drugs. Therefore, it is necessary to adjust the dose, to prevent toxicity [2].

2.1.3.3. Drugs, medicinal plants, and foods

Some drugs and phytochemical compounds present in medicinal plants and foods of plant origin can induce or inhibit the activity of cytochrome P450 [29].

2.2. Phases of drug metabolism

Biotransformation reactions of drugs are divided into reactions of phase I or functionalization and reactions of phase II or conjugation [2].

The chemical reactions of phase I allow the introduction of functional groups such as –OH, –COOH, –SH, –O–, or $–NH_2$. Phase I reactions are very simple chemical reactions such as oxidation, reduction, hydrolysis, alkylation, and dealkylation [2]. Of these chemical reactions, the most important in the metabolism of drugs and that occur more frequently are the oxidation reactions performed by the cytochrome P450 enzymes (CYP450). These enzymes are located mainly in the smooth endoplasmic reticulum [1, 2].

When the addition of the functional groups (–OH, –COOH, –SH, –O–, $–NH_2$) to the drug molecule is not enough to transform it to a more polar molecule, the molecule continues its modification through reactions of phase II. Phase II reactions are called also conjugation reactions. In these reactions, the molecule of the drug or metabolite previously formed in the reactions of phase I is conjugated with a large molecule of polar nature (hydrophilic) as the acid glucuronide, or acetyl Co-A, glycine, glutathione, phosphoadenosyl phosphosulfate, and S-adenosylmethionine [2]. These reactions are carried out by means of specific enzymes called transferases that are generally located in the microsomes and in the cytosol [1–3].

2.3. Role of cytochrome P450 (CYP450) in drug metabolism

Cytochrome P450 (CYP450) is a superfamily of enzymes that contain a heme group, so they are hemoproteins. The iron in the heme group is reduced and forms complexes with the carbon monoxide that absorbs light at a wavelength of 450 nm [30]. They have identified more than 8700 genes that code for their proteins and are found in eukaryotic and prokaryotic cells [31]. They are responsible for metabolizing or biotransforming endogenous substances in the body such as hormones, and different xenobiotics such as drugs. These enzymes perform oxidation reactions and participate in the phase I reactions of drug metabolism [1–3]. They are also known as mixed function oxidases or monooxygenases; they require a reducing agent such as NADPH and molecular oxygen [32].

They have different patterns of specificity for the substrate; for example, acetaminophen is a substrate of both CYP1A2 and CYP2E1, while halogenated anesthetics are substrate only of CYP2E1 [2, 34–36]. This enzyme system is found in different tissues such as kidney, lung, skin, brain, adrenal cortex, placenta, testicles, and other tissues, but the liver and small intestine are the organs that have more CYP450 [33, 34].

2.3.1. Nomenclature of CYP450

The CYP450 is grouped into families and subfamilies depending on the analogy in their amino acid sequences, such that CYPs that present 40% homology in their amino acids belong to a family, and when the analogy is greater than 55%, they form a subfamily, are named with the prefix CYP, and followed by the family number, a capital letter indicating the subfamily, and a number that marks the individual form: for example, CYP1A1, in this way, represents the individual form 1 of subfamily A of family 1 [35]. Eighteen families, 42 subfamilies, and more than 50 individual genes of human origin have been described. However, the most important in the metabolism of drugs are CYP1A1/2, CYP1B1, CYP2A6, CYP2B6, CYP2C9,

CYP2D6, CYP2E1, CYP3A4,5,7 [1–3]. CYP3A4,5,7 is the most abundant and participates in the metabolism of more than 50% of the drugs currently used in the clinic [1–3, 35].

2.4. Induction and Enzymatic inhibition

Many substances such as drugs, environmental toxins, and phytochemicals present in medicinal plants and some foods of plant origin contain substances that act as inhibitors or inducers of cytochrome P450 enzymes; this induction and inhibition can be strong or weak so it can sometimes have relevant clinical implications such as producing toxicity or therapeutic failure [36].

Enzymatic induction refers to the increase of enzymes and/or their activity. Additionally, it increases the metabolic rate of CYP450, and therefore, the concentrations of the drug in blood will decrease, which can cause a decrease in pharmacological effects and with it a therapeutic failure (**Figure 2**) [37].

In enzymatic inhibition, the number of enzymes and/or their activity decreases. There are fewer enzymes available to biotransform the drugs and increase their plasma levels with each administration of the drug will produce toxicity (**Figure 2**) [33].

It is important not to induce or inhibit the activity of CYP450; they directly influence the bioavailability of the drugs. On the other hand, the genetic polymorphism of CYP450 is also responsible for the variability in the response to drugs between each individual [34, 35]. Genetic variability, especially of CYP2C9, CYP2C19, CYP2D6, and CYP3A5, is known to have an important clinical impact on drugs that are metabolized by these enzymes [38–40].

2.5. Effect of bioactive compounds of medicinal plants and foods of vegetable origin on the activity of CYP450

In the literature, there is a lot of information about the effect of drugs to inhibit or induce certain CYP450 isoenzymes. Recently the study of the effect of some phytochemical components that are present in medicinal plants and foods of vegetable origin on the activity of CYP450 has been increasing, because the population makes use of herbal medicine in its traditional practice and, on the other hand, it consumes foods with nutraceutical properties, either to prevent or to control any disease.

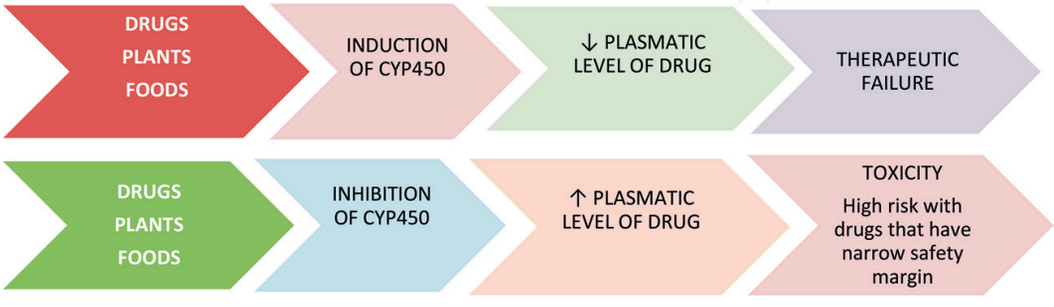

Figure 2. Effect of medicinal plants and foods of vegetable origin on CYP450 activity.

Medicinal plant	Tradicional uses	Phytochemistry compounds	Activity on CYP450	Clinical effect on substrates of CYP450	References
Artemisia annua L.	Antimalaria effect	Artemisinin	↑CYP2C19	↓Plasmatic concentration of I	[3, 41, 42]
Cimicifuga racemosa	Are used as a hormone replacement and antiinflammatory	Triterpene glycosides Fukinolic acid Cimicifugic acid A Cimicifugic acid B	↓CYP1A2 ↓CYP2D6 ↓CYP2C9 ↓CYP3A4	↑Plasmatic concentration of II ↑Plasmatic concentration of III ↑Plasmatic concentration of IV ↑Plasmatic concentration of V	[3, 43]
Centella asiatica	Used for wound healing and maintaining normal blood pressure.	Flavonoids: Quercetin Kaempferol	↓CYP2D6 ↓CYP2C9 ↓CYP3A4	↑Plasmatic concentration of III ↑Plasmatic concentration of IV ↑Plasmatic concentration of V	[3, 44, 45]
Curcuma longa	Antiinflammatory, anticancer and antiarthritic effect.	Curcuminoids: Curcumin Methoxycurcumin, Bisdemethoxy-curcumin	↓CYP1A2 ↑CYP2A6 ↓CYP2C9 ↓CYP3A4	↑Plasmatic concentration of II ↓Plasmatic concentration of VI ↑Plasmatic concentration of IV ↑Plasmatic concentration of V	[3, 46–48]
Echinacea purpurea (L.)	It is used to treat colds, upper respiratory infections, and dermatologic issues	Cichoric acid Caftaric acid Echinacoside Alkylamides	↑CYP1A2 ↓CYP3A4	↓Plasmatic concentration of II ↑Plasmatic concentration of V	[3, 49, 50]
Garcinia cambogia	Obesity treatment	Extract crude	↓CYP2B6	↑Plasmatic concentration of VII	[3, 51]
Gardenia jasminoides Ellis.	Is used as an antioxidant, hypoglycemic , antithrombotic, antiinflammatory, antidepression effect, and improved sleeping quality	Geniposide Genipin	↑CYP2D6 ↓CYP2C19 ↓CYP3A4	↓Plasmatic concentration of III ↑Plasmatic concentration of I ↑Plasmatic concentration of V	[3, 52, 53]
Gingko biloba	It is used as an anti-hypertensive as well as to treat macular degeneration and tinnitus. Are effective in treating cerebral infarction	Ginkgolide A Ginkgolide B Bilobalide Quercetin kaempferol	↓CYP2B6 ↑CYP1A2 ↑CYP3A4	↑Plasmatic concentration of VII ↓Plasmatic concentration of II ↓Plasmatic concentration of V	[3, 54–56]

Medicinal plant	Tradicional uses	Phytochemistry compounds	Activity on CYP450	Clinical effect on substrates of CYP450	References
Panax ginseng	Is believed to enhance cognitive ability and to lower blood sugar levels Ginsenosides and gintonin Ginsenoside F2 and protopanaxadiol	Ginsenosides	↓CYP2C9 ↓CYP3A4	↑Plasmatic concentration of IV ↑Plasmatic concentration of V	[3, 57]
Camellia sinensis	It is consumed to treat cancer, cardiovascular disease, dyslipidemia, inflammation, and weight loss	Catechin (-)-Epigallocatechin -3-gallate	↓CYP1A2 ↓CYP2B6 ↓CYP2C8 ↓CYP2C9 ↓CYP2D6 ↓CYP3A4	↑Plasmatic concentration of II ↑Plasmatic concentration of VII ↑Plasmatic concentration of VIII ↑Plasmatic concentration of IV ↑Plasmatic concentration of III ↑Plasmatic concentration of V	[3, 58–60]
Piper methysticum	Anxiolytic effect	Flavokawain A	↑CYP2C9 ↓CYP1A2 ↓CYP3A4	↓Plasmatic concentration of IV ↑Plasmatic concentration of II ↑Plasmatic concentration of V	[3, 61–64]
Hypericum perforatum	Is used to treat anxiety and depression	Hyperforin	↑CYP2C9 ↑CYP3A4	↓Plasmatic concentration of IV ↓Plasmatic concentration of V	[3, 65–67]

I: Omeprazole, pantoprazole, diazepam, S-mephenytoin, amitriptyline, carisoprodol, citalopram, chloramphenicol, clomipramine, cyclophosphamide, indomethacin, moclobemide, nelfinavir, propranolol, progesterone.

II: Acetaminophen, amitriptyline, phenacetin, tacrine, theophylline, tamoxifen, (R)warfarin, caffeine, verapamil, ondansetron, haloperidol, naproxen, propanolol.

III: Propoxyphene, codeine, oxycodone, dextromethorphan, clozapine, timolol, tamoxifen, tramadol, seleglinide, fluoxetine, phenformin, paroxetine, risperidone, metoprolol, tricyclic antidepressants.

IV: Amitriptyline, celcoxib, ibuprofen, diclofenac, meloxicam, hexobarbital, losartan, S-warfarin, fluvastation, phenytoin, tolbutamide, glipizide, glibenclamide, fluoxetine, tamoxifen.

V: Acetaminophen, amiodarone, cisapride, astemizole, cocaine, cyclosporine, dapsone, diazepam, dihydroergotamine, diltiacem, felodipine, nifedipine, erythromycin, indinavir, lidocaine, methadone, miconazole, quinidine, paclitaxel, mifepristone, spironolactone, verapamil, trazolam, desametaxone, ritonavir, lovastatin, hydrocortisone.

VI: Nicotine.

VII: Bupropion, cyclophosphamide, efavirenz, ifosfamide, methadone.

VIII: Paclitaxel, torsemide, amodiaquine, cerivastatin, repaglinide.

Table 1. Effect of medicinal plants on CYP450 activity.

Fruit or vegetable	Phytochemistry compound	Activity on CYP450	Clinical effect on substrates of CYP450	References
Broccoli	Sulforaphane	↑CYP1A2 ↓CYP2D6	↓Plasmatic concentration of II ↑Plasmatic concentration of III	[3, 68, 69]
Grapefruit	Furanocoumarin	↓CYP3A4	↑Plasmatic concentration of V	[3, 65, 70, 71]
Pomegranate	Flavonoids Tannins Phenolic acids	↓CYP2C9 ↓CYP3A4	↑Plasmatic concentration of IV ↑Plasmatic concentration of V	[3, 72]
Sevillian orange	Furanocoumarin	↓CYP3A4	↑Plasmatic concentration of V	[3, 73]
Star fruit	Catechin Epicatechin	↓CYP3A4	↑Plasmatic concentration of V	[3, 74–76]

II: Acetaminophen, amitriptyline, phenacetin, tacrine, theophylline, tamoxifen, (R)warfarin, caffeine, verapamil, ondansetron, haloperidol, naproxen, propanolol.

III: Propoxyphene, codeine, oxycodone, dextromethorphan, clozapine, timolol, tamoxifen, tramadol, seleglinide, fluoxetine, phenformin, paroxetine, risperidone, metoprolol, tricyclic antidepressants.

IV: Amitriptyline, celcoxib, ibuprofen, diclofenac, meloxicam, hexobarbital, losartan, S-warfarin, fluvastation, phenytoin, tolbutamide, glipizide, glibenclamide, fluoxetine, tamoxifen.

V: Acetaminophen, amiodarone, cisapride, astemizole, cocaine, cyclosporine, dapsone, diazepam, dihydroergotamine, diltiacem, felodipine, nifedipine, erythromycin, indinavir, lidocaine, methadone, miconazole, quinidine, paclitaxel, mifepristone, spironolactone, verapamil, trazolam, desametaxone, ritonavir, lovastatin, hydrocortisone.

Table 2. Effect of fruits or vegetables on CYP450 activity.

Tables 1 and **2** show the effect of the phytochemical compounds present in medicinal plants and foods of vegetable origin. We mentioned principally those natural products that have an important effect on the induction and inhibition of different CYP450 isoenzymes and that have clinical relevance to produce toxicity or therapeutic failure.

3. Conclusions

The induction and inhibition of CYP450, by some bioactive compounds present in medicinal plants or foods, can modify the bioavailability of drugs. The changes in the bioavailability are important in the efficacy and safety of pharmacological management. It is important to consider that when a patient will be in a pharmacologic treatment, the patient should not use any medicinal plants or foods of vegetable origin that can induce or inhibit any CYP450 isoenzymes.

Especially, they should not use the St. John's wort and grapefruit, as their phytochemical compounds have a potent effect to induce or inhibit, respectively, the activity of CYP3A4 with important clinical relevance.

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