Review

Phytochemicals That Interfere With Drug Metabolism and Transport, Modifying Plasma Concentration in Humans and Animals

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Abstract

Phytochemicals (Pch) present in fruits, vegetables and other foods, are known to inhibit or induce drug metabolism and transport. An exhaustive search was performed in five databases covering from 2000 to 2021. Twenty-one compounds from plants were found to modulate CYP3A and/or P-gp activities and modified the pharmacokinetics and the therapeutic effect of 27 different drugs. Flavonols, flavanones, flavones, stilbenes, diferuloylmethanes, tannins, protoalkaloids, flavans, hyperforin and terpenes, reduce plasma concentration of cyclosporine, simvastatin, celiprolol, midazolam, saquinavir, buspirone, everolimus, nadolol, tamoxifen, alprazolam, verapamil, quazepam, digoxin, fexofenadine, theophylline, indinavir, clopidogrel. Anthocyanins, flavonols, flavones, flavanones, flavonoid glycosides, stilbenes, diferuloylmethanes, catechin, hyperforin, alkaloids, terpenes, tannins and protoalkaloids increase of plasma concentration of buspirone, losartan, diltiazem, felodipine, midazolam, cyclosporine, triazolam, verapamil, carbamazepine, diltiazem, aripiprazole, tamoxifen, doxorubicin, paclitaxel, nicardipine. Interactions between Pchs and drugs affect the gene expression and enzymatic activity of CYP3A and P-gp transporter, which has an impact on their bioavailability; such that co-administration of drugs with food, beverages and food supplements can cause a subtherapeutic effect or overdose. Therefore, it is important for the clinician to consider these interactions to obtain a better therapeutic effect.

Keywords

phytochemical, cytochrome (CYP3A), P-glycoprotein, area under the curve, interaction drug, expression, activation/repression or inhibition of activity

Introduction

In recent decades, the quality of dietary and lifestyle habits has changed substantially compared to the second half of the twentieth century. In today's society, the intake of organic foods and food supplements has significantly increased as a result of the generalized concern about healthy lifestyles and disease prevention. The use of dietary supplements continues to increase every year among patients interested in "natural" remedies. It is estimated that the consumption of dietary supplements increased by 42% in people over 20 years of age between 1988 and 1994. Half of the USA adult population has reported using at least one dietary supplement.[1]

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The interaction between drugs and food, such as fruits, vegetables, roots, tubers, honey, olive oil, drinks, wine, tea, and chocolate, has begun to attract the attention of researchers due to compounds present in food that can interact with the enzymes that metabolize and excrete drugs. This occurs because of the similarity in chemical structure between some food compounds and drugs.[2-4] With increasing frequency, medications prescribed by physicians interact with food products, mainly in patients undergoing chronic therapy.[2,5] Until a few decades ago, these interactions were not suspected.

Cases of therapeutic ineffectiveness and adverse drug reactions have been reported as a consequence of the interaction between medications and plant products consumed as an alternative herbal medicine or nutritional supplements. This type of interaction happens whenever the effect of a drug is altered as a result of previous or simultaneous administration with a plant product or nutrient.[3-5]

The influence of dietary components on the effect of drugs depends on numerous variables, including the physicochemical properties and the biological, clinical, and cultural characteristics of the patients, such as age, sex, genetic background, diet quality and dietary patterns, nutritional status, etc.[6]

Food-drug interactions can manifest as changes in the blood levels of drugs due to alterations in the processes of absorption, distribution, metabolism and excretion.[5,7] It has been reported that some plant molecules phytochemicals (Pch) interfere with the modulation of the expression and activity of cytochrome CYP3A and P-gp, changing the pharmacokinetics of drugs.[8] The National Health and Nutrition Examination Survey reported that the most widely used nutritional supplements in the US are coenzyme Q10, cranberries, echinacea, fish oil, garlic, ginseng, *Ginkgo biloba*, glucosamine/chondroitin, green tea, melatonin, methylsulfonylmethane, milk thistle, probiotics/prebiotics, saw palmetto and valerian.[1] Therefore, it is relevant to study how Pchs consumed in the diet can interact with the metabolic and drug transport processes.

Based on the above the purpose this review focuses on the importance os Pchs present in food and nutrients in the daily diet, which can either inhibit or promote the action of *cyp3a*/CYP3A and *abcb1*/P-gp, and the role they have with the metabolism and transport of drugs.

Methods

A systematic review without meta-analysis was conducted in biomedical databases, including the Cochrane Library, Embase, Medline (PubMed), Lilacs, and Web of Science to identify articles providing evidence of phytochemical-drug interaction in preclinical and clinical studies. Likewise, those in which the AUC of the drug alone and in co-administration with Pchs. Additionally, a complementary review was carried out in the same databases to establish which Pchs are present in the plants.

Inclusion criteria: Studies published between 2000 and 2021, no language filters were applied, and the following MeSH terms were used: phytochemical, herb, food, nutrient, drug, AUC, drug concentration, modification, induction, inhibition, CYP3A, P- gp, expression of the *cyp3a*, *abcb1* genes. Excluded manuscripts did not report the pharmacokinetic value of AUC or their results did not show significant differences between controls and co-treatments; duplicate articles were also removed.

Thus, one hundred and thirty-one results were obtained through the search in the databases. After critical reading, 54 articles were included and 77 were eliminated because they did not report the AUC or did not present significant differences between the control and the co-treatment. The remaining 123 articles correspond to the complementary review of the phytomolecules present in plants. Total of 177 articles were included in this review.

Cytochrome

Cytochrome (CYP) is an enzymatic system of heme proteins that catalyze the oxidative metabolism of a large number of exogenous and endogenous compounds.[9-11] Cytochromes are constitutively expressed in the endoplasmic reticulum of hepatocytes and various extrahepatic tissues, including the intestine, kidney, lung, skin, adrenal cortex, testes, placenta, and various brain regions.[10-14]

The main function of CYP is to transform poorly soluble (lipophilic) xenobiotics into water-soluble (hydrophilic) metabolites to accelerate urinary excretion.[3,10] It metabolizes a large number of medications, including neuropsychiatric, antineoplastic, cardiovascular, immunosuppressive, antibiotic, antiviral, and antifungal drugs. The most important property of CYP is that it can be induced and/or inhibited by xenobiotics, including drugs.[10,13] CYP3A is a genetically conserved enzyme. For this reason, it has very little genetic variability and a low frequency of polymorphisms.[10] However, it should be noted that the expression of CYP3A could be affected by exogenous compounds present in different foods and herbs consumed in the daily diet.[5,10,15-17]

P-Glycoprotein Transporter

P-glycoprotein (P-gp) is a protein encoded by the *abcb1* gene (Multridrug resistance 1 or *MDR1*), which belongs to the group of adenosine-triphosphate binding cassette (ABC) transporter genes. It is a membrane protein whose function is to protect cells through the expulsion of unknown toxic substances. P-gp also contains multiple binding sites for xenobiotics (including drugs), and it is

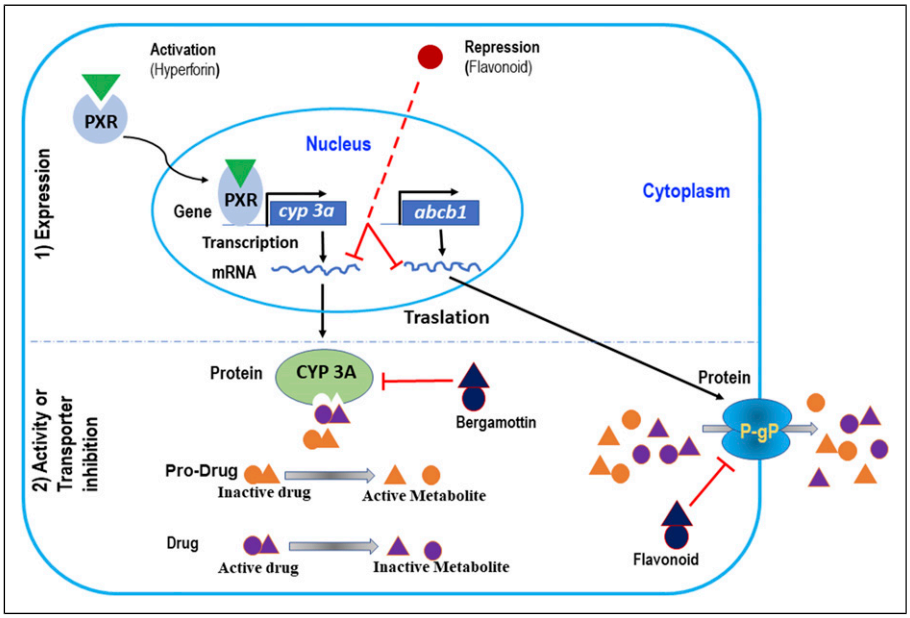


Figure 1. Mechanisms involved in the modulation: (1) Some Pch such as hyperforin and some flavonoids modulate *cyp3a* and *abcb1* gene expression by activation or repression modify mRNA transcription for CYP3A and P-gp.[8,31,35,93,94] However, the exact mechanism by which the repression of both proteins is carried out is unknown.[11,31,95] (2) Flavonoids such as bergamottin and other Pchs bind competitively or noncompetitively to CYP3A and P-gp proteins,[96,97] resulting in inhibition of the activity of both proteins. Both mechanisms result in changes in blood concentration of drugs and prodrugs.

capable of simultaneously binding to multiple substrates at overlapping binding sites.[18]

This transporter is highly expressed in tissues that have direct contact with xenobiotics, such as the epithelium of the gastrointestinal tract, the proximal renal tubule, the pulmonary bronchi, the canalicular surface of hepatocytes, and the surface of the endothelial cells of the blood-brain barrier. Since drugs are expelled from these tissues, P-gp helps to reduce the systemic concentration of drugs.[19]

Due to the importance of P-gp in the transport and excretion of drugs, the concomitant administration of any drug, food, and/or medicinal herb that modifies the expression and activity of P-gp can have important pharmacological consequences[7,20] regarding the concentration and bioavailability of administered drugs.[21-27]

Interaction Mechanisms

The mechanisms that affect the drug concentration can involve the modulation of *cyp3a*/*abcb1* (gene activation or repression) or inhibition of CYP3A and P-gp proteins.[9,11]

Gene Expression (Activation or Repression). Activation of gene expression by Pchs can be done through nuclear receptors such as PXR, PXR is a transcription factor (TF) found in the cytoplasm, Pch as hyperforin can act as a ligand and binds to PXR, this allows that the ligand-TF complex translocates to the nucleus and transcribes target genes such as *cyp3a* and *abcb1*. In repression, Pchs like flavonoids, decrease the mRNA levels of CYP3A and P-gp by unknown mechanisms (Figure 1).[28-41]

Inhibition of Protein Activity (Metabolism or Transport). Some Pchs inhibit CYP3A and P-gp by binding directly to the protein: in the CYP3A, Pchs bind to the catalytic site; meanwhile for P-gp, they bind to the cytosolic site (Figure 1).[27-29,35,39-42]

The inhibition mechanism has been reported mainly in flavonoids, which interact directly through the binding of hydroxyls located on carbons C7, C5, and C4 to the heme group of the catalytic site of CYP3A.[28,40-42] These bonds can be competitive and/or non-competitive. Catechin and piperine, for example, bind to CYP3A non-competitively,[28,43,44] while the Pchs of grapefruit, such as bergamottin and its isomers, bind competitively of cytochrome with a Ki equal to that of ketoconazole, a drug considered as a strong inhibitor of CYP3A.[27,41,43,45] The mechanism of inhibition of P-gp is reportedly similar to that of cytochrome, in which the hydroxyls of the flavonoids located in the carbons C5 and C7 bind to the binding site that carries out the transport activity.[46,47]

The timely identification of interactions between medicinal herbs and food components with the same affinity as certain drugs to bind to CYP3A and/or P-gp would greatly help to avoid possible therapeutic failures or adverse reactions produced by changes in drug concentrations.

Based on the above, it can be summarized that Pchs can modify the therapeutic effect of a number of drugs by affecting the expression and activity of the proteins that metabolize and transport them. For example, some drugs produce their therapeutic effect without being metabolized by CYP3A, as is the case with midazolam, because when it is metabolized by CYP3A, inactive metabolites are generated,[31,48-50] while others, such as carbamazepine, need to be metabolized by CYP3A to generate the active metabolites (10,11 epoxi-carbamazepine) that carry out the therapeutic effect.[51] On the other hand, hyperforin activates the expression of *cyp3a* and *abcb1*, resulting in increased therapeutic effect of pro-drugs.[33] Unlike Pchs, as galangin and capsaicin, which cause the repression of these genes, producing a decrease in the drugs efficacy.[11,31]

Phytochemical Sources and Pharmacological Effects

Pchs are substances naturally present in vegetables, fruits and herbs. Over time, they have been incorporated into various food supplements as adjuvants to prevent numerous diseases, especially degenerative ones. Various health benefits has been attributed to Pchs, and this is a reason which they are widely used as everyday products (Table 1).

A recent intervention study by Fraga et al.,[52] evaluated the metabolism of citrus flavanone and the effect of orange juice on cardiometabolic biomarkers. The authors reported a significant reduction in body fat and blood pressure, suggesting that the consumption of these substances is a good cardioprotective strategy.

Pchs can also have an "anti-diabetic" effect[53] by reducing the absorption of carbohydrates in the small intestine, suppressing tissue gluconeogenesis, increasing tissue glucose uptake, protecting pancreatic beta cells, and increasing insulin secretion.[53] An *in vivo* study showed that oral administration of rutin-loaded nanophytosomes for 4 weeks was more effective than free rutin in controlling hyperglycemia and hyperlipidemia in streptozotocin-induced diabetic rats. This "antidiabetic" effect is also evident in the management of blood glucose.[54]

It should be noted that the beneficial health effects attributed to various Pchs have not yet been fully demonstrated, since there is very little scientific evidence on the pharmacological effect of Pchs. Most of the existing evidence is based on the personal experience of the people who consume them (Table 1).

It is important to consider that consuming Pchs from herbs, fruits, and/or vegetables is not always as safe as it seems. It is generally assumed that "everything natural" is beneficial; however, this is not always true, since it depends on many factors such as dose, characteristics of the population, time of consumption, etc.[55]

Drug interactions involving cytochrome CYP3A enzymes and P-gp transporter are mediated through genes activation/repression or protein inhibition. The therapeutic importance of these mechanisms can be observed in clinical practice when drugs that are metabolized and/or transported by CYP3A and P-gp are co-administered with Pchs, which produces an alteration of the bioavailability of the drug and/or the elimination of its compounds.

Decrease in Drug Concentrations by Modulation *cyp3a*/CYP3A by Phytochemicals

One of the most important pharmacokinetic parameters related to drug metabolism is the area under the curve (AUC), which involves: the relationship between maximum concentration (Cmax), maximum time (Tmax), time in which the drug reaches its maximum concentration, and clearance (Cl), the most important parameters used to evaluate the absorption and bioavailability of drugs.

Different substances found in plants, mainly flavonoids or alkaloids, can change the expression of the *cyp3a* and *abcb1* genes and activity of CYP3A cytochrome and P-glycoprotein.

Tables 2 and 3 show the results of preclinical and clinical studies that demonstrated a decrease in the AUC of different drugs. This interaction is highly relevant because it can result in ineffective treatments.

For example, the AUC of everolimus or cyclosporine decreases after consuming different Pchs, reducing the efficacy of the immunosuppressive treatment (Table 2).[26,56]

Decreased plasma concentrations of celiprolol, talinolol, digoxin, and nadolol, either due to activation/repression of *cyp3a* and *abcb1* or inhibition of CYP3A and P-gp an result in cardiac decompensation, atrioventricular block and acute myocardial infarction.[57-60]

There are also reports of a decrease in the systemic concentration of simvastatin, which is used in the treatment of hypercholesterolemia.[61]

A decrease in the plasma concentration of anxiolytics such as midazolam, alprazolam and buspirone can prevent the desired anxiolytic effect to be achieved, causing patients to suffer anxiety episodes, phobias, panic attacks and intense stress. For midazolam, such a decrease may impair the sedative effect.[50,62]

It has also been reported that a decrease in the plasma concentration of quazepam due to the administration of St John's wort could put epileptic patients at risk by interfering with the control of seizures, which could then increase in number and making difficult to control the disease.[63]

The plasma concentrations of both saquinavir and indinavir decrease in the presence of some Pchs. Treatment failure can be the cause of disease in HIV-positive patients or in those who require antiviral treatment by preventing the viral load to

Table 1. Classification and pharmacological effect of phytocomponents present in vegetables, fruits and herbs.

Classification. Subclassification, presence and pharmacological activities
PHENOLIC COMPOUNDS[98-102]
Hidroxibenzoic acids. Present in raspberries, strawberries, cranberry, cinnamon, cloves, mushrooms, fermented dairy products. **Pharmacological activities.** Antioxidant, anticancer, anti-inflammatory, antiproliferative, antiangiogenic, keratolytic, platelet aggregation moderate antibacterial, antiviral, antifungal, antiprotozoal, nematicidal
Hidroxicinamic acids. Present in chokeberry, cranberry, blueberry, bilberry, tomato, orange, corn, grapes, beans, potatoes. **Pharmacological activities.** Antioxidant, anticancer, anti-inflammatory, antiproliferative, antiangiogenic, keratolytic, platelet aggregation moderate antibacterial, antiviral, antifungal, antiprotozoal, nematicidal
STILBENES[51,64,79,102-105]
Resveratrol. Present in blueberries (*Vaccinium macrocarpon*), (*Polygonum cuspidatum*), Red grape skin and seeds of (*Vitis vinifera*), blackberries, peanuts and red wine. **Pharmacological activities.** Protecting from oxidative stress, cardioprotective, diabetes, and neurodegenerative diseases, cancer prevention, a cholesterol-lowering effect
TANNINS[106-113]
Catechin: Present in green tea (*Camellia sinensis*), Grapeseed oil (*Vitis vinifera*), Pomegranate (*Punica granatum*), Cacao (*Theobroma cacao*), Star fruit (*Averrhoa carambola*). **Pharmacological activities.** Antioxidant, antimicrobial, antifungal, antiviral, anti-inflammatory, antiallergenic, and anticancer.
Epigallocatechin: Present in green tea (*C sinensis*), Grape (*Vitis vinifera*) skin and seeds, Pomegranate (*Punica Granatum*), Cacao (*T cacao*), Star fruit (*A carambola*), and high concentration in blueberries (*Vaccinium macrocarpon*), hazelnuts, pecans nut, apple, peach, mango, pinto beans, red wine and cinnamon. **Pharmacological activities.** Antimicrobial, antibacterial. Antioxidative, anti-inflammatory, and antitumor agent
FLAVONOIDS
Flavonols[41,99,111,114-126]
Quercetin: Pomegranate (*P granatum*), Jamaica flower (*Hibiscus sabdariffa*), Moringa (*Moringa oleifera*), Fabaceae (*Millettia aboensis*), Ginger (*Alpinia galanga*), Onion (*Allium cepa*), Cacao (*T cacao*), Thyme (*Thymus saturoides*), Guava (*Psidium guajava*), Valerian (*Valeriana officinalis*), Fennel (*Foeniculum vulgare*). **Pharmacological activities.** Anticancer, antiviral, antiprotozoal, antimicrobial, treatment of; allergic, inflammatory disorders, eye, cardiovascular diseases, and arthritis
Morin: Present in guava (*P guajava*). **Pharmacological activities.** Anti-inflammatory, antioxidant, anticancer and chemoprotective.
Rutin: Present in onion (*A cepa*) and (*Allium obliquum*). Valerian (*V officinalis*), Fennel (*F vulgare*). **Pharmacological activities.** It has a role as a metabolite and an antioxidant, anti-diabetic, and anticancer
Kaemppherol: Present in green Tea, Delphinium, Broccoli, Witch Hazel (*Hamamelis virginiana*), Grapefruit, Grape, Brussels Sprouts, Apples. **Pharmacological activities.** Attenuate oxidative stress, anti-inflammatory, antimicrobial, cardioprotector and neuroprotective effects.
Myricetin: Present in Jamaica flower (*H sabdariffa*), strawberry (*Fragaria spp.*), peepal (*Ficus religious*), spinach (*Spinaceae oleraceae*), cauliflower (*Brassica oleraceae*). Other: Red wine, citics, curly kale, leeks, broccoli, blueberries, cranberry juices. **Pharmacological activities.** Anti-oxidant, anticancer, antidiabetic, anti-inflammatory, analgesic, antitumor, hepatoprotective and antidiabetic
Flavones[111,114,117,120,122,127-134]
Apigenine: Present in Carambola (*A carambola*), Cacao (*T cacao*), Pomegranate (*P granatum*), Thyme (*T saturoides*), Chamomile (*Matricaria chamomilla*), Doradilla (*Anastatica hierochuntia*), Onion *(A cepa).* Other: Parsley, celery, oranges, maize, rice, tea, wheat sprouts, some grasses. **Pharmacological activities.** Antioxidant, anti-inflammatory, antitoxicant, anticancer, ant-genotoxic, anti-allergic, neuroprotective, cardioprotective, and antimicrobial
Diosmetin: Present in Citrus species and other plants (*Anastatica hirerochuntica).* **Pharmacological activities.** Phlebotropic, venoprotective, oestrogenic, anticancer, anti-inflammatory, antioxidant, and antimicrobial effects.
Chrysin: Present in Blue passion flower (*Passiflora caerulea),* honey and/or propolis and mushrooms. **Diosmetin:** Citrus species and other plants (*A hirerochuntica).* **Pharmacological activities.** Antispasmodic, sedative, antioxidant, anti-inflammatory, anticancer, and antiviral activities
Galangin: Present in Parsley (*Alpinia officinarum*), (*Helichrysum aureonitens*). Other: Honey, propolis, apple. **Pharmacological activities.** Anti-mutagenic, anti-clastogenic, anti-oxidative, antimicrobial, anticancer, anti-inflamatory, radical scavenging, metabolic enzyme modulating and anticancer activity
Luteolin: Present in Cacao (*T cacao*), Pomegranate (*P granatum*), A. hirerochuntica, (*Apium graveolens*), Parsley (*Petroselinum crispum*), Broccoli (*Brassica oleracea*), (*T saturoides)* thyme, onion (*A cepa*) (*A cepa*) leaves, carrots, peppers, cabbages, apple skins, and chrysanthemum flowers are luteolin rich. **Pharmacological activities.** Anti-inflammation, antiallergy and anticancer, estrogenic and anti-estrogenic activity; anti or pro-oxidant
Bergamottin (5-geranoxypsoralen): Present in Grapefruit (*Citrus paradise*), Peel and pulp of orange (*C sinensis*), Lemon (*Citrus aurantifolia*), pulp of pomelos. **Pharmacological activities.** Antioxidative, anti-inflammatory, and anticancer
Flavanones or dihydroflavones[2,28,135-140]
Naringenin: Present in Grapefruit *(C paradise)*, orange (*C sinensis)*, lemon (*C aurantifolia)*. **Pharmacological activities.** Anti-inflammatory, anti-cancer, bone health, metabolic syndrome, oxidative stress, genetic damage and central nervous system (CNS) diseases.
Hesperetin: Present in Tangerine (*Pericarpium citri*), Honeybush (*Cyclopia subternata*). Other sources: Tomatoes, aromatic plants such as mint. **Pharmacological activities.** Antioxidant and anticancer activity, lipid-lowering, treatment of hemorrhoids and prevention of postoperative thromboembolism, reduction of blood pressure and body fat
Isoflavones[65,141]
Biochanin: Present in Oregano (*Origanum vulgare*), Haba (*Vicia faba*), zallouh or Lebanese viagra (*Ferula hermonis*), red clover, cabbage, alfalfa. **Pharmacological activities.** Anti-inflammatory, estrogen-like (estrogenic and/or antiestrogenic activity), treatment: Menopause symptoms, glucose, lipids, cancer, osteoporosis. Cardioprotective and neuroprotective
DIFERULOYLMETHANES[46,56,84,142-144]
Curcumin: Present in several species of Zingiberaceae p/e: (*Curcuma aromatic*), (*Curcuma longa*), (*Curcuma cedoaria*), (*Curcuma wenyujin*), (*Curcuma kwangsiensis*). **Pharmacological activities.** Anticancer (chemopreventative and Chemotherapeutic), antioxidant, anti-inflammatory, cardioprotective, antimicrobial, neuroprotective. Inhibits scarring, cataract, and gallstone formation. Prevents liver injury, kidney toxicity, diabetes, multiple sclerosis, Alzheimer's, HIV disease, septic shock, lung fibrosis, arthritis, and inflammatory bowel disease
Furocoumarin: Present in Citrus-peel oils and a few other essential oils, for example: Angelica (*Angelica archangelica*) root and rue (*Ruta graveolens*). **Pharmacological activities.** Antioxidative, anti-inflammatory, anticancer and bone health

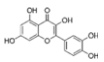
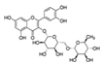
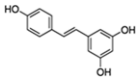
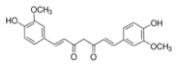
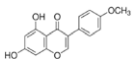
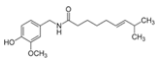
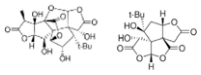
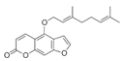
(continued)

Table 1. (continued)

Classification. Subclassification, presence and pharmacological activities
ANTHOCYANIDINS[101,145-151]
Delphinidin: It is found in many brightly colored fruits, vegetables. **Pharmacological activities.** Antioxidant, antimutagenics, anti-inflammatory and antiangiogenic
Cyanidin: Present in Apples red flesh (*Malus domestica*), apple white flesh (*Malus spp*) and berries (*vaccinium corymbosum L*) in particular, ed-skinned, hawthorn, bilberries, cranberries, chokeberries. **Pharmacological activities.** Attributable antioxidant effect
Petunidin: It is found in Plant Petunia (*Petunia axillaris*), blueberries, muscadine (*Vitis rotundifolia*) is the major source. Other sources: Blueberry (*Vaccinium macrocarpon*), Jamaica flower (*H sabdariffa*), Guava (*P granatum*), Cacao (*T cacao*), Grape (*Vitis vinifera*), Raspberry (*Rubus idaeus*), Cherry (*Prunus ceresus*), Blackberry (*Rubus ulmifolius*). **Pharmacological activities.** Antioxidant, reduces the risk of heart attack
HYPERFORIN[30,75,152-154]
It is found in St. John's wort (*Hypericum perforatum, Hypericum elodes, Hypericum calycinum*). **Pharmacological activities**. Antidepressants, antibiotic activity against gram-positive bacteria, antitumoral, in addition to the neuronal uptake of serotonin, norepinephrine, dopamine
PROTOALKALOIDS[11,44,49,132,155,156]
Capsaicin or chili pepper (*Capsicum*): Which can be found in several species of chili (*Capsicum*). Pharmacological activities. Analgesic properties
ALKALOIDS[157-161]
Berberine: Present in Berberis species, Goldenseal (*Hydrastis canadensis*), Coptidis rhizoma (*Rhizomes of Coptis chinensis*), *Phellodendron chinense* Schneid. (Family Rutaceae), genus Mahonia. **Pharmacological activities**. Berberine and its metabolites such as berberrubine, thalifendine, demethyleneberberine and jatrorrhizine were antimicrobial, anti-diabetic, anti-cancer activities
TERPENES[162-167]
Bilobalide contained in *Ginkgo biloba*: Present in *Ginkgo biloba* ginkgo tree. **Pharmacological activities**. Cardioprotective and neuroprotection effect, anticancer activity, in addition, also have toxic effects genotoxicity and carcinogenicity
Baicalin present in (*Scutellaria radix*), from which it is obtained from the dried roots of (*S. baicalensis*) Georgi and other Scutellaria species, including (*S. lateriflora*) and *S. galericulata*. **Pharmacological activities**. Antitumor, antimicrobial, and antioxidant
Ginseng (*Panax ginseng*): Present in several species ginsenosides: (*P ginseng*) Korean ginseng, (*Panax notoginseng)* Chinese ginseng, (*Panax japonicum)* Japan ginseng, and (*Panax quinquefolius)* American ginseng. **Pharmacological activities**. Antioxidation, anti-inflammatory, vasorelaxation, antiallergic, antidiabetic, and anticancer, beneficial effects on cardiac and vascular
***Sophora flavescens* or Ku Shen:** Present in root of Radix (*Sophorae flavescentis)* Kushen. **Pharmacological activities**. Antitumor, antimicrobial, antipyretic, antinociceptive, and anti-inflammatory
Bunge (*Salvia miltiorrhiza*): Present in roots of (*S miltiorrhiza)*. **Pharmacological activities**. Analgesic, anti-cancer, anticoagulant, anti-thrombolitic, anti-allergic, antibacterial, treatment of gastrointestinal hemorrhage, osteoporosis, skin diseases, pyretic stranguria and diuretic agent

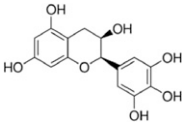
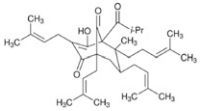
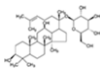
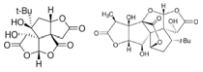
The sources were revised as a complement in.[168]

Table 2. Decrease in drug concentrations by modulation *Cyp3A*/CYP3A by phytochemicals.

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
		INHIBITION IN PRECLINICAL STUDIES IN RATS		
		FLAVONOLS		
	Quercetin (50 mg/kg)	Cyclosporine (CSP) (1.25 mg/kg)	AUC $_{CSP\ alone}$= 65.5 ± 25.8 μg/mL/min AUC $_{CSP+quercetina}$= 37.2 ± 2.2 μg/mL/min	Quercetin decreases (43%) the CSP plasma concentration. Cmax decreased[26]
	Rutin (110 mg/kg)	Cyclosporine (CSP) (1.25 mg/kg)	AUC $_{CSP+rutin}$ = 28 ± 11.1 μg/min/mL	Rutin decreases (57%) the CSP plasma concentration. Cmax decreased[26]
		FLAVONES		
	Galangin (8 mg/kg/day)	Midazolam (MDZ) (5 mg/kg)	AUC $_{MDZ\ alone}$= 6454 ± 134 μg/L/h AUC $_{MDZ+Galangin}$= 1558.15 μg/L/h	Galangin decreases (75%) the MDZ plasma concentration. Tmax and Cmax increase. **The mRNA expression of *Cyp3A* was repressed[31]
		STILBENES		
	Resveratrol (20 mg/kg)	Saquinavir (SQV) (30 mg/kg)	AUC $_{SQV\ alone}$= 258 ± 12 ng/mL/h AUC $_{SQV+RESV}$= 177.92 ± 90 ng/mL/h	Resveratrol decreases (31%) the SQV concentration. Cmax increases and Tmax decreases[64]
	Resveratrol contents in grape seed extract (80 mg/kg)	Midazolam (MDZ) (20 mg/kg)	AUC $_{MDZ\ alone}$= 3.09 ± .79 μg/mL/h AUC $_{MDZ+GSE}$= 2.37 ± .55 μg/mL/h	It decreases (23%) the MDZ concentration. Cmax decrease, Tmax and clearance increase[48]
		DIFERULOYMETHANES		
	Curcumin (200 mg/kg)	Buspirone (BUS) (10 mg/kg)	AUC $_{BUS\ alone}$= 224 μg/mL/min AUC $_{BUS+CUR}$= 208 μg/mL/min	Curcumin decreases (7.5%) the BUS plasma concentration. Clearance increases[170]
	Curcumin (100 mg/kg)	Everolimus (EVL) (.5 mg/kg)	AUC $_{EVL\ alone}$= 1637.7 ± 3 ng/mL/min AUC $_{EVL+cucumin}$= 466 ± 33 ng/mL/min	Curcumin decrease (72%) the EVL concentration. Cmax decreased[56]
		ISOFLAVONES: FLAVANS		
	Biochanin A (100 mg/kg)	Tamoxifen (TMF) (10 mg/kg)	AUC $_{TMF\ alone}$= 1572.3 ± 90 ng/mL/h AUC $_{TMF+Biochanin}$= 1065.94 ± 13 ng/mL/h	Biochanin decreases (32%) the TMF plasma concentration. Cmax and Tmax decreased[25]
	Biochanin (100 mg/kg)	4-hydroxytamoxifen (10 mg/kg of TMF)	AUC $_{TMF\ alone}$= 177.3 ± 90 ng/mL/h AUC $_{TMF+Biochanin\ A}$= 107.8 ± 13 ng/mL/h	Biochanin decreases (40%) the 4-TMF plasma concentration. Cmax and Tmax decreased[25]
		PROTOALKALOIDS		
	Capsaicin (30 mg/kg	Midazolam (MDZ) (10 mg/kg)	AUC $_{MDZ\ alone}$ = 3418.6 ± 26 μg/L/h AUC $_{MDZ+Capsaicin}$= 2683.46 ± 151 μg/L/h	Capsaicin decreases (21.5%) the MDZ plasma concentration. Cmax and Tmax decreased and clearance increase[49]
		TERPENES		
	Bilobalide and ginkgolide Contained in 100 mg/kg of ginkgo extract	Theophylline (TPL, 10 mg/kg)	AUC $_{TPL\ alone}$= 148.3 ± 8.7 μg g/mL/h AUC $_{TPL+ginkgo}$= 92.2 ± 2 μg/mL/h	Ginkgo decreases (37%) the TPL plasma concentration[67]
		INHIBITION IN CLINICAL STUDIES IN HEALTHY VOLUNTEERS		
		FLAVANONES		
	Bergamottin contents in 600 mL of grapefruit juice (GFJ)	Celiprolol (CPL) (100 mg)	AUC $_{CPL\ alone}$= 814 ± 21 ng/mL/h AUC $_{CPL+(GFJ)}$= 200 ± 125 ng/mL/h	Bergamottin decreases (75%) the CPL plasma concentration. Cmax decreases and Tmax increases[59]

(continued)

Table 2. (continued)

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
			TANNINS	
	Epigallocatechin contents in commercial green tea (700 mL)	Nadolol (NDL) (30 mg)	AUC $_{NDL\ alone}$ = 708.9 ± 56 ng/mL/h AUC $_{NDL+Green\ tea}$= 106.6 ± 67 ng/mL/h	Epigallocatechin decreases (85%) the NDL plasma concentration. Cmax and Tmax decreased and clearance increase[60]
			EFECT IN PROTEIN ACTIVITY IN PRECLINICAL STUDIES (RAT)	
			FLAVONOIDS AND TERPENES	
	Sophora extract (.316 g/kg/day)	Indinavir (IDN) (40 mg/kg)	AUC $_{IND\ alone}$= 16.07 ± .99 μg/mL/h AUC $_{IND+Sophora}$= 7.23 ± .83 μg/mL/h	Sophora extract decreases (55%) the IND plasma concentration. Cmax decreases and Tmax and clearance increases.**The expression of CYP3A was increased at nivel mRNA and protein[8]
			EFFECT IN PROTEIN ACTIVITY IN CLINICAL STUDIES IN HUMANS IN HEALTHY VOLUNTEERS	
			Phenolic compounds	
	Hyperforin (8 mg) content in tablet with 900 mg of SJW	Digoxin (DGN) (.25 mg)	AUC $_{DGN\ alone}$= 7.8 ± 1.6 ng/mL/h AUC $_{DGN+SJW}$= 6.0 ± 1.3 ng/mL/h	Hyperforin decreases (23%) the plasma DGN concentration. Cmax and Tmax decreases[58]
	Hyperforin (.88 mg) contents in 60 mg of SJW	Alprazolam (ALP) (1 mg)	AUC $_{ALP\ alone}$ = 149 μg/L/h AUC $_{ALP+SJW}$ = 14.4 μg/L/h	Hyperforin decreases (90%) the ALP plasma concentration. Cmax and Tmax[171]
	Hyperforin contents in tablet with 300 mg of SJW	Alprazolam (ALP) (2 mg)	AUC $_{ALP\ alone}$= 522 ng/mL/h AUC $_{ALP+SJW}$ = 254 ng/mL/h	It decreases (51%) the ALP plasma concentration. Cmax decreases and Tmax increases[62]
	Hyperforin (3% to 6%) contents tablet with 900 mg of SJW.	R-Verapamil (VPM) (120 mg/L)	AUC $_{VPM\ alone}$= 2406 ± 17 ng/mL/min AUC $_{VPM+SJW}$= 420 ± 24 ng/mL/min	Hyperforin decreases (82.5%) the plasma concentration of verapamil when co-administered orally. Cmax and Tmax decreases.[172]
	Hyperforin (3% to 6%) contents tablet with 900 mg of SJW	S-Verapamil (VPM) (120 mg/L)	AUC $_{VPM\ alone}$ = 413 ± 31 ng/mL/min AUC $_{VPM+SJW}$ = 56 ± 32 ng/mL/min	It decreases (86%) the VPM plasma concentration. Cmax and Tmax decreases[172]
	Hyperforin contents in tablet with 900 mg SJW	Quazepam (QZM) (15 mg)	AUC $_{QZM\ alone}$ = 217 ± 28 ng/mL/h AUC $_{QZM+SJW}$= 161 ± 25 ng/mL/h	Hyperforin decreases (26%) the QZM plasma concentration. Cmax decreases and Tmax increases[63]
	Hyperforin contents in tablet with 600 mg day of SJW. ***Kidney transplant patients	Cyclosporin (CSP) Constant blood concentration in a range of 100-150 μg/L	AUC $_{CSP\ alone}$= 3319 ± 36 μg/L/h AUC $_{CSP+SJW}$= 2832 ± 38 μg/L/h	It decreases (14.7%) the CSP plasma concentration. Cmax decreases[173]
	Hyperforin contents in tablet with 900 mg/day of St. John's wort (SJW) ***Kidney transplant patients	Cyclosporine (CSP) (80-150 μmg/L) unchanged for at least 2 months	AUC $_{CSP\ alone}$= 3473 ng/mL/h AUC $_{CSP+SJW\ high}$= 1671 ± 313 ng/mL/h	Hyperforin decreases (52%) the CSP plasma concentration. Cmax and Tmax decreases[174]
			TERPENES	
	Ginsenosides contents in capsules with 500 mg	Midazolam (MDZ) (8 mg)	AUC $_{MDZ\ alone}$= 120 ng/mL/h AUC $_{MDZ+Ginseng}$= 79 ng/mL/h	Ginsenosides decreases (34%) the MDZ plasma concentration. Cmax decreases and clearance increase[50]
	Ginsenosides contents in capsules with 500 mg	Fexofenadine (FDN) (120 mg)	AUC $_{FDN\ alone}$= 2036 ng/mL/h AUC $_{FDN+Ginseng}$= 1860 ng/mL/h	Ginsenosides decreases (9%) the FDN plasma concentration. Cmax decreases, Tmax increases and clearance increase[50]
	Bilobalide and ginkgolide in tablets with 240 mg of ginkgo leaf (GBE)	Simvastatin (SMV) (40 mg)	AUC $_{SMV\ alone}$= 86.44 ± 35 μg/L/h AUC $_{SMV+GBE}$= 49.55 ± 2 μg/L/h	Bilobalide decreases (43%) the plasma concentration of SMV. Cmax decreases and Tmax increases[61]
			Other plants	
	Capsules of danshen (DSC). *Salvia miltiorhirza* with .56 g	Clopidogrel (CLP) (300 mg)	AUC= $_{CLP\ alone}$ 16.67 ± 3.39 ng/mL/h AUC $_{CLP+DSC}$=8.28 ± 1.81 ng/mL/h	*S miltiorhirza* decreases (50%) plasma concentration of CLP. Cmax, Tmax decrease and clearance increase[66]

*AUC value of drug administered alone (control) and co-administered with (Pch). ** Article reporting expression of cyp3a genes.
***Kidney transplant patients. All PCH were co-administered orally with drug in both preclinical or clinical studies. The Pch structure were obtained from the database of Sigma-Aldrich.[168]

be adequately reduced, thus failing to stop the disease progression.[8,64]

Patients receiving antineoplastic therapy must take special care with the type and amount of Pchs that are consumed, to avoid a possible therapeutic failure. Some studies have found that biochanin A, present in oregano and broad beans, causes a reduction in the systemic concentration of tamoxifen and its metabolite 4-hydroxytamoxifen (Table 1).[25,65]

The plasma concentration of the antiplatelet clopidogrel decreases when co-administered with the flavonoids found in *Salvia miltiorrhiza*,[66] which could increase the risk of blood thrombosis and cause cerebrovascular disease or coronary heart disease.

The bioavailability of the antihistamine fexofenadine is affected by the consumption of Ginseng,[50,67] which reduces its plasma concentration and increases its Tmax and clearance, diminishing its therapeutic effect (Tables 2 and 3).

The components of *Ginkgo biloba* affect the bioavailability of theophylline,[67] reducing its blood concentration. It is important to avoid co-administration of these two substances since it could lead to asthmatic attacks, bronchospasms, and lack of ventilation, among other conditions.[68]

Increase in Drug Concentrations by Modulation cyp3a/CYP3A by Phytochemicals

An increase in the AUC of a drug can also be a consequence genes activation/repression *cyp3a/abcb1* or inhibition CYP3A/P-gp as shown in Tables 4 and 5.

Concomitant use of Pchs and medications that are CYP3A substrates may expose the patient to drug interactions and severe side effects, thereby affecting treatment adherence, safety and clinical outcome.

Cardiovascular drugs such as verapamil, norverapamil, losartan, diltiazem, felodipine, nicardipine, dihydrofelodipine and nifedipine increase their plasma concentration when combined with some Pchs, which can lead to severe arterial hypotension, bradycardia, and high toxicity, among others.[21,28,31,46,57,69-79]

An increase in the plasma concentration of anticonvulsants such as triazolam and carbamazepine can produce ataxia, hypotonia, hypotension, respiratory depression, coma, arrhythmia, hemodynamic instability, and death. Carbamazepine, an antiepileptic drug with a narrow therapeutic window, is metabolized to carbamazepine-10,11-epoxide, active metabolite generated by CYP3A. Resveratrol markedly increased the systemic exposure and brain concentration of carbamazepine and its metabolite by inhibiting the CYP3A and P-gp activities. Co-administration of resveratrol with carbamazepine increase the concentration of the drug and its active metabolite in plasma, brain, liver and kidney.[51,80,81]

An unplanned increase in the plasma concentration of the anxiolytics midazolam, alprazolam and buspirone could cause serious problems: increased respiratory rate, lightheadedness, confusion, depression of superficial reflexes, slightly decreased alertness, ataxia, slurred speech, postural instability and even death.[48,59,82-85]

An increase in the plasma concentration of immunosuppressants such as cyclosporine could produce toxicity in kidneys and brain.[11,86]

For some antineoplastic drugs such as methotrexate, doxorubicin, paclitaxel and tamoxifen an increase in their plasma concentrations can cause hematological or myeloid alterations (toxicity) associated with fever, infections, septicemia, septic shock, hemorrhages, tissue hypoxia or death.[22-24,33,87-89]

An increase in the concentration of the antidepressant aripiprazole can produce mild side effects such as blurred vision, fatigue, headache, insomnia, tremors, but also serious side effects such as suicidal tendencies, cardiovascular disorders (hypotension, venous thromboembolism), seizures, neuroleptic malignant syndrome, among others[90] (Tables 4 and 5).

Some terpenes presents in the extract of *S. flavescens* produces a transcriptional activation of *cyp3A* and *abcb1* genes, meanwhile, capsaicin compounds exhibit *cyp3A/abcb1* repression[8] (Table 6).

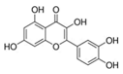
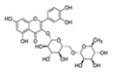
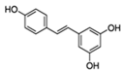
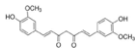
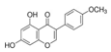
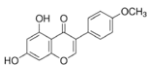
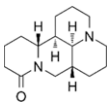
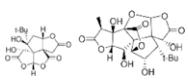
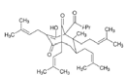
On the other hand, quercetin, bergamottin, myricetin, naringenin, resveratrol, curcumin, baicalein and capsaicin exhibit inhibition of CYP3A and P-gp proteins; this inhibition affects the AUC of different drugs (increase/decrease), for example: quercetin and rutin reduce the cyclosporine plasma concentration by inhibiting both CYP3A and P-gp,[26] however, baicalein increases the tamoxifen concentration by inhibiting the same proteins[88]

Pchs are popularly associated with various beneficial effects such as antioxidant, anticancer and antidiabetic activity and/or good health in general. However, the existing evidence shows that the co-administration of Pchs with some drugs should be further studied to avoid interactions that cause an increase or decrease in the systemic concentrations of the drug and impact in the effectiveness and/or safety of the treatment.

The evidence also shows that interactions between drugs and Pchs have their origin in the modulation of genes *cyp3a/abcb1* or in the inhibtion of both proteins CYP3A/P-gp.

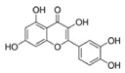
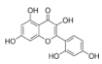
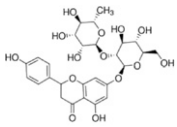
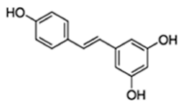
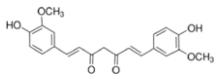
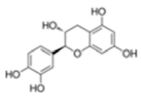
These interactions influence the bioavailability of different drugs that are co-administered with food, fruits, vegetables, beverages, and/or food supplements containing different Pchs, and can cause an underdose or an overdose of the drug.[3-5] It is well known that phytomolecules are metabolized through various pathways by phase 1 and 2 enzymes and that they can serve as substrates for drug transporters.[91,92] However, further studies are required to evaluate the influence of the various

Table 3. Decrease in drug concentrations by modulation *abcb1*/P-PG BY phytochemicals.

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
		INHIBITION IN PRECLINICAL STUDIES IN RAT		
			FLAVONOLS	
	Quercetin (50 mg/kg)	Cyclosporine (CSP) (1.25 mg/kg)	AUC $_{CSP\ alone}$= 65.5 ± 25.8 μg/mL/min AUC $_{CSP+quercetina}$= 37.2 ± 2.2 μg/mL/min	Quercetin decreases (43%) the CSP plasma concentration. Cmax decreased[26]
	Rutin (110 mg/kg)	Cyclosporine (CSP) (1.25 mg/kg)	AUC $_{CSP\ alone}$= 65.5 ± 25.8 μg/min/mL AUC $_{CSP+rutin}$= 28 ± 11.1 μg/min/mL	Rutin decreases (57%) the CSP plasma. Cmax decreased[26]
			STILBENES	
	Resveratrol (RESV) (20 mg/kg)	Saquinavir (SQV) (30 mg/kg)	AUC $_{SQV\ alone}$= 258 ± 12 ng/mL/h AUC $_{SQV+RESV}$= 177.92 ± 90.5 ng/mL/h	Resveratrol decreases (31%) the SQV plasma concentration. Cmax increases, Tmax decreases and clearance increase[64]
			DIFERULOYMETHANES	
	Curcumin (100 mg/kg)	Everolimus (EVL) (.5 mg/kg)	AUC $_{EVL\ alone}$= 1637.7 ± 3 ng/mL/min AUC $_{EVL+curcumin}$= 466 ± 33 ng/mL/min	Curcumin decreases (72%) EVL the plasma concentration. Cmax decreased[56]
			FLAVANS	
	Biochanin (100 mg/kg)	Tamoxifen (TMF) (10 mg/kg)	AUC $_{TMF\ alone}$= 1572.3 ± 90 ng/mL/h AUC $_{TMF+\ Biochanin}$= 1065.9 ± 2 ng/mL/h	Biochanin decreases (32%) the TMF plasma concentration. Cmax and Tmax decreased[25]
	Biochanin (100 mg/kg)	4-hydroxytamoxifen (10 mg/kg TMF)	AUC $_{TMF\ alone}$= 177.3 ± 90 ng/mL/h AUC $_{TMF+Biochanin}$= 107.8 ± 13 ng/mL/h	Biochanin decreases (40%) the 4-TMF plasma concentration. Cmax and Tmax decreased[25]
		INHIBITION IN CLINICAL STUDIES IN HUMANS		
			FLAVANONES: (bergamottin)	
	Bergamottin in 600 mL of grapefruit juice (GFJ)	Celiprolol (CPL) (100 mg)	AUC $_{CPL\ alone}$= 814 ± 21 ng/mL/h AUC $_{CPL+GFJ}$= 200 ± 125 ng/mL/h	Bergamottin decreases (75%) the CPL plasma concentration. Cmax decreased and Tmax increases[59]
			TANNINS: (Epigallocatechin)	
	Epigallocatechin contents in commercial green tea (700 mL)	Nadolol (NDL) (30 mg)	AUC $_{NDL\ alone}$ = 708.9 ± 56 ng/mL/h AUC $_{NDL+Green\ tea}$= 106.6 ± 67 ng/mL/h	Epigallocatechin decreases (85%) the NDL plasma concentration. Cmax, Tmax decreased, and clearance increases[60]
		EFFECT IN PROTEIN ACTIVITY IN PRECLINICAL STUDIES IN RAT		
			FLAVONOIDS AND TERPENES	
	Sophora extract (.316 g/kg/day)	Indinavir (IND) (40 mg/kg)	AUC $_{IND\ alone}$= 16.07 ± .99 μg/mL/h AUC $_{IND+Sophora}$= 7.23 ± .83 μg/mL/h	Sophora decreases (55%) the IND plasma concentration. Cmax decreases, Tmax and clearance increase. **The expression of P-gp was increased at nivel mRNA and protein[8]
		EFFECT IN PROTEIN ACTIVITY IN CLINICAL STUDIES IN HEALTHY VOLUNTEERS		
			TERPENES	
	Bilobalide and ginkgolide in tablets with 240 mg of ginkgo leaf (GBE)	Simvastatin (SMV) (40 mg)	AUC $_{SMV\ alone}$= 86.44 ± 35 μg/L/h AUC $_{SMV+GBE}$= 49.55 ± 2 μg/L/h	Bilobalide decreases (43%) the SMV plasma concentration. Cmax decreases and Tmax increases[61]
			PHENOLIC COMPOUNDS	
	Hyperforin present in table with 900 mg of St John's wort (SJW)	Talinolol (TLOL) (50 mg)	AUC $_{TLOL\ alone}$= 834 ± 45 ng/mL/h AUC $_{TLOL+SJW}$ = 564 ± 36 ng/mL/h	Hyperforin decreases (32%) the plasma concentration of TLOL. Cmax decreases and Tmax increases[57]

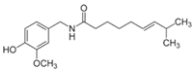
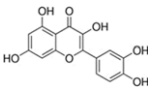
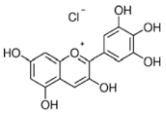
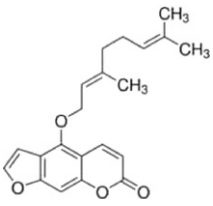
*AUC value of drug administered alone (control) and co-administered with (Pch). **Article reporting expression of *abcb1* genes. All PCH were co-administered orally with drug in both preclinical or clinical studies. The Pch structure were obtained from the database of Sigma-Aldrich.[168]

Table 4. Increase in drug concentrations by modulation of *cyp3a*/CYP3A by phytochemicals.

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
		PRECLINICAL STUDIES IN RAT		
		FLAVONOLS		
	Quercetin (20 mg/kg/day)	Losartan (LSN) (10 mg/kg)	AUC $_{LSN\ alone}$= 7.34 ± .75 mg/mL/h AUC $_{LSN+quercetin}$= 13.9 ± 1,2 mg/mL/h	Quercetin increases (89%) the LSN plasma concentration. Cmax increased and Tmax decreased[74]
	Quercetin in 400 mg/kg of *Millettia aboensis* (EMA)	Simvastatin (SMV) (20 mg/kg)	AUC $_{Dx+vehicle+SMV}$= 29.5 ± .48 μg/mL/h AUC $_{DX+EMA+SMV}$= 69.6 ± .6 μg/mL/h	Quercetin increased (135%) the SMV plasma concentration. Increased Tmax and decreases clearance[175]
	Myricetin (8 mg/kg)	Losartan (LSN) 9 mg/kg	AUC $_{LSN\ alone}$= 283 ± 57 ng/mL/h AUC $_{LSN+myricetin}$= 456 ± 88 ng/mL/h	Myricetin increases (61%) the LSN plasma concentration. Cmax and Tmax increase[21]
	Morin (15 mg/kg)	Diltiazem (DTZ) (7.5 mg/kg)	AUC $_{DTZ\ alone}$= 358 ± 56.9 ng/mL/h AUC $_{DTZ+morin}$= 642 ± 76.6 ng/mL/h	Morin increased (79%) the DTZ plasma concentration. Cmax increase and decreases clearance[77]
	Kaempferol (10 mg/kg)	Nifedipine (NFNE) (10 mg/kg)	AUC $_{NFNE\ alone}$= 5930 ± 107 μg/mL/min AUC $_{NFNE+Kaempferol}$ = 9234 ± 1569 μg/min/mL	Kaempferol increase (56%) the NFNE plasma concentration when co-administered orally[73]
		FLAVONOIDS GLYCOSIDES		
	Naringin (7.5 mg/kg). In rabbit	Verapamil (VPM) (9 mg/kg)	AUC $_{VPM\ alone}$= 18.4 ± 4.2 μg/mL/min AUC $_{VPM+naringin}$= 28.4 ± 6.3 μg/mL/min	Naringin increased (54%) the VPM plasma concentration. Cmax increase[78]
	Naringin (7.5 mg/kg). In rabbit	Norverapamil (NVPM) (9 mg/kg of verapamil)	AUC $_{NVPM\ alone}$= 16.6 ± 4.2 μg/mL/min AUC $_{NVPM+naringin}$= 19.1 ± 6.3 μg/mL/min	Naringin increased (15%) the NVPM plasma concentration. Cmax increase[78]
		STILBENES		
	Resveratrol contents in 2 g/kg of *P. cuspidatum* (PC)	Carbamazepine (CBZ) (200 mg/kg)	AUC $_{CBZ\ alone}$= 13.3 ± 1.4 mg/mL/min AUC $_{CBZ+PC}$= 30.3 ± 1.7 mg/mL/min	Resveratrol increased (127%) the CBZ plasma concentration and also in brain, liver and kidney. Cmax increase[51]
	Resveratrol contents in 2 g/kg of *P. cuspidatum* (PC)	Carbamazepine 10,11-epoxide (200 mg/kg of CBZ)	AUC $_{CBZ\ alone}$ = 25.4 ± 2.6 mg/mL/min AUC $_{CBZ+PC}$ = 44.7 ± 3 mg/mL/min	Resveratrol increased (75.9%) the plasma concentration of CBZ-10,11-epoxide and also in brain, liver, and kidney. Cmax increases[51]
	Resveratrol (10 mg/kg)	Diltiazem (DTZ)(15 mg/kg)	AUC $_{DTZ\ alone}$= 283 ± 65 ng/mL/min AUC $_{DTZ+resveratrol}$= 439 ± 98 ng/mL/min	It increased (55%) the DTZ plasma concentration. Cmax increase[79]
	Resveratrol (200 mg/kg)	Aripiprazole (APZ) (3 mg/kg)	AUC $_{APZ\ alone}$= 158 ± 36 μg/L/h AUC $_{APZ+resveratrol}$= 634 ± 11 μg/L/h	Resveratrol increased (301%) the APZ plasma concentration. Cmax increases and clearance decreases[90]
		DIFERULOYMETHANES		
	Curcumin (60 mg/kg)	Midazolam (MDZ) (20 mg)	AUC $_{MDZ\ alone}$= 255 ± 27 ng/mL/h AUC $_{MDZ+Curcumin}$= 470 ± 88.3 ng/mL/h	Curcumin increased (84%) the MDZ plasma concentration. Cmax increases and clearance decreases twice[84]
		TANNINS		
	Catechin in green tea extract (GTE) (400 mg/kg)	Midazolam (MDZ) (20 mg/kg)	AUC $_{MDZ\ alone}$= 3.09 ± .79 μg/mL/h AUC $_{MDZ+GTE}$= 9.16 ± 2.5 μg/mL/h	Catechin increased (196%) the MDZ plasma concentration. Cmax and Tmax increase and clearance decreases[48]

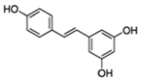
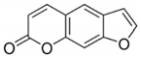
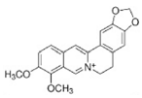
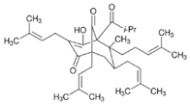
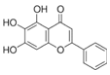
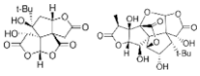
(continued)

Table 4. (continued)

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
		PROTOALKALOIDS		
	Capsaicin (3.0 mg/kg)	Cyclosporin (CSP) (50 mg/kg)	AUC $_{CSP\ alone}$= 97.7 ± 26 μg/mL/h AUC $_{CSP+capsicin}$= 140.4 ± 18.9 μg/mL/h	Capsaicin increases (44%) the CSP plasma concentration. Cmax and Tmax increased. Clearance decreases. **The mRNA expression of CYP3A was repressed in the intestine and liver[11]
		CLINICAL STUDIES IN HEALTHY VOLUNTEERS		
		FLAVONOLS		
	Quercetin contents in valerian tablets (1.0 g)	Alprazolam (ALP) (2 mg)	AUC $_{ALP\ alone}$= 472.18 ng/mL/h AUC $_{ALP+Valerian}$= 538 ± 240 ng/mL/h	Quercetin increases (14%) the ALP plasma concentration. Cmax increased[83]
		ANTHOCYANINS		
	300 mL of juice (BBJ) contained a concentration of 700- 2100 mg/mL of total anthocyanins predominated: Delphinidin 44.5 μg/mL, Cyanidin 22.7 μg/mL, Petunidin 29.5 μg/mL)	Buspirone (BUS) (10 mg)	AUC $_{BUS\ alone}$= 3.11 ± 4.52 ng/mL/h AUC $_{BUS+\ BBJ}$= 4.06 ± .59 ng/mL/h	Anthocyanins increased (30%) the BUS plasma concentration of buspirone. Cmax and clearance decreases and Tmax increases[85]
		FLAVONONES		
	Bergamottin (25-100 μM)contained in 250 mL grapefruit juice (GFJ)	Felodipine (FDP) (10 mg tablets)	AUC $_{FDP\ alone}$= 36 ± 8 mol/L/h AUC $_{FDP+GFJ}$ = 65 ±11 mol/L/h	Bergamottin increased (80%) the FDP plasma concentration. Cmax decreased[28]
	Bergamottin in 300 mL of grapefruit juice (GFJ)	Felodipine (FDP) (10 mg)	AUC $_{FDP\ alone}$= 13 ± 1.6 ng/mL/h AUC $_{FDP+GFJ}$= 25 ± 4.3 ng/mL/h	Bergamottin increased (92.3%) the FDP plasma concentration. Cmax increased and Tmax decreased[176]
	Bergamottin in 250 mL of grapefruit juice (GFJ)	Felodipine (FDP) (5 mg)	AUC $_{FDP\ alone}$= 20.1 ± 4.4 nmol/L/h AUC $_{FDP+GFJ}$= 29.8 ± 7.8 nmol/L/h	Bergamottin increased (48%) the FDP plasma concentration. Cmax increased and Tmax decreased[76]
	Bergamottin (12 mg)	Felodipine (FDP) (5 mg)	AUC $_{FDP\ alone}$= 20.1±4.4 nmol/h/L AUC $_{FDP+Bergamottin}$= 26.7 ±8.3 mol/h/L	Bergamottin increased (32.8%) the FDP plasma concentration. Cmax increased and Tmax decreased[76]
	Bergamottin in 300 mL of grapefruit juice (GFJ)	Dehydrofelodipine (DFDP) (10 mg Felodipine)	AUC $_{DFDP\ alone}$= 16.9 ± 2.6 ng/mL/h AUC $_{DFDP+GFJ}$= 21 ± 4.2 ng/mL/h	Bergamottin increased (24.2%) the DFPD plasma concentration. Cmax increased and Tmax decreased.[176]
	Bergamottin in 300 mL of grapefruit juice (GFJ)	Midazolam (MDZ) (6 mg)	AUC $_{MDZ\ alone}$= 64.9 ± 7 ng/mL/h AUC $_{MDZ+GFJ}$= 106.8 ± 12 ng/mL/h	Bergamottin increased (64%) the MDZ plasma concentration. Cmax increased, clearance is reduced[82]
	Bergamottin in 600 mL of grapefruit juice (GFJ)	Midazolam (MDZ) 15 μg/kg	AUC $_{MDZ\ alone=}$ 11.3 ± 6.18 nmol/L/h AUC $_{MDZ+GFJ}$= 22.9 ± 13.8 nmol/L/h	Bergamottin increased (100%) the MDZ plasma concentration. Cmax increase[59]
	Bergamottin in 240 mL of grapefruit juice (GFJ)	Cyclosporine (CSP) (5 mg/kg)	AUC $_{CSP+Orange\ juice\ (control)}$= 11.3 nmol/L/h AUC $_{CSP+GFJ}$= 15.6 nmol/L/h	Pch increased (38%) the CSP plasma concentration. Cmax increased, clearance is reduced[86]
	Bergamottin in 300 mL of grapefruit juice (GFJ)	Triazolam (TZL) (.1875 mg)	AUC $_{TZL\ alone}$= 10.0 ± 3.5 ng/mL/h AUC $_{TZL+GFJ}$= 16.0 ± 4.7 ng/mL/h	It increases (60%) the TZL plasma concentration. Cmax increased, clearance is reduced[81]
	Bergamottin (7.3 mg/mL) in 300 mL of grapefruit juice (GFJ)	Buspirone (BUS) (10 mg)	AUC $_{BUS\ alone}$= 3.11 ± 4.06 ng/mL/h AUC $_{BUS+GFJ}$= 6.15 ± .92 ng/mL/h	Bergamottin increased (97%) the BUS plasma concentration. Cmax, Tmax increased and clearance reduction[85]

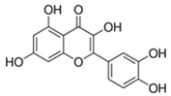
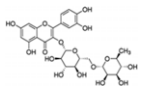
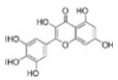
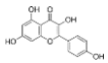
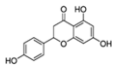
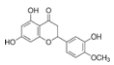
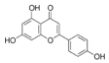
(continued)

Table 4. (continued)

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
		STILBENES		
	Resveratrol (500 mg)	Carbamazepine (CBZ) (200 mg/kg)	AUC $_{CBZ\ alone}$= 195.6 ± 39 mg/mL/min AUC $_{CBZ+Resveratrol}$= 288.7 ± 35 mg/mL/min	Resveratrol increased (48%) the CBZ plasma concentration. Cmax increased, Tmax and clearance decreased[80]
		DIFERULOYMETHANES		
	Furanocoumarin in 240 mL of grapefruit juice (GFJ)	Felodipine (FDP) (10 mg)	AUC $_{FDP+Orange\ juice\ (control)}$= 54 nmol/L/h AUC $_{FDP+GFJ}$= 110 nmol/L/h	Furanocoumarin increased (104%) the FDP plasma concentration. Cmax increased and clearance reduction[46]
		ALKALOIDS		
	Berberine (76.8 mg) in commercial extract Goldenseal	Midazolam (MDZ)	AUC $_{MDZ\ alone}$= 107.9 ± 43 ng/mL/h AUC $_{MDZ+Goldenseal}$= 175.3 ± 74.8 ng/mL/h	The commercial extract containing berberine increased (62%) the MDZ plasma concentration. Cmax increased and clearance reduction[177]
		PRECLINICALS STUDIES IN RAT		
		PHENOLIC COMPOUNDS		
	Hyperforin in 300 mg/kg of St John's wort (SJW)	Methotrexate (MTX) (5 mg/kg)	AUC $_{MTX\ alone}$= 163 ± 16.5 μg/mL/h AUC $_{MTX+SJW}$= 429 ± 56.4 μg/mL/h	Hyperforin increased (163%) the MTX plasma concentration. Cmax increased[33]
		TERPENES		
	Baicalein (10 mg/kg)	Tamoxifen (TMF) (10 mg/kg)	AUC $_{TMF\ alone}$= 1834 ± 51 ng/mL/h AUC $_{TMF+baicalein}$= 3468 ± 898 ng/mL/h	Baicalein increased (89%) the plasma concentration of TMF. Cmax increased and clearance reduction[88]
	Baicalein (10 mg/kg)	4-Hydroxy-tamoxifen (TMF) (10 mg/kg of TMF)	AUC $_{TMF\ alone}$= 284 ± 65 ng/mL/h AUC $_{TMF+baicalein}$= 359 ± 95 ng/mL/h	Baicalein increased (26.6%) the plasma concentration of 4-hydroxytamoxifen when co-administered baicalein-TMF. Cmax increased[88]
	Bilobalide and ginkgolide in tablets with 80 mg/kg/day ginkgo leaf (GLT)	Losartan (LSN) (10 mg/kg)	AUC $_{LSN\ alone}$= 6.99 ± 1.05 mg/L/h AUC $_{LSN+GLT}$= 11.94 ± 1.8 mg/L/h	Bilobalide increased (70%) the LSN plasma concentration. Cmax, Tmax increased and clearance decreased[72]

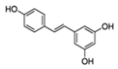
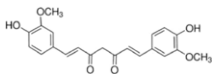
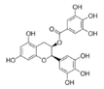
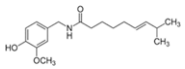
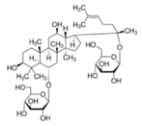
*AUC value of drug administered alone (control) and co-administered with (Pch). ** Article reporting expression of *cyp3a* genes. All PCH were co-administered orally with drug in both preclinical or clinical studies. The Pch structure were obtained from the database of Sigma-Aldrich.[168]

Table 5. Increase of drug by modulation of *abcb1*/P-gp by phytochemical.

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
			PRECLINICALS STUDIES IN RAT	
			FLAVONOLS	
	Quercetin (15 mg/kg)	Doxorubicin (DXB) (50 mg/kg)	AUC $_{DXB\ alone}$= 186 ± 44 ng/mL/h AUC $_{DXB+Quercetin}$= 439 ± 107 ng/mL/h	Quercetin increase (136%) the DXB plasma concentration. Cmax increased[22]
	Quercetin (20 mg/kg/day)	Losartan (LSN) (10 mg/kg)	AUC $_{LSN\ alone}$= 7.34 ± .75 mg/mL/h AUC $_{LSN+quercetin}$= 13.9 ± 1.2 mg/mL/h	Quercetin increases (89%) the LSN plasma concentration. Cmax increased and Tmax decreased[74]
	Rutin (40 mg/kg)	Paclitaxel (PCX) (40 mg/kg)	AUC $_{PCX\ alone}$= 1544.32 ± 24 ng/mL/h AUC $_{PCX+Rutin}$= 3193.53 ± 36 ng/mL/h	Rutin increased (106%) PCX plasma concentration. Cmax and Tmax increased[23]
	Myricetin (8 mg/kg)	Tamoxifen (TMF) (10 mg/kg)	AUC $_{TMF\ alone}$= 1832 ± 34 ng/mL/h AUC $_{TMF+Myricetin}$= 3195 ± 60 ng/mL/h	Myricetin increased (174%) the TMF plasma concentration. Cmax and Tmax increased[24]
	Myricetin (8 mg/kg)	Tamoxifen (TMF) (10 mg/kg of TMF)	AUC $_{TMF\ alone}$= 284 ± 51 ng/mL/h AUC $_{4\text{-}TMF+Myricetin}$= 352 ± 60 ng/mL/h	Myricetin increased (24%) plasma concentration of 4-TMF. Cmax and Tmax increased[24]
	Myricetin (10 mg/kg)	Doxorubicin (DXB) (40 mg/kg)	AUC $_{DXB\ alone}$= 179 ± 34 ng/mL/h AUC $_{DXB+myricetin}$= 390 ± 77 ng/mL/h	Myricetin increased (117%) the DXB plasma concentration. Cmax increased[87]
	Myricetin (8 mg/kg)	Losartan (LSN) 9 mg/kg	AUC $_{LSN\ alone}$= 283 ± 57 ng/mL/min AUC $_{LSN+myricetin}$= 456 ± 88 ng/mL/min	Myricetin increase (61%) the LSN plasma concentration. Cmax and Tmax increased[21]
	Kaempferol (10 mg/kg)	Nifedipine (NFNE) (10 mg/kg)	AUC $_{NFNE\ alone}$= 5930 ± 107 μg/mL/min AUC $_{NFNE+Kaempferol}$= 9234 ± 1569 μg/mL/min	Kaempferol increase (56%) the NFNE plasma concentration[73]
			FLAVONONES	
	Naringenin (100 mg/kg)	Felodipine (FDP) (10 mg/kg)	AUC $_{FDP\ alone}$= 2361.7 ± 34 ng/mL/h AUC $_{FDP+naringenin}$= 6086.4 ± 47 ng/mL/h	Naringenin increase (157%) the FDP plasma concentration. Cmax increased and clearance decreased[70]
	Hesperetin (100 mg/kg)	Felodipine (FDP) (10 mg/kg)	AUC $_{FDP\ alone}$= 2361.7 ± 20 ng/mL/h AUC $_{FDP+Hesperetin}$= 4386.3 ± 38 ng/mL/h	Hesperetin increased (86%) the FDP plasma concentration. Cmax increased and clearance decreased[71]
			FLAVONES	
	Apigenin (40 mg/kg)	Paclitaxel (PCX) (40 mg/kg)	AUC $_{PCX\ alone}$= 1300 ± 12 ng/mL/h AUC $_{PCX+apigenin}$= 4391.67 ± 55 ng/mL/h	Apigenin increased (237%) the PCX plasma. Cmax increased and clearance decreased[23]
			STILBENES	

(continued)

Table 5. (continued)

Structure Pch	Pch (dose of administration)	Drug (dose of administration)	AUC drug-Pch*	Effect of inhibition
	Resveratrol contents in 2 g/kg of *P. cuspidatum* (PC)	Carbamazepine (CBZ) (200 mg/kg)	AUC $_{CBZ\ alone}$= 13.3 ± 1.4 mg/mL/min AUC $_{CBZ+PC}$= 30.3 ± 1.7 mg/mL/min	Resveratrol increased (127%) the CBZ plasma concentration and also in brain, liver and kidney. Cmax increased[51]
	Resveratrol contents in 2 g/kg of *P. cuspidatum)* (PC)	Carbamazepine 10,11-epoxide (200 mg/kg of CBZ)	AUC $_{CBZ\ alone}$= 25.4 ± 2.6 mg/mL/min AUC $_{CBZ+PC}$= 44.7 ± 3 mg/mL/min	Resveratrol increased (75.9%) the plasma concentration of CBZ-10,11 and also in brain, liver, and kidney. Cmax increased[51]
	Resveratrol (10 mg/kg)	Diltiazem (DTZ) (15 mg/kg)	AUC $_{DTZ\ alone}$= 283 ± 65 ng/mL/min AUC $_{DTZ+resveratrol}$= 439 ± 98 ng/mL/min	Resveratrol increased (55%) the DTZ plasma concentration. Cmax increased[79]
			DIFERULOYMETHANES	
	Curcumin (60 mg/kg)	Midazolam (MDZ) (20 mg/kg)	AUC $_{MDZ\ alone}$= 255 ± 27 ng/mL/h AUC $_{MDZ+Curcumin}$= 470 ± 88.3 ng/mL/h	Curcumin increased (84%) the MDZ plasma concentration. Cmax increased and clearance decreased[84]
	Curcumin (60 mg/kg)	Celiprolol (CPL) (30 mg/kg)	AUC $_{CPL\ alone}$= 2140.04 ± 187 ng/mL/h AUC $_{CPL+Curcumin}$= 2347.63 ± 287 ng/mL/h	Curcumin increased (9%) the CPL plasma concentration. Cmax increased and clearance and t_{max} decreased[84]
			TANNINS	
	Epigallocatechin gallate (EGCG) (10 mg/kg)	Nicardipine (NCP) (12 mg/kg)	AUC $_{NCP\ alone}$= 371 ± 67 ng/mL/h AUC $_{NCP+\ EGCG}$= 663 ± 133 ng/mL/h	Epigallocatechin gallate increased (79%) the NCP plasma concentration. Cmax increased[69]
			PROTOALKALOIDS	
	Capsaicin (3.0 mg/kg)	Cyclosporin (CSP) (50 mg/kg)	AUC $_{CSP\ alone}$=97.7 ± 26 μg/mL/h AUC $_{CSP+capsaicin}$= 140.4 ± 18.9 μg/mL h	Capsaicin increases (44%) the CSP plasma concentration. Cmax and Tmax increased, Clearance is decreased. **The mRNA expression of *abcb1* was repressed in the intestine and liver[11]
			TERPENES	
	Ginseng extract (KRG) (100 mg/kg)	Paclitaxel (PCX) (25 mg/kg)	AUC $_{PCX\ alone}$= 50.9 ± 12.6 μg/mL/min AUC $_{PCX+KRG}$= 80.6 ± 14 μg/mL/min	Ginseng increased (57%) the PCX plasma concentration. Cmax, Tmax increased and clearance decreases[89]

*AUC value of drug administered alone (control) and co-administered with (Pch). ** Article reporting expression of *abcb1* genes. All Pch were co-administered orally with drug in both preclinical or clinical studies. The Pch figures were obtained from the database of Sigma-Aldrich.[169]

Table 6. Phytochemicals That Act in the Same Interaction Of CYP3A and P-gp, Mechanisms That Modify the Concentration of Drugs.

Pch	Effect interaction on CYP3A	Effect interaction on P-gp	Efect on Drug
INHIBITION IN CLINICAL STUDIES IN HUMAN			
Bergamottin	Inhibition evaluated with enzymatic activity. Midazolam was used as a specific substrate.	Inhibition transport was assessed celiprolol as a probe substrates.	Midazolam increase (100%) Celiprolol decrease (75%)[59]
INHIBITION IN PRECLINICAL STUDIES IN RATS			
Quercetin	Inhibition of enzymatic activity produced reduces bioavailability. Ketoconazole was a control of CYP3A inhibition.	Inhibition of transport was assessed with rhodamine 123 in cell cultures which showed a decrease in rhodamine due to quercetin.	Cyclosporine decrease (43%)[26]
Quercetin	Inhibition. Enzymatic activity.Quercetin inhibited the CYP IC50% = 14.8 μMol.	Inhibition. Transport evaluated with rhodamine 123 in cell cultures.	Doxorubicin increase (136%)[22]
Rutin	Inhibition of enzymatic activity produced reduces bioavailability. Ketoconazole was used as control of CYP3A inhibition.	Inhibition of transport was assessed with rhodamine 123 in cell cultures which showed a decrease in rhodamine due to quercetin	Cyclosporine decrease (57%)[26]
Myricetin	Inhibition enzymatic activity. Myricetin inhibited the CYP IC50% = 7.81 μMol.	Transport inhibition was observed by rhodamine 123 accumulation in MCF-7/ADR cells.	Losartan increase (61%)[21]
Myricetin	7.8 μM of myricetin was enough to inhibit the 50% the enzymatic activity CYP3A4	Inhibition transport was evaluated with rhodamine 123 in MCF-7/ADR cell cultures.	Doxorubicina increase (117%)[87]
Resveratrol	Inhibition evaluated with enzymatic activity. Ketoconazole was control of CYP3A inhibition.	The inhibition of Saquinavir transport was shown using verapamil as a control.	Saquinavir decrease (31%)[64]
Resveratrol	Inhibition. Evaluated with enzymatic activity. Ketoconazole inhibition control.	The inhibition of Carbamazepine transport was shown using verapamil as a control.	Carbamazepine increase (127%)[51]
Curcuma	Inhibition evaluated with enzymatic activity. Midazolam was used as a specific substrate.	Inhibition transport was assessed celiprolol as a probe substrates.	Midazolam increase (84%) Celiprolol increase (9%)[84]
Curcuma	Inhibition evaluated with enzymatic activity. Ketoconazole as an inhibition control.	Inhibition transport was observed with accumulation of rhodamine 123 in LS 180 cells.	Everolimus decrease (72%).[56]
Capsaicin	Inhibition observed in mRNA and protein CYP3A in liver and intestine. Induction control was dexamethasone, while the inhibition control was ketoconazole.	Inhibition observed in mRNA and protein P-gp in liver and intestine, verapamil was positive control of P-gp inhibitor, 100 mg/mL.	Cyclosporine increase (44%)[11]
Baicalein	Inhibition evaluated with enzymatic activity. Baicalein inhibited the CYP IC50% = 9.6 μMol and ketoconazole inhibition IC50% = 0.3 μMol.	Inhibition transport was assessed with rhodamine 123 in MCF-7/ADR cells cultures.	Tamoxifen increases (89%).[88]
Flavonoids present in *(Sophora flavescens)*	Activation mRNA and protein of *cyp3a*/CYP3A in intestine and liver.	Activation mRNA and protein of *abcb1*/P-gp in intestine and liver tissues.	Indinavir decrease (55%)[8]

compounds present in the vegetables consumed in the diet, in medicinal herbs, and generally in any food supplement of vegetable origin.

Conclusion

The identification of drugs that interact with Pchs is of great clinical importance. Mainly, for any drug that is a substrate of CYP3A and/or P-gp caution may need to be exercised when prescribing them. This review provides evidence that drug-Pchs interactions may be as important as drug-drug interactions.

A decrease in drug concentration can lead to therapeutic failure, whereas an increase in concentration for some drugs can lead to toxicity. The information gathered in the present review leads to suggest a better understanding of a patient's diet to make appropriate recommendations for when to take their medication, if drug-food interactions are possible. Additional research is needed to determine the "dose" of the food that provides sufficient concentrations of these compounds to lead to clinically significant interactions.

Limitations of this Literature Review

A limitation was the impossibility to cover all information that has been reported in the literature about the interaction between Pchs and drugs that are substrates of CYP3A and P-gp. This review included data from the last 2 decades. Thus, significant references on this subject may have been omitted.

Abbreviations

Pch. Phytochemical
CYP. Cytochrome
AUC. Area under the curve
P-gp. P-glycoprotein

Authors' Contributions

All authors meet the following criteria for authorship: (i) made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data, (ii) drafted the article or revised it critically for important intellectual content, and (iii) approved the version to be published. (iv) All author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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