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, prazepam, digoxin, fexofenadine, theophylline, indinavir, clopidogrel. Anthocyanins, flavonols, 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. With increasing frequency, medications prescribed by physicians interact with food products, mainly in patients undergoing chronic therapy. 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.

The influence of dietary components on the effect of drugs depends on numerous variables, including the physiochemical 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. 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. 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. 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.

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 of this review focuses on the importance of 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. 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.

The main function of CYP is to transform poorly soluble (lipophilic) xenobiotics into water-soluble (hydrophilic) metabolites to accelerate urinary excretion. 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. CYP3A is a genetically conserved enzyme. For this reason, it has very little genetic variability and a low frequency of polymorphisms. 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.

**P-Glycoprotein Transporter**

P-glycoprotein (P-gp) is a protein encoded by the abcb1 gene (Multidrug 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...
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 regarding the concentration and bioavailability of administered drugs. 7,20-27

**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. 8,11

**Gene Expression (Activation or Repression).** Activation of gene expression by Pch 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, while others, such as carbamazepine, need to be metabolized by CYP3A to generate the active metabolites (10,11 epoxycarbamazepine) that carry out the therapeutic effect. On the other hand, hyperforin activates the expression of cyp3a and abcb1, resulting in increased therapeutic effect of pro-drugs. Unlike Pchs, as galangin and capsaicin, which cause the repression of these genes, producing a decrease in the drugs efficacy.

**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. 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 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. 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.

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.

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). 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, can result in cardiac decompensation, atrioventricular block and acute myocardial infarction.

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

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.

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.

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 phytoconstituents present in vegetables, fruits and herbs.

| Classification | Subclassification | Presence and pharmacological activities |
|----------------|------------------|------------------------------------------|
| PHENOLIC COMPOUNDS | **Hydroxibenzoic acids** | Present in raspberries, strawberries, cranberry, cinnamon, cloves, mushrooms, fermented dairy products. Pharmacological activities: Antioxidant, anticancer, anti-inflammatory, antiproliferative, antithrombic, platelet aggregation moderate antibacterial, antiviral, antifungal, antiprotozoal, nematocidal |
| | **Hydroxycinamic 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, nematocidal |
| | **STILBENES** | 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** | Camellia sinensis, Theobroma cacao, Star fruit (Averrhoa carambola). Pharmacological activities: Antioxidant, antimicrobial, antifungal, antiviral, anti-inflammatory, antiproliferative, antiangiogenic, keratolytic, platelet aggregation moderate antibacterial, antiviral, antifungal, antiprotozoal, nematocidal |
| | **Flavonoids** | Quercetin, Pomegranate (P granatum), Jamaica flower (Hibiscus sabdariffa), Moringa (Moringa oleifera), Fabaceae (Millettia oblonga), Ginger (Alpinia galanga), Onion (Allium cepa), Cacao (T cacao), Thyme (Thymus sativus), Guava (Psidium guajava), Valerian (Valeriana officinalis), Fennel (Foeniculum vulgare). Pharmacological activities: Anticancer, anti-inflammatory, antiviral, antiprotozoal, antiallergic, treatment of allergic, inflammatory disorders, eye, cardiovascular diseases, and arthritis |
| | **Flavonols** | Morin: Present in guava (Psidium guajava), Fabaceae (Millettia oblonga), Valerian (Valeriana officinalis), Fennel (Foeniculum vulgare). Pharmacological activities: Anti-inflammatory, anti-oxidant, anticancer and chemoprotective |
| | **Flavanols** | Rutin: Present in onion (Allium cepa) and Allium obliquum. Valerian (Valeriana officinalis), Fennel (Foeniculum vulgare). Pharmacological activities: It has a role as a metabolite and an antioxidant, anti-diabetic, and antioxidant |
| | **Myricetin** | Present in Jamaica flower (Hibiscus sabdariffa), strawberry (Fragaria spp), peepal (Ficus religiosa), spinach (Spinacea oleracea), cauliflower (Brassica oleracea): Other: Red wine, oregano, kale, leeks, broccoli, blueberries, cranberry juice. Pharmacological activities: Anti-oxidant, anticancer, antidiabetic, anti-inflammatory, analgesic, antiasthma, hepatoprotective and anti-diabetic |
| | **Apigenin** | Pomegranate (A cerasus) Cacao (T cacao), Pomegranate (P granatum), Thyme (T sativus), Chamomile (Matricaria chamomilla), Doradilla (Anastatica hierochuntica). Onion (A cepa). Other: Parsley, celery, oranges, maize, rice, tea, wheat sprouts, some grasses. Pharmacological activities: Antioxidant, anti-inflammatory, anti-oxidant, anticancer, anti-genotoxic, anti-allergic, neuroprotective, cardioprotective, and antimicrobial |
| | **Myrcetin** | Present in Jamaica flower (Hibiscus sabdariffa), strawberry (Fragaria spp), peepal (Ficus religiosa), spinach (Spinacea oleracea), cauliflower (Brassica oleracea): Red: Wine, oregano, kale, leeks, broccoli, blueberries, cranberry juice. Pharmacological activities: Anti-oxidant, anticancer, antidiabetic, anti-inflammatory, analgesic, antiasthma, hepatoprotective and anti-diabetic |
| | **Flavanones** | Apigenin: Present in Carambola (A cerasus). Cacao (T cacao), Pomegranate (P granatum). Thyme (T sativus), Chamomile (Matricaria chamomilla), Doradilla (Anastatica hierochuntica). Onion (A cepa). Other: Parsley, celery, oranges, maize, rice, tea, wheat sprouts, some grasses. Pharmacological activities: Antioxidant, anti-inflammatory, anti-oxidant, anticancer, anti-genotoxic, anti-allergic, neuroprotective, cardioprotective, and antimicrobial |
| | **Flavonones** | Diosmetin: Present in Citrus species and other plants (A hirerochuntica). Pharmacological activities: Antioxidative, anti-inflammation, antioxidant, and antimicrobial effects. |
| | **Chrysin** | Present in Blue passion flower (Passiflora caerulea), honey and for propolis and mushroom. Diosmetin: Citrus species and other plants (A hirerochuntica). Pharmacological activities: Antispasmodic, sedative, antioxidant, anti-inflammatory, antacid, and antiviral activities |
| | **Galangin** | Present in Parsley (Alpinia officinarum), (Helichrysum aureonatum). Other: Honey, propolis, apple. Pharmacological activities: Anti-mutagenic, anti-digestive, anti-oxidative, antimicrobial, antioxidant, anti-inflammatory, radical scavenging, metabolic enzyme modulating and anticaner activity |
| | **Luteolin** | Present in Cacao (T cacao), Pomegranate (P granatum), A hirerochuntica, (A hirerochuntica), Parsley (Petroselinum crispum), Broccoli (Brassica oleracea), (T sativus) thyme, onion (A cepa) leaves, carrots, peppers, cabbages, apple skin, and chrysanthemum flowers are luteolin rich. Pharmacological activities: Anti-inflammation, antiallergy and anticancer, estrogenic and anti-estrogenic activity; anti or pro-oxidant |
| | **Bergamottin** | S 5-geranyloxypsoralen: Present in Grapefruit (Citrus Paradisi), Peel and pulp of orange (C sinensis), Lemon (Citrus aurantifolia), pulp of pomelos. Pharmacological activities: Antioxidative, anti-inflammatory, and anticancer |
| | **Flavonones or dihydroflavonones** | Naringenin: Present in Grapefruit (C paradoxa), 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. |
| | **Hesperitin** | 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 hyperlipidemia and prevention of postoperative thromboembolism, reduction of blood pressure and body fat |
| | **Isoflavones** | Biochanin: Present in Oregano (Origanum vulgare), Haba (Vicia faba), zollou or Lebanese viara (Fenuls hemonis), red clover, cabbage, alfalfa. Pharmacological activities: Anti-inflammatory, estrogen-like (estrogenic and/or anti-estrogenic activity), treatment Menopause symptoms, gliomas, lipids, cancer, osteoporosis. Cardioprotective and neuroprotective |
| | **Feruloyltymethanes** | Curcumin: Present in several species of Zingiberaceae p/e: (Curcuma aromatica), (Curcuma longa), (Curcuma edoina). (Curcuma wenyujin), (Curcuma kwangsiensis). Pharmacological activities: Anticancer (chemopreventative and Chemotherapeutic), antioxidant, anti-inflammatory, cardioprotective, antimalarial, neuroprotective. Inhibits scarring, cancer, and gallstone formation. Prevents liver injury, kidney toxicity, diabetes, multiple sclerosis, Alzheimer’s. HIV disease, septic shock, lung fibrosis, arthritis, and inflammatory bowel disease |

(continued)
| Classification, Subclassification, presence and pharmacological activities |
|---|
| **ANTHOCYANIDINS** |
| Delphinidin: It is found in many brightly colored fruits, vegetables. Pharmacological activities. Antioxidant, antimutagens, anti-inflammatory and antiangiogenic activities. Attributable antioxidant effect. |
| Cyanidin: Present in apples red flesh (Malus domestica), apple white flesh (Malus spp) and berries (Vaccinium vinifera L.) in particular, ed-skinned, hawthorn, bilberries, cranberries, chokeberries. Pharmacological activities. Antioxidant, antimutagens, anti-inflammatory and antiangiogenic activities. |
| Petunidin: It is found in Petunia (Petunia axillaris), blueberries, muscadine (Vitis rotundifolia) is the major source. Other sources: Blueberry (Vaccinium macrocarpon), Jamaica flower (Habandosifola), Guava (Psidium guajava), Grape (Vitis vinifera), Raspberry (Rubus idaeus), Cherry (Prunus cerasus), Blackberry (Rubus ulmifolius). Pharmacological activities. Antioxidant, reduces the risk of heart attack. |
| **HYPERFORIN** |
| 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** |
| Capsaizin or chili pepper (Capsicum): Which can be found in several species of chili (Capsicum). Pharmacological activities. Analgesic properties. |
| **ALKALOIDS** |
| Berberine: Present in Berberis species, Goldenseal (Hydrastis canadensis), Coptids rhizoma (Rheum officinale), 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** |
| 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, anti-allergic, anti-diabetic, and anticancer, beneficial effects on cardiac and vascular. |
| Sophora flavescens or Ku Shen: Present in root of Radix (Sophora flavescens) Kushen. Pharmacological activities. Antitumor, antimicrobial, anti-inflammatory, anti-allergic, and diuretic agent. |
| Bunge (Salvia miltiorrhiza): Present in roots of (S miltiorrhiza). Pharmacological activities. Analgesic, anti-cancer, anti-coagulant, anti-thrombotic, 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-Pch⁸ | Effect of inhibition |
|--------------|------------------------------|------------------------------|---------------|---------------------|
| **FLAVONOLS**|                              |                              |               |                     |
| Quercetin    | 50 mg/kg                     | Cyclosporine (CSP) (1.25 mg/kg) | AUC<sub>CSP alone</sub> = 65.5 ± 25.8 μg/mL/min | Quercetin decreases (43%) the CSP plasma concentration. Cmax decreased¹⁴ |
| Rutin        | 110 mg/kg                    | Cyclosporine (CSP) (1.25 mg/kg) | AUC<sub>CSP+rutin</sub> = 28 ± 11.1 μg/min/mL | Rutin decreases (57%) the CSP plasma concentration. Cmax decreased¹⁴ |
| Galangin     | 8 mg/kg/day                  | Midazolam (MDZ) (5 mg/kg)     | AUC<sub>MDZ</sub> alone = 6454 ± 134 μg/L/h | Galangin decreases (75%) the MDZ plasma concentration. Tmax and Cmax increase. **The mRNA expression of Cyp3A was repressed³¹ |
| **FLAVONES** |                              |                              |               |                     |
| Resveratrol  | 20 mg/kg                     | Saquinavir (SQV) (30 mg/kg)   | AUC<sub>SQV alone</sub> = 258 ± 12 ng/mL/h | Resveratrol decreases (31%) the SQV concentration. Cmax increases and Tmax decreases⁴⁸ |
| Resveratrol  | contents in grape seed extract (80 mg/kg) | Midazolam (MDZ) (20 mg/kg) | AUC<sub>MDZ</sub> alone = 3.09 ± 79 μg/mL/h | Resveratrol decreases (23%) the MDZ concentration. Cmax decrease, Tmax and clearance increase⁴⁸ |
| Curcumin     | 200 mg/kg                    | Buspirone (BUS) (10 mg/kg)    | AUC<sub>BUS</sub> alone = 224 μg/mL/min | Curcumin decreases (7.5%) the BUS plasma concentration. Clearance increases⁷⁰ |
| Curcumin     | 100 mg/kg                    | Everolimus (EVL) (5 mg/kg)    | AUC<sub>EVL</sub> alone = 1637.7 ± 3 ng/mL/min | Curcumin decrease (72%) the EVL concentration. Cmax decreases⁴⁹ |
| **STILBENES**|                              |                              |               |                     |
| Resveratrol  | 20 mg/kg                     | Saquinavir (SQV) (30 mg/kg)   | AUC<sub>SQV</sub> alone = 258 ± 12 ng/mL/h | Resveratrol decreases (31%) the SQV concentration. Cmax increases and Tmax decreases⁴⁸ |
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| Curcumin     | 100 mg/kg                    | Everolimus (EVL) (5 mg/kg)    | AUC<sub>EVL</sub> alone = 1637.7 ± 3 ng/mL/min | Curcumin decrease (72%) the EVL concentration. Cmax decreases⁴⁹ |
| **ISOFLAVONES: FLAVANS** |                              |                              |               |                     |
| Biochanin A  | 100 mg/kg                    | Tamoxifen (TMF) (10 mg/kg)    | AUC<sub>TMF</sub> alone = 1572.3 ± 90 ng/mL/h | Biochanin decreases (32%) the TMF plasma concentration. Cmax and Tmax decreased³³ |
| Biochanin A  | 100 mg/kg                    | 4-hydroxytamoxifen (10 mg/kg of TMF) | AUC<sub>4-hydroxytamoxifen</sub> alone = 177.3 ± 90 ng/mL/h | Biochanin decreases (40%) the 4-TMF plasma concentration. Cmax and Tmax decreased³³ |
| **PROTOALKALOIDS** |                              |                              |               |                     |
| Capsaicin    | 30 mg/kg                     | Midazolam (MDZ) (10 mg/kg)    | AUC<sub>MDZ</sub> alone = 3418.6 ± 26 μg/L/h | Capsaicin decreases (21.5%) the MDZ plasma concentration. Cmax and Tmax decreased and clearance increase⁹⁹ |
| **TERPENES** |                              |                              |               |                     |
| Bicololate and ginkgolide Contained in 100 mg/kg of ginkgo extract | Theophylline (TPL, 10 mg/kg) | AUC<sub>TPL</sub> alone = 148.3 ± 8.7 μg/mL/h | Ginkgo decreases (37%) the TPL plasma concentration⁶⁷ |
| **INHIBITION IN CLINICAL STUDIES IN HEALTHY VOLUNTEERS** |                              |                              |               |                     |
| Bergamottin contents in 600 mL of grapefruit juice (GFJ) | Celiprolol (CPL) (100 mg) | AUC<sub>CPL</sub> alone = 814 ± 21 ng/mL/h | Bergamottin decreases (75%) the CPL plasma concentration. Cmax decreases and Tmax increases⁶⁹ |
| Structure | 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 | Epigallocatechin decreases (85%) the NDL plasma concentration. Cmax and Tmax decreased and clearance increases49 |
| FLAVONOIDS AND TERPENES |                             |                              |               |                     |
| Sophora extract (.316 g/kg/day) | Indinavir (IDN) (40 mg) | AUC IND alone = 16.07 ± .99 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 protein8 |
| 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 | Hyperforin decreases (23%) the plasma DGN concentration. Cmax and Tmax decreases68 |
| Hyperforin (88 mg) contents in 60 mg of SJW | Alprazolam (ALP) (1 mg) | AUC ALP alone = 14.9 μg/L/h | Hyperforin decreases (90%) the ALP plasma concentration. Cmax and Tmax71 |
| Hyperforin contents in tablet with 300 mg of SJW | Alprazolam (ALP) (2 mg) | AUC ALP alone = 522 ng/mL/h | It decreases (51%) the ALP plasma concentration. Cmax decreases and Tmax increases65 |
| 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 | Hyperforin decreases (82.5%) the plasma concentration of verapamil when co-administered orally. Cmax and Tmax decreases.170 |
| 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 | It decreases (86%) the VPM plasma concentration. Cmax and Tmax decreases72 |
| Hyperforin contents in tablet with 900 mg SJW | Quazepam (QZM) (15 mg) | AUC QZM alone = 56 ± 32 ng/mL/min | Hyperforin decreases (26%) the QZM plasma concentration. Cmax and Tmax increases64 |
| 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 | It decreases (14.7%) the CSP plasma concentration. Cmax decreases173 |
| Hyperforin contents in tablet with 900 mg/day of St. John’s wort (SJW) **Kidney transplant patients | Capsules of danshen (DSC). Salvia miltiorrhiza with .56 g | | | |
| Ginsenosides contents in capsules with 500 mg | Midazolam (MDZ) (8 mg) | AUC MDZ alone = 120 ng/mL/h | Ginsenosides decreases (34%) the MDZ plasma concentration. Cmax decreases and clearance increases50 |
| Ginsenosides contents in capsules with 500 mg | Fexofenadine (FDN) (120 mg) | AUC FDN alone = 2036 ng/mL/h | Ginsenosides decreases (9%) the FDN plasma concentration. Cmax decreases, Tmax increases and clearance increases50 |
| Bilobalide and ginkgolide in tablets with 240 mg of ginkgo leaf (GBE) | Simvastatin (SMV) (40 mg) | AUC SMV alone = 86.44 ± 35 μg/L | Bilobalide decreases (43%) the plasma concentration of SMV. Cmax decreases and Tmax increases84 |
| Capsules of danshen (DSC). Salvia miltiorrhiza with .56 g | Clopidogrel (CLP) (300 mg) | AUC CLP alone = 16.67 ± 3.39 ng/mL/h | S miltiorrhiza decreases (50%) plasma concentration of CLP. Cmax, Tmax decrease and clearance increases66 |

* 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.6,64

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 antiangiotics midazolam, alprazolam and buspiron 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, septicaemia, 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 others90 (Tables 4 and 5).

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

On the other hand, quercetin, bergamottin, myricetin, naringenin, resveratrol, curcumin, baicalein and capsacin 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 anti diabetic 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 inhibition 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.1-5 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 | Quercetin decreases (43%) the CSP plasma concentration | Cmax decreased |
| 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 |
| **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 |
| **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 |
| 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 |
| **TANNINS** |
| Bergamottin in 600 mL of grapefruit juice (GF) | Celiprolol (CPL) (100 mg) | AUC CPL alone = 814 ± 21 ng/mL/h AUC CPL+GF = 200 ± 125 ng/mL/h | Bergamottin decreases (75%) the CPL plasma concentration. Cmax decreased and Tmax increases |
| 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 |
| **INHIBITION IN CLINICAL STUDIES IN HUMANS** |
| **FLAVANONES:** (bergamottin) |
| Bergamottin in 600 mL of grapefruit juice (GF) | Celiprolol (CPL) (100 mg) | AUC CPL alone = 814 ± 21 ng/mL/h AUC CPL+GF = 200 ± 125 ng/mL/h | Bergamottin decreases (75%) the CPL plasma concentration. Cmax decreased and Tmax increases |
| 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 |
| **TERPENES** |
| Sophora extract (.316 g/kg/day) | Indinavir (IND) (40 mg/kg) | AUC IND alone = 16.07 ± 9.9 μg/mL/h AUC IND+Sophora = 7.23 ± 8.3 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 |
| **PHENOLIC COMPOUNDS** |
| 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 |
| Hyperforin present in tablet with 900 mg of St John’s wort (SJW) | Talinolol (TLOL) (50 mg) | AUC TLOL alone = 834 ± 45 ng/mL/h AUC TLOL+Hyperforin = 564 ± 36 ng/mL/h | Hyperforin decreases (32%) the plasma concentration of TLOL. Cmax decreases and Tmax increases |

*aAUC 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.*
Table 4. Increase in drug concentrations by modulation of cytochrome P450 by phytochemicals.

| Structure | 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 | Quercetin increases (89%) the LSN plasma concentration. Cmax increased and Tmx decreased | |
| | | AUC$_{LSN+quercetin}$ = 13.9 ± 1.2 mg/mL/h | | |
| Quercetin in 400 mg/kg of Millettia aboensis (EMA) | Simvastatin (SMV) (20 mg/kg) | AUC$_{SMV+quercetin}$ = 29.5 ± 48 μg/mL/h | Quercetin increased (135%) the SMV plasma concentration. Increased Tmx and decreases clearance | |
| | | AUC$_{SMV+DX+quercetin}$ = 69.6 ± .6 μg/mL/h | | |
| Myricetin (8 mg/kg) | Losartan (LSN) 9 mg/kg | AUC$_{LSN}$ alone = 283 ± 57 ng/mL/h | Myricetin increases (61%) the LSN plasma concentration. Cmax and Tmx increase | |
| | | AUC$_{LSN+myricetin}$ = 456 ± 88 ng/mL/h | | |
| Morin (15 mg/kg) | Diltiazem (DTZ) (7.5 mg/kg) | AUC$_{DTZ}$ alone = 358 ± 56.9 ng/mL/h | Morin increased (79%) the DTZ plasma concentration. Cmax increase and decreases clearance | |
| | | AUC$_{DTZ+morin}$ = 642 ± 76.6 ng/mL/h | | |
| Kaempferol (10 mg/kg) | Nifedipine (NFNE) (10 mg/kg) | AUC$_{NFNE}$ alone = 5930 ± 107 μg/mL/min | Kaempferol increase (56%) the NFNE plasma concentration when co-administered orally | |
| | | AUC$_{NFNE+kaempferol}$ = 9234 ± 1569 μg/mL/min | | |
| FLAVONOID GLYCOSIDES | | | | |
| Naringin (7.5 mg/kg). In rabbit | Verapamil (VPM) (9 mg/kg) | AUC$_{VPM}$ alone = 18.4 ± 4.2 μg/mL/min | Naringin increased (54%) the VPM plasma concentration. Cmax increase | |
| | | AUC$_{VPM+naringin}$ = 28.4 ± 6.3 μg/mL/min | | |
| Naringin (7.5 mg/kg). In rabbit | Norverapamil (NVPM) (9 mg/kg of verapamil) | AUC$_{NVPM}$ alone = 16.6 ± 4.2 μg/mL/min | Naringin increased (15%) the NVPM plasma concentration. Cmax increase | |
| | | AUC$_{NVPM+naringin}$ = 19.1 ± 6.3 μg/mL/min | | |
| 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 | Resveratrol increased (127%) the CBZ plasma concentration and also in brain, liver and kidney. Cmax increase | |
| | | AUC$_{CBZ+PC}$ = 30.3 ± 1.7 mg/mL/min | | |
| 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 | Resveratrol increased (75.9%) the CBZ plasma concentration. Cmax increase and decreases clearance | |
| | | AUC$_{CBZ+PC}$ = 44.7 ± 3 mg/mL/min | | |
| Resveratrol (10 mg/kg) | Diltiazem (DTZ) (15 mg/kg) | AUC$_{DTZ}$ alone = 283 ± 65 ng/mL/min | It increased (55%) the DTZ plasma concentration. Cmax increase | |
| | | AUC$_{DTz+resveratrol}$ = 439 ± 98 ng/mL/min | | |
| Resveratrol (200 mg/kg) | Aripiprazole (APZ) (3 mg/kg) | AUC$_{APZ}$ alone = 158 ± 36 μg/L/h | Resveratrol increased (301%) the APZ plasma concentration. Cmax increases and clearance decreases | |
| | | AUC$_{APZ+resveratrol}$ = 634 ± 11 μg/L/h | | |
| Curcumin (60 mg/kg) | Midazolam (MDZ) (20 mg) | AUC$_{MDZ}$ alone = 255 ± 27 ng/mL/h | Curcumin increased (84%) the MDZ plasma concentration. Cmax increases and clearance decreases twice | |
| | | AUC$_{MDZ+curcumin}$ = 470 ± 88.3 ng/mL/h | | |
| TANNINS | | | | |
| Catechin in green tea extract (GTE) (400 mg/kg) | Midazolam (MDZ) (20 mg) | AUC$_{MDZ}$ alone = 3.09 ± 0.79 μg/mL/h | Catechin increased (196%) the MDZ plasma concentration. Cmax and Tmx increase and clearance decreases | |
| | | AUC$_{MDZ+GTE}$ = 9.16 ± 2.5 μg/mL/h | | |

(continued)
Table 4. (continued)

| Structure | 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 |              | Capsaicin increases (44%) the CSP plasma concentration. Cmax and Tmax increased. Clearance decreases. **The mRNA expression of CYP3A was repressed in the intestine and liver11 |
|           |                              | 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 liver11 |
|           |                              | 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 | Quercetin increases (14%) the ALP plasma concentration. Cmax increased |
|           | 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 | Anthocyanins increased (30%) the BUS plasma concentration of buspirone. Cmax and clearance decreases and Tmax increases83 |
|           | 300 mL of juice (GFJ) | Felodipine (FDP) (10 mg tablets) | AUC FDP alone = 36 ± 8 mol/L/h | Bergamottin increased (80%) the FDP plasma concentration. Cmax decreased |
|           | 250 mL of grapefruit juice (GFJ) | Felodipine (FDP) (10 mg) | AUC FDP alone = 13 ± 4.4 ng/mL/h | Bergamottin increased (92.3%) the FDP plasma concentration. Cmax increased and Tmax decreased |
|           | 250 mL of grapefruit juice (GFJ) | Felodipine (FDP) (5 mg) | AUC FDP alone = 20.1 ± 7.8 ng/mL/h | Bergamottin increased (48%) the FDP plasma concentration. Cmax and Tmax decreased |
|           | 12 mg | Felodipine (FDP) (5 mg) | AUC FDP alone = 29.8 ± 7.8 ng/mL/h | Bergamottin increased (32.8%) the FDP plasma concentration. Cmax increased and Tmax decreased |
|           | 300 mL of grapefruit juice (GFJ) | Dehydrofelodipine (DFDP) (10 mg Felodipine) | AUC DFDP alone = 16.9 ± 2.6 ng/mL/h | Bergamottin increased (24.2%) the DFDP plasma concentration. Cmax increased and Tmax decreased |
|           | 300 mL of grapefruit juice (GFJ) | Midazolam (MDZ) (6 mg) | AUC MDZ alone = 64.9 ± 7 ng/mL/h | Bergamottin increased (64%) the MDZ plasma concentration. Cmax increased, clearance is reduced |
|           | 600 mL of grapefruit juice (GFJ) | Midazolam (MDZ) 15 μg/kg | AUC MDZ alone = 106.8 ± 12 ng/mL/h | Bergamottin increased (100%) the MDZ plasma concentration. Cmax increase59 |
|           | 240 mL of grapefruit juice (GFJ) | Cyclosporine (CSP) (5 mg/kg) | AUC CSP + Orange juice (control) = 11.3 nmol/L/h | Pch increased (38%) the CSP plasma concentration. Cmax increased, clearance is reduced86 |
|           | 230 mL of grapefruit juice (GFJ) | Triazolam (TZL) (1.075 mg) | AUC TZL alone = 10.0 ± 3.5 ng/mL/h | It increases (60%) the TZL plasma concentration. Cmax increased, clearance is reduced81 |
|           | 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 | Bergamottin increased (97%) the BUS plasma concentration. Cmax, Tmax increased and clearance reduction85 |

(continued)
Table 4. (continued)

| Structure Pch | Pch (dose of administration) | Drug (dose of administration) | AUC drug-Pch* | Effect of inhibition |
|---------------|-------------------------------|-------------------------------|---------------|---------------------|
| Resveratrol (500 mg) | Carbamazepine (CBZ) (200 mg/kg) | AUC$_{CBZ}$ alone$^{20}$ = 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$^{25}$ |
| Furanocoumarin in 240 mL of grapefruit juice (GFJ) | Felodipine (FDP) (10 mg) | AUC$_{FDP+Orange juice}$ (control$^{26}$) = 54 nmol/L/h, AUC$_{FDP+GFJ}$ = 110 nmol/L/h | Furanocoumarin increased (104%) the FDP plasma concentration. Cmax increased and clearance reduction$^{68}$ |
| Berberine (76.8 mg) in commercial extract Goldenseal | Midazolam (MDZ) | AUC$_{MDZ}$ alone$^{46}$ = 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$^{77}$ |
| Hyperforin in 300 mg/kg of St John’s wort (SJW) | Methotrexate (MTX) (5 mg/kg) | AUC$_{MTX}$ alone$^{33}$ = 163 ± 16.5 μg/mL/h, AUC$_{MTX+Hyperforin}$ = 429 ± 56.4 μg/mL/h | Hyperforin increased (163%) the MTX plasma concentration. Cmax increased$^{3}$ |
| Baicalein (10 mg/kg) | Tamoxifen (TMF) (10 mg/kg) | AUC$_{TMF}$ alone$^{46}$ = 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 (10 mg/kg of TMF) | AUC$_{TMF}$ alone$^{49}$ = 284 ± 65 ng/mL/h, AUC$_{TMF+bacalein}$ = 359 ± 95 ng/mL/h | Baicalein increased (26.6%) the plasma concentration of 4-hydroxytamoxifen when co-administered baicalein-TMF. Cmax increased$^{68}$ |
| 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.$^{168}$

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

| Structure | Pch (dose of administration) | Drug (dose of administration) | AUC drug-Pch | Effect of inhibition |
|-----------|-------------------------------|-------------------------------|--------------|---------------------|
| FLAVONOLS |                               |                               |              |                     |
| Quercetin (15 mg/kg) | Doxorubicin (DXB) (50 mg/kg) | AUC DXB alone = 186 ± 44 ng/mL/h | Quercetin increase (13%) 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 | Quercetin increases (89%) the LSN plasma concentration. Cmax increased and Tmax decreased | 24 |
| Rutin (40 mg/kg) | Paclitaxel (PCX) (40 mg/kg) | AUC PCX alone = 1544.32 ± 24 ng/mL/h | Rutin increased (106%) PCX plasma concentration. Cmax and Tmax increased | 25 |
| Myricetin (8 mg/kg) | Tamoxifen (TMF) (10 mg/kg) | AUC TMF alone = 1832 ± 34 ng/mL/h | Myricetin increased (174%) the TMF plasma concentration. Cmax and Tmax increased | 26 |
| Myricetin (8 mg/kg) | Tamoxifen (TMF) (10 mg/kg) | AUC TMF alone = 284 ± 51 ng/mL/h | Myricetin increased (24%) plasma concentration of 4-TMF. Cmax and Tmax increased | 4 |
| Myricetin (10 mg/kg) | Doxorubicin (DXB) (40 mg/kg) | AUC DXB alone = 179 ± 34 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 | 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 | Kaempferol increase (56%) the NFNE plasma concentration | 74 |
| Naringenin (100 mg/kg) | Felodipine (FDP) (10 mg/kg) | AUC FDP alone = 2361.7 ± 34 ng/mL/h | Naringenin increase (157%) the FDP plasma concentration. Cmax increased and clearance decreased | 6 |
| Hesperetin (100 mg/kg) | Felodipine (FDP) (10 mg/kg) | AUC FDP alone = 2361.7 ± 20 ng/mL/h | Hesperetin increased (86%) the FDP plasma concentration. Cmax increased and clearance decreased | 6 |
| Apigenin (40 mg/kg) | Paclitaxel (PCX) (40 mg/kg) | AUC PCX alone = 1300 ± 12 ng/mL/h | Apigenin increased (237%) the PCX plasma. Cmax increased and clearance decreased | 8 |

(continued)
Table 5. (continued)

| Pch (dose of administration) | Drug (dose of administration) | AUC drug-Pch<sup>a</sup> | Effect of inhibition |
|-----------------------------|--------------------------------|-------------------------|---------------------|
| Resveratrol contents in 2 g/kg of P. cuspidatum (PC) | Carbamazepine (CBZ) (200 mg/kg) | AUC<sub>CBZ</sub> alone = 13.3 ± 1.4 mg/mL/min, AUC<sub>CBZ+PC</sub> = 30.3 ± 1.7 mg/mL/min | Resveratrol increased (127%) the CBZ plasma concentration and also in brain, liver and kidney. Cmax increased<sup>54</sup> |
| Resveratrol contents in 2 g/kg of P. cuspidatum (PC) | Carbamazepine 10.11-epoxide (200 mg/kg of CBZ) | AUC<sub>CBZ</sub> alone = 25.4 ± 2.6 mg/mL/min, AUC<sub>CBZ+PC</sub> = 44.7 ± 3.9 mg/mL/min | Resveratrol increased (75.9%) the plasma concentration of CBZ-10.11 and also in brain, liver, and kidney. Cmax increased<sup>51</sup> |
| Resveratrol (10 mg/kg) | Diltiazem (DTZ) (15 mg/kg) | AUC<sub>DTZ</sub> alone = 283 ± 65 ng/mL/min, AUC<sub>DTZ+Resveratrol</sub> = 439 ± 98 ng/mL/min | Resveratrol increased (55%) the DTZ plasma concentration. Cmax increased<sup>79</sup> |
| Curcumin (60 mg/kg) | Midazolam (MDZ) (20 mg/kg) | AUC<sub>MDZ</sub> alone = 255 ± 27 ng/mL/h, AUC<sub>MDZ+Curcumin</sub> = 470 ± 88.3 ng/mL/h | Curcumin increased (84%) the MDZ plasma concentration. Cmax increased and clearance decreased<sup>84</sup> |
| Curcumin (60 mg/kg) | Celiprolol (CPL) (30 mg/kg) | AUC<sub>CPL</sub> alone = 2140.04 ± 187 ng/mL/h, AUC<sub>CPL+Curcumin</sub> = 2347.63 ± 287 ng/mL/h | Curcumin increased (9%) the CPL plasma concentration. Cmax increased and clearance and <i>t<sub>max</sub></i> decreased<sup>84</sup> |
| Epigallocatechin gallate (EGCG) (10 mg/kg) | Nicardipine (NCP) (12 mg/kg) | AUC<sub>NCP</sub> alone = 371 ± 67 ng/mL/h, AUC<sub>NCP+EGCG</sub> = 663 ± 133 ng/mL/h | Epigallocatechin gallate increased (79%) the NCP plasma concentration. Cmax increased<sup>69</sup> |
| Capsaicin (3.0 mg/kg) | Cyclosporin (CSP) (50 mg/kg) | AUC<sub>CSP</sub> alone = 97.7 ± 26 μg/mL/h, AUC<sub>CSP+Capsaicin</sub> = 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 <i>abcb1</i> was repressed in the intestine and liver<sup>71</sup> |
| Ginseng extract (KRG) (100 mg/kg) | Paclitaxel (PCX) (25 mg/kg) | AUC<sub>PCX</sub> alone = 50.9 ± 12.6 μg/mL/min, AUC<sub>PCX+KRG</sub> = 80.6 ± 14 μg/mL/min | Ginseng increased (57%) the PCX plasma concentration. Cmax, Tmax increased and clearance decreased<sup>89</sup> |

<sup>a</sup>AUC value of drug administered alone (control) and co-administered with (Pch).<sup>**</sup> Article reporting expression of <i>abcb1</i> 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.<sup>169</sup>
Table 6. Phytochemicals That Act in the Same Interaction Of CYP3A and P-gp, Mechanisms That Modify the Concentration of Drugs.

| Phytochemical | Effect interaction on CYP3A | Effect interaction on P-gp | Effect 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%) | Ceprolol decrease (75%) |
| 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%) |
| 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%) |
| Myricetin     | Inhibition enzymatic activity. Myricetin inhibited the CYPIC50% = 7.81 µMol. | Transport inhibition was observed by rhodamine 123 accumulation in MCF-7/ADR cells. | Losartan increase (61%) |
| 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. | Doxorubicin increase (117%) |
| 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%) |
| Resveratrol   | Inhibition. Evaluated with enzymatic activity. Ketoconazole inhibition control. | The inhibition of Carbamazepine transport was shown using verapamil as a control. | Carbamazepine increase (127%) |
| 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%) | Ceprolol increase (9%) |
| Capsaicin     | 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%) |
| Baicalein     | 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%) |
| Flavonoids present in (Sophora flavescens) | Activation mRNA and protein of cyp3a/CYP3A in intestine and liver. | Inhibition transport was assessed with rhodamine 123 in MCF-7/ADR cells cultures. | Tamoxifen increase (89%) |
|               | Activation mRNA and protein of abcb1/P-gp in intestine and liver tissues. | | Indinavir decrease (55%) |
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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**References**

1. Matura JM, Shea LA, Bankes VA. Dietary supplements, cytochrome metabolism, and pharmacogenetic considerations. *J Med Sci*. 2021;20-21. doi:10.1007/s11845-021-02828-4.

2. Choi J, Ko C. Food and drug interaction. *J Lifestyle Med*. 2017; 7(1):1-9. doi:10.15280/jlm.2017.7.1.1.

3. Samano-S Miguel M, Méndez-Sánchez J. Interacciones alimentario/medicamento. *Inf Ter Sist Nac Salud*. 2011;35(1):3-12. https://www.mscbs.gob.es/biblioPublic/publicaciones/recursos_propios/infMedic/docs/vol35_1_Interacciones.pdf

4. Zhou SF, Zhou ZW, Li CG, et al. Identification of drugs that interact with herbs in drug development. *Drug Discov Today*. 2007;12(15-16):664-673. doi:10.1016/j.drudis.2007.06.004.

5. Jensen K, Ni Y, Panagiotou G, Kouskoumvekaki I. Developing a molecular roadmap of drug-food interactions. *PLoS Comput Biol*. 2015;11(2):1-16. doi:10.1371/journal.pcbi.1004048.

6. Martin-Hernandez I, Cordero-Eiriz A. Interacciones fármaco-nutritivo en el paciente con daño neurológico. *Rev Cub Aliment Nutr*. 2008;18(2):257-264. http://www.revalnutricion.sld.cu/index.php/rcan/article/view/915

7. Zhou S, Koh HL, Gao Y, Gong ZY, Lee EJD. Herbal bioactivation: the good, the bad and the ugly. *Life Sci*. 2004;74(8):935-968. doi:10.1016/j.lfs.2003.09.035.

8. Yang JM, Ip SP, Xian Y, et al. Impact of the herbal medicine Sophora flavescent on the oral pharmacokinetics of indinavir in rats: the involvement of CYP3A and P-Glycoprotein. *PLoS One*. 2012;7(2):e31312. doi:10.1371/journal.pone.0031312.

9. van Watershoot RAB, Schinkel AH. A critical analysis of the interplay between cytochrome P450 3A and P-glycoprotein: recent insights from knockout and transgenic mice. *Pharmacol Rev*. 2011;63(2):390-410. doi:10.1124/pr.110.002584.

10. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther*. 2013;138(1):103-141. doi:10.1016/j.pharmthera.2012.12.007.

11. Zhai X, Shi F, Chen F, Lu Y. Capsaicin pretreatment increased the bioavailability of cyclosporin in rats: involvement of P-glycoprotein and CYP 3A inhibition. *Food Chem Toxicol*. 2013;62:323-328. doi:10.1016/j.fct.2013.08.068.

12. Hernández-Martínez N, Caballero-Ortega H, Donado-González V, et al. Tissue-specific induction of the carcinogen-inducible cytochrome P450 isoforms in the gastrointestinal tract. *Environ Toxicol Pharmacol*. 2007;24(3):297-303. doi:10.1016/j.etap.2007.07.004.

13. Sills GJ, Brodie MJ. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia*. 2007;48(3):435-441. doi:10.1111/j.1528-1167.2007.00983.x.

14. Vences-Mejía A, Labra-Ruiz N, Hernández-Martínez N, et al. The effect of aspartame on rat brain xenobiotic-metabolizing enzymes. *Am J Pharmacol Toxicol*. 2011;6(2):93-99. doi:10.1165/atap.2011.07.001.

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enzymes. *Hum Exp Toxicol*. 2006;25:453-460. doi:10.1191/0960327106het0460a.

15. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. *Drugs*. 2009;69(13):1777-1798. doi:10.2165/11317010-000000000-00000.

16. Liu KH, Kim MJ, Jeon BH, et al. Inhibition of human cytochrome P450 isofoms and NADPH-CYP reductase in vitro by 15 herbal medicines, including Epimedi herba. *J Clin Pharm Ther*. 2006;31(1):83-91. doi:10.1111/j.1365-2710.2006.00706.x.

17. Ramanathan MR, Penzak SR. Pharmacokinetic drug interactions with Panax ginseng. *Eur J Drug Metab Pharmacokinet*. 2017;42(4):545-557. doi:10.1007/s13318-016-0387-5.

18. Lund M, Petersen TS, Dalhoff KP. Clinical implications of P-Glycoprotein modulation in drug–drug interactions. *Drugs*. 2017;77(8):859-883. doi:10.1007/s40265-017-0729-x.

19. Lazarowski A, Czornyj L, Lubienieki F, Girardi E, Vazquez S, D’Giano C. ABC transporters during epilepsy and mechanisms underlying multidrug resistance in refractory epilepsy. *Epilepsia*. 2007;48(suppl 5):140-149. doi:10.1111/j.1528-1167.2007.01302.x.

20. Zhou SF. Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. *Xenobiotica*. 2008;38(7-8):802-832. doi:10.1080/00498250701867889.

21. Choi D-H, Li C, Choi J-S. Effects of myricetin, an antioxidant, on the pharmacokinetics of losartan and its active metabolite, EXP-3174, in rats: possible role of cytochrome P450 3A4, cytochrome P450 2C9 and P-glycoprotein inhibition by myricetin. *J Pharm Pharmacol*. 2010;62(7):908-914. doi:10.1211/jpp.62.07.0012.

22. Choi JS, Piao YJ, Kang KW. Effects of quercetin on the bioavailability of doxorubicin in rats: role of CYP3A4 and P-gp inhibition by quercetin. *Arch Pharm Res (Seoul)*. 2011;34(4):607-613. doi:10.1007/s12272-011-0411-x.

23. Kumar KK, Priyanka L, Gnananath K, Babu PR, Sujatha S. Pharmacokinetic drug interactions between apigenin, rutin and paclitaxel mediated by P-glycoprotein in rats. *Eur J Drug Metab Pharmacokinet*. 2015;40(3):267-276. doi:10.1007/s13318-014-0203-z.

24. Li C, Lim SC, Kim J, Choi JS. Effects of myricetin, an anticancer compound, on the bioavailability and pharmacokinetics of tamoxifen and its main metabolite, 4-hydroxytamoxifen, in rats. *Eur J Drug Metab Pharmacokinet*. 2011;36(3):175-182. doi:10.1007/s13318-011-0036-y.

25. Singh SP, Wajahuddin, Raju KSR, Ali MM, Kohli K, Jain GK. Reduced bioavailability of tamoxifen and its metabolite 4-hydroxytamoxifen after oral administration with Biochanin A (an Isoflavone) in rats. *Phyther Res*. 2012;26(2):303-307. doi:10.1002/ptr.3652.

26. Yu CP, Wu PP, Hou YC, et al. Quercetin and rutin reduced the bioavailability of cyclosporine from Neoral, an immunosuppressant, through activating P-glycoprotein and CYP3A4. *J Agric Food Chem*. 2011;59(9):4644-4648. doi:10.1021/jf104786t.

27. Zhao Y, Helhum BH, Liang A, Nilsen OG. Inhibitory mechanisms of human CYPs by three alkaloids isolated from traditional chinese herbs. *Phyther Res*. 2015;29(6):825-834. doi:10.1002/ptr.5285.

28. Bailey DG, Dresser GK, Bend JR. Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: Comparison with grapefruit juice. *Clin Pharmacol Ther*. 2003;73(6):529-537. doi:10.1067/sp009-9236(03)00051-1.

29. Chu V, Einolf HJ, Evers R, et al. In vitro and in vivo induction of cytochrome P450: a survey of the current practices and recommendations: a pharmaceutical research and manufacturers of America perspective. *Drug Metab Dispos*. 2009;37(7):1339-1354. doi:10.1124/dmd.109.027029.

30. Moore LB, Goodwin B, Jones SA, et al. St. John’s wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Pro Natl Acad Sci USA*. 2000;97(13):7500-7502. doi:10.1073/pnas.30.15.5097.

31. Ma YL, Zhao F, Yin JT, et al. Two approaches for evaluating the effects of galangin on the activities and mRNA expression of seven CYP450. *Molecules*. 2019;24(6):1171. doi:10.3390/molecules24061171.

32. Zhai X, Feng Y, Liu J, et al. Pharmacokinetic effects of capsaicin on vinblastine in rats mediated by CYP3A and MRP2. *Fundam Clin Pharmacol*. 2019;33(4):376-384. doi:10.1111/fcp.12448.

33. Yang SY, Juang SH, Tsai SY, Chao PDL, Hou YC. St. John’s wort significantly increased the systemic exposure and toxicity of methotrexate in rats. *Toxicol Appl Pharmacol*. 2012;263(1):39-43. doi:10.1016/j.taap.2012.05.020.

34. Kluth D, Banning A, Paar I, Blomhoff R, Brigelius-Flohé R. Modulation of pregnane X receptor and electrophile responsive element-mediated gene expression by dietary polyphenolic compounds. *Free Radic Biol Med*. 2007;42(3):315-325. doi:10.1016/j.freeradbiomed.2006.09.028.

35. Lemmen J, Tozkidis IE, Gallia HJ. Pregnan X receptor upregulates ABC-transporter Abcg2 and Abcb1 at the blood-brain barrier. *Brain Res*. 2013;1491;1-13. doi:10.1016/j.brainres.2012.10.060.

36. Sachar M, Ma X. Nuclear receptors in herb-drug interactions. *Drug Metab Rev*. 2013;45(1):73-78. doi:10.3109/03602532.2012.753902.

37. Viswakarma N, Jia Y, Bai L, et al. Coactivators in PPAR-regulated gene expression. *PPAR Res*. 2010;2010:250126. doi:10.1155/2010/250126.

38. Xu C, Huang M, Bi H. PXR- and CAR-mediated herbal effect activation by quercetin. *Biomol Ther*. 2019;24(6):1171. doi:10.3390/biomolther.2019.122.

39. Lee KY, Choi HS, Choi HS, et al. Quercetin directly interacts with vitamin D Receptor (VDR): structural implication of VDR activation by quercetin. *Biomol Ther*. 2011;29(2):191-198. doi:10.4062/biomolther.2011.222.

40. Ho P, Saville D, Wamimoinrak S. Inhibition of human CYP3A4 activity by grapefruit flavonoids, flavanocumarins and related compounds. *J Pharm Pharm Sci*. 2001;4(3):217-227.
41. Tsujimoto M, Horie M, Honda H, Takara K, Nishiguchi K. The structure-activity correlation on the inhibitory effects of flavonoids on cytochrome P450 3A activity. *Biol Pharm Bull.* 2009;32(4):671-676. doi:10.1248/bpb.32.671.

42. Kent UM, Lin H, Noon KR, Harris DL, Hollenberg PF. Metabolism of bergamottin by cytochromes P450 2B6 and 3A5. *J Pharmacol Exp Ther.* 2006;318(3):992-1005. doi:10.1124/jpet.105.099887.

43. Misaka S, Kawabe K, Onoue S, et al. Effects of green tea catechins on cytochrome P450 2B6, 2C8, 2C19, 2D6 and 3A activities in human liver and intestinal microsomes. *Drug Metab Pharmacokin.* 2013;28(3):244-249. doi:10.2133/dmpk.DMPK-12-9G-101.

44. Shamsi S, Tran H, Tan RSJ, Tan ZJ, Lim LY. Curcumin, and its anti-diabetic effects: cellular mechanisms and effects to improve blood sugar levels. *Biomolecules.* 2019;9(9):430-435. doi:10.3390/biom9090430.

45. Amjadi S, Shahnaz F, Shokouhi B, et al. Nanophytosomes for enhancement of rutin efficacy in oral administration for diabetes treatment in streptozotocin-induced diabetic rats. *Int J Pharm.* 2021;610(Cd):121208. doi:10.1016/j.ijpharm.2021.121208.

46. Tsujimoto M, Horie M, Honda H, Takara K, Nishiguchi K. The structure-activity correlation on the inhibitory effects of flavonoids on cytochrome P450 3A activity. *Biol Pharm Bull.* 2009;32(4):671-676. doi:10.1248/bpb.32.671.

47. Sheu MT, Liou YB, Kao YH, Lin YK, Ho HO. A quantitative structure-activity correlation on the inhibitory effects of flavonoids on cytochrome P450 3A4. *Drug Metab Dispos.* 2013;41:430-435. doi:10.1124/dmd.130.506857.

48. Nishikawa M, Ariyoshi N, Kotani A, et al. Effects of con- jugates and minor extension by phenolic acid after long-term intake of grapefruit juice on organic anion-transporting polypeptide and cytochrome p450 3A4. *Biochem Pharm.* 2013;86(12):1936-1941. doi:10.1016/j.bcp.2013.10.001.

49. Zhu HD, Gu N, Wang M, Kong HR, Zhou MT. Effects of capsicin on rat cytochrome P450 isoforms CYPIA2, CYP2C19, and CYP3A4. *Drug Dev Ind Pharm.* 2015;41(11):1824-1828. doi:10.3109/03639045.2015.1011166.

50. Malati CY, Robertson SM, Hunt JD, et al. Influence of panax ginseng on cytochrome P450 (CYP)3A and p-glycoprotein (P-gp) activity in healthy participants. *J Clin Pharmacol.* 2012;52(6):932-939. doi:10.1177/0091270011407194.

51. Chi YC, Lin SP, Hou YC. A new herb-drug interaction of Polygonum cuspidatum, a resveratrol-rich nutraceutical, with carbamazepine in rats. *Toxicol Appl Pharmacol.* 2012;263(3):315-322. doi:10.1016/j.taap.2012.07.003.

52. Fraga LN, Coutinho CP, Rozenbaum AC, et al. Blood pressure and body fat % reduction is mainly related to flavanone phase II conjugates and minor extension by phenolic acid after long-term intake of orange juice. *Food Funct.* 2021;12(22):11278-11289. doi:10.1039/d1ff02664j.

53. Al-ishaq RK, Abotaleb M, Kubatka P, Kajo K, Büßelberg D. Flavonoids and their anti-diabetic effects: cellular mechanisms and effects to improve blood sugar levels. *Biomolecules.* 2019;9(9):430-435. doi:10.3390/biom9090430.

54. Amjadi S, Shahnaz F, Shokouhi B, et al. Nanophytosomes for enhancement of rutin efficacy in oral administration for diabetes treatment in streptozotocin-induced diabetic rats. *Int J Pharm.* 2021;610(Cd):121208. doi:10.1016/j.ijpharm.2021.121208.

55. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J Am Coll Cardiol.* 2010;55(6):515-525. doi:10.1016/j.jacc.2009.07.074.

56. Hsieh YW, Huang CY, Yang SY, et al. Oral intake of curcumin markedly activated CYP 3A4: in vivo and ex vivo studies. *Sci Rep.* 2014;4:1-7. doi:10.1038/srep06587.

57. Schwarz UI, Hanso H, Oertel R, et al. Induction of intestinal P-glycoprotein by St John’s wort reduces the oral bioavailability of talinolol. *Clin Pharmacol Ther.* 2007;81(5):669-678. doi:10.1038/sj.cpt.6100191.

58. Gurley B, Swain A, Williams DK, Barone G, Battu KS. Gauging the significance of P-glycoprotein mediated herb-drug: Comparative effects of StJohn’s wort, echinacea, claritromycin, and rifampin on digoxin pharmacokinetics. *Mol Nutr Food res.* 2008;52(7):772-779. doi:10.1002/mnfr.200700081.

59. Tanaka S, Uchida S, Miyakawa S, et al. Comparison of inhibitory duration of grapefruit juice on organic anion-transporting polypeptide and cytochrome p450 3A4. *Biol Pharm Bull.* 2013;36(12):1936-1941. doi:10.1248/bpb.b13-00538.

60. Misaka S, Yatabe J, Müller F, et al. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. *Clin Pharmacol Ther.* 2014;95(4):432-438. doi:10.1038/clpt.2013.241.

61. Dai LL, Fan L, Wu HZ, et al. Assessment of a pharmacokinetic and pharmacodynamic interaction between simvastatin and Ginkgo biloba extracts in healthy subjects. *Xenobiotica.* 2013;43(10):862-867. doi:10.3109/00498254.2013.773385.

62. Markowitz JS, Donovan JL, DeVane CL, et al. Effect of St John’s wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *J Am Med Assoc.* 2003;290(11):1500-1504. doi:10.1001/jama.290.11.1500.

63. Kawaguchi A, Ohmori M, Tsuruoka SI, et al. Drug interaction between St John’s wort and quazepam. *Br J Clin Pharmacol.* 2004;58(4):403-410. doi:10.1111/j.1365-2125.2004.02171.x.

64. Li J, Liu Y, Zhang J, Yu X, Wang X, Zhao L. Effects of resveratrol on P-glycoprotein and cytochrome P450 3A in vitro and on pharmacokinetics of oral saquinavir in rats. *Drug Des Devel Ther.* 2016;10:3699-3706. doi:10.2147/DDDT.S118723.

65. Saeed IA, Ali L, Jabeen A, Khasawneh M, Rizvi TA, Ashraf SS. Estrogenic activities of ten medicinal herbs from the Middle east. *J Chromatogr Sci.* 2013;51(1):33-39. doi:10.1093/chromsci/bms101.

66. Zhouchua C, Xu M, Yu HB, Zheng XT, ZhongZF, Zhangtong L. Effects of Danshen capsules on the pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. *Food...
20

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67. Choi JS, Burm JP. Effects of oral epigallocatechin gallate on the pharmacokinetics of theophylline in rats. Food Chem Toxicol. 2007;45(12):2441-2445. doi:10.1016/j.fct.2007.05.023.

68. Euflora venosa 200 mg (Teofila anhida 200 mg). Data Sheet. https://cima.aemps.es/cima/pdfs/es/ft/1891_FichaTecnica_1891.html.pdf (accessed 31 October 2021).

69. Choi J, Han H. Pharmacokinetic interaction between diltiazem and morphine, in rats. Pharmacol Res. 2005;52(5):386-391. doi:10.1016/j.phrs.2005.05.011.

70. Kim HJ, Choi JS. Effects of naringin on the pharmacokinetics of verapamil and one of its metabolites, norverapamil, in rabbits. Biopharm Drug Dispos. 2005;26(7):295-300. doi:10.1002/bdd.459.

71. Sridhar V, Sandeep MS, Babu PR, Babu KN. Evaluation of first-pass cytochrome P4503A (CYP3A) and P-glycoprotein activities using Felodipine and Hesperetin in combination in wistar rats and everted rat gut sacs in vitro. Phyther Res. 2014;28(5):699-705. doi:10.1002/ptr.5040

72. Dong B, Yuan S, Hu J, Yan Y. Effects of Ginkgo leaf tablets on the pharmacokinetics of losartan and its metabolite EXP3174 in rats and its mechanism. Pharm Biol. 2018;56(1):333-336. doi:10.1080/13880209.2018.1481107.

73. Park J-won, Choi J. Role of kaempferol to increase bioavailability and pharmacokinetics of nifedipine in rats. Chin J Nat Med. 2019;17(9):690-697. doi:10.1007/s11875-5364(19)30083-4.

74. Zhao Q, Wei J, Zhang H. Effects of quercetin on the pharmacokinetics of losartan and its metabolite EXP3174 in rats. Xenobiotica. 2019;49(5):563-568. doi:10.1080/00498254.2018.1478168.

75. Cantoni L, Rozio M, Mangolini A, Hauri L, Caccia S. Hypoferolin contributes to the hepatic CYP3A-inducing effect of Hypericum perforatum extract in the mouse. Toxicol Sci. 2003;75(1):25-30. doi:10.1093/toxsci/kfg174.

76. Goosen TC, Ciliéi D, Bailey DG, et al. Bergamottin contribution to the grapefruit juice-felodipine interaction and disposition in humans. Clin Pharmacol Ther. 2004;76(6):607-617. doi:10.1016/j.clpt.2004.08.019.

77. Choi J, Han H. Pharmacokinetic interaction between diltiazem and morin, a flavonoid, in rats. Pharmacol Res. 2005;52(5):386-391. doi:10.1016/j.phrs.2005.05.011.

78. Kim TJ, Choi JS. Effects of naringin on the pharmacokinetics of verapamil and one of its metabolites, norverapamil, in rabbits. Biopharm Drug Dispos. 2005;26(7):295-300. doi:10.1002/bdd.459.

79. Hongpyo S, Choi D-J, Choi J-S. Effects of resveratrol on the pharmacokinetics of Diltiazem and its major metabolite, desacetyldiltiazem, in rats. Cardiovasc Ther. 2008;26(4):269-275. doi:10.1111/j.1755-5922.2008.00060.x.

80. Bedada SK, Neerati P. Effect of resveratrol on the pharmacokinetics of Carbamazepine in healthy human volunteers. Phyther Res. 2015;29(3):701-706. doi:10.1002/ptr.5302.

81. Culum-Merdek K, Von-Moltke L, Gan L, et al. Effect of extended exposure to grapefruit juice on cytochrome P450 3A activity in humans: Comparison with ritonavir. Clin Pharmacol Ther. 2006;79(3):243-254. doi:10.1016/j.clpt.2005.11.009.

82. Greenblatt DJ, Von Moltke LL, Harmatz JS, et al. Time course of recovery of cytochrome P450 3A function after single doses of grapefruit juice. Clin Pharmacol Ther. 2003;74(2):121-129. doi:10.1016/S0009-9236(03)00118-8.

83. Donovan JL, Devane CL, Chavkin KD, et al. Multiple nighttime doses of valerian (Valeriana officinalis) had minimal effects on CYP3A4 activity and no effect on CYP2D6 activity in healthy volunteers. Drug Metab Dispos. 2004;32(12):1333-1336. doi:10.1124/dmd.104.001164.

84. Zhang W, Tan TMC, Lim LY. Impact of curcumin-induced changes in P-glycoprotein and CYP3A expression on the pharmacokinetics of peroral celiprolol and midazolam in rats. Drug Metab Dispos. 2007;35(1):110-115. doi:10.1124/dmd.106.011072.

85. Hanley MJ, Masse G, Harmatz JS, et al. Effect of blueberry juice on clearance of buspirone and flurbiprofen in human volunteers. Br J Clin Pharmacol. 2011;75(4):1041-1052. doi:10.1111/j.1365-2125.2012.04450.x.

86. Paine MF, Widmer WW, Pusek SN, et al. Further characterization of a furanocoumarin-free grapefruit juice on drug disposition: studies with cyclosporine. Am J Clin Nutr. 2008;87(4):863-871. doi:10.1093/ajcn/87.4.863.

87. Choi SI, Shin SC, Choi JS. Effects of myricetin on the bioavailability of doxorubicin for oral drug delivery in rats: possible role of CYP3A4 and P-glycoprotein inhibition by myricetin. Arch Pharm Res (Seoul). 2011;34(2):309-315. doi:10.1007/s12272-011-0217-x.

88. Li C, Kim M, Choi H, Choi J. Effects of baicalein on the pharmacokinetics of tamoxifen and its main metabolite, 4-hydroxytamoxifen, in rats: possible role of cytochrome p450 3A4 and P-glycoprotein inhibition by baicalein. Arch Pharm Res (Seoul). 2011;34(11):1965-1972. doi:10.1007/s12272-011-1117-9.

89. Bae JK, Kim YJ, Chae HS, et al. Korean red ginseng extract enhances paclitaxel distribution to mammary tumors and its oral bioavailability by P-glycoprotein inhibition. Xenobiotica. 2017;47(5):450-459. doi:10.1080/00988254.2016.1182233.

90. Zhan YY, Liang BQ, Li XY, et al. The effect of resveratrol on pharmacokinetics of aripiprazole in vivo and in vitro. Xenobiotica. 2016;46(5):439-444. doi:10.3109/00988254.2015.1088175.

91. Venkataramanan R, Komoroski B, Strom S. In vitro and in vivo assessment of herb drug interactions. Life Sci. 2006;78(18):2105-2115. doi:10.1016/j.lfs.2005.12.021.

92. Sjögren E, Abrahamsson B, Augustijns P, et al. In vivo methods for drug absorption - Comparative physiologies, model selection, correlations with in vitro methods (IVIVC), and applications for formulation/API/excipient characterization including food effects. Eur J Pharm Sci. 2014;57(1):99-151. doi:10.1016/j.ejps.2014.02.010.
93. Šemeláková M, Jendželovský R, Fedoročko P. Drug membrane transporters and CYP3A4 are affected by hypericin, hyperforin or aristoforin in colon adenocarcinoma cells. *Biomed Pharmacother*. 2016;81:38-47. doi:10.1016/j.biopha.2016.03.045.

94. Moya M, José Gómez-Lechón M, Castell JV, Jover R. Enhanced steatosis by nuclear receptor ligands: a study in cultured human hepatocytes and hepatoma cells with a characterized nuclear receptor expression profile. *Chem Biol Interact*. 2010; 184(3):376-387. doi:10.1016/j.ceb.2010.01.008.

95. Bogacz A, Mrozikiewicz PM, Karasiewicz M, et al. The influence of standardized valeriana officinalis extract on the CYP3A1 gene expression by nuclear receptors in in vivo model. *BioMed Res Int*. 2014;2014:819093. doi:10.1155/2014/819093.

96. Saljé K, Lederer K, Oswald K, Assfeld R, Siegmund 81.9093.

97. Stark T, Bareuther S, Hofmann T. Sensory-guided decomposition of roasted cocoa nibs (Theobroma cacao) and structure determination of taste-active polyphenols. *J Agric Food Chem*. 2005;53(13):5407-5418. doi:10.1021/jf050457y.

98. Hosoi S, Shimizu E, Arimori K, et al. Analysis of CYP3A inhibitory components of star fruit (Averrhoa carambola L.) using liquid chromatography-mass spectrometry. *J Nat Med*. 2008;62(3):345-348. doi:10.1007/s11418-008-0239-y.

99. Chou T, Yang M, Tseng S, Lee S, Chang C. Tea silkworm droppings as an enriched source of tea flavonoids. *J Food Drug Anal*. 2018;26(1):41-46. doi:10.1016/j.jfda.2016.11.011.

100. Salami M, Rahimmalek M, Ehtemam MH. Inhibitory effect of different fennel (Foeniculum vulgare) samples and their phenolic compounds on formation of advanced glycation products and comparison of antimicrobial and antioxidant activities. *Food Chem*. 2016;213:196-205. doi:10.1016/j.foodchem.2016.06.070.

101. Pereira-Caro G, Borges G, Nagai C, et al. Profiles of phenolic compounds and purine alkaloids during the development of seeds of Theobroma cacao cv. Trinitario. *J Agric Food Chem*. 2013;61(2):994-1001. doi:10.1021/jf304397m.

102. Calderón-Montaño J, Burgos-Morón E, Pérez-Guerrero C, Hernández G. Los *Calceolaria* y sus efectos en la salud. *Rev LA Fac QUÍMICA Farm*. 2014; 55-66. doi:10.1111/j.1755-5922.2008.00060.x.

103. El-Saber BG, Magdy Beshbishy AG, Wasef L, et al. Chemical constituents and pharmacological activities of garlic (Allium sativum L.): a review. *Nutrients*. 2020;12(3):872. doi:10.3390/nu12030872.

104. Enogieru AB, Haylett W, His DC, Bardien S, Ekpo OE. Rutin as a potent antioxidant: Implications for neurodegenerative disorders. *Oxid Med Cell Longev*. 2018;27:6241017. doi:10.1155/2018/6241017.

105. García-Zebadúa JC, Reyes-Chipala R, Huerta-Reyes M, et al. El árbol tropical Calophyllum brasiliense: una revisión botánica, química, y farmacológica. *Rev LA Fac QUÍMICA Farm*. 2014; 21(2):126-145.

106. Olivas-Aguirre FJ, Wall-Medrano A, González-Aguilar GA, et al. Hydrolyzable tannins; biochemistry, nutritional & analytical aspects and health effects. *Nutr Hosp*. 2015;31(1): 55-66. doi:10.3305/nh.2015.31.1.7699.

107. Cheynier V. Polyphenols in foods are more complex than often thought. *Am J Clin Nutr*. 2005;81(1 suppl):15640485. doi:10.1093/ajcn/ajn.81.1.223s.

108. Sharifi-rad M, Redaelli M, Zorzan M, Cho WC, Sharifi-rad J. Preclinical activities of Epigallocatechin Gallate in signaling pathways in cancer. *Molecules*. 2020;25(467):1-29.

109. Bae J, Kim N, Yunyoung S, Woo-Yeon K, You-Geong K. Activity of catechins and their applications. *Biomed Dermatol*. 2020;8(4):1-35. doi:10.1186/s41702-020-0057-8.
pharmacological review. *Food Chem.* 2014;165(165):424-443. doi:10.1016/j.foodchem.2014.05.002.

122. Brahmi Z, Niwa H, Yamasato M, et al. Effective cytochrome P450 (CYP) inhibitor isolated from thyme (Thymus saturosoides) purchased from a Japanese market. *Biosci Biotechnol Biochem.* 2011;75(11):2237-2239. doi:10.1271/bbb.110328.

123. Rodriguez-Pérez C, Gilbert-López B, Mendiola JA, Quirantes-Piné R, Segura-Carretero A, Ibáñez E. Optimization of microwave-assisted extraction and pressurized liquid extraction of phenolic compounds from Moringa oleifera leaves by multiresponse surface methodology. *Electrophoresis.* 2016;37(13):1938-1946. doi:10.1002/elps.201600071.

124. Rattanachaikunsopon P, Phumkhachorn P. Contents and anti-inflammatory activity of hepatocytes-treated extracts of valerian and St. John’s wort. *Fitoterapia.* 2011;82(1):24-31. doi:10.1016/j.fitote.2010.07.003.

125. Albert NW, Lewis DH, Zhang H, Irving LJ, Jameson PE, Davies KM. Light-induced vegetative anthocyanin pigmentation in Petunia. *J Exp Bot.* 2011;62(5):1717-1726. doi:10.1093/jxb/erq097.

126. Piñol-Roig E, Codony-Senent X, Peralta J, et al. Anthocyanin-less pomegranate (Punica granatum L.) caused by an insertion in the coding region of the leucoanthocyanidin dioxygenase (LDOX; ANS) gene. *PLoS One.* 2015;10(11):1-16. doi:10.1371/journal.pone.0142777.

127. Brahimi Z, Niwa H, Yamasato M, et al. Effective cytochrome P450 (CYP) inhibitor isolated from thyme (Thymus saturosoides) purchased from a Japanese market. *Biosci Biotechnol Biochem.* 2011;75(11):2237-2239. doi:10.1271/bbb.110328.

128. Rodríguez-González M, Rodríguez-Pérez C, Gilbert-López B, Mendiola JA, Quirantes-Piné R, Segura-Carretero A, Ibáñez E. Optimization of microwave-assisted extraction and pressurized liquid extraction of phenolic compounds from Moringa oleifera leaves by multiresponse surface methodology. *Electrophoresis.* 2016;37(13):1938-1946. doi:10.1002/elps.201600071.

129. Cazarolli LH, Kappel VD, Pereira DF, et al. Optimization of microwave-assisted extraction and pressurized liquid extraction of phenolic compounds from Moringa oleifera leaves by multiresponse surface methodology. *Electrophoresis.* 2016;37(13):1938-1946. doi:10.1002/elps.201600071.

130. Cazarolli LH, Kappel VD, Pereira DF, et al. Optimization of microwave-assisted extraction and pressurized liquid extraction of phenolic compounds from Moringa oleifera leaves by multiresponse surface methodology. *Electrophoresis.* 2016;37(13):1938-1946. doi:10.1002/elps.201600071.

131. Algamdi N, Mullen W, Crozier A. Tea prepared from *Ananas comosus* var. `Flavacolor` purchased from a Japanese market. *J Agric Food Chem.* 2010;58(15):6185-6205. doi:10.1021/jf1006568.

132. Fahad S, Bajwa AA, Nazir U, et al. Crop production under drought and heat stress: Plant responses and management options. *Front Plant Sci.* 2017;8:1-16. doi:10.3389/fpls.2017.01147.

133. Benavente-Garcia O, Castillo J. Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. *J Agric Food Chem.* 2008;56(15):6185-6205. doi:10.1021/jf8006568.

134. Patel K, Gadewar M, Tahilyani V, Patel DK. A review on pharmacological and analytical aspects of diosmetin: a concise report. *Chin J Integr Med.* 2013;19(10):792-800. doi:10.1007/s11655-013-1595-3.

135. Llanes PR, Villamil AP, López CO. Determinación por HPLC de flavononas en jugos cítricos de variedades cultivadas en Santander. *Sci Tech.* 2007;33(3):293-294.

136. Rodríguez-González M, Rodríguez-Pérez C, Gilbert-López B, Mendiola JA, Quirantes-Piné R, Segura-Carretero A, Ibáñez E. Optimization of microwave-assisted extraction and pressurized liquid extraction of phenolic compounds from Moringa oleifera leaves by multiresponse surface methodology. *Electrophoresis.* 2016;37(13):1938-1946. doi:10.1002/elps.201600071.

137. Di Majo D, Giammanco M, La Guardia M, Tripoli E, Gianmancio S, Finetti O. Flavanones in citrus fruit: structure-antioxidant activity relationships. *Food Res Int.* 2005;38(10):1161-1166. doi:10.1016/j.foodres.2005.05.001.

138. Simmen U, Saladin C, Kaufmann P, Poddar M, Wallimann C, Schaffner W. Preserved pharmacological activity of galangin-a concise report. *Phytochemistry.* 2008;79(5):727-747. doi:10.1016/j.phytochem.2007.11.017.

139. Dugrand-Judek A, Olry A, Hehn A, et al. The distribution of coumarins and furanocoumarins in citrus species closely matches citrus phylogeny and reflects the organization of biosynthetic pathways. *PloS One.* 2015;10(11):1-25. doi:10.1371/journal.pone.0142757.

140. Yu C, Zhang P, Lou L, Wang Y. Perspectives regarding the role of biochanin A in humans. *Front Pharmacol.* 2011;2(1):143-149. doi:10.3389/fphar.2011.00093.

141. Yu C, Zhang P, Lou L, Wang Y. Perspectives regarding the role of biochanin A in humans. *Front Pharmacol.* 2011;2(1):143-149. doi:10.3389/fphar.2011.00093.

142. Bamba Y, Yun YS, Kunugi A, Inoue H. Compounds isolated from *Psidium guajava*. *Planta Med.* 2011;77(11):2237-2239. doi:10.1271/bbb.110328.

143. Beevers C, Huang S. Pharmacological and clinical properties of curcumin. *Bot Targets Ther.* 2011;1:5-18. doi:10.2147/btat.s17244.

144. Hung WL, Suh JH, Wang Y. Chemistry and health effects of furanocoumarins in grapefruit. *J Food Drug Anal.* 2017;25(1):71-83. doi:10.1016/j.jfda.2016.11.008.

145. Albert NW, Lewis DH, Zhang H, Irving LJ, Jameson PE, Davies KM. Light-induced vegetative anthocyanin pigmentation in Petunia. *J Exp Bot.* 2009;60(7):2191-2202. doi:10.1093/jxb/er907.

146. Ben-Simhon Z, Judeinstein S, Trainin T, et al. A “white” anthocyanin-less pomegranate (Punica granatum L.) caused by an insertion in the coding region of the leucoanthocyanidin dioxygenase (LDOX; ANS) gene. *PLoS One.* 2015;10(11):1-21. doi:10.1371/journal.pone.0142777.

147. Leusink GJ, Kitts DD, Yaghmaee P, Durance T. Retention of antioxidant capacity of vacuum microwave dried cranberry. *J Food Sci.* 2010;75(3):311-316. doi:10.1111/j.1750-3841.2010.01563.x.
149. Liang Z, Liang H, Guo Y, Yang D. Cyanidin 3-o-galactoside: a natural compound with multiple health benefits. *Int J Mol Sci*. 2021;22(5):1-23. doi: 10.3390/ijms22052261.

150. Patel K, Jain A, Patel DK. Medicinal significance, pharmacological activities, and analytical aspects of anthocyanidins ‘delphinidin’: a concise report. *J Acute Dis*. 2013;2(3):169-178. doi: 10.1016/s2221-6189(13)60123-7.

151. Rajan VK, Ragi C, Muraleedharan K. A computational exploration into the structure, antioxidant capacity, toxicity and drug-like activity of the anthocyanidin “Petunidin”. *Heliyon*. 2019;5(7):e02115. doi: 10.1016/j.heliyon.2019.e02115.

152. Beheres L. Hyperforin. *Phytochemistry*. 2006;67(20):2201-2207. doi: 10.1016/j.phytochem.2006.08.017.

153. Madabushi R, Frank B, Drewelov B, Derendorf H, Butterweck V. Hyperforin in St. John’s wort drug interactions. *Eur J Clin Pharmacol*. 2006;62(3):225-233. doi: 10.1007/s00228-006-0096-0.

154. Zanoli P. Role of hyperforin in the pharmacological activities of St. John’s wort. *CNS Drug Rev*. 2004;10(3):203-218. doi: 10.1111/j.1527-3458.2004.tb00022.x.

155. Vidal MA, Calderón E, Román D, Pérez-Bustamante F, Torres LM. Capsaicina tópica en el tratamiento del dolor neuropático. *Rev la Soc Esp del Dolor*. 2004;11(5):306-318.

156. Frias B, Merighi A. Capsaicin, nociception and pain. *Molecules*. 2016;21(797):3-33. doi: 10.3390/molecules21067097.

157. Wang K, Feng X, Chai L, Cao S, Qiu F. The metabolism of berberine and its contribution to the pharmacological effects. *Drug Metab Rev*. 2017;49(2):139-157. doi: 10.1080/03602532.2017.1306544.

158. Zhou M, Deng Y, Liu M, et al. The pharmacological activity of berberine, a review for liver protection. *Eur J Pharmacol*. 2021;890(1166):172655. doi: 10.1016/j.ejphar.2020.172655.

159. Zhi D, Feng PF, Sun JL, et al. The enhancement of cardiotoxicity by concomitant administration of Berberine and marolcides. *Eur J Pharm Sci*. 2015;76:149-155. doi: 10.1016/j.ejps.2015.05.009.

160. Wang Y, Jiang YM, Wang YT, et al. Inhibition of cytochrome P450 isoforms and P-gp activity by multiple extracts of Huang-Lian-Jie-Du decoction. *J Ethnopharmacol*. 2014;156:175-181. doi: 10.1016/j.jep.2014.08.044.

161. Shan YQ, Zhu YP, Pang J, et al. Tetrandrine potentiates the hypoglycemic efficacy of berberine by inhibiting P-glycoprotein function. *Biol Pharm Bull*. 2013;36(10):1562-1569. doi: 10.1248/bpb.b13-00272.

162. He X, Fang J, Huang L, Wang J, Huang X. Sophora flavescescens Ait.; traditional usage, phytochemistry and pharmacology of an important traditional Chinese medicine. *J Ethnopharmacol*. 2015;172:10-29. doi: 10.1016/j.jep.2015.06.010.

163. Huang T, Liu Y, Zhang C. Pharmacokinetics and bioavailability enhancement of Baicalin: a review. *Eur J Drug Metab Pharmacokinet*. 2019;44(2):159-168. doi: 10.1007/s13318-018-0509-3.

164. Kum KY, Kirchhof R, Luick R, Heinrich M. Danshen (Salvia miltiorrhiza) on the global market: what are the implications for products’ quality? *Front Pharmacol*. 2021;12:1-14. doi: 10.3389/fphar.2021.621169.

165. Li Y, Wang Q, Yao X, Li Y. Induction of CYP3A4 and MDR1 gene expression by baicalin, baicalein, chlorogenic acid, and ginsenoside Rf through constitutive androstane receptor- and pregnane X receptor-mediated pathways. *Eur J Pharmacol*. 2010;640(1):46-54. doi: 10.1016/j.ejphar.2010.05.017.

166. Mei N, Guo X, Ren Z, Kobayashi D, Wada K, Guo L. Review of Ginkgo biloba-induced toxicity, from experimental studies to human case reports. *J Ethnopharmacol*. 2015;172:1-29. doi: 10.1016/j.jep.2015.06.010.1278298.

167. Rajaraman G, Chen J, Chang TKH. Ginkgolide A contributes to the potentiation of acetaminophen toxicity by Ginkgo biloba extract in primary cultures of rat hepatocytes. *Toxicol Appl Pharmacol*. 2006;217(2):225-233. doi: 10.1016/j.taap.2006.08.005.

168. Bhagwat S, Haytowitz BD, Holden JM. *USDA Database for the Flavonoid ContenBhagwat, Seemat of Selected Foods Release 3; 2011. https://www.ars.usda.gov/ARSUserFiles/80400525/Data/Flav/Flav3.3.pdf.

169. Sgma-Aldrich. https://www.sigmaaldrich.com/MX/es/substance. https://www.sigmaaldrich.com/MX/es/substance (accessed 31 October 2021).

170. Kim S-B, Cho S-S, Cho H-J, Yoon I-S. Modulation of hepatic cytochrome p450 enzymes by curcumin and its pharmacokinetic consequences in sprague-dawley rats. *Pharmacogn Mag*. 2015;11(44):580. doi: 10.4103/0973-1296.172965.

171. Arol G, Donath F, Maurer A, et al. No relevant interaction with alprazolam, caffeine, tobutamide, and digoxin by treatment with a low-hyperforin St John’s wort extract. *Planta Med.* 2005;71(4):331-337. doi: 10.1055/s-2005-864099.

172. Tannergren C, Engman H, Knutson L, Hedeland M, Bondesson U, Lennernäs H. St John’s wort decreases the bioavailability of R- and S-verapamil through induction of the first-pass metabolism. *Clin Pharmacol Ther*. 2004;75(4):298-309. doi: 10.1016/j.cpt.2003.12.012.

173. Bauer S, Störmer E, Johne A, et al. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John’s wort in renal transplant patients. *Br J Clin Pharmacol*. 2003;55(2):203-211. doi: 10.1046/j.1365-2125.2003.01759.x.

174. Mai I, Bauer S, Perloff ES, et al. Hyperforin content determines the magnitude of the St John’s wort-cyclosporine drug interaction. *Clin Pharmacol Ther*. 2004;76(4):330-340. doi: 10.1016/j.cpt.2004.07.004.

175. Nduka SO, Okonta MJ, Ajaghaku DL, Amorha KC, Ukwe CV. Inhibition of cytochrome P450 3A enzyme by Millettia aboesis: its effect on the pharmacokinetic properties of efavirenz and nevirapine. *Rev Bras Farmacogn*. 2017;27(2):228-235. doi: 10.1016/j.bjp.2016.10.008.

176. Dresser GK, Urcuhatl BL, Proniuk J, et al. Coffee inhibition of cytochrome P450 isoenzymes and P-gp activity by multiple extracts of *Planta Med.* 2013;80(1):61-69. doi: 10.1055/s.1016/j.cpt.2004.07.004.

177. Gurley BJ, Swain a, Hubbard Ma, et al. Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity in vivo. *Clin Pharmacol Ther.* 2008;83(1):61-69. doi: 10.1038/sj.clpt.6100222.