ISSN: 2754-5008

Journal of Pharmaceutical Research and Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Concept of Drug Metabolism and Pharmacokinetics with Special Focus on Herbal-Drug Interaction

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ABSTRACT

The study of how xenobiotics undergo the process of absorption, distribution, metabolism, and excretion (ADME) is conceptualized as pharmacokinetics. An understanding therefore of the PK properties is crucial and plays an important contribution in the drug discovery and development of new chemical entities. Drug metabolism is linked to the metabolic breakdown of drugs (xenobiotic metabolism) by enzyme or living organisms. The pathway involved in this process can lead to the bio-transformations that occurs in most living organisms. The drug metabolic action facilitates the detoxification process except in special circumstances where the metabolites (break down products) can lead to toxic effects. Under such circumstances the study of drug metabolism is termed as pharmacokinetics, which constitutes an important discipline as a branch of pharmacology. Herbal natural products have been used to prevent and treat diseases worldwide since the creation of mankind. However, the efficacy, safety and quality of herbal bioactive metabolites depends on the multiple components absorbed in the body and their pharmacokinetics. This review attempts to give an insight into the concept of drug metabolism and pharmacokinetics with special consideration on PK drug-herbal interactions, mechanisms, metabolizing enzymes involved and transporters implicated in the determination of the PK of xenobiotics.

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Received: September 25, 2023; **Accepted:** October 04, 2023; **Published:** October 09, 2023

Keywords: Drug Metabolism, Pharmacokinetics, absorption, distribution, metabolism and excretion, Herbal-drug interactions, metabolic enzymes

Introduction

Pharmacokinetics (PK) is defined as the quantitative study of drug absorption, distribution, metabolism, and excretion (ADME) [1]. It gives an understanding of the ways the body process a drug as the drug exerts its actions in the body [2]. The scope of PK embodies more studies on healthy participants and to do with wider research on variations under a cascade of physiologic or pathologic conditions, with the underlying mechanisms, potential drug-drug interactions (DDI), and different management approaches such as dose adjustment in order to achieve precision medication (Pharmacogenomics). In a wider sense, PK studies concerns customization of drug dosage regimens for the improvement of better therapeutic outcomes [1]. PK study is an important instrument for establishing the relations and the underlying mechanisms of a drug to its activities and clinical therapeutic output. The outcome of PK studies is relevant for lead compound identification and optimization in the drug discovery process, and in addition understanding the dosage regimen design and adjustment in clinical practice [2]. The complexity of PK has evolved, thanks to the rapid developments in analytical chemistry, computer science, molecular biology and biochemistry. With more studies done so far on the PK of many drugs, and the possible establishment of many technologies for PK research, recent studies have revealed the existence of new mechanisms on how drugs are metabolized and how PK can be regulated. There is an increasing understanding of the development of new experimental models and computational modeling algorithms opening up better understanding of the significance of PK in a whole-body system, though with many research challenges faced by scientists. The application of PK in Chinese traditional medicine is well illustrated by Kunming et al. in Table 1.

Table 1: The Application of Pharmacokinetics in Traditional Chinese Medicine [1].

Name of plant	Analytical Method	Active Components	Compartment method	Parameters	PK behavior
Schisandra chinensis	UFLC-MS/MS	Schisandrin, Schisandrol B, Schisantherin A, Deoxyshisandrin, Schisandrin, gomisin N	Non- Compartmental	AUC, Cmax, T1/2, MRT, CLZ/F	The better absorption of the six analyses in model group
Rhizoma copidis	UHPLC-ESI-MS/MS	Berberine, coptisine, Palmatine, jatrorrhizine, Epiberberine, magnoflorine, Columbamine, noroxyhydrastine, oxyberberine, 8-oxocoptisine		$T_{1/2,}$ $C_{max,}$ $T_{max,}$ AUC_{0-1}	Wine processing did exert limited effects on the absorption of of columbamine, noroxyhydrastinine, oxyberberine and 8-oxocoptisine
Pueraria lobata	UFLC-MS/MS	Puerarin, 3-methoxypuerarin, hydroxypuerin, hydroxypuerarin, daidzein, daidzein-8-C-apiosyl-(1-6) glycoside	Non- Compartmental	$T_{max,}$ C0, AUC_{0-1}, $T_{1/2}$, etc	Puerarin, 3-methoxypuerarin, hydroxypuerin, hydroxypuerarin, daidzein and daidzein-8-C-apiosyl-(1-6) glycoside can quickly penetrate the brain through the blood brain barrier
Angelica Pubescens Maxim	HPLC	columbianetin	Non- Compartmental	C_{max},V/F, T1/2	Columbianetin has rapid oral absorption, quick clearance and good absolute bioavailability
Herba Ephedrae Radix Aconiti Lateralis	UPLC-MS	norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, methylephedrine, aconitine, benzoyylaconine and benzoylhypaconine	Non- Compartmental	$T_{max,}$ $C_{max.}$ $AUC_{0-1,}$ $T_{1/2,}$ etc	Alkaloids (except methylephedrine, benzoyylaconine and benzoylhypaconine) showed slower elimination.
Radix Aconiti Lateralis	LC-MS/MS	aconitine, hypaconitine, mesaconitine, benzoylaconine, benoylhypaconine, benzoylmesaconine		T1/2, AUC0-1, Cmax, Tmax	Ganjiang could promote the elimination of aconitine and hypaconine and enhance the absoption of benzoylhyaconine and benzoylmesaconine
Rhubarb peony Decoction (RPD)	LC-MS	Alo-emodin, rhein, emodin		$T_{1/2,}$ C_{max} T_{max}	The absorption of rhein in rats was suppressed after oral administration

The Advantages of Pharmacokinetics

The application of PK on herbal natural products has gained the interest of many researchers who are dedicated to developing improved traditional medicine (ITM). There are three advantages for applying PK on ITM. First, the possibility of identifying and screening multi-components of herbal products could clearly explain its bioactive effects. Many compounds can be screened as in earlier studies by Wang X., et al. who screened 9 compounds selecting a candidate component to explain the pharmacological effects via comparing the dynamic process of each composition in vivo [1,2].

Research Platform of Pharmacokinetics Applications in Drug-Herbal Interaction

Several data mining references involved application of PK on components research of single herbs. In order to discover the reason why main components in single herb could treat diseases, comparing its PK parameters *in vivo* is a good choice of techniques [1]. Wei B. et al. discovered that the absorption of six sedative and hypnotic lignans in an insomniac group were all significantly higher than in a normal group by comparing their PK parameters [3]. Furthermore, the study also showed that six lignans were distributed mainly in the hypothalamus and a comparative study of the PK parameters of the six lignans indicated that their absorptions in the insomniac group were higher than in the normal group [4,5].

Drug Metabolizing Enzyme and Transporters as Determinants of Pk

Drug-metabolizing enzymes and transporters play a very important role in the control of PK. In addition, transcriptional and post-transcriptional factors such as nuclear receptors and noncoding RNAs (ncRNAs) are crucial in the modulation of PK and can provide an understanding on the regulatory mechanisms to solve the PK problems [6,7]. These mechanism-driven PK studies can enhance the success of drug development related to its efficacy and safety and an improvement on the rational use of drugs in clinical practice [8].

The Influence of Drug-Metabolizing Enzymes in The Mediation and Control of Pk

Drug-metabolizing enzymes regulate the metabolism of exogenous and endogenous substances. Most drugs can reduce their pharmacological activities mainly through metabolic transformation, producing metabolites with high water solubility that can be readily excreted [9,10]. Therefore, metabolizing enzymes have shown to play a very important role in the control of drug PK. The biotransformation of xenobiotics by xenobiotic-metabolizing enzymes (XMEs) may be classified into Phase I and Phase II reactions. A more complex and advanced characterizations of enzymes for human drug metabolism are highly needed, in order to reduce and minimize severe adverse drug reactions [11,12]. There has been advancement in the understanding of drug-metabolizing enzymes role in the mediation of PK, involving individual isoforms of many enzymes such as cytochrome P450s (CYPs) and uracil diphosphate (UDP)-glucuronosyltransferases (UGTs), and their selective substrates, inducers and inhibitors. Other non-P450 oxidative enzymes and conjugative enzymes are also important since an increasing number of drugs are metabolized via these enzymes [13-15].

Cyps Role in The pk Process

CYPs can oxidize exogenous substances, enhance the water solubility and facilitate drugs to be easily eliminated from the body. Most drugs are metabolized by CYPs, that are located mainly at the inner membrane of mitochondria or the endoplasmic reticulum of cells [14,15]. There is a total of 57 known human CYP genes in 18 families. The members of the CYP1 to CYP4 families oxidize thousands of exogenous and endogenous substrates, whereas all members of CYP5 family and higher, mainly metabolize endogenous substrates in a highly substrate-specific manner [16]. Most known chemical carcinogens, such as aromatic amines and polycyclic aromatic hydrocarbons (PAHs), are substrates of CYP1 family, and their metabolism often results in the formation of active carcinogenic metabolites. Some studies conducted in 2018, indicated that CYP1B1 was found in the mitochondria of cancer cells, where it reportedly metabolizes melatonin to form the metabolite N-acetyl serotonin (NAS), which has antitumor effects [14]. CYP2D6, another important metabolic enzyme, is involved in the metabolism of many anti-cancer drugs, such as cyclophosphamide, tamoxifen, and gefitinib [15].

Other research has found that in brain, CYP2D6 can metabolize both m-tyramine and p-tyramine into dopamine [16]. The CYP4 family has been widely studied and shown for its potential to generate useful metabolites and dispose of endogenous substrates. CYP4F11, together with CYP4F2, are known to play an important role in the synthesis of 20-hydroxyeicosatetraenoic acid (20HETE) from arachidonic acid, and participates in the metabolism of vitamin K [14,15]. Cyp2A5, the mouse correlate of human CYP2A6, encodes an enzyme that can exhibit circadian regulation [16,17]. An understanding on the variation in the mechanism-based enzyme activity is important for the improvement of the clinical use of drugs. Highly selective inducers and inhibitors of CYPs have been reported in the Guidance for Industry by FDA (https://www.fda.gov/drugs/drug-interactionslabeling/drug-development-and-drug-interactions-table-substrates inhibitors-and-inducers).

New studies have shown new chemicals and herbal natural products as inducers or inhibitors of CYPs. For instance, CYP7A1 is upregulated by an intestinal HIF-2a inhibitor called PT238517. The ketene intermediate of erlotinib can also inactivate CYP3A4 and CYP3A5, resulting to liver injury [18]. Due to the complexity of bioactive metabolites in the herbal extracts it has been reported that herb products can exhibit different effects on the regulation of multiple enzymes. For example, *Sophora flavescens* are known to inhibit CYP2B6, CYP2C8, CYP2C9, and CYP3A activities, while catalpol can inhibit the activity of CYP3A4, CYP2E1 and CYP2C919,20. Some regulatory factors such as tumor suppressor p53 can also alter the expression of CYPs, like Cyp2B10 directly and thereby attenuate APAP-induced hepatotoxicity [19,20].

Herbal Natural Products

Herbs may be used singly or in combination for the treatment of diseases [21]. It is very important to understand how drug exposure can affect molecular mechanisms underlying many complex drug interactions. For example, studies have shown that ellagic acid from pomegranate peel, guava leaf extract can significantly increase the AUC of warfarin with concomitant use. A significant reduction in CYP2C8, 2C9, and 3A4 activity can be the main reason for this interaction [22].

Based on research findings, new information on the relative state of individual isoforms of P450 has been reported and there is a significant difference between total CYP concentrations between Chinese and Caucasian populations and the metabolic potentials of CYPs in Chinese liver microsomes are known to be significantly lower (<50%) in the CL int for substrates of CYP1A2, CYP2C9, CYP2C19 and CYP2E1 than those of Caucasian populations [23]. Large variations in protein content, mRNA levels, and intrinsic activities of ten P450s (CYP3A4, 1A2, etc.) revealed that some single nucleotide polymorphisms had significant impact on P450 expression; for instance, CYP2C19 activity varied more than 600-fold [24].

Other organs such as the kidney and intestine also have significant metabolic potentials. There is strong evidence for CYP2B6 and CYP3A5 expression in human kidney, while multiple CYPs have shown to be expressed in intestine [25-27]. The role of renal and intestinal enzymes in herbal product metabolism has been studied. Aminoglycoside antibiotics are leading causes for

nephrotoxicity; combination with herbs or dietary supplements at reduced dosage is possible to reduce the risk of drug-mediated renal toxicity. Other studies have shown that Moringa oleifera seed oil could limit gentamicin-induced oxidative nephrotoxicity [28]. Additional herbs have been identified as having effects on intestinal metabolism, such as the extracts of Yin-Chen-Hao Tang (YCHT), a very popular hepatoprotective three-herb formula in China and Japan [29]. These findings contribute to the understanding of the metabolic characteristics of renal and intestinal metabolism.

The Role of non-p450 Oxidative Enzymes in pk

The contribution of non-P450 enzymes to drug metabolism can be very important and can affect the overall development of drugs. Non-CYP enzymes can be divided into four general categories: namely oxidative, reductive, conjugative, and hydrolytic. Non-CYP oxidative enzymes include flavin-containing monooxygenases (FMOs), monoamine oxidases (MAOs), peroxidases, xanthine oxidases (XO), aldehyde oxidase (AO), alcohol dehydrogenase (ADHs) and aldehyde dehydrogenase (ALDHs) [30]. There is a gap of information on the regulation of content and activity of non-P450 oxidative enzymes. Some studies on selective substrates and inhibitors of non-P450 enzymes have been identified in natural products and other sources. FMOs are involved in the metabolism of a wide varieties of xenobiotics. Important inhibitors of FMOs include indole-3-carbinol and methimazole, and 2-mercaptobenzimidazole [31]. Classified into two different isoforms (MAO-A, MAO-B), MAOs are enzymes involved in the catabolism of monoamines. Benextramine and its derivatives has been identified as novel human monoamine oxidases inhibitors, which could be considered as candidate drugs for the treatment of neurodegenerative diseases [32].

Furthermore, 3-(3-(-(dimethyl amino) propanoyl)-7-hydroxy-5-methyl-2H-chromen-2-one hydrochloride has been reported to function as a novel selective hMAO-B inhibitor, showing a promising multifunctional Parkinson's disease treatment agent [33]. XO and AO are involved in the oxidation of aldehydes and heterocycles, and carbazeran was used as a selective probe substrate of AO in hepatocytes [34]. Allopurinol and Sallyl cysteine (SAC) are XO inhibitors used in the treatment of gout and hyperuricemia [35]. A single-nucleotide polymorphism of human cytochrome P450 oxidoreductase (POR) in the Chinese population can regulate the content of POR and P450 isoforms [36]. Identifying specific inhibitor compounds will greatly facilitate investigation of enzyme-mediated drug disposition and drug interactions.

Current Status of Research on Drug-Drug Interactions

Drug-drug interactions (DDIs) may result in efficacious or toxic effects. Patients frequently use more than one medication at a time and depending on the clinical settings and the number of drugs prescribed, the incidence of potential DDIs can range between 15% and 80% [37]. DDIs can be classified mechanistically into 3 major types: physio-chemical incompatibility, PK interactions, and pharmacodynamic interactions [38]. Physio-chemical interactions usually occur when positively and negatively charged compounds are mixed before they are administrated or absorbed. Pharmacokinetics-based DDIs, are characterized by altered concentration of unbound drugs that exert pharmacological effects, and can be caused by several mechanisms, such as:

1. Alteration of drug metabolizing enzymes (e.g., CYPs) [39].
2. Alteration of transporters involved in the absorption, distribution and excretion of drugs (e.g., MDR1, OAT, OCT, etc.)
3. Influence on plasma protein binding affinity, and
4. Changes in the organ function (e.g., gut motility or stomach content pH) [38,39].

Pharmacodynamics-based DDIs are characterized by a shift of the unbound drug concentration versus response curve [38]. New responses that are not present when either of the drugs is given alone may also be observed when drugs are used in combination. *In vitro*, *in vivo* and clinical studies are usually conducted to identify any potential DDIs. The *in vitro* studies are usually simple systems that can be used for high throughput screening and provide mechanistic information for potential DDIs. *In vivo* animal studies on the other hand, are often conducted using clinically relevant dosages and pharmacodynamic endpoints to confirm the *in vitro* observations. If evidence obtained from *in vitro* and *in vivo* animal models suggests a strong DDIs potential further clinical trials are recommended [39,40]. Recently, mathematical modeling, particularly physiologically-based pharmacokinetic (PBPK) modeling has also been used to investigate potential pharmacokinetic-based DDIs. A review by Min et al. [41,42] showed how pharmacokinetic modeling improves and simplifies the investigation on DDIs.

Although DDIs between small molecule drugs have been well investigated and documented, knowledge on interactions between drugs and herbs, interactions between therapeutic biologics, and interactions mediated by the gut microbiome are currently not well understood [43,44].

Current Research Status on Herb-Drug Interactions

Herbal plants and herbal products are commonly used as therapeutic agents and dietary supplements. When herbs are simultaneously administered with drugs, unrecognized herb-drug interactions (HDIs) can occur leading to side effects and toxicity. HDIs basically share the same mechanisms as DDIs, and to avoid physio-chemical interactions between herbal components and drugs, it is usually recommended that herbs should be taken at two hours before or after the drugs. Furthermore, herbs may sometimes alter the PK and/or pharmacodynamics of the concurrently administered drugs. PK and pharmacodynamic interactions have been reported between herbs and drugs with narrow therapeutic windows, especially drugs for CNS and cardiovascular diseases [43]. For example, St John's wort (Hypericum perforatum) has been reported to decrease warfarin plasma concentrations via inducing the activity of CYPs, leading to the loss of anticoagulant activity [44].

Pharmacokinetic Interactions Between Herbal Medicines

It is understood that the metabolites of the medicinal plant are able to induce or inhibit transporters or metabolic enzymes, and this could be useful to predict potential pharmacokinetic interactions between herbal medicines and drugs [45]. A number of *in vitro* studies have approached the potential of selected herbal extracts and/or specific constituents to induce or inhibit transporters or drug-metabolizing enzymes, mainly P-glycoprotein (P-pg) and cytochrome P450 (CYP450) isoforms. In addition, transporters belonging to the ATP-binding cassette transporters (ABC transporters) and solute carrier (SLC) transporters as well as phase I and II enzymes can be targeted by plant secondary metabolites. Unfortunately, the translation of *in vitro* results in clinical data is difficult to achieve, and differences are commonly observed between the results of controlled clinical studies and *in vitro* results. Different factors can be responsible for this discrepancy like the high concentrations of extracts or their metabolites that

are used in vitro to inhibit or to induce transporters or drug-metabolizing enzymes, are not obtained in humans after the administration of the conventional dose [45, 46].

Some other factors to be considered would be the modification of enzyme activity in the incubation setting, induced by ionic strength, pH changes or by the solvent used to dissolve the herbal extract. Other *in vitro* studies do not consider the parameters, such as bioavailability, protein-binding properties or *in vivo* formation of metabolites. The lack of medicinal plant standardization makes the scenario more complex and in different studies, the same natural products may show quantitative and qualitative differences in the chemical composition [46, 47].

Mechanisms of Action of Herbal Medicines-Drugs Interactions

The induction or inhibition of metabolic enzymes and transporters are the main mechanisms of action of the bioactive compounds in the herbal medicines. It is well understood that a receptor-mediated mechanism is involved in the induction of drug-metabolizing enzymes and transporters, especially orphan nuclear receptors, including pregnane X receptor (PXR) (Nuclear Receptor Subfamily 1 Group I Member 2, NR1I2) and constitutive androstane receptor (CAR) (Nuclear receptor subfamily 1 group I member 3 protein, *NR1I3*) [48]. P-gp is expressed in normal human tissues such as liver, kidney, intestine and the endothelial cells of the blood–brain barrier [49].

The apical (or luminal) expression of P-gp in these tissues results in reduced drug absorption from the gastrointestinal tract, enhanced drug elimination into bile and urine, and hinders the entry of certain drugs into the central nervous system. In addition, the expression of CYP is ubiquitous and in the liver, the activation of PXR stimulates the expression of the CYP3A family members [47-49] and CYP2, including CYP2B6, CYP2C8, CYP2C9 and CYP2C19 [50]. Moreover, Phase II genes that are up-regulated by PXR ligands include members of the UDP-glucuronosyltransferase (UGTs), glutathione-S-transferase and sulfotransferase (SULTs) families. In the intestine, PXR stimulates the expression of ABCB1, while, in the liver, PXR stimulates the expression of organic anion transporting polypeptide (OATP)2B1 and multidrug resistance-associated protein (MRP)2 [50].

The four types of enzyme inhibitions can be differentiated by monitoring Km and Vmax values of the substrate.

St John's Wort (Sjw)

Miliar stone of the herb–drug interactions refer to the capacity of St John's wort (*Hypericum perforatum*; SJW) to induce the expression of several members of CYPs and P-gp (Table 1). In particular, the National Institutes of Health (NIH) conducted the first pharmacokinetic study that was suggested for SJW acting as an inducer of CYP3A4. That study was performed to verify whether hypericum extract may affect the plasma level of the HIV protease inhibitor indinavir, a substrate of CYP3A4. The results of that study indicated that a 2-week treatment with SJW reduced the area under the curve (AUC) of indinavir by a mean of 57% and decreased the extrapolated 8-h indinavir trough by 81% in healthy volunteers [51]. Examples of clinical evidence of St John's Wort (SJW)-drug interaction mediated mainly by induction in healthy volunteers or patients is illustrated in table 2.

Table 2: Examples of Clinical Evidence of St John's Wort (Sjw)-Drug Interaction Mediated Mainly by Induction in Healthy Volunteers or Patients [46]

Hypericum Extract Dose 3 x 300 mg/day	Duration	Subject number	Drug Pharmacokinetic Parameters	Protein Involved
L1160	10 days	13 males and 12	↓AUC and C_{max} of digoxin	P-gp
Rex Sund	12 days	Females	AUC and C_{max} of midazolam	CYP3A4
Jarsin L1160		12 females	AUC of bosentan	CYP2C9/3A4
Jarsin L1160		13 subjects	AUC and C_{max} of ambrisentan	CYP3A4/5
Jarsin L1160		16 male and 4 females	Cmax of midazolam and fexofenadine	CYP2C19
Jarsin L1160		10 males and 11 females 9 males	AUC and C_{max} of talinolol	CYP3A4 and P-gpCYP3A4, P-gp
Buyers	14 days	6 males and 2 females	AUC of indinavir	CYP3A4
Jarsin L1160		7 males and 5 females	AUC of midazolam	CYP3A4
TruNatur		8 males	AUC of simvastatin	CYP2C8/3A4
L1160		12 subjects*	AUC of amitriptyline	CYP3A4
Kira		6 males and 6 females	AUC and C_{max} of imatinib	CYP3A5, P-gp
Buyers		12 males	AUC and C_{max} of omeprazole	CYP2C19
Buyers		12 males	AUC and C_{max} of mephenytoin	CYP2C19
Solaray 3 x 325 mg/day		15 males	AUC and C_{max} of no change of repaglinide	CYP2C8/3A4
Movina		8 males	AUC and C_{max} of verapamil	CYP3A4
Jarsin L1160		16 males	AUC and C_{max} of voriconazole	CYP3A4/5, P-GP
Kira		14 males	AUC and C_{max} of zolpidem	CYP2C19
Kira		15 males and 6 females	AUC and C_{max} of gliclazide	CYP3A4
Willmar Schwabe Pharm		14 subjects	AUC and C_{max} of nifedipine	CY-2C9
Jarsin L1160		6 males and 6 females	AUC and C_{max} of S-ketamine	CYP3A4
Hyper plant		4 males and 7 females*	AUC of decetaxel	CYP3A4/22B6 CYP3A

Oral bioavailability and the renal clearance of digoxin and SJW are regulated by P-gp activity and other clinical studies have shown supporting evidence that has suggested that SJW acts as an inducer of CYP metabolic and P-gp pathways. More *in vitro* and *in vivo* studies have also demonstrated the molecular mechanism underling the ability of SJW to decrease oral availability and/or accelerate the metabolism of drugs co-administered with the extract. The Glaxo Wellcome Research and Development group identified orphan nuclear receptor PXR as the target of SJW, the same as rifampicin, a well-known activator of this receptor and CYP3A4 expression. Hyperforin, one of the major constituents present in the dried flowering tops or aerial parts of SJW can mediate transactivation and coactivator recruitment by steroid and xenobiotic receptor (SRX) and was an activator of PXR with a half-maximal effective concentration (EC_{50}) of 23 nM making it one of the most potent PXR activators to be reported so far [52-55]. Successively, it has been shown that genes other than CYP3A4 [47-49] are induced by PXR in humans following activation by xenobiotics, including CYP2B6 CYPlA1 and 1A2 CYP2C8 and 2C9 as well as ABCB1 and MRP2 [56-60].

It has been reported that the induction of CYP3A and P-gp by SJW, in healthy volunteers, depends on hyperforin dose levels in the different types of extracts studied and, in particular, it has been suggested that a daily dose of 1 mg of hyperforin is an important dose necessary for clinically significant interactions [61-64]. Studies using the randomized, double-blind, parallel-arm, clinical trial with 16 healthy volunteers recruited, evaluated the effect of SJW on fentanyl, which is metabolized by hepatic CYP3A4 and transported by P-gp [65]. In this study, the pharmacokinetics and pharmacodynamics of fentanyl was not affected. Therefore, several controlled clinical studies have been done to show that SJW and midazolam significantly modifies the pharmacokinetics of drugs that are substrate of CYP3A, 2C9, 2C19, 2E1 or transported by P-gp or both including midazolam simvastatin amitriptyline chlorzoxazone methadone ethinyl estradiol/norethindrone combination oral contraceptives fexofenadine warfarin imatinib omeprazole mephenytoin tacrolimus verapamil voriconazole talinolol gliclazide nifedipine ketamine zolpidem bosentan ambrisentan and docetaxel [66-91]. Even though hyperforin of SJW has been reported as the first herbal constituent to activate PXR, other herbal products, such as *Ginkgo biloba* and garlic extracts, are now known to activate this nuclear receptor and induce in vitro transporter proteins and/or metabolizing enzymes as indicated in table 3.

Table 3: Studies on Clinical Pharmacokinetics of Gingko Biloba-Drug Interaction Modulated by The Induction in Healthy Subjects or Patients' Participants [45, 46]

Herbal Extract		Subject number	Drug Pharmacokinetic Parameters	Protein Involved
Dose	**Duration**			
Ginkgo biloba extract 240 mg standardized to 0.12% to 0.3 hypericin	14 days	12 subjects	AUC of alprazolam on effect half-life of elimination	CYP3A4
Ginkgo biloba extract 240 mg	28 days	14 subjects	AUC and Cmax of midazolam	CYP3A4
Ginkgo biloba extract mg no available	Some months	1 HIV-infected*	Plasma concentrations of efavirenz	CYP2B6
Ginkgo biloba extract 120 mg, twice daily	12 days	7 males	Voriconazole no pharmacokinetic change of	Extensive (2C19*1/2C19*1) and poor (2C19*2/2C19*2) metabolizers
Ginkgo biloba extract 120 mg, twice daily	14 DAYS	14 males	Bupropion no pharmacokinetic change	CYP2B6
Ginkgo biloba extract 120 mg, twice daily	28 days	12 males	Diazepam No pharmacokinetics change	CYP2C19
Ginkgo biloba extract 360mg/day	14 days	10 males	Cmax and AUC of talinolol No effects elimination half-life	P-gp inhibition

There are some research challenges that make the understanding of the clinical relevance of available data sometimes questionable due to the lack of correlation between the high concentrations of extracts or their metabolites necessary to activate nuclear receptors and to induce transporters or drug metabolizing enzymes *in vitro*, with those effectively obtained at standard dosage in humans [45]. It is important to note that *in vitro* studies do not include important factors such as bioavailability or the generation of active metabolites [46]. All the limitations of *in vitro* studies may help in understanding the gap, often documented, between outcomes predicted by *in vitro* studies and the data of controlled clinical studies. These differences can arise from the study design (dosage, duration of treatment), the variability in phytochemical composition of commercially available herbal supplements, the selection of substrate drug used to predict enzyme activity, and also the choice of pharmacokinetics performed to assess the occurrence of herb–drug interactions (e.g., single-time point versus canonical AUC analysis) [45,46]. The metabolites associated with the reported activation of nuclear receptors are not identified and only a hypothesis about the candidate bioactive compounds is known and has been studied.

Ginkgo Biloba

Studies using in *vitro* cell-based luciferase reporter gene assay have shown that an extract of *Ginkgo biloba* can activate human PXR, in a dose-dependent manner [92]. This extract included metabolite concentrations of ginkgolide A, B, C, and J, bilobalide and flavonols similar to those found in the standardized extract EGb 761 [92]. In particular, G. biloba extract at 200 µg/mL increased by 9.5-fold human PXR activation [92] and the expression of PXR target genes, i.e., CYP3A4, CYP3A5 and ABCB1 (encoding P-gp) in human LS180 colon adenocarcinoma cells [92]. Further studies by Li and colleagues [92] confirmed that *G. biloba* extract (EGb 761, 100 µg/mL) activated human PXR by identifying the compounds responsible for this effect [93]. In human HepG2 cells studies, the cell-based reporter assays indicated that ginkgolide A (GA; 50 µM) and ginkgolide B (GB; 50 µM) activated PXR; quercetin (25 µg/mL) and kaempferol (20 µg/mL) activated PXR, CAR, and aryl hydrocarbon receptor (AhR), whereas bilobalide (BB; 50 µM) did not induce effects on these nuclear receptors [93]. In human primary hepatocytes, it was reported that only EGb 761, GA, and GB were capable of inducing CYP3A4, CYP2B6, UGTI A1, ABCB1 and MRP2, unlike BB and the flavonoids kaempferol and quercetin that were inactive [93].

Recent studies on molecular docking analysis has shown that the PXR binding energy was high for GA and GB [94]. The study compared the GA effect with hyperforin, indicating that the ginkgolide had less effectiveness (EC_{50} = 16.2 µM) than hyperforin (EC_{50} = 0.02–0.2 µM) but both showed similar efficacy (Emax = 11. 5-fold for GA vs. 6- to 12-fold for hyperforin) [94]. Furthermore, it was demonstrated that the flavonoidic fraction of EGb761 inhibited the enzyme activity of CYP 3A4, 2C9, 1A2, 2El with Ki between 4.9 and 55 microg/mL [95]. No elaborate and contrasting data were obtained in vivo after exposing rats with *G. biloba*, where it was reported that the extract increased metabolic [96] and inhibited P-gp activity [97]. The administration of *G. biloba* extract (100 mg/kg for 5 days) significantly reduced the AUC (0-12) of tolbutamide by 53% in low-protein diet-fed rats and by 38% in normal rats [96]. On the contrary, the treatment with *G. biloba* extract for 30 days with a dose of 100 mg/kg increased tissue venlafaxine levels in kidney tissue measured as a tissue/serum drug ratio, while a dose of 200 mg/kg of extract increases fluoxetine availability in liver, kidney and brain tissues [97]. The extrapolation of the *in vitro* or rodent results to human situation is complicated and contrasting evidence of interactions comes also from clinical studies using *G. biloba*. Treatment with *G. biloba* extract (240 mg/day for 2 weeks), in healthy volunteers, significantly decreased by 17% the AUC of alprazolam, CYP3A4 substrate, but did not affect the $t_{1/2}$ [98].

The involvement of P-gp transporter in *G. biloba*–drug interaction has been well demonstrated by Blonk and colleagues [99] with raltegravir, a weak P-gp substrate [100]. In healthy volunteers, *G. biloba* extract (120 mg twice daily for 14 days) induced a geometric mean ratio (90% confidence intervals) difference (1.44 vs. 1.21) of C_{max} and $AUC_{(0-\infty)}$ when raltegravir was administered alone or with the extract trials [99]. Clinical pharmacokinetic studies of interactions between garlic extracts and drugs mediated by induction in healthy volunteers or patients has been better illustrated and described in table 4.

Table 4: Clinical Pharmacokinetic Studies of Interactions Between Garlic Extracts and Drugs Mediated by Induction in Healthy Volunteers or Patients*[46]

Herbal Extract Dose	Duration	Subject number	Drug Pharmacokinetic Parameters	Protein Involved
Garlic oil 500mg three times daily	28 days	6 males and 6 females	6-hydroxychlorzoxazone/ chlorzoxazone serum ratios (2-h) in young and elderly subjects Paraxanthine/caffeine serum ratios (6-h) 1-dydroxymidazolam/midazolam Serum ratios (1-h) Debrisoquine urinary recovery ratios no change	CYP2 E1 CYP1A2 CYP3A4 CY2D6
Garlic power tablets (kwai) 3 x 600 mg tablets twice daily	14 days	9 males and 6 females	AUC, C_{max}, T_{max}, half-life of elimination of alprazolam urinary Dextromethorphan/dextrorphan ratios activity no changes	CYP3A4
Garlic powder caplets twice daily	19 days	4 males and 6 females	C_{max} and AUC of squinavir	CYP2B6
Garlic capsules twice daily	4 days	5 males and 5 females	Not pharmacokinetics changes of ritonavir	

It is postulated that the decrease in the bioavailability of statins is associated with the capacity of G. biloba extract to induce OATP1B1 activity if no effects have been observed on the cholesterol-lowering efficacy of these drugs [102,103]. Furthermore, although, in the study of Guo and co-workers [101], subjects with the 521TT genotype were included, the data should be achieved on the activity or expression of intestinal and hepatic transporters after treatment with *G. biloba* in humans [102]. It was concluded that, the *in vitro* results obtained by Zhou and colleagues [99] indicated that ginkgolides were active on metabolic enzymes only at a high concentration [101], not achievable after the administration of standard doses of *G. biloba* extract in a healthy subject. These results can be explained by the lack of effect of the extract on pharmacokinetics of co-administered drugs (Table 2). Other recent studies highlight the capacity of gingkolides to affect intestinal and/or hepatic transporters suggesting some precaution in G. biloba extract administration with their substrates.

Allium Sativum

Different data have resulted from controlled clinical studies for garlic (*Allium sativum*) interactions. These inconclusive results are linked to differences in the duration of treatment and/or the use of different garlic-derived materials (Table 3). Many varieties of commercial garlic products are now available, including aged garlic extract (AGE), garlic essential oil and garlic powder. AGE includes water soluble sulphur compounds such as S-allylmercaptocysteine (SAMC) and S-allylcysteine (SAC) and small amounts of oil-soluble allyl sulphides. Garlic essential oil includes only oil-soluble sulphur components, such as diallyl trisulfide (DATS) and diallyl sulfide (DAS), with no allicin or water-soluble fraction. Garlic powder contains alliin and a small amount of oil-soluble sulphur compounds. The amounts of alliin present in different strains of garlic range from 2.8 to 7.7 $mg \bullet g^{-1}$[104]. Garlic and garlic powder do not contain allicin but it is produced through an enzymatic reaction catalyzed by alliinase. This enzyme is present in high concentrations in garlic cloves: at least 10% of the total protein content (10 $mg \bullet g^{-1}$ fresh weight). Alliinase is localized in vascular bundle sheath cells, whereas alliin is compartmentalized in mesophyll cells. By wetting the powder or crushing the clove of garlic can induce tissue disruption and consequently alliin is released from compartments and interacts with alliinase resulting to the synthesis of allicin in few seconds. Garlic cloves yield about 2.5 to 4.5 mg of allicin per gram of fresh weight when crushed [104]. Several *in vitro* studies refer to the potential of garlic, or selected garlic constituents, to inhibit P450 enzymes but they do not allow for the elucidation of data achieved in controlled clinical studies using garlic.

It has been previously shown, by using an in vitro assay, that both fresh garlics extracts and various commercial garlic products can inhibit the activities of cytochrome P4503A4, 2C9 *1, 2C19, 3A5, and 3A7 but not that of CYP2D6 and show moderate effectiveness on P-gp activity [105]. Some known water-soluble constituents of aged garlic were analyzed for their ability to inhibit the activity of CYP2C9, 1A2, 2CJ1, 2B6, 2D6, and 3A in human liver microsomes; and only S-allyl-L-cysteine and S-methyl-L-cysteine at 100 µmol/L produced a modest inhibition of CYP3A, reducing activity to 20–40% of the control [106]. Considering the limitations relative to *in vitro* studies, these data have indicated that garlic may cause inhibition during acute dosing. Many useful information about the *in vivo* effects of garlic on drug metabolizing enzymes may be inferred from animal studies that elucidated the molecular mechanisms underlying the capacity of garlic or related bio-active metabolite, including diallyl sulphide (DAS), diallyl disulphide (DADS) and its CYP2El-derived metabolites, diallyl sulphone (DASO2) and diallyl sulphoxide (DASO), to reduce the incidence of a number of chemically induced tumours in animal models. In addition to efficiently inhibiting CYP2El in rat liver, DADS and DAS also had the capacity to induce CYP enzymes, including CYP3A, CYP1A and CYP2B families, and phase II detoxification enzymes such as gluthatione S-transferase (GST), NAD(P)H: quinone oxidoreductase (NQO), epoxide hydrolase (EH) and UDP-glucuronosyltransferase (UGT) in rat liver [107-109]. Clinical pharmacokinetic studies of herbal-drug interactions mediated mainly by inhibition in healthy volunteers, cancer or HIV patients is well illustrated in table 5.

Table 5: Clinical Pharmacokinetic Studies of Herbal-Drug Interactions Mediated Mainly by Inhibition in Healthy Volunteers, Cancer* Or Hiv Patients

Herbal Extract		Subject number	Drug Pharmacokinetic Parameters	Protein Involved
Dose	**Duration**			
Hydrastis canadensis root extract [Goldenseal] 900 mg, 3 times daily (no standardization claim	28 days	6 males and 6 females	Debrisoquin and midazolam Pre- and post-supplementation Phenotypic ratio means	CYP2D6 and CYP3A4/5
Echinacea purpurea extract from root 400 mg, 4 times daily	8 days	6 males and 6 females	Dose/AUC (0-∞), C_{max}, T_{max}, of caffeine	CYP1A2
Echinacea purpurea whole plant extract 800 mg 2 times daily	28 days	6 male and 6 females	6-h serum Paraxanthine-to-caffeine Concentration ratio	CYP1A2
Echinacea purpurea extract from root 400 mg, 4 times daily	8 days	6 males and 6 females	AUC (0-∞) by 23% and Of $t_{1/2}$ of midazolam, administered intravenously.	CYP3A4
Echinamide Natural Factors capsule 250 mg 2 times daily	28 days	8 males and 5 females	AUC of midazolam by 37% and a reduction of half-life by 45%	CYP3A4
Silymarin (Thisilyn) 153 mg 3 times daily	21 days	12 subjects	C_8 ($_{ug/mL}$) of indinavir	CYP3A4
Silymarin 160mg	14 days	7 males and 3 females	C_{max}, AUC of indinavir	CYP3A4
Milk thistle 175 mg 2 daily (standardized to 80% silymarin	28 days	6 males and 6 females	1-hydroxymidazolam/ midazolam serum ratios (1-h sample) No effect	CYP3A4
Milk thistle 300 mg 3 times daily (standardized to 80% silymarin	14 days	10 males and 10 females	AUC (0-∞), C_{max} and T_{max} CL/F, $t_{1/2}$ of midazolam No effect	CYP3A4

Milk thistle extract 200 mg 3 times daily (standardized to 80% silymarin	4 or 12 days	2 males and 4 females*	No effect on irinotecan Clearance	CYP3A4 UGTIA1
Silymarin 420 mg/day	14 days	12 males	AUC ($_{0-24}$), AUC (0-∞) and C_{max} Dose/AUC (0-∞) of losartan	CYP2C9*1/*1
Silymarin 140 mg three times daily	14 days	18 males	AUC ($_{0-36}$), AUC (0-∞) and C_{max} Oral clearance (CL/F) of talinolol	P-gp

Garlic intake (3 × 600 mg tablets twice daily for 2 week) did not modify the AUC, C_{max}, T_{max}, $t_{1/2}$, of alprazolam, CYP34 substrate drug, nor the urinary dextromethorphan/dextrorphan ratios used as an index of CYP2D6 activity [110-115]. This evidence would indicate that garlic supplements have a low risk for CYP-mediated herb-drug interactions; however, quite different results have been previously shown by Piscitelli and co-workers [116-119]. Specifically, in a clinical study, they evaluated the effect on the pharmacokinetics of saquinavir after treatment for 21 days with garlic powder caplets, administered twice daily. It was highlighted that garlic supplementation decreased drug C_{max} by 54%, AUC by 51%, and levels at 8 h after dosing (post dose C_8) by 49% [111-120]. Moreover, saquinavir pharmacokinetics did not return to baseline values after a 10-day washout period; indeed, the mean AUC returned to 65%, the C_{max} to 61% and the C_8 to 70% of baseline values, respectively.

As the AUC for saquinavir did not return to baseline values after the washout period, a direct impairment of absorption in the gastrointestinal tract can be supposed. By comparing saquinavir and darunavir effects on P-gp binding sites, the same has been reported that darunavir and phytochemicals in AGE bind the same sites, suggesting that no pharmacokinetic modification is expected with darunavir [112,121]. The divergent results achieved by Piscitelli et al [111] and Markowitz et al. [110] (Table 3) could be attributed to a different dosing period (3 weeks versus 2 weeks) used.

These studies can be supported by another study, indicating that the intake of garlic capsules over 4 days did not modify significantly the single-dose pharmacokinetics of ritonavir (a drug with a high binding affinity for P-gp and CYP3A substrate) in healthy volunteers, although there was a trend for a decrease in ritonavir concentrations [113,212]. Furthermore, the authors had also indicated that two HIV-infected patients taking garlic or garlic supplements for more than 2 weeks showed serious gastrointestinal toxicity after beginning ritonavir-containing antiretroviral therapy (400 or 600 mg twice daily); the symptoms disappeared after discontinuing garlic or ritonavir [113]. However, the lack of data for the plasma levels of ritonavir when administered with garlic constituents does not allow for speculation about the possible underlying mechanism. On many instances, it has been indicated that garlic supplementation (600 mg tablets twice daily) does not significantly alter the disposition of docetaxel, a CYP3A4 substrate drug [114,123]. However, in patients carrying a CYP3A5*1A allele, on average, over a 12-day period, garlic decreased the clearance of docetaxel [114,124]. These data suggest that the genotyping of drug-metabolizing enzymes that exhibit clinically relevant polymorphisms should represent an integral part of herb–drug interaction studies to overcome some inconsistent results obtained from clinical studies. Generally, what can be anticipated is that special attention must be given when garlic supplements are employed by patients concurrently treated with drugs whose disposition depends on P-gp and/or CYP3A and CYP2E1 (Table 3).

The ability of *Echinacea* extracts to inhibit the activity of human cytochrome P450 enzymes is unequivocally reported in several studies in vitro [116-119]. However, different variables including the species (E. angustifolia, E. purpurea, E. pallida), plant parts (aerial parts, whole plants, roots or a combination of them), and the kind of preparations (such as infusion, tincture, tablets, capsules, methanolic extract or liquid capsules) do not allow comparison of the various studies. Specifically, when considering CYP inhibition by 10 different commercially available *Echinacea* preparations, it was shown that all tested extracts were capable of inhibiting CYP3A4, but inhibitory potencies (expressed as median inhibitory concentration, IC_{50}) changed by a factor of 150 [118]. Then, a lack of information or insufficient characterization regarding the investigated extract, definitely preclude any translation of *in vitro* results to clinical setting. Actually, different studies examined in humans the effects of various *Echinacea* extracts on cytochrome P450 activity [119-124].

Although additional studies are very much needed before an assertion can be done about the ability of *Echinacea* to inhibit the metabolism of CYP1A2 substrate drugs in humans, it is recommended to take with caution *Echinacea* extracts with such drugs. Similar conclusions can be made when Echinacea supplementation is assumed with CYP2C9 substrate drugs following the observation that the administration of *Echinacea purpurea* extract (400 mg four times a day for 8 days) increased the AUC of oral tolbutamide and reduced its oral clearance [120]. However, intake for 2 weeks (four times daily) of MediHerb Premium Echinacea TM tablets (a mixture of *Echinacea angustifolia* and *Echinacea purpurea*) weakly increased the apparent clearance of (S)-warfarin [122-125]. No significant modifications were observed in CYP2D6 activity in three different studies after the administration of *Echinacea* extracts [116-121]. Likewise, no significant changes in CYP2E1 activity were observed by Gurley et al [121]. following the oral administration of Echinacea. On the contrary, conflicting results have been shown on the effects of *Echinacea* administration on the disposition of drugs substrate of CYP3A4 isoform. *Echinacea purpurea* whole plant extract (800 mg, two times daily) for 28 days did not induce changes in pre- and post-supplementation values of l-hydroxymidazolam/midazolam serum ratio 1 h after oral administration of midazolam (8 mg) to 12 healthy volunteers [121-127].

Medicinal plant extracts, useful for different therapeutic purposes, e.g., aromatherapy in dementia, may influence the pharmacokinetics of co-administered drugs by inducing modifications in plasma drug levels. Consequently, it may not reach a therapeutic response or, alternatively, it may cause drug-induced toxicity [125,126].

Interaction happens usually during all the pharmacokinetic phases of a drug (intestinal absorption, distribution, hepatic elimination and/or renal excretion). Several clinical studies report that herbal extracts may alter oral availability and/or the systemic hepatic clearance of drugs co-administered but the effects on drug distribution and renal excretion are not yet largely investigated. Different mechanisms are involved in herb–drug interactions as membrane transport, drug metabolizing enzymes or both. While many clinical studies carried out have investigated the potential for P-gp- and/or CYP-mediated interaction, there is a gap of information regarding interaction involving a drug transporter other than P-gp and phase II metabolism. The attempt made to increase the knowledge on the induction or inhibition of transporters or metabolic enzymes by natural extract compounds can allow for the anticipation of potential drug–herbal interactions and minimizes the risk of therapeutic failure or drug toxicity [45].

The SJW extracts and their components, hypericin, hyperforin, and quercetin, have been recorded to be competitive or non-competitive inhibitors of several CYP enzymes *in vitro* [127]. Indeed, SJW is the herbal medicine for which extensive data mining indicates its ability to induce P-gp and CYP3A4 in humans. However, SJW poses the risk of interaction with indinavir or other drugs metabolized by cytochrome P450. The example provided by SJW demonstrates that only one herbal medicine can induce interactions through several mechanisms. Moreover, Silybum marianum influences other drugs both at the level of cytochrome P450 and of P-gp. Another aspect refers to the contrasting results often shown in clinical studies. In fact, discrepancy between *in vitro* and clinical results may occur and this can be explained by several reasons: (1) the use of high concentrations of herbal product in vitro not achievable in humans after the administration of the conventional dose; (2) the modification of enzyme activity in the *in vitro* setting (ionic strength, pH changes, use of solvents, etc.) respect to clinical administration; (3) the lack of oral bioavailability, protein-binding properties or *in vivo* formation of metabolites during in vitro studies. For all the listed reasons, well-designed clinical trials, a suitable choice of substrate drugs for transporters and phase I and phase II enzymes, the standardization of herbal extracts along with the genotyping of drug-metabolizing enzymes that display clinically important polymorphisms, should aid to overcome in the near future some inconsistent results originating from clinical studies [128].

Clinical studies are necessary to ensure safety on the use of medicinal plants in combination with conventional medicine. However, it is important to indicate that it is very necessary to comply with existing guidelines on how to conduct clinical trials on the interactions between natural extracts and synthetic drugs. More studies are also needed to elucidate all possible mechanisms of herbal medicine–drugs interactions, most of the actual data being focused on interactions involving metabolic enzymes and carriers. DMPK research is essential for understanding the efficacy and safety of medications. Integrated studies on drug-metabolizing enzymes and transporters underlying the ADME processes as well as their transcriptional and post-transcriptional regulation mechanisms can provide a comprehensive understanding of inter-individual diversity in pharmacotherapy. More future research in herbal-drug interaction will hopefully advance the understanding for achieving a better prediction of pharmacokinetics properties.

Future Prospective

The increasing global economic evolution has caused a shift to focus on societal health situation and growing alternative therapy on improved traditional medicine (ITM) more impact in developing economy beyond that of Western countries [107]. It is evident that to guarantee the safety and effectiveness of herbal medicines, studies in pharmacokinetics are necessary. Safety and effectiveness of ITM are vital aspects in order to investigate herbal medicines. It is not feasible that clinical rational use of ITM can mainly depend on pharmacokinetic parameters of bioactive metabolites derived from herbal products. The usage and dosage of ITM have to originate from a large exploration development of clinical trials studies. Although the PK studies of herbal products have significantly contributed in unlocking some vital problems with the application of ITM

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