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Review article

Pharmacokinetics-Based Herb-Drug Interactions: Current Status in Experimental Models in Nigeria

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SUMMARY

Introduction/Aim. Herbs have been a vital renewable source of medicine throughout human history as a large proportion of the global population still depends on them for their health benefits. The increasing popularity of herbal supplements has raised an obvious concern about the overall safety and potential interaction with other drugs in situ. The intent was to spur future research on herb-drug interactions as well as the mechanisms of interaction to understand the consequences of such interactions.
Methodology. The review was conducted by a systematic search of relevant literature using the databases of Google Scholar, Science Direct, Mendeley, Scopus, and PubMed. Publications written in English were used.
Results. Many herbal products are reported to exhibit herb-drug interaction with known orthodox medicines. The inhibition-induction mechanism triggers chain reactions which often result in reduced drug bioavailability, toxicities, or undesirable side effects. Some herbal phytoconstituents reportedly bind CYP2C9, CYP2C19, CYP2E1, and CYP3A1 among numerous others temporarily or irreversibly.
Conclusion. The study was concluded by reiterating the imperativeness to routinely and regularly inform both physicians and patients of the inherent dangers such as reduced efficacy and increased toxicities associated with herb-drug interactions (HDI). Herb users should be regularly advised on the appropriate use of herbal supplements to avoid the risk of adverse drug interactions during co-administrations or in combination therapies. As both synergistic and antagonistic effects could be observed in HDI, further preclinical and clinical empirical studies are required to underscore the mechanism and extent of HDI.

Keywords: **herb-drug interaction, enz**

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INTRODUCTION

The upsurge in the global application of complementary and alternative medicines which heavily relies on herbal preparations calls for urgent attention with respect to interactions of the chemical constituent of a plant with prescription medicines (1). Herb-drug interactions (HDIs) are interactions that occur between herbal product/ dietary supplement and a conventional drug when administered together. This interaction could involve either pharmacokinetic or pharmacodynamic mechanisms. While pharmacokinetic interaction refers to the effect of a herbal drug on the absorption, distribution, metabolism and excretion of a conventional drug, pharmacodynamic interactions are associated with the pharmacological activity of the drug and may affect an enzyme, receptor site, or organ system. Thus, the outcomes could be additive, synergistic, or antagonism.

Pharmacokinetics (PK) is simply defined as the action of the body on the drug while exerting its action in the body. It is the quantitative study of drug absorption, distribution, metabolism, and excretion (2). It does not study only healthy individuals but also includes research on PK variations under a variety of physiological (e.g. pregnancy) and disease conditions. It also covers the underlying mechanisms, potential drug-drug interactions (DDIs), dietary-drug interactions, HDIs, and strategies (dose adjustment) to achieve precise dosage regimens for better therapeutic outcomes (3). Thus, PK study is always required to determine the relations and underlying mechanisms of drug actions and its clinical benefits and is important for lead identification and optimization in drug discovery (4).

Despite the advancement in drug metabolism and pharmacokinetics (DMPK) research, it is largely due to the advancement in bio-analytical chemistry, pharmacology, molecular biology, medicinal chemistry, biochemistry, and computer science. Research involving herb-drug interaction seems not to have fully utilized these technologies. This is largely due to complex constituents of herbs, study designs (e.g. dose and treatment periods) and assay systems (e.g. *in vitro*, or *in vivo* preclinical studies or clinical studies). These are the reasons for the inconsistent predictions and/or results associated with HDIs studies (5 - 7).

Our previous studies on combinations of a medicinal plant and a natural product with a versatile pharmaceutical excipient revealed that bioavailability and efficacy can be altered through interaction (8 - 10). This impelled us to carry out a review on herb and drug interaction.

This review provides a comprehensive overview of current trends in pharmacokinetics and further discusses the trends in PK-based HDIs and its underlying mechanisms as well as the clinical relevance in Nigeria.

LITERATURE SEARCH/METHODOLOGY

Literature search from 2003 up to 2023 was undertaken using a range of scientific databases (Google Scholar, PubMed, Science Direct, Mendeley, and Scopus) using the keywords: pharmacokinetics, herb-drug interaction, mechanism of Pharmacokinetic action, clinical relevance, and experimental models.

FACTORS DETERMINING PHARMACOKINETICS-BASED HDIs

Absorption is the movement of a drug from its site of administration into the blood from where it is distributed to its site of action and permeates through different body barriers until the drug is inactivated and finally excreted from the body. Alterations in the absorption, distribution, metabolism and excretion of a drug affect its pharmacokinetic profile (8). Hence, drug metabolizing enzymes (DMEs) and transporters (e.g. P-glycoprotein) are key determinants in pharmacokinetics. Drug transporters are usually present in the intestine where they are involved in drug absorption, an important parameter of pharmacokinetics (9). Drug-metabolizing enzymes are largely present in the liver where most drug metabolism occurs. Most of the herbal drug interactions are metabolism-based and mediated by the cytochrome P450 system that is largely involved in phase 1 reaction (10, 11). Also, transcriptional and posttranscriptional factors (e.g. nuclear receptors, noncoding RNA) are important determinants of PK. Studies exploring these determinants can explain the mechanism of HDIs, improve the success of drug development, and prevent drug recall post market. However, herbal products and other natural products are not usually considered during the process of drug development either

at the preclinical or clinical stages of development. Nonetheless, some significant clinical HDIs were reported (12).

DRUG METABOLIZING ENZYMES MODULATION OF PHARMACOKINETICS

Drug metabolizing enzymes mediate the metabolism of exogenous (drugs, herbs, chemicals) and endogenous (e.g. bilirubin) substances. Most drugs become inactive mainly through metabolic transformation, producing more polar metabolites that are readily excreted. Hence, DMEs play a crucial role in the mechanism mediating pharmacokinetic-based herb-drug interaction. For instance, induction of DMEs may lead to a decrease in drug concentration in the body and consequent efficacy reduction. The metabolism of drugs/herbs by the metabolizing enzymes may be classified into phase I, phase II, and phase III reactions (13). The phase I reactions usually involve enzymes such as cytochrome P450 oxidases (CYPs) that introduce reactive or polar groups into drugs/herbs. This is usually followed by phase II reactions; the enzymes involved in this reaction are transferases (e.g. uridine glucuronyl transferase, UGTs). Lastly, in phase III reactions, the product of phase III reactions may be further processed, before it is recognized and pumped out of the cells by the efflux transporter (13). There is a better understanding of the roles played by DMEs in the modulation of PK. These include identifications of more isoforms of metabolizing enzymes and their selective substrates, inducers, and inhibitors. The roles of other non-CYPS oxidative enzymes (e.g. flavin monooxygenases) and conjugative enzymes (e.g. carboxylases) are now being considered in PK studies (14).

Herbal products also undergo phase I and phase II reactions to be excreted from the body. If a herbal product is co-administered with a drug, it may inhibit or induce the activity or the expression of specific DMEs that could be the same enzymes responsible for the metabolism of that drug, leading to herb-drug interactions (15).

PHASE 1 DRUG-METABOLIZING ENZYME CRITICAL FOR PK

Phase 1 enzymes may be grouped as CYPs and non-CYPs oxidative enzymes. CYPs are responsible for many drug metabolisms, mainly located in the inner membrane of mitochondria or the smooth endoplasmic reticulum of the liver cells (16). However, some CYPs are found outside the liver cells (e.g. CYP1A1); they can also be found in the cells of the lungs, kidneys as well as in the intestine. They are classified based on their amino acid sequence homology into families, subfamilies, and isoforms (14). When two CYPs have about 40% similarity in their amino acid sequence, then they belong to the same family. The families are numbered, such as CYP1, CYP2, and CYP3 etc. Subfamilies are identified based on 55% similarities in sequence homology; it is usually represented with a capital letter, for example CYP1A, CYP1B, CYP2A, etc (17). Lastly, individual 'isoforms' that originated from a single are represented by the number which usually follows the letters that represent subfamilies, such as

Table1. *Endogenous and exogenous substrates of CYPs*

Family	Number of subfamilies	Endogenous/Exogeneous substrates
CYP1A	2	Aflatoxin, estrogen, melatonin, and naproxen
CYP2	13	Arachidonic acid, coumarin, diazepam, halothane, and paracetamol
CYP3A	2	Erythromycin, nifedipine, and testosterone
UGT1A	8	Bilirubin, eicosanoids, imipramine, and p-Nitrophenol
UGT2A	3	Hydeoxycholic acid, tobacco carcinogens
UGT2B	7	Carvedilol, efavirenz, diclofenac, and bile acids
UGT3	1	N-acetylglucosamine
UGT8	1	Bile acid

CYPs- cytochrome P450. Adapted from Liu et al. (2)

CYP1A1, CY1A2 and others (17 - 19). A total of 57 human CYP genes in 18 families have been identified (13, 2, 20). CYP1 to CYP4 families oxidized several exogenous and endogenous chemicals (Table 1), while CYP5 and higher families majorly metabolize endogenous substrate in a highly substrate-specific manner (20).

The understanding of differences in mechanism of metabolism-mediated DDI/HDIs involving the metabolizing enzyme activities is very critical for improving clinical use of drugs either with herbs or another drug. Recent studies have shown several herbs and chemical entities as inhibitors/inducers of CYPs. For example, *Styrax liquidus* (resin of *Liquidambar orientalis* Mill) inhibits CYP3A (21). The complexity of phyto-constituents of herbs is the reason for the differences seen in the effects of the herbal remedy on the regulation of multiple enzymes. For instance, *Sophora flavescens* inhibit CYP2B6, CYP2C8, CYP2C9 and CYP3A activities (22). Other regulatory factors such as nuclear factor (Pregnane X receptor) can alter the expression of CYPs. Tumor suppressor p53 is known to regulate CYP2B10 directly (23).

It is important to understand how drug/herb exposure could alter drug metabolism mechanism underlying many HDIs. For example, the area under the curve (AUC) of glibenclamide was markedly increased when co-administered with *Tinospora cordifolia* extracts (24). This was due to a significant inhibition of CYP2C9, the enzyme involved in the metabolism of this drug.

The extrahepatic CYPs also have an important role in drug metabolism. There is evidence that C1A1 and CYP1B1 expressed in the lungs have a role in the metabolism of dolutegravir (25). Likewise, CYPs found in the intestine and kidneys are implicated in the metabolism of some herbs (26). More studies have shown the role of renal enzymes in herbs metabolism. Precisely, gentamicin-induced renal toxicity was shown to be alleviated by *Moringa oleifera* seed oil (27).

Lastly, CYP polymorphisms also play a critical role in PK. Recent data are now available on the relative content of individual CYPs isoforms. Total CYP concentrations are significantly varied between the Chinese and Caucasian populations, and the metabolic capabilities of CYPs in Chinese liver microsomes was significantly lower (< 50%) in the clearance of substrates for CYP1A2, CYP2C9, CYP2C19, and CYP2E1 than those of Caucasian populations (28).

NON-CYPs OXIDATIVE ENZYMES

The non-CYP oxidative enzymes also contribute immensely to drug metabolism. Hence, they are also important for consideration during drug development and PK study. They can be broadly classified based on the type of reactions they catalyze, they can be oxidative, hydrolytic, reductive and conjugative. Examples of non-CYP oxidative enzymes are: flavin-containing monooxygenases (FMOs), monoamine oxidases (MAOs), hydrolase (e.g. carboxyesterases), aldehyde oxidase (AO) and others (29, 30).

CES (carboxylesterase)-mediated reactions have been overlooked; it belongs to the family of α/β- hydrolase and about five of them have been identified in humans (CES1, CES2, CES3, CES5and CES6). They are ubiquitous but the human liver predominantly contains CES1 with smaller quantities of CES2, while the intestine almost only contains CES1 (30). Substrates and inhibitors have been identified for some of these enzymes (Table 2). Recently, scientists found that corylifolinin, a flavonoid found in *Fructus psoraleae*, inhibits carboxylesterase-1 (CES1), while bavachinin, found in the same plant species, inhibits carboxyesterae-2 (CES2) (31, 32).

Table 2. *Examples of different drugs that are substrates and modulators of Carboxylesterases*

Family	Substrates	**Inhibitors**	Inducers
CES1	Clopidogrel, enalapril, oseltamivir	**Curcumin, caffeic acid**	Trinitrobenzene, sulfonate, sulforaphane
CES2	Flutamide, irinotecan	**Loperamide, Telmisartan**	Urethane dimethacrylate

CES- carboxylesterase. Adapted from Wang et al. (161)

FMOs are involved in the metabolism of ethionamide, a second-line anti-tuberculosis drug (33). 2-mercaptobenzimidazole, indole-3-carbinol, and methimazole are known inhibitors of FMOs (34). Another non-CYPs oxidative enzyme is human monoamine oxidase (hMAO). There are two different isoforms, namely, hMAO-A and hMAO-B. These enzymes are involved in the metabolism of monoamines. Herniarin, a phytochemical obtained from *Artemsia dracunculus* were identified as inhibitors of hMAO (35).

IMPORTANCE OF PHASE II ENZYMES IN PK

Phase II enzymes (glucuronyl transferases, glutathione –S-transferases and N-acetyltransferases, etc.) play a major role in exogenous and endogenous substance metabolism (36). Uridine diphosphoglucuronosyl transferases (UGTs) are the most important enzymes in phase 2 metabolisms and glucuronidation is the most common reaction of phase II metabolisms (37). UGTs are present in the smooth endoplasmic reticulum, especially in the liver; they are classified into four gene families (UGT1, UGT2, UGT3 and UGT8). UGT1 and 2 play a major role in xenobiotics glucuronidation, while UGT4 and 8 roles are minimal (38). Chemicals either natural or synthetic with functional groups such as –OH, -COOH, -SH2 and –NH2 are generally suitable substrates for UGTs (39). Several substrates and inhibitors have been identified for different isoforms of UGTs (Table 3). Diosmetin, a naturally occurring flavonoid (mainly extracted from *Galium verum*) is metabolized by the UGTs (2). Also, UGT1A3 is involved in the glucuronidation of alpinetin, while metizolam (a depressant) is metabolized by UGT1A4 (40, 41). UGTs are diverse and have weak specificity for their substrates, hence, herb-drug interactions easily occur with UGTs (2). Highly selective and specific inhibitors/substrates have been identified in herbs and other sources; for example, resveratrol activates the expression of UGT1A8 and emodin inhibits UGT2B7 activity in various reports (42, 43).

Polymorphism in the genes encoding UGTs plays a critical role in the regulation of its contents and activity. Consequently, the variation could either be normal or abnormal metabolic activities with resultant alterations in the PK parameters (2, 44). Most of the findings on gene polymorphism are extrapolated for use in African populations, even when variant frequencies can differ significantly in different populations (45). The UGT1A4*3 genetic polymorphism is associated with low posaconazole

Table3. *Exogeneous and endogeneous chemicals metabolized by UGTs. Reproduced (47)*

Family	Enzymes	Endogeneous/exogeneous substrate
UGT1A	UGT1A1	Estradiol, Bilirubin, axitinib
	UGT1A3	Bile acid, NSAIDS
	UGT1A4	Eicosanoids, imipramine
	UGT1A6	Serotonin, 1- Napthol 4- nitrophenol
	UGT1A7	Icaritin
	UGT1A8	Fatty acids, opiods, coumarins
	UGT1A9	Steroids, Niflumic acid
	UGT1A10	Estrogens, dopamine, nitrosamine
UGT2A	UGT2A2/3	Hyodeoxycholic acid, tobacco carcinogens
UGT2B	UGT2B4	Arachidonic acid, Naftopidil
	UGT2B7	Sex steroids, zidovudine, codeine
	UGT2B10	Eicosanoids, amitryptiline
	UGT2B11	Hydroxlestrogens
	UGT2B15	Sex steroid hormones, lorazepam
	UGT2B17	Sex steroid hormones, flavonoids
	UGT2B28	Sex steroid hormones
UGT3	UGT3	N- acetylglucosamine
UGT8	UGT8A1	Bile acids

plasma concentrations in patients with hematological malignancies (46).

Other phase II enzymes such as glutathione S-transferase (GST) and sulfonyl transferase (SULT) are also important in mediating phase II reactions. Although these enzymes are being overlooked, recent studies have shown that they play an important role in metabolism-based HDIs and drugs PK (44). GST catalyzed the binding of glutathione to many electrophilic compounds in phase 2 reactions. About seven classes of GST isoforms have been identified in humans - alpha, zeta, theta, mu, pi, sigma, and omega (47). Endogenous substrates such as heme are metabolized by these enzymes. Xenobiotics substances such as busulfan are metabolized by GST (48).

REGULATORS OF DRUG METABOLIZING ENZYMES (DMEs)

Drug metabolizing enzyme expressions are regulated by human nuclear receptors. They are transcription factors that regulate target genes involved in drug metabolism (2). The transcription factors (peroxisome proliferators-activated receptor (PPAR), liver X-receptor (LXR), hepatocyte nuclear factor (HNF)) have been of interest lately regarding drug disposition because they are now found to regulate many drug-metabolizing enzymes (44). LXR controls the transcription of CYP7A1, CYP3A11and CYP2E1 (49).

Traditional transcription such as pregnane X-receptor (PXR), constitutive androstane/activated receptor (CAR), and microRNA (miRNAs) are the factors that control gene expressions by directly binding to specific DNA sequences (50). However, UGTs and CYPs are modulated mainly via epigenetic regulation by changing the chromatin architecture (51). This form of regulation accounts for gender specific regulations; for example, UGT1A gene repression is mediated by recruitment of histones in females (51).

In summary, drug metabolizing enzyme expression and activities are regulated by multiple factors, such as drug or herb chemical constituents, gene polymorphisms, nuclear receptors, ethnic variations, and even gender. These factors have critical effects on PK. Recently, non-CYP oxidative and UGT metabolizing enzymes have gained attention in DMPK research. It is important to comprehend the factors associated with the modulation of DME expression and its activities in predicting potential pharmacokinetic herb-drug interactions.

TRANSPORTERS' MODULATION OF PK

This review focused more on DMEs role in PK herbs-drug interactions. However, it is important to mention the role of drug transporters in pharmacokinetics. Drug transporters are membrane-bound proteins that act like gatekeepers for cells and control the uptake and efflux of drugs. They are very crucial in the pharmacokinetics, efficacy, and toxicity of drugs/herbal product. Any factor that can cause alteration in the expression and/or activity of drug transporter will have consequences on the PK of the affected drug. Co-administration of herbal product with drugs may lead to induction or inhibition of drug transporters resulting in a change in drug pharmacokinetics, which may potentially cause HDIs.

There are two major families of drug transporters — ABC (ATP-binding cassette) and SLC (solute carriers) (52). The ABC transporters act as exporter, pumping drugs out of the cells with the aid of energy produced from the hydrolysis of ATP, while SLT transporters mainly utilize energy stored in ions across the membrane (52, 53). About 49 ABC transporters have been identified and classified into seven subfamilies: ABC1/ABCA, multidrug resistance (MDR)/TAP/ABCB, MRP/ABCC, ALD/ABCD, OABP/ABCE, GCN20/ABCF and white/ABCG (44). Among ABC transporters, P-glycoprotein (P-gp) is the most widely studied, expressed mainly in the intestine, liver, kidneys, brain and placenta. Many substrates of P-gp (e.g. immunosuppressants, antibiotics and antineoplastics drugs) overlap with the substrates of CYPs. Transcription factors (vitamin D (VDR) and CCAAT/miRNAs) regulate P-gp expression (54).

Cancer cells usually over-express P-gp and this has been attributed to multidrug resistance (MDR) seen in antineoplastic chemotherapy (55). There are 360 SLC superfamily members which are organized into 55 SLC families. Organic anion transporting proteins (OATP), organic anion, and cation transporters (OATs and OCTs/SLCO) are the major SLC that play vital roles in drug disposition (54, 56).

The expression and activity of drug transporters are regulated by herbs/drugs. Co-administration of drugs with multiple drugs or herbal pro-

duct may lead to inhibition or induction of the transporters. Also, disease states may regulate the expression of transporters with consequent modification of drug pharmacokinetics (2).

HERB-DRUG INTERACTIONS

Herb-drug interactions (HDIs) are pharmacological or clinical responses to co-exposure to a conventional drugs and herbal medicine that exceed what is expected based on the known effects of each agent when administered alone. The outcome of HDIs may affect either the drug/herb pharmacokinetics (quantitative alteration) or pharmacodynamic (qualitative alteration) (Figure 1). The pharmacokinetic-mediated interactions occur due to an alteration in one or more processes of pharmacokinetics (ADME). The potential outcomes of this alteration include changes in pharmacokinetic (PK) parameters (C_{max}, T_{max}, and AUC), changes in drug efficacy, and changes in toxicity. Approximately 43% of HDI cases were related to PK-based interactions and contraindication cases arising from herb-drug combination occurred (57, 7). HDIs do not always lead to unfavorable effects. Favorable effects such as increased efficacy or reduced toxicity have been observed, and sometimes no effect is noticed when herbs are co-administered with drugs (58).

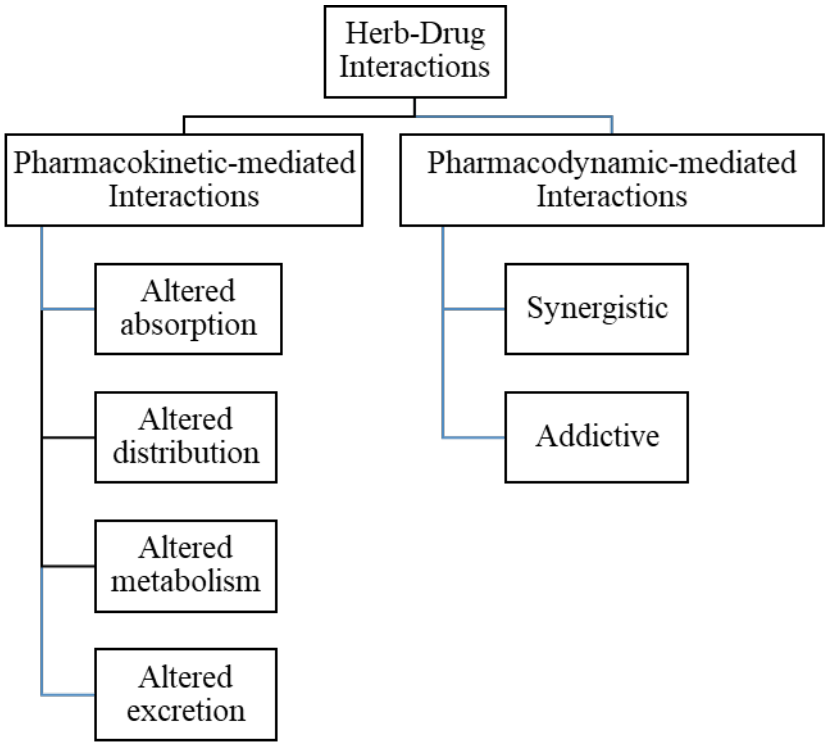

Figure 1. *Quantitative and qualitative outcome of Herb-Drug interactions*

MECHANISM OF HDIs

The mechanism of HDIs is very complex due to the presence of numerous herbs and phytochemicals. Pharmacokinetic and pharmacodynamic alterations are the major mechanistic pathways through which HDIs occur (Figure 1). The ability of phytochemicals in herbs to alter drug absorption, distribution, metabolism, and excretion (ADME) is the major mechanism underlying PK interactions (Figure 1). Thus, HDIs arise from modulation of metabolizing enzymes and/or transporters that mediate ADME of drugs in the liver, kidneys, and intestine (59).

METABOLIZING-ENZYME MEDIATED HDIs

Modulation (inhibition or induction) of drug metabolizing enzymes is the main mechanism of action of the bioactive constituents in the herbs (Figure 2). Studies have reported more CYP inhi-

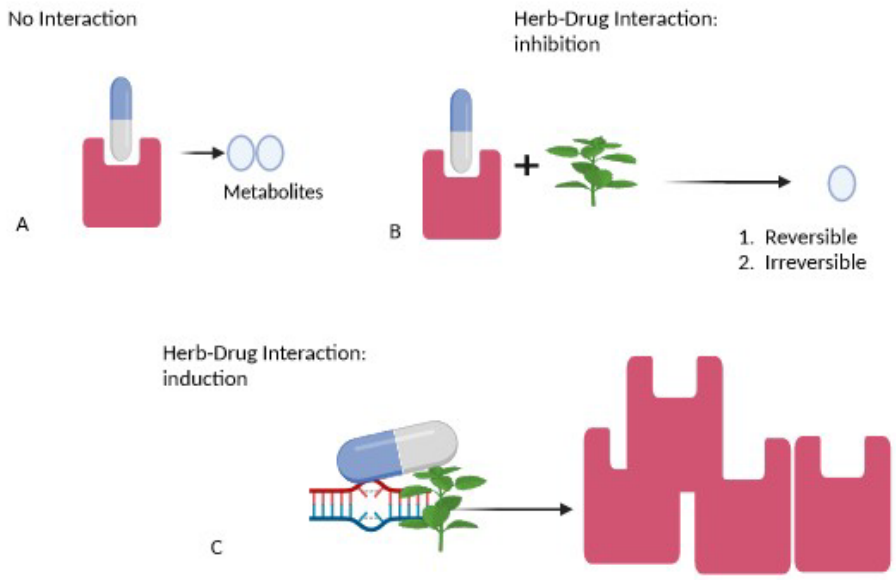

Figure 2. *Mechanisms underlying metabolism-mediated HDIs*

A) The drug-metabolizing enzyme interacts with the drug to produce expected metabolites in the absence of herbal constituents. B) In the presence of herbal constituents, there is a decrease in the activity of drug metabolizing enzymes that results in a reduction in metabolite formation. C) Interactions of herbal constituents with drug-metabolizing enzymes may increase enzyme expression or activity, which may result in the rapid metabolism of a co-administered drug. Both events in A and B may lead to significant herb-drug interactions, with a consequent decrease in drug efficacy or increase in drug toxicity.

bition than induction as a mechanism of PK-based HDIs (60). Inhibition of metabolic enzymes can either be reversible or irreversible (Figure 2). Reversible inhibition occurs as competition for DMEs (CYPs, UGTs) binding sites between the substrate (victim drug) and the perpetrators (i.e. inhibitors). Reversible inhibition can be further divided into competitive, non-competitive, uncompetitive, and mixed-type inhibition (61, 62). Irreversible inhibition occurs when the perpetrators bind covalently to the active site of the DMEs. For example, a co-administration of green tea leaves with ticagrelor (a P2Y12 receptor antagonist), a drug used in the management of acute coronary syndrome, may lead to a decrease in its bioavailability. This is due to the inhibition of CYP3A involved in ticagrelor metabolism by tea polyphenol extract (TPE) found in green tea leaves (63). In another study, aqueous and methanolic extracts of *Ocimum basilicum* using human liver microsomes *in vitro* assays reduced the activity of CYP2B6 by less than 50% at 200 μg/mL concentrations (64). The methanolic extracts of *Ocimum basilicum* strongly inhibit the rifampicin metabolism pathway (64). *Fructus autantii*, one of the herbal components of the Chinese decoction used in the management of COVID-19 disease (QFD; Qingfei Paidu decoction), was found to strongly inhibit CYP3A4 that catalyzes testosterone 6β hydroxylation in HLMs (65). Also, the significance of phase II enzyme inhibition in PK-based HDIs cannot be undermined; several studies have shown the relevance of these enzymes in HDIs (66, 37, 2).

Induction-mediated interaction is of major concern in clinical practice and drug development due to the possibility of herbal product consumption and multi-drug therapy. This is because enzyme induction may lead to a decrease in the efficacy of the co-administered drug by increasing the drug's elimination, lowering drug concentration, and reducing the pharmacological effects. It may also lead to an increase in reactive metabolite formation, resulting in increased toxicity (67). A common mechanism of DME induction is nuclear receptor (NR)-

mediated, leading to increased gene transcription, mRNA stabilization, or active protein (68).

The major nuclear receptor-mediators involved in metabolic enzyme induction are pregnane X receptor (PXR) (nuclear receptor subfamily 1 group 1 member 2, NR1I2) and constitutive androstane receptor (nuclear receptor subfamily 1 group I Member 3 protein, NR1I3). The activation of PXR in the liver stimulates the expression of CYP3A and CYP2 (CYP2B6, CYP2C8, CYP2C9 and CYP2C19) family members. Likewise, UGTs, GST and SULTs families are expressed upon activation of PXR (62). Other NRs involved in the regulation of genes related to drug ADME are fatty acid peroxisome proliferator-activated receptor (PPARα), retinoid-related orphan receptors (RORα), bile acid-activated farnesoid X receptor (FXR) and oxysterol activated liver X receptor (LXRα) (69), ligand-dependent transcription factor is involved in the induction of CYP1A1 and CYP1B1 (70). The binding of perpetrators (herbs) to any of these nuclear receptors activates it and then binds to the xenobiotic response element (XRE) that is located on the gene promoter region. This cascade of events will lead to increased transcription and translation of mRNA to proteins (67). There are many reports of PK-based HDIs resulting from the induction of metabolic enzymes. Thus, *Hypericum perforatum* (St John's wort; SJW) extracts induced CYP3A4 when co-administered with indinavir (antiretroviral drug; protease inhibitor). There was a reduction in the area under curve (AUC) of indinavir by a mean of 57% in healthy volunteers (62). Likewise, the extract of *Cordalis rhizoma*, commonly used in traditional Chinese medicine, was reported to induce the expression of CYP2E1 and 3A1 (71).

CURRENT EXPERIMENTAL MODELS IN PK-BASED HDIs

In the past twenty years, many studies have been conducted to unravel the mechanism of HDIs, especially that of enzymes-mediated PK-based HDIs (72). Experimental models usually comprising the combination of *in vitro* and *in vivo* studies are used to assess HDIs with the aim of identifying pharmacokinetic interactions. The study design involved the initial *in vitro* screening followed by *in vivo* (preclinical and clinical) studies (73, 74). Currently, fewer studies are reported using *in silico* and physiologically based pharmacokinetic (PBPK) simulation models (75, 76). In metabolic enzyme-mediated PK based HDI models, herbs, either single or multiple constituents, are assumed to be perpetrators (inducer or inhibitor), while the conventional drug is a substrate (i.e. victim drug) for the DMEs (62). This is because herbs contain numerous phytochemicals and sometimes unknown compounds which makes it difficult to analyze the concentration changes of all the phytochemicals representing their PK properties.

IN VITRO METABOLIC MODELS

The philosophy of 'fail early, fail cheaply' is very relevant in the process of drug development (16). *In vitro* models allow early screening of drugs for possible HDIs and provide a fast, simple and convenient route for detecting metabolic-mediated HDIs. It also provides platform for human-based *in vitro* assay which gives more accurate predictability of human clinical outcomes than animal studies during preclinical studies. Thus, current guidelines on drug development recommend that *in vivo* studies will be required when *in vitro* studies provide positive outcomes (77 - 79). Also, the results obtained from *in vitro* studies are used for physiology-based pharmacokinetic (PBPK) modeling to improve *in vitro* to *in vivo* extrapolation of HDIs (76).

Several *in vitro* test systems which range from whole cell system (e.g. intact perfused liver, primary human hepatocytes, and transfected cell lines) to enzyme preparations (e.g. liver microsomes (humans or animals), cytosolic and S9 fractions) can be used for *in vitro* metabolic studies. Each of these test systems has its advantages and limitations. According to the United State Food and Drug Administration Agency (FDA), the use of microsomes or supersomes (human lymphoblast cells containing expression of CYPs enzymes) is preferred and recommended for *in vitro* inhibition assay and primary human hepatocytes are recommended for *in vivo* induction assay (80, 81). However, the choice of the test system should be based on the goal of the evaluation, *in vivo* resemblance, ethical consideration, cost, and availability (16).

Almost all the *in vitro* models reviewed either for induction or inhibition assay followed this basic principle: the ability of herbs or their constituents to inhibit or induce DMEs is determined by treating cells, microsomes, superstores, or hepatocytes with known substrate for any of the DMEs in the absence or presence of herbal extracts or known potent inhibitors of the enzyme. Enzyme activities are deter-

mined by monitoring the changes in metabolite formation. However, for induction assay detection of mRNA levels using real-time polymerase chain reaction (RT-PCR) and the protein expression assay using Western blot are recommended in addition to the changes in enzyme activities (82). The most common analytical methods used to quantify metabolites formed in the *in vitro* assay are liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) or a fluorescence assay. Recently, molecular imprinting polymers (MIP) have drawn the interest of researchers in bioanalytical methods (83). There is no report on its application in an *in vitro* experimental model for herb-drug interaction studies.

IN VIVO METABOLIC MODELS

The *in vitro* model demonstrates only one aspect of the whole PK, thus, *in vivo* model provides more multi-factorial results and the combined effects of ADME. Irrespective of the thoroughness of *in vitro* models, *in vivo* studies are required to measure drug exposure and to determine DDI/HDIs. Preclinical animal studies can be used to predict HDIs, but they have poor extrapolative value to humans. This is due to interspecies variations and the use of dosage regimens that are not applicable in humans (84). In addition, since data on herbs absorption is limited, it is therefore difficult to determine if the phytochemicals will be absorbed enough to affect the PK parameters of the co-administered drugs. While the common laboratory animal for HDI study is the rat, the advent or development of gene editing technology, animal models of special ADME genes are used to study the mechanisms of HDIs (85 - 87). The current trend to improve the interspecies variation is the use of engineered/humanized mouse models (88). For example, humanized CYP2C19 mice for drug metabolism, humanized CYP3A4, and humanized CYP2D6 mice for drug interactions were constructed (89 - 91). The most recent is the novel clustered regularly interspaced short palindromic repeat (CRISPR/CRISPR-9) associated Cas 9-based animal model for the DMPK study (85, 87, 92).

This genetic editing technology has improved the extrapolative values of data from animal models, however, the challenges of the complexity of ADME and the involvement of multiple human organs in herbs/drug metabolism persist (84). Hence, clinical studies are the most reliable model to investigate PK-based HDIs. In designing and conducting clinical pharmacokinetics HDI studies, the following must be considered: experimental design, PK parameters, herbal product quality, and appropriate dosage (93). Typically, a subject (usually healthy volunteers) will be administered a single dose of a test or "probe" drug or cocktail of drugs that are substrates for different DMEs/transporters (e.g. orally administered dolutegravir is a substrate for UGT1A1 and CYP3A4) and followed by PK assessments to determine the baseline DMEs activities (94). This is usually followed by daily multiple administrations of the test herbs extracts/products over a period usually 2 weeks to 1 month and the test drugs will be administered again. The pre-and post-herbal extracts administration data will be compared to providing a probability of an HDI (84). *In vitro* and *in vivo* animal studies are useful in determining the potential of herbs to cause HDIs, but only human studies (*in vivo*) can establish clinically relevant HDIs (92).

IN SITU MODEL

It is also known as the organ perfusion model; this experimental model almost mimics *in vivo* drug ADME (95). The liver perfusion model is the most studied of all the different organ perfusion models. Unlike in the *in vitro* test systems (hepatocytes and sub-cellular), the liver structure and architecture are maintained and all the cell populations (e.g. Kupffer cells), including transporters, are preserved. This feature makes it very close to the *in vivo* systems. This model requires minimal organ preparation therefore reducing organ damage. One of these model limitations is the very short cell viability due to poor cell oxygenation and nutrients. Other limitations are scarce human liver source, poor reproducibility, and low thoroughput (84).

EX VIVO METABOLIC MODEL

In this model, drug and/or herbal extracts are administered to animals followed by organ harvest (e.g. liver to prepare liver microsomes) and it is used to determine changes in activities or expression of DMEs. This model has been reported for HDIs studies (96), however, it is commonly used in induction and toxicity studies. The liver is often studied for the effect of herbs co-administered with conventional drugs on DMEs activities and/or levels

because it is the organ that is mostly exposed to drugs and other xenobiotics. These changes in DME expression or activities could in turn explain the changes in drug PK or be linked to the toxicities (95).

IN SILICO PREDICTION

This model is becoming popular because it is less expensive and not time-consuming unlike the other models. It is also known as dry laboratory because the experiment is largely done on computers. Most often it is done early by the researcher because its outcome usually determines if there is a need to proceed to the *in vivo* study. Although this method and the others have their limitations, it is better to combine these methods to have a holistic view of HDIs (Figure 3). *In silico* method is commonly used to study the interactions of bioactive components of the medicinal plant and cytochrome P450 (97, 98). Several free online tools are available (99).

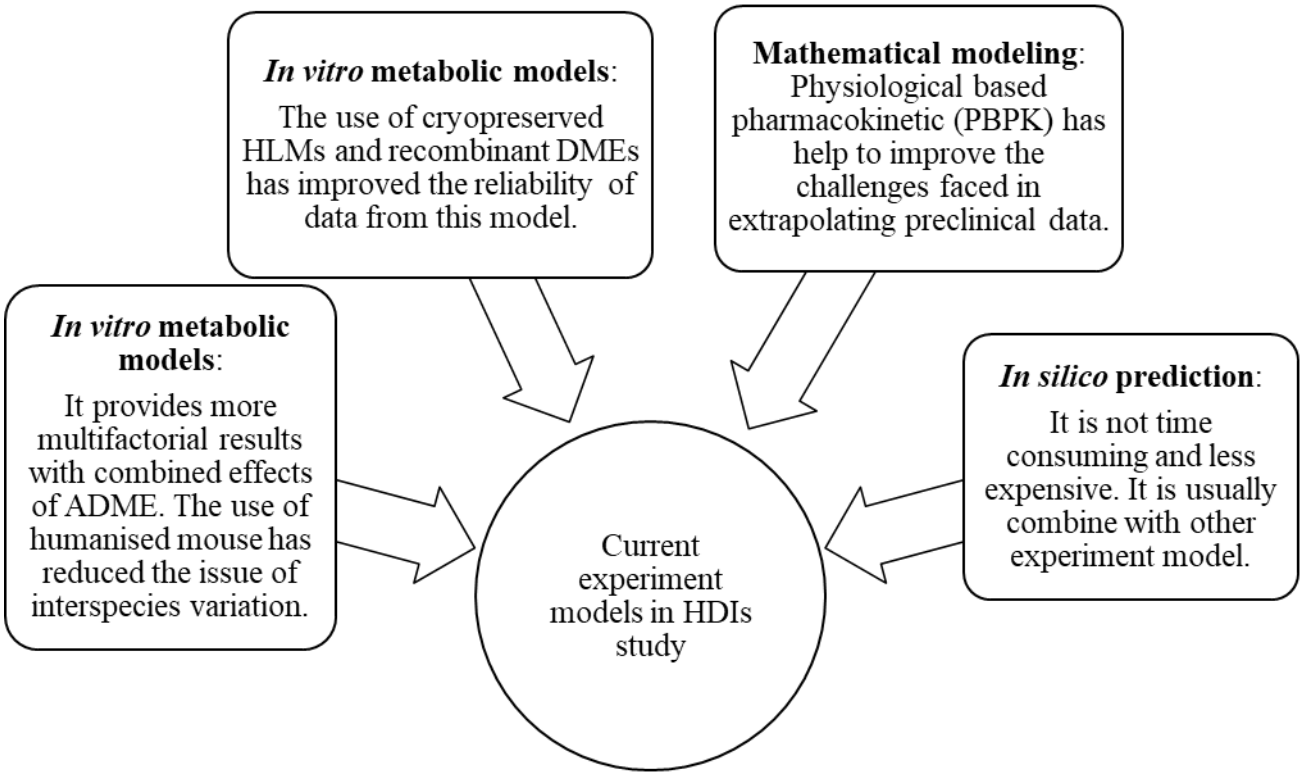

Figure 3. *Current tools of herb-drug interactions study*

CURRENT TRENDS OF RESEARCH ON HDIs

Herbal products are commonly used for treatment of some ailments and as dietary supplements (100). Co-administration with conventional drugs may lead to clinically relevant HDIs resulting in either increased/decreased efficacy or toxicities. Drugs such as digoxin with narrow therapeutic window are usually associated with HDIs (57). HDIs with both pharmacokinetics and pharmacodynamic consequences were reported (101).

Reported cases of HDIs are largely based on *in vitro* and *in vivo* animal studies that do not have significant clinical relevance (102, 7, 103). One of the challenges in HDIs research is the inconsistencies in preclinical data and low clinical relevance of results reported from preclinical studies. This is due to poor standardization of herbal products and interspecies variation in DMEs especially between rodents and humans (5). To improve on the challenges faced in extrapolating preclinical (*in vitro* and *in vivo* animal studies) data, PBPK mathematical simulation were developed to predict HDIs (104, 67). For example,

PBPK mathematical simulation was used to predict HDIs between tacrolimus and *Schisandra sphenanthera* extracts mediated by CYP3A4 inhibition (105). However, limited human PK data of herbs phytochemicals restrict the application of PBPK model in HDIs studies (76). Thus, very well-designed clinical studies are required to evaluate the efficacy and safety of the concurrent use of herbs and conventional drug.

CLINICALLY RELEVANT HERB-DRUG INTERACTION STUDIES

Herb-drug pharmacokinetic interactions become clinically relevant when significant changes occur in the pharmacokinetic parameters of the co-administered conventional drug. These parameters, which are directly related to the efficacy and toxicity of the drug, include the area under the curve (AUC), maximum concentration (C_{max}) or time to reach maximum concentration (T_{max}). Herb-drug pharmacokinetic interactions associated with high risks and severe adverse reactions may be experienced with drugs that have narrow therapeutic indices (e.g. digoxin, phenytoin, and warfarin) (106, 107). Many of the herb-drug pharmacokinetic interactions are difficult to anticipate in clinical practice as they often occur through multiple mechanisms and are usually dependent on many factors. In some cases, insufficient clinical evidence exists to confirm pharmacokinetic effects of herbs on drug molecules that were observed during *in vitro* and *in vivo* animal studies.

Some HDIs have been reported in *in vitro* and *in vivo* studies as well as with clinical cases. In this section, some empirical examples of PK-based influence of herbal drugs on conventional medicines with significant clinical relevance are highlighted as follow:

1. *Allium sativum L.* (Alliaceae) bulb is commonly called garlic (local name: Ayu).

Ethnomedicinally, A. sativum is used for flatulence, intestinal worms, dysentery, diabetes, and cough (108 - 110). It has been scientifically validated as an antimicrobial, anti-hypertensive, hypolipidaemic, and immune booster (111). It contains sulphur-containing compounds such as allicin, alliin, and flavonoids e.g. quercetin, rutin, as well as terpenes, saponins etc.

Garlic was reported to have no effect on the PK of alprazolam, caffeine, ciclosporin, debrisoquine, paracetamol, simvastatin, ritonavir, docetaxel, and midazolam (112, 113). However, it decreased the AUC and C_{max} of saquinavir, an antiviral drug, and chlorzoxazone as well as warfarin (101, 113, 114).

2. *Actaea racemosa* (Ranunculaceae), commonly called Black cohosh, is a herbal medication for post-menopausal symptoms. It did not affect the PK of midazolam, caffeine, and digoxin. However, it showed a weak inhibition of CYP2D6 resulting in an increased urinary ratio of debrisoquine (115).

3. The roots of *Echinacea purpurea*, and *Echinacea pallida* are commonly called purple root and pale coneflower root, respectively. They are used as adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract such as the common cold and influenza (116). They possess a similar phytochemical profile of which alkyl amides, implicated in the HDIs, are the major compounds.

Echinacea was reported not to affect the pharmacokinetics of darunavir-ritonavir, although there was slight decrease with this drug when co-administered with *Echinacea purpurea (117).*

*4. Gingko biloba (*Gingkoaceae) is commonly known as gingko. It is used for cerebral insufficiency and memory enhancement (118 - 120). Gingko contains flavonoids such as quercetin, kaempferol, isorhamnetin, and terpene trilactones (e.g. Ginkgo bilobalides A, B and C; and bilobalide) (119, 121).

Gingko showed no PK effect on bupropion, caffeine, chlorzoxazone, clopidogrel, debrisoquine, diazepam, digoxin, lopinavir, metformin, and nifedipine (122). However, gingko altered the plasma concentrations of omeprazole and alprazolam by induction of CYP 2C19 and CYP3A4, respectively (123, 124). Also, induction of CYP2C19 is also responsible for the life-threatening seizures reported in a patient on valproic acid (125). Therefore, the consumption of gingko should be monitored or avoided in patients receiving drugs metabolized by CYP2C19, while the effect of gingko on CYP3A4 or P-gp requires additional study (126).

5. *Piper methysticum G*. Forst root (Piperaceae) commonly known as kava kava is used in the treatment of depression, anxiety, insomnia, and restlessness. The bioactive compounds include kavalactones including methysticin and dihdryomethysticin (127-129).

Kava kava has no significant effect on the PK of midazolam, digoxin, debrisoquine, caffeine, however, by possible additive effect on GABA receptors, it cases disorientation and lethargy with alprazolam

(110, 130). By the inhibition of CYP2E1, it causes a decrease in serum ratios of 6-hydroxychlorzoxazone to chlorzoxazone by 40%, thus, it must not be co-administered with chlorzoxane (12, 131).

6. *Silybum marianum* (Compositae/Asteraceae) with synonym as Carduus marianus, is commonly called Milk-thistle.

Ethnomedicinally, it is used in some parts of Europe as an effective liver remedy. This claim has been scientifically justified as several flavonolignans have been isolated from the leaf and fruit (132). The major bioactive constituent from the seed is silymarin which is composed of three isomer flavonolignans (silybin, silydianin, and silychristin). Silybin has the most pronounced biological activity, and it is the major component (50 – 70%) of silymarin (133).

S. marianum caused an induction of intestinal P-gp and CYP3A4 leading to the increased clearance and decreased half- life, C_{max} and AUC of metronidazole (134, 135). Also, by inhibition of P-gp, it led to an increased C_{max} and AUC of talinolol (135, 136). Its inhibition of CYP2C9 led to increased AUC and decreased metabolic ration of losartan (135). However, milk-thistle had no effect on the PK of caffeine, debrisoquine, midazolam, nifedipine, ranitidine, digoxin, and indinavir (137, 131, 135, 138, 139, 140).

7. *Panax ginseng* (*Araliaceae*) commonly called ginseng, has its root in high use in traditional Chinese medicine. Its major active components are dammarane-type saponins named ginsenosides by Japanese scientists and panaxosides by Russian scientists (141). However, the two series of chemical constituents are not completely identical, especially about the sugar moieties. Ginseng contains a mixture of both steroidal and pentacyclic triterpenoids saponins (142). These saponins are implicated in HDIs involving ginseng. Ginseng has various pharmacological activities, including effects on the central nervous system, antineoplastic effects, and immunemodulatory effects. *In vitro* studies have shown that ginseng can inhibit CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (143). In rats, *P. ginseng* (150 mg/kg/day) for 14 days decreased the AUC from 0 to 12 hours of oral fexofenadine, decreased the C_{max} and significantly reduced the ratios of brain to plasma concentrations (144). Available clinical evidence shows that the probability of an HDI involving ginseng is low (145).

8. *Hypericum perforatum L.* (Hypericaceae), known as St John's Wort (SJW), is the most extensively investigated herbal medicine involved in HDIs. Ethnomedicinally, it is used as antidepressant, and this has been scientifically validated as useful in mild to moderate depression (146, 147). It contains bioactive constituents such as flavonoids including quercitrin, quercetin, naphthodianthrones, and hypericin (148, 149).

In vitro studies have suggested that SJW extracts can inhibit CYP3A4, CYP2C9, CYP1A2, CYP2D6 and CYP2C19 (150). Individual constituents of SJW have different inhibitory effects on CYP isoenzymes, for example, hyperforin is a non-competitive inhibitor of CYPs, while quercetin and some other flavonoids are more selective for CYP1B1. Hypericin is a potent inhibitor of many CYP enzymes.

SJW has the potential for both PK and PD interactions, and clinically, it depends on the duration, dosage, and therapeutic range. As found in the case of oral contraceptives failure, it was reported that concurrent use of SJW with oral contraceptive pills significantly increases the clearance of these pills (150, 151). Since the potential of HDIs with SJW is high, patients should be discouraged from taking SJW when on prescription medicines (126, 152).

In Nigeria, the following cases of HDIs have been reported both in *in vitro* and clinical cases, and quite a few in animal studies. For this review, natural products taken as beverage or foods are excluded, and only plants or herbal products taken for medicinal purposes are included.

1. In an *in vitro* study, quinine was adsorbed onto *Garcinia kola*, and it resulted in decreased quinine availability (153). In this study, concurrent oral administration of quinine and *G. kola* seed resulted in a decrease in the T_{max} of quinine ,which led to the reduction in the C_{max}, exposure of quinine and its major metabolite (3-hydroxyquinine). The absorption of quinine was delayed as evidenced from an increase in the T_{max} of quinine. A significant herb-drug interaction was reported in this study; caution must be taken by individual on quinine oral therapy and *Garcinia Kola* (153).

2. Ciklavit, a liquid herbal formulation made from the extracts of *Cajanus cajan* seeds, used for the management of sickle cell anemia disease in Nigeria, significantly decreased the dissolution of proguanil tablets *in vitro* (154). However, the animal or clinical studies on this observation have not been reported.

3. Manix, made from the extracts *Asparagus racemosus, Tribulus terrestris; Tinospora cordifolia;*

Semecarpus anacardium; Pueraria tuberose; Plumbago zeylanica; Cinnamomum zeylanicum; Elettaria cardamomum; Cinnamomum tamala; Dioscorea bulbifera; and *Sesamum indicum* are used in the management of male infertility in Nigeria was reported to have effect on the pharmacokinetics of perfloxacin, an antibiotic, in the rat. Concurrent usage of perfloxacin with this herbal product significantly reduced the C_{max}, T_{max}, and AUC of this antibiotic (155).

4. The leaf of *Moringa oleifera* (Moringaceae) is taken as food and as medicine in Nigeria. In rat system, it was observed that it altered the PK of amodiaquine by reducing the C_{max} but increasing the AUC on coadministration and pre-treatment with Moringa. This implied PK interaction with effect on absorption (156). In another study in human volunteers, the concurrent administration of the *Moringa oleifera* leaf extract resulted in a significant decrease in the C_{max} of amodiaquine, an antimalarial drug (157).

5. A study conducted in mice to investigate MAMA Decoction (MD), an antimalarial product prepared from the leaves of *Mangifera indica* L., *Alstonia boonei* De Wild, *Morinda lucida* Benth and *Azadirachta indica*, revealed an increase in the C*max* of amodiaquine with the concurrent administration of MD. There was an increase in the exposure and half-life of amodiaquine and its metabolite, desethyl-amodiaquine (158).

6. *Cola nitida* commonly known as kolanut is commonly chewed in Nigeria. The *Cola nitida* was shown to have implications on the PK of halofantrine in healthy volunteers. There was a significant decrease in the plasma concentrations of halofantrine and its active metabolite desbutylhalofantrine when kolanut was simultaneously used with halofantrine. Thus, caution must be taken whenever halofantrine is used along with caffeine-containing substances such as kolanut (159).

7. In addition, the effect of the administration of chloroquine and aqueous leaf extract of *Azadirachta indica* was investigated in rabbits. This study revealed a significant decrease in serum concentration, slower absorption, elimination and prolonged half-life of chloroquine. Other pharmacokinetic parameters such as area under the curve, C_{max}, absorption rate and volume of distribution were significantly reduced when chloroquine was co-administered with *A. indica* (160).

CONCLUSION

Substantial progress has been made in the methods used to evaluate PK-based HDIs, however, the progress is incomparable to the achievements made in DDIs studies. This is not far from the challenges of extrapolative values and inconsistencies of outcome of most of the HDIs preclinical studies. However, there is still demand for well-designed preclinical and clinical studies that will improve understanding of the underlying mechanisms of HDIs. A lot needs to be done in communicating clinically relevant findings to provide well-informed clinical decision with respect to herb-drug combination. It is important to understand the complexity of herbs and phytochemicals, various intrinsic factors present in respective experimental models, and diverse factors considered in study designs to improve the evaluation methodologies and interpretations of HDIs.

Nevertheless, efforts have been made to improve the extrapolation of research findings during preclinical (*in vitro* and *in vivo* animal studies) HDI studies. Such attempted efforts include the genetically modified animals that have been transfected with human genes to express the same enzymes as humans (e.g. humanized mice) and PBPK simulation of both *in vitro* and *in vivo* preclinical data to predict clinically relevant HDIs. This review adds credence to the existing knowledge of HDI and encourages that more preclinical and clinical studies be conducted to further ascertain the associated complexities of the interactions between herbs components and drugs co-administered. While the additive or synergistic interaction could be exploited for further development, the antagonistic should be ultimately discouraged. As the mechanism of metabolism of herbal supplements and the PK of HDI remains obscured, users and herbs/drug administrators must take caution to minimize incidences of fatalities.

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Conflict of Interest

Authors declare no conflict of interest.

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Interakcije između biljaka i lekova zasnovane na farmakokinetici: eksperimentalni modeli u Nigeriji

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SAŽETAK

Uvod/Cilj. Biljke su vitalni obnovljivi izvor koji se kroz istoriju koristio u medicinske svrhe; veći deo globalne populacije i dalje zavisi od njih i koristi ih za očuvanje zdravlja. Sve veća popularnost biljnih suplemenata izazvala je očiglednu zabrinutost zbog ukupne bezbednosti i potencijalne interakcije sa drugim lekovima *in situ*. Cilj ovog rada bio je da se podstaknu buduća istraživanja o interakcijama biljaka i lekova, kao i o mehanizmima interakcija kako bi se razumele njihove posledice.
Metode. Pregled je sproveden sistematskom pretragom relevantne literature iz baza podataka *Google Scholar*, *Science Direct*, *Mendelei*, *Scopus* i *PubMed*. U obzir su uzeti radovi napisani na engleskom jeziku.
Zaključak. Pokazalo se da mnogi biljni proizvodi stupaju u reakciju sa najčešće primenjivanim lekovima. Mehanizam inhibicije–indukcije izaziva lančane reakcije koje često dovode do smanjene bioraspoloživosti lekova, toksičnosti ili neželjenih sporednih efekata. Pojedini biljni fitokonstituenti navodno se vezuju za enzime CIP2C9, CYP2C19, CIP2E1 i CIP3A1 privremeno ili trajno. U zaključku ovog rada ukazano je na neophodnost rutinskog i redovnog obaveštavanja i lekara i bolesnika o opasnostima poput smanjene efikasnosti i povećane toksičnosti povezanim sa interakcijama biljaka i lekova. Potrebno je da se osobe koje koriste biljne suplemete informišu o njihovoj odgovarajućoj upotrebi kako bi se izbegao rizik od neželjenih interakcija lekova u toku istovremene primene ili u kombinovanim terapijama. S obzirom na to da se u interakcijama između biljaka i lekova mogu uočiti sinergistički i antagonistički efekti, treba sprovesti naknadne pretkliničke i kliničke empirijske studije da bi se naglasio mehanizam i obim ovih interakcija.

Ključne reči: **interakcija između biljaka i lekova, enzimi, farmakokinetičke interakcije, tradicionalna medicina, citohrom P450**