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Pharmacokinetics and Drug Interactions of Herbal Medicines: A Missing Critical Step in the Phytomedicine/Drug Development Process

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1. Introduction

Discovering and developing safe and effective new medicines is a long, difficult and expensive process involving multi-billion dollar investments in Research and Development by research-based pharmaceutical industries yearly. On average, it will cost a pharmaceutical company up to \$800m and upwards of 15 years to get one new medicine from the laboratory to the pharmacist's shelf. Only five in 5,000 compounds that enter preclinical testing will actually progress into human clinical trials, and of these five, only one is likely to be approved by the regulatory authorities using new drug approvals systems that are extremely rigorous, costly and time-consuming (1).

One of the regulatory requirements for an investigational new drug (IND) approval is pre-clinical pharmacokinetics of the new drug entity. However, for the majority of herbal remedies used in ethnomedical or conventional medical practice, data on their disposition and biological fate in humans are lacking or in paucity. It is vital in the drug development chain, to understand the disposition of these herbal products and how they interact with conventional drugs before their launch in the market, in order to ensure the rational use of herbal medicines. For natural products, the additional challenge currently is in their pharmacokinetics, arising from the multiplicity of components, inability to identify biological markers and lack of knowledge of the fate of the agents and/or their metabolites *in vivo*. Are these processes currently largely ignored in drug development, due to the rigor, cost and time consumption of the conventional drug development process? The clinical consequences of diminished drug efficacy can be as devastating as those of enhanced drug toxicity. Also sometimes, the clinical effect may not be obvious in a short term study and therefore may go unrecognized, possibly leading to the inappropriate discontinuation of an effective medication or the unnecessary addition of other drugs. Does the extent and volume of botanical - drug interactions observed in today's medical care and understanding the processes involved therein, make it a critical area for in-depth attention in pharmaceutical research & development?

Herbal medicines are classified as dietary supplements and the Food and Drug Administration (FDA) regulatory requirements for their approval are not as stringent as those for new chemical entities yet these are products with pharmacological properties with the potential to cause harm.

The term 'Herbal products' has become a colloquial term which commonly refers to all types of preparations obtained from herbs, spices, roots, stems, leaves and other non-botanical materials of natural origin. They can be used therapeutically as prescription or over-the-counter medicines or even as cosmetics orally or topically. Plants are important sources of medicines and plant derived drugs came into use in modern medicine through the uses of plant materials as indigenous cure in folklore or traditional systems of medicine. The use of plant extracts and herbs as medicines preparations has been since the beginning of recorded time, probably originating from ancient China and Egypt. Over 80,000 species of plants are in use throughout the world. In the last century, roughly 121 pharmaceutical products were formulated based on the knowledge of plant use in traditional medicine from various sources and presently about 25% of pharmaceutical prescriptions in the United States contain at least one plant-derived ingredient.

Herbal medicine, phytotherapy, phytomedicine, nutraceuticals, natural product medicine, complimentary & alternative medicine, ethnomedicine, botanicals, herbal medicinal product, dietary supplements and phytopharmaceuticals are all terms used interchangeably to denote the use of botanicals in healthcare and are therefore used as such in this text. Increasing number of patients and consumers are using plant-based therapeutic products as complementary therapy in the treatment and management of chronic ailments such as tuberculosis, diabetes, hypertension, HIV/AIDS, cancer and diseases of endemicity and high recrudescence especially malaria, as well as other social conditions like obesity, cigarette smoking and drug abuse. This upsurge in the use of phytomedicines is a global phenomenon, with more than 80% of people in Africa and Asia using herbal medicines and an increasing number in the Western world. It is estimated that 60% to 70% of the American population is taking botanical products (2).

The World Health Organisation promotes the use of herbal medicine, thus herbal medicine has become big business. Many Americans use complementary and alternative medicine (CAM) to prevent or alleviate common illnesses, with the effect that in the United States, botanical products are now a \$1.5 billion per year industry. In 2005, trade in herbal medicine was worth 14 billion USD in China, 5 billion USD in Western Europe in 2003-2004 and 160 million USD in Brazil in 2007. In Africa where all types of plant derived medicines and dietary supplements (both domestic and foreign) are seen, the volume of trade in botanicals is unquantified.

In recent times many factors have contributed to the current surge in phytomedicine use. The therapeutic superiority of many plant extracts over single isolated constituents, as well as the bioequivalence of many phytopharmaceuticals with synthetic chemotherapeutics is well documented (3). The gradual transition from the long-standing use of monodrug therapy in classical medicine to the new concept of a multidrug and multitarget therapy is greatly promoting phytotherapeutics. There is a gradual shift from the orthodox use of mono-substance therapy and an increasing transition to multidrug therapy of patients with

drug combinations, such as is done presently for the treatment of diabetes, cancer, acquired immune deficiency syndrome (AIDS), malaria, tuberculosis or hypertension (4, 5).

The rationalization for this strategy is based on therapeutic experiences that the use of drug combinations can target the multiple aetiologies, disease dynamics and/or complications that are seen in many ailments better than each of the components separately, while promoting patient compliance. Also there is the consideration that a complex pathophysiological process can be influenced more effectively and with fewer or no severe side-effects by a combination of several low-dosage compounds or the corresponding extracts than by a single large dosage isolated compound. Phytotherapy has long followed and developed these strategies by using mono-extracts or extract combinations containing mixtures of bioactive compounds that complement one another to elicit an efficacy of superior power. It is also believed that these components do primarily activate self-healing and protective processes of the human body (especially the immune system, which can then properly fight foreign invaders), promote the balancing of regulatory process in the body and help to destroy offending pathogens without toxic side effects, rather than attacking and directly destroying the damaging agents.

Most consumers often consider herbal therapies as accessible and affordable therapeutic alternatives to orthodox therapy without any safety concerns and sometimes even as the only effective therapeutic way left to treat certain disorders that have defied conventional drugs or promote and maintain health. The above factors have led to a situation where the concomitant administration of phytomedicines and orthodox drugs has become inevitable. One of the consequences of concurrent use of herbal medicines and orthodox drugs is the possibility of interactions. The interaction of drugs with herbal medicines is a significant safety concern, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin), drugs with long-term regimens and drugs used in the management of life-threatening conditions due to the fact that an alteration in the pharmacokinetics and/or pharmacodynamics of the drug by herbal remedies could bring about potentially severe and perhaps even life-threatening adverse reactions. Because of the clinical significance of drug interactions with herbs, it is important to identify drugs and compounds in development that may interact with herbal medicines. This can be achieved by incorporating timely herb-drug interaction studies using appropriate *in vitro* and *in vivo* approaches in order to identify such drugs has important implications for drug development.

With the availability of over 30000 over-the-counter products, more than 1000 different chemical substances that are constituents of prescription drugs and hundreds of herbs, vitamins, and minerals, the possibilities of drug interaction are endless. A drug interaction is defined as any modification caused by another exogenous chemical (drug, herb, or food) in the diagnostic, therapeutic, or other action of a drug in or on the body. The risk for drug interactions increases with the number of products consumed: for 2 products, the risk is 6%; for 5 products, 50%; and for 8 or more products, 100% (6). The use of complimentary alternative medicine alongside conventional therapy continues to grow rapidly especially in the developed countries. It is estimated that less than a third of Americans taking botanical products inform their physicians of such use (7). In oncology therapy alone, about 72% of cancer patients taking herbal medicines with their conventional treatments do not inform their physicians (8) and 27% of them were at risk for developing herb - drug interaction (9).

Because the issue of botanical-drug interaction has not been well appreciated and is definitely under-studied, today, our understanding of the interactions between drugs and herbs and between drugs and food has not advanced much, therefore much research is still required in herbal therapy to examine individual plant constituents and to determine how plants interact with drugs and foods. Therefore in our effort to understand the potential therapeutic role of botanicals and promote their safe use, one must not only focus on evaluating toxicity, efficacy, mechanism of action but also on their safe and appropriate use particularly with respect to the research and knowledge on botanical-drug interactions.

A general lack of knowledge of the interaction potentials of concurrent use of botanicals with prescription and/or over-the-counter medicines, poses a great challenge for health care professionals and a safety concern for consumers. Although most people especially in developing countries believe that herbs are harmless plants, about a third of our drugs (including digitalis, morphine, atropine, and several chemotherapeutic agents) were developed from plants. So, indeed, herbs can be potent products. Herbs can affect body functions; therefore, when they are taken concurrently with orthodox drugs, interactions are possible, impacting on the clinical effects of the latter. That natural products are largely unregulated contributes to the misconception that they are safe, with the effect that patients don't feel the need to tell their physicians that they are using them, and physicians don't routinely ask patients if they are taking them.

2. Selected clinically relevant botanical–drug interactions

Although our knowledge of interactions of phytomedicines with conventional drugs in patients is still relatively young and not well understood, many case reports, controlled clinical and in vitro studies constitute strong evidence that support the assumption that significantly more of the large inter-individual variations in the response to treatment seen in medical practice can be attributed to botanical-drug interactions. This assumption is supported by several studies which show that some herbal medicinal products have the capacity to influence plasma levels of drugs (10, 11), giving rise to clinical problems of unexpected toxicities and under-treatment seen in different groups of patients. Factors relating to co-administered drugs (dose, dosing regimen, administration route, pharmacokinetic and therapeutic range), herbs (species, dose, dosing regimen, and administration route) and patients (genetic polymorphism, age, gender and pathological conditions) largely determine the extent and thus the clinical relevance of drug interactions with herbs (12). In general terms, the appearance of enhanced drug effects and/or adverse effects is usually associated with a doubling or more in drug plasma concentration (13). However, less marked changes may still be clinically important for drugs with a steep concentration–response relationship or a narrow therapeutic index. In most cases, the extent of drug interactions with herbs varies markedly among individuals, depending on inter-individual differences in drug metabolizing enzymes and transporters, co-medication with other drugs, age and many of other factors (14).

Several clinically important botanical-drug interactions have been reported leading to altered efficacy and/or toxicity, adverse reactions that are sometimes life threatening or lethal (15). Often times, the evidence of interactions with dietary supplements is often based on presumed pharmacologic activity, data derived from in vitro or animal studies, or anecdotal single case

reports and to a lesser extent, well-designed clinical studies. Tamarind, an Asian fruit used not only in ayurvedic medicine but also as a food flavouring agent, has been shown to significantly increase the extent of absorption of a single 600mg dose of aspirin in six healthy volunteers, posing potential danger if a large amount of aspirin is ingested concomitantly with tamarind. Ginseng induced mania when used concomitantly with phenelzine (16). An enhanced hypoglycemic effect has also been reported when a meal containing garlic and *Mormodica charantia* L. (balsampear) family: *curcubitaceae*, a herb traditionally used in the treatment of type 2 diabetes was consumed with chlorpropamide (17).

The over-the-counter antidepressant herb St John's Wort (SJW) is probably the most studied of all herbal preparations when considering interactions with orthodox drugs. Several clinically relevant drug-drug interactions have been reported between SJW and a wide range of drugs. Chronic administration of SJW together with cyclosporin A has been associated with a significant reduction in cyclosporin plasma levels and a higher risk for acute organ rejection in transplanted patients (18, 19). In healthy volunteers, administration of SJW together with the protease inhibitor indinavir produced an approximately 57% lower plasma AUC of indinavir (20). Co-administration of SJW with digoxin produced an 18% lower plasma AUC of digoxin and a 40% higher expression level of intestinal P-gp (21). Other drugs with reported clinically relevant interactions with St. John's Wort include tacrolimus, warfarin, verapamil, fexofenadine, imatinib, (ethinylestradiol/desogestrel), loperamide, or selective serotonin-reuptake inhibitors (e.g. sertraline, paroxetine, and nefazodone) with attendant clinical implications such as under-treatment and failure of therapies (22, 23)

Ginkgo is a popular herbal product used to improve cognitive function in Alzheimer and dementia as well as to improve blood flow and improve impaired memory in vascular disease. Several reports of bleeding associated with its concurrent use with drugs like aspirin, warfarin, acetaminophen, or an ergotamine caffeine preparation have been documented (24, 25). Matthew MK, reported the association of a recent use of Ginkgo biloba with the occurrence of cerebral haemorrhage in a patient who had been stabilized for five years on warfarin (26). Also, a combined use of ginkgo with a thiazide diuretic may precipitate high blood pressure and coma when combined with trazodone (27, 28). Grapefruit juice is another botanical product that has widely been reported to affect the plasma concentrations and bioavailabilities of conventional drug products ingested with it, such that the FDA includes documented information on drug-grape fruit juice interactions in the product insert of certain medications including statins, drugs for blood pressure reduction, some antiretroviral agents (29) and the Health Canada in 2002 advised the public not to consume grape fruit juice with medications for anxiety, depression among others (30).

As part of the drug development process, before studies from our laboratories have investigated possible interactions of the concomitant administration of various natural products being developed as phytomedicines and various drugs routinely used in the treatment of co-morbidities in the respective disorders. The alteration in bioavailability and pharmacokinetic parameters of paracetamol by an investigational antimalarial phytomedicine (AM-1), when concomitantly administered in humans was reported by us (31). AM-1 an extract from the plant *Nauclea latifolia* Smith (family: Rubiaceae) used in the treatment of uncomplicated malaria was orally administered to healthy volunteers with and without 500mg of acetaminophen. Almost a 50% reduction in the area under the curve of paracetamol was observed in the presence of 500mg capsules of AM-1

Niprisan® an anti-sickling phytomedicine has been shown to also significantly affect the systemic concentrations of paracetamol when both products were concomitantly administered (32), as well as the pharmacokinetic disposition of chloroquine and metronidazole in animal studies (33).

Pharmacokinetic Parameters	Metronidazole alone	Metronidazole + Niprisan	% Diff.	Metronidazole + Nifadin	% Diff.	Metronidazole + AM1	% Diff.
$t_{1/2a}$ (h)	1.788 ± 0.08	2.145 ± 0.21	20↑	1.908 ± 0.12	7 ↑	3.062 ± 0.41	71 ↑
Ka (h^{-1})	0.392 ± 0.02	0.340 ± 0.04	13 ↓	0.351 ± 0.02	10 ↑	0.255 ± 0.04	35 ↓
Cmax (µg/ml)	3.109 ± 0.11	4.989 ± 0.16	60 ↑	7.243 ± 0.25	133 ↑	5.490 ± 0.66	77 ↑
tmax (h)	0.833 ± 0.11	2.417 ± 0.43	190↑	1 ± 0.00	20↑	0.583 ± 0.08	30 ↓
AUC _{0→24} (µg.h/ml)	13.135 ± 0.41	19.781 ± 1.10	50↑	29.520 ± 0.91	124 ↑	21.553 ± 0.77	64 ↑
AUC _{0→∞} (µg.h/ml)	18.794 ± 0.76	28.364 ± 2.02	51↑	42.111 ± 2.03	124 ↑	28.424 ± 3.50	51 ↑
Vd (L)	2.449 ± 0.12	1.875 ± 0.11	25↓	1.208 ± 0.03	50↓	1.791 ± 0.13	27 ↓
Cl _T (L/h)	0.427 ± 0.02	0.231 ± 0.04	45↓	0.180 ± 0.01	57↓	0.188 ± 0.05	56 ↓

Table 1. Effect of Niprisan, AM-1, and Nifadin on the pharmacokinetic parameters of Metronidazole in rats.

Pharmacokinetic parameters	Chloroquine alone value	Chloroquine + Niprisan	% Diff.	Chloroquine + Nifadin	% Diff.	Chloroquine + AM1	% Diff.
$t_{1/2a}$ (h)	4.5612 ± 0.69	5.2760 ± 0.71	3↑	35.567 ± 2.5147	680 ↑	2.7301 ± 0.21	40↓
Ka (h^{-1})	0.1691 ± 0.02	0.1454 ± 0.05	14↓	0.020 ± 0.0011	88↓	0.2610 ± 0.0178	54 ↑
Cmax (µg/ml)	5.2287 ± 0.69	1.8709 ± 0.19	64 ↓	2 ± 0.00	62 ↓	2.9785 ± 0.10	43 ↑
tmax (h)	0.9167 ± 0.06	2.3333 ± 0.33	155	1.4139 ± 0.11	54↑	0.9167 ± 0.08	0
AUC _{0→24} (µg.h/ml)	30.1470 ± 0.18	17.3477 ± 0.38	42 ↓	19.5059 ± 0.59	35↓	18.8178 ± 1.21	38 ↓
Vd (L)	1.4978 ± 0.19	3.5924 ± 0.22	139 ↑	5.7563 ± 0.11	284 ↑	2.2360 ± 0.24	49 ↑
Cl _T (L/h)	0.1531 ± 0.04	0.247 ± 0.01	61↑	0.0908 ± 0.04	40↓	0.2472 ± 0.01	61 ↑
$t_{1/2\beta}$ (h)	9.5048 ± 1.73	10.9652 ± 0.64	15↑	88.9772 ± 13.49	836↑	6.2434 ± 0.52	34 ↓
k_{β} (h^{-1})	0.07351 ± 0.01	0.0632 ± 0.001	14↓	0.0086 ± 0.001	88↓	0.1144 ± 0.01	56 ↑

Table 2. Effect of Niprisan, AM-1, and Nifadin on the pharmacokinetics parameters of chloroquine (CQ) in rats

Not all botanical-drug interactions result in undesirable effect, while some studies have shown a lack of interaction in the concurrent use of some botanical-drug combinations, other interactions may have beneficial effect on drug therapy. In the presence of the extract of Chinese medicinal plant *Tripterygium wilfordi*, the dose of cyclosporine needed for 100% kidney allograft survival in animals was reduced by 50% - 75% (34). The adverse effect of 'statins' therapy arises from a decreased biosynthesis of endogenous coenzyme Q10 leading to depleted tissue levels, the co-administration of coenzyme Q10 with statin in this therapy reduces the adverse effect (35). In women receiving long-term phenothiazine or buyrophenone therapy, researchers found that intake of 800 mg daily of mistletoe extract silymarin was associated with a significant improvement in liver function tests due to a decrease in malondialdehyde (a polyunsaturated fatty acid oxidation product). Thus the coadministration of this herbal product in the psychoactive therapy has the potential to prevent drug-induced hepatotoxicity (36).

Recently, we have also shown that the concomitant administration of three first line antiretroviral drugs (lamivudine, stavudine and nevirapine) and a plant - based immune booster from *Andrographis paniculata* Nees (Acanthaceae) known in north-eastern India as 'king of bitters', used in the management of HIV/AIDS as an immune stimulant, precipitated interactions observed as beneficial changes in food and water intake as well as the haematological and biochemical indices including CD4, in the presence of the herb (37). There was observed steady increase in red blood cells, white blood cells, food and water intake without an associated increase in cholesterol and high density lipoprotein levels and a decrease in platelet counts. Concomittant administration of this herb with the first line antiretrovirals can ameliorate the anemia and lipodystrophy associated with the use of these drugs. A good review of reported cases and clinical studies of drugs that interact with herbal medicinal products can be found in (38, 13).

3. Challenges to botanical-drug interactions research

In spite of growing concern and examples of herb-drug interactions, little systematic research has been published or funded in this area. An important limiting factor that has majorly led to this situation is the reliability of the existing evidence. A survey of 44 of the leading dietary supplement manufacturers in 2003 revealed that only 10 of 15 respondents considered interactions to be an important issue, and only 2 allocated funds to study herbal-drug interactions (39). Poor reliability of the It was reported in a study that of one hundred and eight cases of suspected interactions studied, 68.5% were classified as 'unable to be evaluated', 13% as 'well-documented' and 18.5% as 'possible' interactions (40). One of the major reasons for this unreliability of reports of the clinical evidence on interactions between herbal and conventional drugs is the inherent scientific and clinical challenges in the use of herbal medicines.

3.1 Predictability of herb-drug interactions

Predicting the potential for a botanical medicine to interact with other drugs can be possible, applying the same principles and study designs as for new chemical entities (NCEs) to evaluate the potential inductive/inhibitory effects of herbal extracts on metabolic enzymes and transporters. However, while it may be easier to define the overall pharmacokinetic and/ or pharmacodynamic mechanisms of interactions for NCEs, especially with those

drugs mainly metabolized by CYPs, the prediction of drug interactions with herbs appears to be more difficult and complex (41). Predictability is complexed by factors mainly associated with the drug, and herb (active ingredients complex and not well characterised as well as poorly understood mechanisms of action). Every herbal product is a complex mixture of multiple secondary metabolites / constituents contained in a preparation regarded as one single active substance, even when the preparation is made from a single herb. Masimirembwa et al, using LC MS/MS analysis of six herbal extracts, observed peaks predictive of over 300 chemical species for each herb (42). Each constituent may have a different modulatory potential for the same enzyme and/or modulate a different enzyme. Potentially therefore, a herb may increase, reduce or not affect the effect of a co-administered drug through a combination of simultaneous activities on the same drug target. The inhibition/induction of metabolic enzymes by herbal medicines may vary depending on the herb's method of preparation (different extraction methods may yield different types and quantities of constituents from the same herb). In the work of Gwaza et al, 2mg/ml methanolic extract of the African potato *Hypoxis obtuse* had greater inhibitory effects than same concentration of the water extract. Similar effect was also obtained with the extracts of *Dicoma anomala* (43). Dosing, route of administration, oral bioavailability of the product and other factors are equally confounding factors.

Most often, herbal medicinal products are ingested in a chronic manner by its users, thus a predicted interaction outcome from a single exposure with a target conventional drug may be different in clinical situation. Other drug and patient related factors such as presence of extra-hepatic metabolism; and active transport in liver, age, disease, renal and hepatic functions and genetic polymorphisms are as for conventional drugs and all contribute to the final outcome of drug interaction with herbal medicines. A pharmacological basis of qualitative prediction may be on the 'rule of thumb' simply by comparing the biological effects of the drugs that is, if both products are expected to give similar response, then a potentiation of effect may be expected and vice versa. Also if a drug is a substrate for CYP3A4 and P-gp, its potential for interaction with herbal medicines would be high.

3.2 Lack of consistency in the quality of herbal medicinal products

In a study of 81 published studies on randomized controlled trials of herbal drug interactions, only 15% reported performing tests to quantify actual contents of the herbal supplements used in the studies (43). There are reports of disparity in content of constituents among different brands of echinacea, ginseng, St John's Wort and of particular concern is the fact that inconsistency is also observed even within the same product and same batch (45). Conflicting results of studies of the effect of St John's wort on CYP3A4 are evident. While three enzyme marker studies indicated a potent inducing effect of St John's wort (300 mg three times daily × 14 days) on CYP3A4 activity (46, 47) two others found no effect (both 300 mg three times daily, one for 3 days (48), the other for 8 days (49) on CYP2D6 or 3A4 activities. Lack of batch-to-batch uniformity in the composition and quality of the herbal medicinal products used might explain the discrepancy. Most of these inconsistencies can be attributed to the fact that when compared with conventional drugs, herbal medicines present additional challenges related to quality;

- No established methods to establish the quality of herbal medicines
- Lack of stringent methods for Batch - to - Batch controls
- Susceptibility to environmental contamination

- Herbal medicines are prone to counterfeit practises
- Quality of product prone to seasonal variation & regional source

Thus, there is often great disparity in reported patient response to the use of same herbal medicinal product. The results from many of the published interaction studies therefore may be of little value, since the identity, purity, quality, strength, and composition of the supplements is not always confirmed.

3.3 Lapses in the phytomedicine drug development process

The current phytodrug development process has introduced gaps and lapses that are unfavourable to botanical – drug interaction studies as an integrated step. The argument often is concerning the usefulness of such studies especially where these products have been used therapeutically for centuries without such information. The World Health Organization promotes drug development from traditional medicines partly due to the saving in time and cost that makes the products affordable and accessible, leading to cheaper and cost-effective primary healthcare it offers its teeming population of users. The fast tracking is based on the assumption that the substantial experience from the long history of human use increases the chances that a remedy will be effective and safe, and that precautions will be known. Conventional drug development is slow and expensive and often the finished products are unavailable and unaffordable to resource-limited countries, unless when made available by donors from high-income countries, under heavily subsidized schemes (50). For most phytomedicines, drug development from complimentary and alternative medicines usually follows a “reverse pharmacology” approach (51, 52).

The first step is to select a remedy for development, through a retrospective treatment-outcome study or an ethnobotanical survey to identify medicinal plants used in the treatment of target disease conditions. This step usually will yield insufficient clinical information but is often a good guide to identification of plants and remedies for a given ailment (53, 54). This is because the traditional medicine practitioners often do not have enough records as regards observed patient status as well as progress and treatment outcome and their perception of the efficacy and limitations of their remedies is subjective. Generally also their ability to accurately diagnose a disease condition may be inadequate because a lot of similar symptoms which may present in entirely different disease conditions may be treated with the same remedy. Thus often times, same remedies are employed in the treatment of ‘fevers’, ‘stomach pains’, et cetera. Therefore a lot of the information collected at this stage is largely vague, needing evidence-driven scientific evaluation.

The second step usually spins off the first. Following the analyses of the collated remedies, treatment claims and subsequent plants identification, two essential elements are added to the ethnobotanical survey by performing an organized treatment of a fairly large sample size, aimed at generating clinical information and evidence of efficacy in the presentation and progress of an episode of the target disease and statistically correlating treatment with reported clinical recovery as the marker of effectiveness.

Step three involves further research on a selected candidate remedy, to determine the possible pharmacological basis for the therapeutic claim through bioassays. Also at this pre-clinical stage, standardization and characterization of raw materials, intermediates and extracts are commenced, to generate quality control specifications data and chemical finger printing and identification of markers that can be used for monitoring of batch - to - batch uniformity.

The last step is clinical studies, usually involving a dose optimization observational study that will help select the safest and most efficacious dose through a dose-response phenomenon and finally a randomized controlled trial to compare the phytomedicine to the gold standard treatment for the target disease is conducted.

This 'short - cut' approach facilitates the production of standardized phytomedicines faster and more cheaply than conventional drugs. In recent times, advances in this drug development strategy employs great efforts in standardization of mono- and multi-component phyto-preparations using all available high-tech methods, screening of extracts and their constituents by integration of modern molecular biological bioassays and controlled clinical studies, aimed at evidence based phytotherapy. However, it is still deficient in pertinent steps that involve systematic studies in the systemic effect of the phytomedicines inclusive of pharmacokinetic, bioavailability and drug interaction investigations.

For any medicine, efficacy and safety are the major issues thus before proceeding to clinical studies, it is important to establish that the remedy is safe. Safety of medicines in comprehensive sense would consist of not just the absence of toxicity but also the ability to use it effectively in a manner that avoids adverse reactions, therapeutic failure, minimizing risk-benefit ratio associated with its use while promoting rational drug use. WHO guidelines state that: "If the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment." The guideline relies heavily on evidence of traditional use or recent clinical experience as sufficient proof for safety (55, 56) and also arguing that often times, the same plants are traditionally used both as a food and as a medicine and no toxicological tests are required for foods, which are usually consumed in greater quantities than medicines (57). This may not be sufficient reason to de-emphasize detailed safety studies for herbal medicinal products because, one may argue that most often herbs are used as spices and condiments in foods at smaller quantities than when used as medicines, meaning that they will be consumed in smaller quantities as foods than as medicines. The differences in dosing can introduce variation in an observed response. For example, *Zingiber officinale* has been used and tested as an antinauseant and antispasmodic agent with very good results (58). Ginger has been shown to be a potent inhibitor of thromboxane synthetase and thus prolongs bleeding time and persons taking warfarin or other drugs that affect platelet activity have been advised to refrain from taking ginger in tablet form (59). Using ginger as a spice does not give same effect. Therefore, even when preliminary field studies show that a herbal medicinal preparation is of common and ancient use, with no known important side effects, to avoid or minimize toxic drug-herb interactions, it is important to identify the interaction potential of such herb(s) using proper in vitro and in vivo models in the early stages of drug development. The essence is to obtain enough information that may be useful for providing warning and proper advice to patients in clinical practice and improve the safe utilization of the herb.

In the past, the focus to address the above issues has been on scientific standardization and appropriate regulatory controls in the manufacture of phytomedicines in the following areas:

- application of all available modern, high-tech methods to standardize phytopreparations before conducting systematic pharmacological investigations and clinical studies

- using new molecular biological assays for screening of extracts and plant constituents to evaluate their exact pharmacological profiles, to elucidate the pharmacological basis of the claimed actions of the constituents of an extract and bioassay guided fractions thereby gain a better understanding of the various mechanisms underlying these pharmacological effects
- controlled clinical studies paralleled by pharmacokinetic and bioavailability studies (60).

However in addition, we propose one more research focus in the area of;

- incorporation of conventional principles in studies addressing additional safety concerns such as herb-drug interaction for the clinical use of herbal medicines, early in the drug development process

3.4 Poor knowledge of pharmacokinetics of botanicals

There is limited information on the pharmacokinetics of herbal medicines even though their use either alone or in addition to conventional drugs is increasing. One of the major reasons is that for most of these multicomponent mixtures, their active ingredient(s) are not known. In addition, there is the difficulty of measuring the quantities of the actives in systemic circulation due to very low concentrations, arising from the very small amount per dose in the final product. These challenges have led to the situation that most herb – drug interaction studies and case reports in literature only evaluate the outcome of adding a herbal medicinal product to an existing conventional drug therapy and monitoring changes in pharmacokinetics and/or clinical response of the orthodox drug. The reverse is rarely the case. Therefore, a better understanding of the pharmacokinetics of herbal medicines is needed to support the predictability of botanical – drug interactions. Giant strides in the availability of specific high-tech analytical methods and equipment has resulted to the fact that complex extracts and phytopreparations can be analyzed today, to quantify the major active compounds, which are supposed to be responsible for the efficacy of an extract. The effectiveness of these modern tools and processes has been illustrated in several reports (61). Also, they meet the quality standards of drug authorities with high reproducibility of pharmacological studies subjected to good clinical practice (GCP) and conform to clinical trials requirements (62).

4. Mechanisms of herbal-drug interactions

Basically, the same principles and mechanisms responsible for drug-drug interactions are still involved in interactions between phytomedicines and drugs, resulting in pharmacokinetic and pharmacodynamic interactions. Herbal medicinal products or botanicals share the same metabolic and transport proteins, including cytochrome P450 enzymes (CYP), glucuronosyltransferases (UGTs), and P-glycoprotein (Pgp), with over-the-counter and prescription medicines increasing the likelihood of drug–botanical interactions. In other words, herbal products can interact with drugs by affecting the biological processes that regulate their metabolism and elimination.

The family of enzymes known as the cytochrome P450s (CYPs) are involved in 75% of drug metabolism. These monooxygenase enzymes are located mainly in intestinal and liver cells and catalyzes several phase I metabolic processes of many prescription drugs. Of its many subtypes, CYP3A4 is one of the most important, being responsible for about 50% of CYP450

- mediated metabolism. Thus natural products interfering with actions and/or quantities of CYP3A4 have the potential to affect a high percentage of drugs to variable extents. One way that a natural product can alter the action of an enzyme is to modulate by up or down regulating it. Also precipitators may affect bioavailability by modulating absorption or first pass metabolism, altered protein binding, or pharmacological effect. Interactions between herbals and medications can be caused by either pharmacodynamic or pharmacokinetic mechanisms.

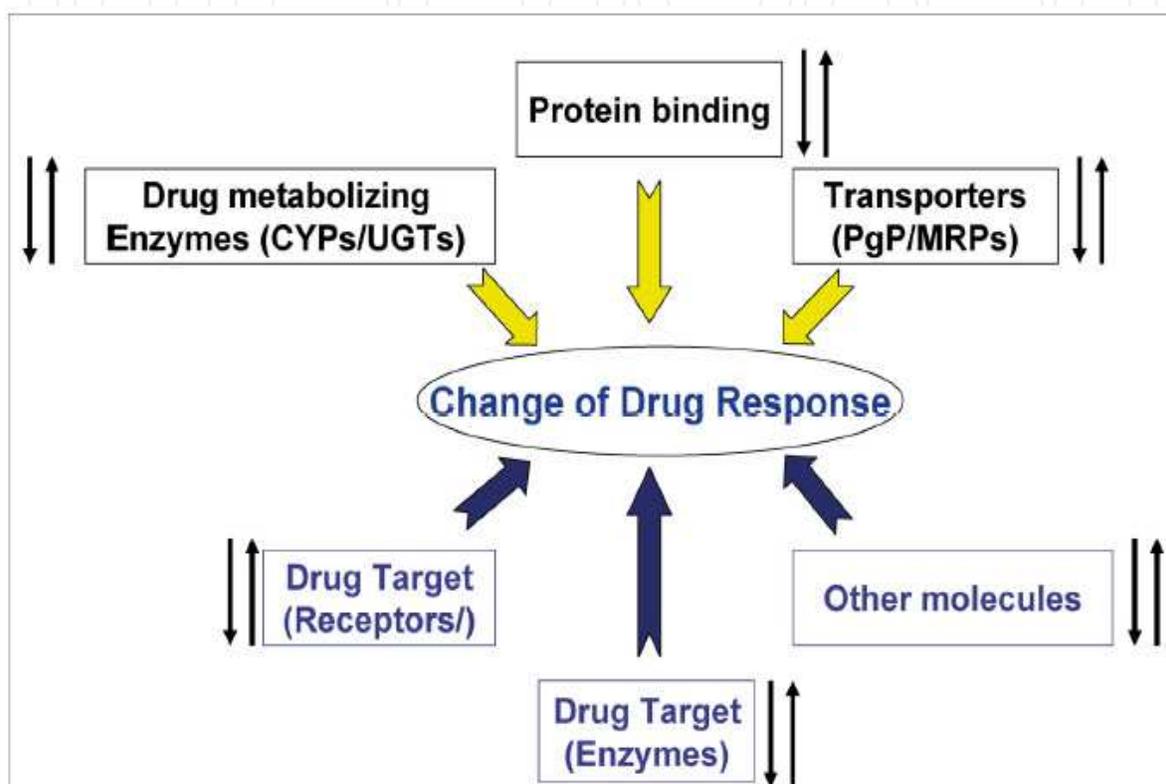


Fig. 1. Possible mechanisms for drug interactions with combined herbal medicines. (ref 63)

Pharmacodynamic interactions can occur when a herbal product produces additive, synergistic, or antagonist activity in relation to the conventional drug with no change in the plasma concentration of either herbal product or drug. Such interactions are related to the pharmacological activity of the interacting agents and can affect organ systems, receptor sites, or enzymes. A pharmacodynamic interaction may occur when herbals that possess antiplatelet activity are administered with antiplatelet/ anticoagulant drugs, thus increasing the risk for bleeding. When Kava, a herbal that depresses the central nervous system (CNS) was administered concomitantly with CNS depressant drug alprazolam, a semicomatose state was induced (64). When a sedative botanical like valerian is co-administered with diazepam or other such sleep inducing agents, a potentiation of sleeping effect could occur. In addition, herbals with the potential to cause organ toxicity may cause further risk of toxicity when drugs with similar toxicity are administered concurrently, such as when the hepatotoxic herbal comfrey is given with large and prolonged doses of acetaminophen (65). An example of an antagonistic interaction is when an herbal with high caffeine content, such as guarana, is administered with a sedative-hypnotic.

In pharmacokinetic interactions on the other hand, the herbal changes the absorption, distribution, metabolism, protein binding, or excretion of a drug which results in altered levels of the drug or its metabolites. The resultant alterations caused by the combination of drugs may or may not alter the dose-response relationship despite the change in the plasma levels and /or drug disposition profile of the drugs because an observable pharmacodynamic change will depend on the degree of change in systemic concentration.

Absorption. Absorption of drugs can be impaired when herbs that contain hydrocolloidal fibers, gums, and mucilage are taken together. Examples of such herbs include psyllium, rhubarb, flaxseed, marshmallow and aloe gel. These herbals can bind to drugs preventing their absorption and, subsequently, reduce systemic availability of the compounds. Psyllium a herb with high content of mucilage, used in the treatment of constipation, inhibits the absorption of lithium (66). Herbal laxatives such as aloe latex, buckthorn, cascara sagrada, rhubarb, and senna can cause loss of fluids and potassium and can potentially increase the risk of toxicity with digoxin (67) as well as reduction in the action of drugs that have a narrow therapeutic index (eg, digoxin, warfarin) due to the diarrhea (68).

Distribution. Salicylates can displace highly protein-bound drugs such as warfarin and carbamazepine from plasma proteins thereby increasing the adverse/toxic effects of the drugs. Meadowsweet and black willow herbs contain salicylates and can potentially interact with such drugs (69). Potential pharmacokinetic interactions can occur with displacement of a drug from protein binding sites. Drug displacement of highly protein-bound drugs by another compound may result in increased activity of the displaced drug. Although displacement of protein-bound drugs has been described as a mechanism for potential drug interactions, there are no documented reports of herbal-drug interactions attributable to displacement of drugs from protein-binding sites.

Metabolism. Licorice when used as an herb, not a sweetener decreases the metabolism of corticosteroids and the anticoagulant action of warfarin is enhanced by ginkgo and possibly by many other herbs (70). Change in renal clearance of a drug is another potential mechanism for producing herbal-drug interactions. Herbals that can inhibit tubular uptake or in other ways that can interfere with the renal clearance of a drug should be considered as having potential to produce pharmacokinetic herbal drug interactions (71).

Two important processes involved in drug disposition in man have been implicated in most of the current evidence of herbal-drug interactions. Several of the documented herb-drug interactions are pharmacokinetic in nature, involving metabolizing enzymes related to oxidative metabolism by the cytochrome P-450 system (CYP) and / or the efflux drug transporter P-glycoprotein, with fewer evidence of the involvement of other enzymes such as glutathione S-transferases and uridine diphosphoglucuronyl transferases (UGTs) and more than half of all medications undergo metabolism by CYP3A4 substrates (72). Besides CYP3A4 which has been shown to be involved in most herbal - drug interactions, other CYP isoenzymes, which have been found to be involved in significant pharmacokinetic reactions in humans, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E. Because some herbals and various drugs may be substrates of the same CYP isoenzyme, either of them may inhibit or induce the activity of the enzyme when ingested concomitantly, the choice of which is dependent on the enzyme -substrate affinity and concentration among other factors.

The other important system that significantly contributes to drug disposition in human is the P-glycoprotein drug transporter. It is a glycoprotein encoded by the MDR1 gene and

functions as a transmembrane efflux transporter that pumps drugs out of cells as they try to get into the intestinal wall from the gut lumen where they again become available for oxidative elimination from the body. They are found mainly in organs responsible for drug absorption or elimination, such as the intestine, liver, and kidneys and also present in many tissues. This drug efflux therefore limits the rate and extent of drug absorption from the intestinal tract. Altered expression or activity of several drug transporters and drug-metabolizing enzymes can lead to lower therapeutic efficacy or greater toxicity. The P-glycoprotein has high transport capacity and broad substrate specificity thus it can transport a wide number of clinically relevant drugs with structurally different features and belonging to different classes such as several anticancer drugs, some HIV protease inhibitors, H₂ receptor antagonists, antiarrhythmics—(cardiac glycosides and calcium channel blockers), immunosuppressive immunosuppressive agents, corticosteroids, antiemetic and antidiarrheal agents, analgesics, antibiotics, anthelmintics, antiepileptics, sedatives, antidepressants.

Drugs that are substrates of CYP3A4 often affect P-glycoproteins as well (73), thus the interplay of both intestinal P-gp and CYP3A4 has a strong effect on the bioavailability of most orally administered drugs including proton pump inhibitors (PPIs), cyclosporine, midazolam, talinolol, statins, HIV protease inhibitors and verapamil (74, 75, 76). Therefore concomitant intake of herbal medicinal products that are P-gp and/or CYP3A4 substrates with orthodox drugs has a higher potential for interaction. Studies have shown that in cancer therapy several anticancer drugs (such as vincristine, vinblastine, vinorelbine, irinotecan, etoposide, docetaxel, and paclitaxel), as well as certain supportive care agents concomitantly and commonly used by cancer patients, such as ondansetron, fentanyl, morphine, loperamide, and domperidone can modulate P-glycoprotein and/or CYP isoenzymes (77). Thus, the modulation of intestinal and hepatic Pgp and CYP enzymes by herbal medicines represents a potentially important mechanism by which the bioavailability of co-administered drugs can be modulated.

Inhibition or induction of metabolizing enzymes or drug transporters involved in the systemic disposition of drugs is the mechanism of most pharmacokinetic interactions elicited by herbs or their active constituents. Inhibition occurs when herb is able to decrease the normal activity level of a metabolic enzyme or drug transporter via a competitive or noncompetitive mechanism. Induction on the other hand is a much slower process involving gene regulation and expression. The herbal product activates increase in the mRNA leading to increased expression of the corresponding gene or drug transporter. Discontinuation of the precipitator usually brings enzyme levels back to normal, making the process reversible. Induction of the enzymes involved in the metabolism and transport of chemotherapeutic drugs irinotecan or imatinib is responsible for the lower plasma levels observed when each is concurrently administered with St John's Wort (78, 79). On the other hand, inhibition of CYP3A4 by grapefruit juice was responsible for the increase in plasma levels of felodipine when a 5mg tablet was taken with the juice (80). Some botanicals that actively inhibit CYP enzymes include evening primrose oil, kava, garlic, *Ginkgo biloba*, *Echinacea purpurea*, milk thistle, while Pgp activity was shown to be inhibited by curcumin, , piperine, green tea, quercetin, and silymarin (81 - 83). Ginseng and ginsenosides inhibit both CYP enzyme and Pgp.

In a broad sense, the mechanisms behind induction of metabolizing enzymes will include processes that involve enhanced translational efficiency, increased gene transcription rates, improved enzyme stability and ligand binding / other enzyme-related actions. However, the most commonly encountered is that involving the activation of certain nuclear receptors in man. This mechanism has been further elucidated, giving rise to new possibilities for the identification of herbal preparations capable of causing induction because the mechanistic knowledge about induction processes can be an aid in the prediction of clinically relevant interactions.

Pregnane X receptor (PXR), the constitutive androstane receptor (CAR), and the vitamin D-binding receptor (VDR) are nuclear receptors that have been identified to be involved in the induction of metabolizing enzymes and some drug transporters. After activation by endogenous or exogenous ligands, these receptors form heterodimers with the 9-*cis* retinoic acid receptor (RXR) and bind to xenobiotic response elements in the target genes (84). Because of this, the transcription of the target genes is increased, leading to detoxification and elimination of xenobiotics.

PXR, is one of the main transcriptional regulators of CYP3A4 and Pgp, while possessing some transcriptional control over CYP2B6, CYP2C9, sulfotransferase (SULT), UGT1A1, glutathione S-transferases (GST), and MRP-2. Studies have shown that the activation of PXR is one of the main mechanisms behind induction of metabolizing enzymes and drug transporters by herbal medicines (85). The inductive capacity of SJW is mediated via this mechanism. Hyperforin, a bioactive constituent in St John's wort, forms a complex with the ligand-binding domain of human PXR thereby activating the PXR and consequently inducing CYP3A4 and CYP2C9 expression (86, 87). Studies using gene reporter assays or measuring mRNA levels of CYP3A4 in human hepatocytes have also shown that guggulipid, or its chemical constituents guggulsterones, derived from the Mukul myrrh tree, hops, two traditional Chinese medicines (TCMs), Wu Wei Zi (*Schisandra chinensis* Baill) and Gan Cao (*Glycyrrhiza uralensis* Fisch), and their selective constituents, carotenoids, especially β -carotene, and retinol have the potential to induce CYP3A4 by activation of PXR (88-90).

Both P-gp and CYP3A4 are abundantly expressed in the villus tip of enterocytes and hepatocytes, correspondingly, both intestine and liver express significant concentrations of PXR. This is important because the transcriptional regulation of drug metabolizing enzymes is cell-mediated and tissue-selective, thus significant inductions will not be found in tissues that have low concentrations of the receptors and enzymes when in contact with the relevant ligands. Known ligands of human PXR include rifampicin, dexamethasone, clotrimazole, and paclitaxel and all are established inducers of CYP3A4 (91).

Metabolizing enzymes are also induced to a lesser extent by other nuclear receptors such as CAR and VDR. CYP2B gene is the main target of CAR but the expression of other hepatic genes, such as UGT1A1 and CYP2C9 and MDR-1 is also modulated by this receptor (92, 93). VDR is the receptor responsible for modulating cytogenesis and cell death in response to 1 α , 25-dihydroxy vitamin D₃ as the ligand. In addition, it also regulates CYP3A4, CYP2B6 and CYP2C9 (94). Though PXR has been shown to mainly regulate CYP3A4 expression while CAR regulates CYP2B expression, it is clear that one type of nuclear receptor has the ability to modulate the expression of several enzymes, meaning that the specificity is not absolute but rather there is some overlap in both the nuclear transcription function as well as the ligand-binding capacity and the extent of induction will vary depending on the ligand, tissue

involved. Consequently, more than one enzyme modulated by different receptors may be responsible for an observed effect in a herb induced interaction. For example, PXR, CAR and the aryl hydrocarbon receptor (AhR) are all known to modulate the overall UGT1A1 response to flavonoids, though the AhR is mainly responsible for the UGT1A1 expression (95).

In vitro screening for potential inhibition or induction of CYP enzymes by various herbals is gaining momentum (96), but data about the inductive capacity of herbal medicinal products and their interaction with nuclear receptors is scarce and mainly focused on PXR. However, with the discovery of the mechanistic processes involving nuclear receptors in the induction of metabolizing enzymes and drug transporters drug transporters, recent efforts to address these challenges are more optimistic.

5. Investigating herb–drug interaction

FDA requires that the extent of metabolism for all new drugs be defined, the CYP enzymes involved in the formation of its major metabolite be identified and their potency for enzyme inhibition evaluated. This is with a view to complying with the regulatory requirement that a warning towards such interactions be added in the product insert and label (97). Thus, in the discovery of conventional drugs, new chemical entities (NCEs) are tested for inhibitory effects on CYP3A4, potent inhibition is associated with a potential for drug-drug interactions. Similarly, there is a need to identify the potentials for herbal medicinal products to interact with drugs in the early stages of drug development using proper in vitro and in vivo models, so as to improve their safe use in clinical practice.

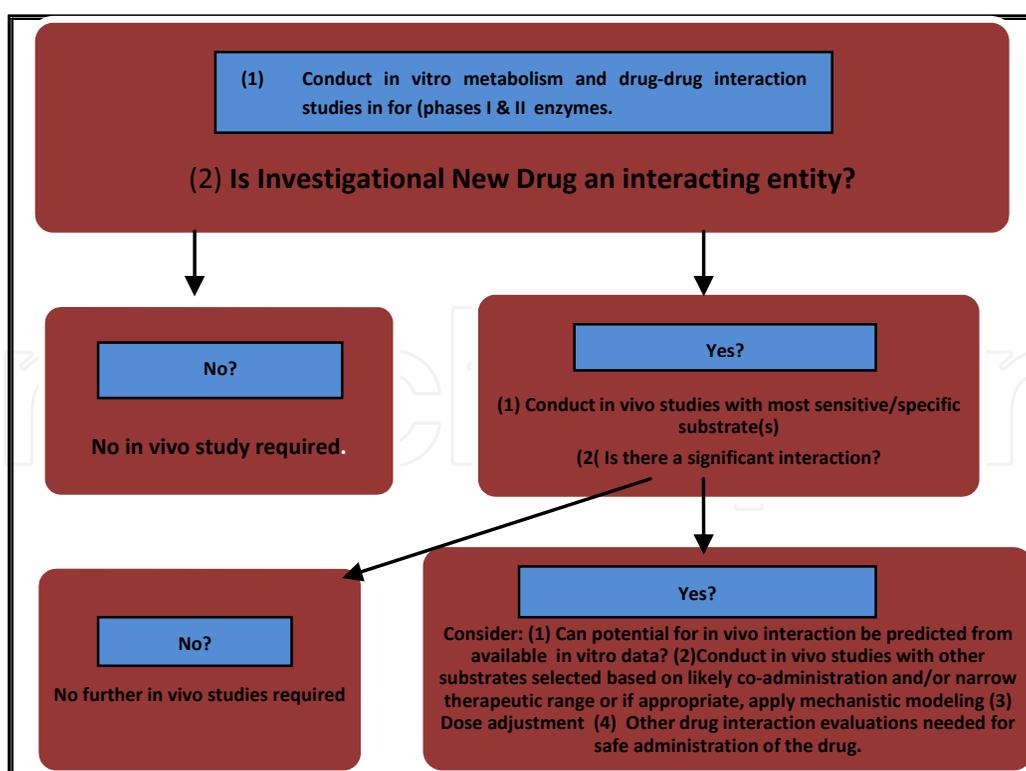


Fig. 2. Simplified schematic representation of the FDA recommended approach to evaluating Investigational New Drugs for possible drug-drug interactions (DDIs).

Although there are challenges of content of numerous constituents of unknown pharmacokinetics and pharmacology inherent in herbal agents that limit the application of methods used in screening conventional drugs, several of these methods can be adapted for determining whether a phytomedicine will affect metabolic enzymes and drug transporter systems thereby deduce its interaction potential. For example, an inhibition study can be adapted from the FDA guidance document on drug / drug interaction as shown in figure 3.

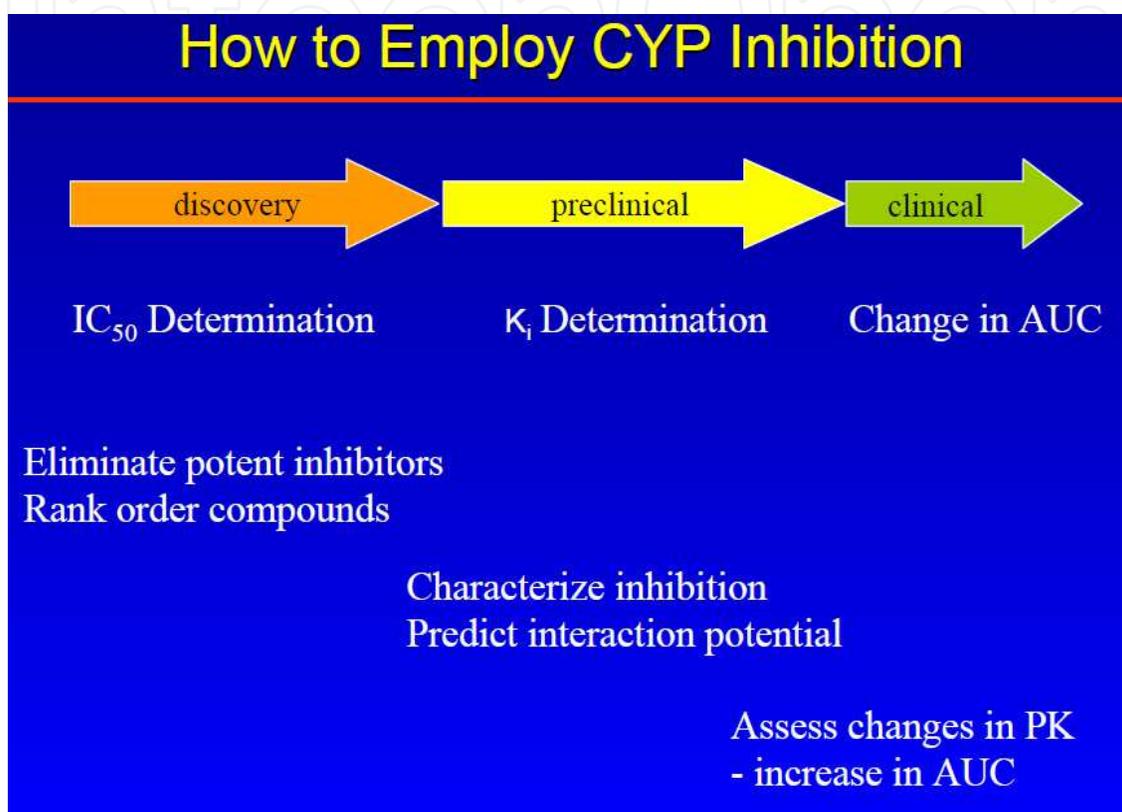


Fig. 3. Schematic representation on how to employ CYP inhibition at different stages of drug development process

Likelihood	K_i (μM)	I/K_i
Probable	<1	>1
Possible	$1 < K_i < 50$	$0.1 < I/K_i < 1$
Unlikely	>50	<0.1

Table 3. Inhibition studies Interpretation: Potential for in vivo inhibition.

Compounds with $K_i < 1\mu\text{M}$ are generally predicted to cause drug / drug interaction hence in vivo studies recommended. Hyperforin one of the constituents of St John's wort, purported to be the active constituent and the most potent agonist of PXR, has a K_i of 27nM (98).

In vitro models generally use subcellular fractions of human liver tissues, whole-cell models of isolated human hepatocytes, liver slices, or human cell lines (99). Changes in the activity or concentration of enzymes or transporters can be demonstrated through use of selective

chemical inhibitors of specific CYP enzymes or transporter systems. For metabolic studies, the major models usually are subcellular fractions (liver microsomes, cytosols and homogenates), precision-cut liver slices, isolated and cultured hepatocytes or liver cell lines, and cDNA-expressed enzymes while human gastrointestinal absorption and cancer cell lines, as well as membrane vesicles and cDNA expressed drug transporters are widely used for transport studies (100, 101).

High throughput screening has been successfully adapted to the study of drug-herb, herb-CYP and herb/P-gp interactions (102). This has an advantage that a large number of herbs, their bioactive fractions and constituents can be screened at the same time in a multiple well plate (see figure 4), thereby providing *in vitro* inhibition data as a criterion for further investigation. This method has been used in our laboratories to study *in vitro*, inhibition studies involving the inhibition of CYP-specific marker reactions by test herbal medicinal products. These phytomedicines are being developed for use in the treatment and management of malaria, HIV infection, diabetes and sickle cell disease respectively.

The products were investigated at two concentrations for CYP-specific marker reactions using recombinant CYP3A4 and fluorescent based marker reactions. Inhibition of the CYP activity by more than 20% was considered significant and in such cases, the IC_{50} (the concentration of product bringing about 50% inhibition of enzyme activity) value was determined. All the products had inhibition greater than 50%, some comparable to the troleandomycin, a known inhibitor of CYP3A4. Their IC_{50} ranged from 0.004 - 0.060mg/ml and was compared with that of ketoconazole, a potent inhibitor of CYP3A4 with an IC_{50} of 0.016mg/ml (Obodozie et al, unpublished data).

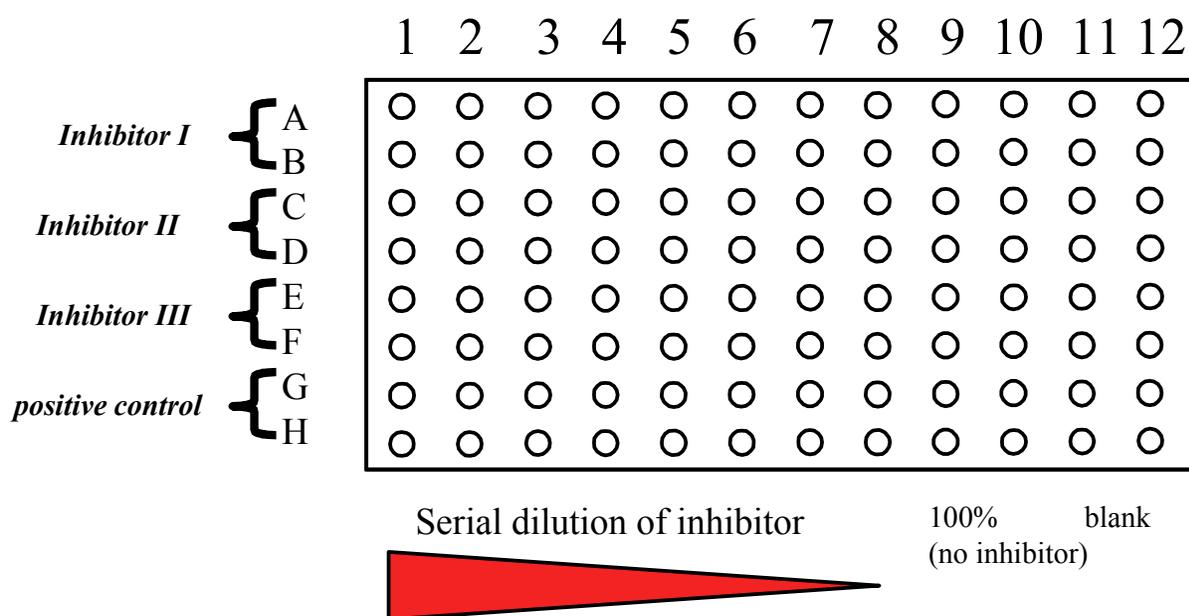


Fig. 4. Design of HTS for CYP Inhibition (*ref. 102*)

The IC_{50} curves for four of the five products and control inhibitor is shown in figures 5a - 5e

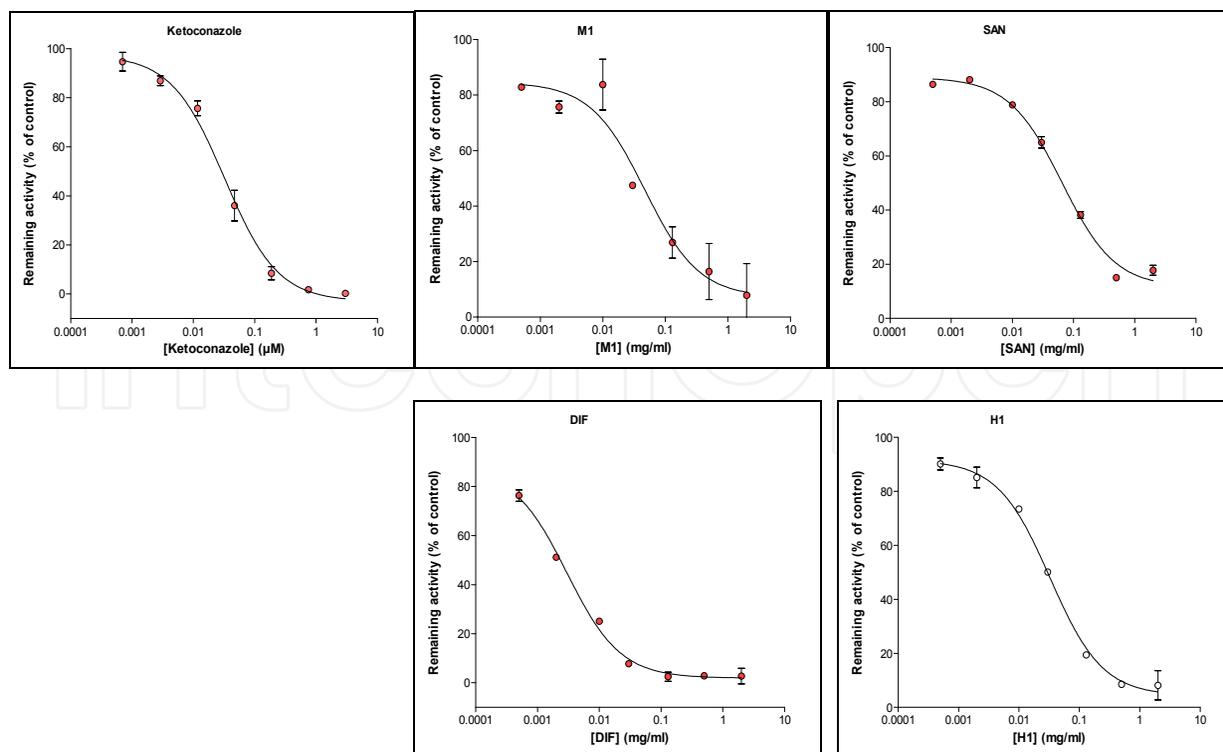


Fig. 5. (a – e): IC₅₀ Curves for some natural products and control inhibitor. [a] M1=AM-1 extract from *Nauclea latifolia*, [b] SAN=NIPRISAN [c] D1F= Fraction component of the extract of *Vernonia amygdalina* and [d] HI=extract *Andrographis paniculata*

If absorbed, these products are predicted to result in significant clinical drug-herb interactions. Therefore further in vivo studies are necessary as recommended by FDA approach (see figure 2).

Other in vitro methods involve the use of in silico methods to determine the interactions potential of CYPs, Phase II enzymes, P-gp with botanicals, often by the use of rule-based modelling, and structure-activity relationships (103, 104).

Often times, to obtain enough information that is useful for a test herbal product in evaluating how the herb may affect CYPs and P-gp, various methods may be used in combination. For example, in an in vitro study performed to investigate the inductive properties of several flavonoids, including quercetin, resveratrol, and curcumin to activate nuclear receptors and to induce metabolizing enzymes using primary cultures of human hepatocytes of 17 individuals, it was found that only quercetin led to an increase in the quantity of CYP3A4 mRNA. To further elucidate the involvement of PXR, a reporter gene assay with hPXR was used. Quercetin did not show a significant increase in luciferase activity, suggesting that CYP3A4 was induced by mechanisms not involving PXR (105). Kava-kava also increases CYP3A4 mRNA levels in hepatocytes with enhanced luciferase activity, others like grapeseed extract, ginseng and garlic stimulates only CYP3A4 mRNA without increasing luciferase activity indicating that that the induction CYP3A4 by some herbs may not always be mediated via PXR.

Each of these models has very different cost, reliability, advantages and limitations. For example, some models will maintain the structure and integrity of isolates and cellular

cultures with a loss in quality and quantity of the target enzymes. Thus they may be useful for the study of Phase I and II reactions (106, 107) but not suitable for inhibition and transport studies (108) due to the rapid down regulation of certain enzymes and transporters which occurs after isolation of hepatocytes. Primary liver cell cultures have been used for a long time to study inductive potentials of products but its major set back is the availability, quality and inter-individual variation of human liver tissue and the fact that it can only give information about the inductive capacity and not about the nuclear receptor involved. The development of reporter gene assays has reduced some of the challenges associated with the use of human liver tissue.

Making decisions on whether an herbal-drug interaction occurs based on data from *in vitro* or animal test models is inadequate. When drug interactions with a herbal medicinal product is suspected to be likely based on *in vitro* results or significant in animal studies, they should be confirmed with further well conducted *in vivo* studies and in human to validate the clinical significance. Such studies are needed because most often *in vitro* assays do not necessarily correlate with *in vivo* and human metabolism. This is most important for herbal medicines which usually contain multiple constituents because the entity that is precipitating enzyme modulation *in vitro* may not be systemically available due to instability in the GIT, unabsorbed or is inactive prodrug.

As reported earlier, the *in vitro* studies using rCYP3A4 and paracetamol as the substrate showed AM-1 as a potent inhibitor of the enzyme indicating that an increase in paracetamol (acetaminophen) blood levels will be likely if both drugs are co-administered. However, further *in vivo* studies in human volunteers showed reduction in AUC of paracetamol when both products were concurrently administered (31). Grapefruit juice, a potent inhibitor of intestinal CYP3A4 precipitated lower AUC of etoposide when both were taken concomitantly orally in humans, contrary to the expected increase in oral bioavailability of the CYP3A4 substrate. The involvement of another mechanism, possibly an inductive effect of grapefruit juice on Pgp-mediated transport of etoposide may have been responsible for this lower AUC (109). Another example is the use of *in vitro* preparations of liver microsomes to predict drug interaction potentials. These results may not agree with *in vivo* studies because human liver microsomes are not able to predict enzyme induction due to inability of microsomal preparations to synthesize new proteins thus may not give an indication of potential induction *in vivo*. An example of this is the case of St John's Wort which has been shown to induce both CYP3A4 through an action on PXR *in vivo*, as well as Pgp and CYP2C19 but *in vitro*, it inhibits CYP2D6, CYP 2C9 and CYP3A4 (110, 111).

Animal models are widely used for the evaluation of drug-herb interactions. Such models include the use of wistar rats, rabbits, mice, transgenic mice et cetera. Caution should be exercised in the interpretation and extrapolation of *in vivo* results obtained from animal models to humans because the species differences in nuclear receptors and inductive processes make extrapolation difficult. Also there are observed species differences in the ligand-binding domains (LBDs), especially in the LBD of PXR of wild-type laboratory animals that may produce discrepancies between *in vivo* animal and human study data. The report by Bakare-Odunola et al (112), showed that metronidazole pharmacokinetic parameters were significantly altered by concomitant administration of the antimalaria phytomedicine AM-1, such that AUC and maximum serum concentration were increased by over 100% and Vd and Cl were similarly reduced in rats, another study showed no

significant alteration in the oral bioavailability of the same drugs when concurrently administered to healthy human volunteers (113).

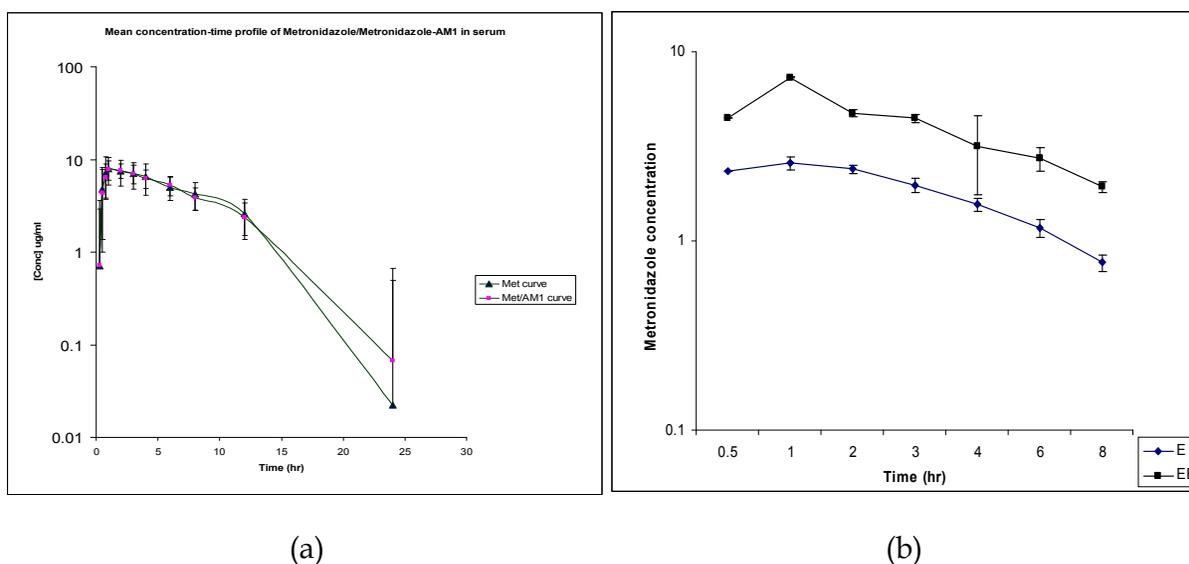


Fig. 6. (a – b): (a) Serum concentration-time curve of metronidazole in human volunteers following oral administration of two tablets of 200mg metronidazole (flagyl®) alone and after concurrent administration with 400mg AM1 (b) Serum concentration-time curve of metronidazole in rats following oral administration of 7.5mg/kg metronidazole alone and after co-administration with 16mg/kg NIPRD AM-1

Not with standing, results from animal studies can also be source of useful information especially when human transgenic animals are used (114).

Clinical studies on drug-herb interaction usually employ the use of human participants and most are designed to monitor pharmacokinetic interactions. The studies follow principally three basic designs, while the first and third give an idea of the involvement of specific enzyme in an interaction, the second provides general information on the effect of the herb on a target drug. Several well conducted clinical studies some popularly used botanicals demonstrate these methods.

(I) The use of probe drugs that are known to be metabolized by specific enzymes and monitoring the change in AUC of the probe drug with and without the test herbal product.

The effect of different herbal drugs on various metabolizing enzymes and transporters in humans have been shown. Artemisinin was shown to be a potent inhibitor of CYP1A2 activity by decreasing the paraxanthine levels when co-administered with caffeine in humans (115). *Citrus aurantium*, *Panax ginseng*, *Echinacea purpurea*, milk thistle, and saw palmetto extracts taken by healthy volunteers all had no effect on the activity of CYP3A4, CYP1A2, CYP2E1, and CYP3A4 measured using model substrates (116). Meanwhile the disposition profile of some substrates for other enzymes CYP3A4, CYP1A2, CYP2E1, and CYP2D6 were not affected by ginkgo when administered to healthy volunteers or elderly patients (117, 118). FDA recommended substrates for specific enzymes include Theophylline/caffeine for CYP 1A2, S-warfarin/Lorstan for CYP 2C9, Desipramine for CYP2D6, mizodolam, buspirone, felodipine, simvastatin, lovastatin for CYP3A4 while fexofenadine and digoxin are P-gp substrates.

(II) Administering the test herbal product with and without a target conventional drug and monitoring the change in pharmacokinetic profile of the latter.

Mills et al have given a good review the effects of St John's Wort on the pharmacokinetics of some conventional drugs (119). One of the renowned cases of herb - drug interaction is the effect of garlic preparations on the plasma concentrations of antiretroviral drugs saquinavir and ritonavir. The effect of garlic supplements on the pharmacokinetics of saquinavir was reported by Piscitelli et al. Garlic preparations decreased the mean AUC and the mean C_{max} of saquinavir by 51% and 54% respectively (120), while not having effect on neither ritonavir concentrations nor the metabolism of acetaminophen in healthy volunteers (121, 122). Ritonavir is now known to be a CYP3A4 inhibitor, an effect that has prompted its use in antiretroviral therapy with positive therapeutic benefit in boosting (by inhibition of CYP3A4) other protease inhibitors and enhancing their bioavailability (saquinavir, lopinavir) as well as reducing hepatic clearance (indinavir, amprenavir, and atazanavir).

Administering the test herbal without a target conventional drug or enzyme probe and monitoring the change in an enzyme activity marker before and after treatment.

Omeprazole hydroxylation, a CYP2C19 mediated action was shown to be induced in healthy male subjects by *Ginkgo biloba*, one of the most widely used herbal products, indicating that the effect of omeprazole could be reduced with the concurrent administration of Ginkgo (123). The effect of P. Ginseng on the 6-B-hydroxycortisol to cortisol ratio, a marker of CYP3A4 activity was evaluated in twenty healthy human participants before and after a 14 day intake of 100mg of P. Ginseng standardized to contain 4% ginsenosides. The results suggested that there was no induction of CYP3A4 activity (124)

6. Risk factors for herbal-drug interactions

The risk of having an herbal-drug interaction is based on a variety of factors related to patient, dosing regimen, co-administered drug and herb, and not solely based on the pharmacologic and pharmacokinetic characteristics of the herbal. One important factor that increases the likelihood of having a herbal-drug interaction is concomitant use of a herbal product with drugs that have a narrow therapeutic index because while a doubling or more in drug plasma concentration has the potential for enhanced drug effects and/or appearance of adverse effects (125), less marked changes may still be clinically important for such drugs with steep concentration-response relationship. Drugs in this category include digoxin, antiepileptic drugs, antineoplastic agents, immunosuppressants and warfarin.

Patient populations who are at increased risk for having herbal-drug interactions include the elderly, critical care patients, patients undergoing surgical procedures, patients with liver or renal disease, and patients receiving multiple medications. In most cases, the extent of drug interactions with herbs varies markedly among individuals, with gender and genetic polymorphism as additional factors for the inter-individual differences.

In persons using herbal products chronically, hepatic and intestinal metabolism or drug transport may be affected by the same herb differently for the same substrate. In vitro data obtained in human hepatocyte cultures, showed that St John's Wort a known CYP3A4 inhibitor, can induce greater docetaxel metabolism in patients using the herb chronically (126). The oral bioavailability of midazolam after echinacea intake was significantly greater, while in contrast, multiple dosing of the same herb in volunteers for 8 days resulted in a

significantly lower AUC and 34% increase in systemic clearance of the drug (127). CYP3A4 was inhibited by single dose administration of ritonavir, chronic administration resulted in an induction of same enzyme (128). Herb related factors that are risk factors in drug interactions with herbal medicinal product include species, dose, dosing regimen, and administration route (13)

7. Conclusion

The metabolism of a drug can be altered by another drug or foreign chemical, and such interactions can often be clinically significant. Cytochrome P450 (CYP) enzymes, a superfamily of enzymes found mainly in the liver, are involved in the metabolism of a plethora of xenobiotics and have been shown to be involved in numerous interactions between drugs and food, herbs and other drugs. The observed induction and inhibition of CYP enzymes by natural products in the presence of a prescribed drug has (among other reasons) led to the general acceptance that natural therapies can have adverse effects, contrary to the popular beliefs in countries where there is an active practice of ethnomedicine. Majority of the classes of conventional drugs have been shown to be affected by different types of botanical preparations leading to various consequences, including treatment failure, adverse / toxic effects and even death. In order to improve the safety of ethnomedicines use alongside conventional therapies in public healthcare, it is necessary to understand how the former will interact with the latter, early in drug development. It is also necessary to predict early so as to eliminate regulatory obstacles and avoid market pressure for recalls that may have been induced by adverse effects linked to interactions.

It is possible and highly recommended that the conventional industrial preclinical platform be used to evaluate herbal extracts for metabolism based drug-herb interactions, thereby incorporating such studies into drug development for phytomedicines. Although the presence of numerous active ingredients in herbal medicines, foods and dietary supplements complicate experimentation, the observable interactions with CYP enzymes warrant systematic studies, so that metabolism-based interactions can be predicted and avoided more readily. Over the years, there has been great advances in the availability of "high tech" tools, in vitro and in vivo study designs and analytical equipment that can be adapted for use in such studies. Pharmaceutical research must go beyond focusing on pharmacological efficacy of botanicals but also in studies that improve their effectiveness in order for humanity to fully benefit from their inherent therapeutic potentials.

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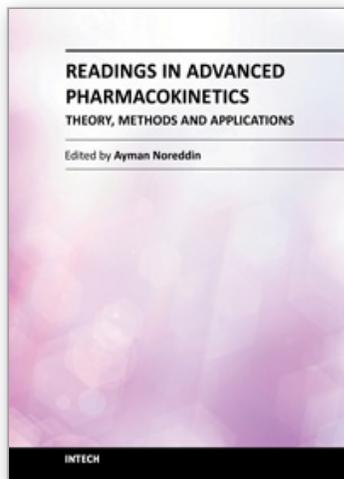
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