DRUG-DRUG AND HERB-DRUG INTERACTIONS-A COMMENT

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Abstract
Clinically relevant drug-drug interactions may be pharmacodynamic or pharmacokinetic. And herbal medicinal products are becoming increasingly popular. Drug interactions can be in vivo or in vitro. Pharmacodynamic outcomes take such forms as Additive, Synergistic, Antagonistic or Indifferent. The paper reviews and presents drug-drug and herb-drug interactions of public health importance in the face of growing patronage of trado-medical products, often purported to be without side-effects.

Keywords: Pharmacokinetics, pharmacodynamics, in vivo, in vitro

Introduction

Drug interactions are said to occur when the pharmacokinetics and/or the pharmacodynamics of a drug are altered by the presence of another drug, food, drink or herb. This definition, in effect, refers to *in vivo* interactions which is the bane of drug therapy. *In vitro* interactions also do occur, and may involve complexation, adsorption, inactivation, antagonisms or potentiation of the effects of one drug in the presence of other drugs, food or chemical agents. Such *in vitro* interactions may or may not affect the pharmacokinetics and pharmacodynamics of the drug.

For convenience, *in vivo* drug interactions could be classified as either *pharmacokinetic* or *pharmacodynamic* interactions. Pharmacokinetic interactions are those which can affect the processes by which drugs are absorbed, distributed, metabolised and/or excreted. Pharmacodynamic interactions involve those that affect the pharmacological activities of drugs.

Drug Interactions can also be described in terms of the resultant Pharmacodynamic outcome as *Additive, Synergistic, Antagonistic or Indifferent.*

Apart from causing outright systemic toxicity, drug-drug and herb-drug interactions could also reduce or increase the bioavailability of the co-administered synthetic drugs. Reduction in bioavailability may result in therapeutic failure while increase in bioavailability may result in over-dose (and so necessitates dose adjustment).

Therefore, as African ethnomedicine is gaining global acceptance, an emerging challenge would be the possibility of identifying and documenting beneficial and non-beneficial interactions between these herbs and conventional drugs. On the other hand, consumers ought also to be aware of the demerits of taking two drugs concomitantly without counsel from the proper health professionals.

This presentation will attempt to present a global appraisal of documented evidences of clinically relevant drug-drug and herb-drug interactions as well as empirical reports of some *in-vitro* and *in-vivo* herb-drug interactions involving African ethnomedicinal agents.

Drug – drug interactions

Clinically relevant drug-drug interactions may be pharmacodynamic or pharmacokinetic**.** Pharmacokinetic interactions sometimes affect the pharmacodynamics of the drug. Pharmacokinetic drug interactions may occur as a result of one drug affecting the gastrointestinal absorption, the metabolism or the renal excretion of the other.

Many factors, which affect gastrointestinal absorptions such as pH of fluid in the gastrointestinal lumen, gastrointestinal motility and blood flow to the intestines are known to be influenced by some drugs. Also, absorption can be influenced by physico-chemical interactions between drugs following oral administration. For instance, antacids have been implicated in reduced absorption of a wide range of drugs including tetracyclines, fluoroquinolones, azithromycin, nitrofurantoin, chloroquine, proguanil and halofantrine. Ferrous salts (blood tonics) also reduce the absorption of tetracycline, fluoroquinolones (such as Ciprofloxacin, ofloxacin and perfloxacin).

Many drugs including barbiturates, most anti-epileptics, glutethimide and rifampicin induce hepatic drug metabolism. Such drugs (especially the barbiturate, phenobarbitone) have been shown to, through induction of hepatic metabolism, decrease plasma levels of several different drugs including quinidine, chloramphenicol, metronidazole, corticosteroids, etc. Drug interactions involving this mechanism are gradual (not immediate) and continue for some time after withdrawal of the inducing agent. There is also a wide range of drugs that inhibit metabolism of other drugs. Cimetidine (a popular anti-ulcer drug) for instance, inhibits the biotransformation, and hence increases the plasma levels of a variety of drugs including opioid analgesics, mebendazole, warfarin, imipramine, nortriptylline, metronidazole, chloroquine, phenytoin and theophylline. Inhibition of drug metabolism resulting in serious cases of drug intoxication in man has been reported. For example, the metabolism of tolbutamide is inhibited by chloromphenicol, phenylbutazone and sulphaphenazole; accordingly, there are reported cases of hypoglycaemic collapse due to the elevated tolbutamide plasma level resulting from the interactions.

Although renal excretion is not a step in "bioavailability pathway" (since the amount of drug reaching the systemic circulation is not affected by renal excretion), the bioavailability parameters, which measure the extent of drug availability, can be significantly altered by this process, because of a change in drug elimination.

Drugs are eliminated by renal excretion through glomerular filtration, tubular reabsorption and active tubular secretion. A co-administered drug can influence any of these processes and the resultant change in drug elimination will increase or decrease some pharmacokinetic parameters.

Herb – drug interactions

Herbal medicinal products are becoming increasingly popular. At the same time, the safety issues related to herbal drugs continue to be ignored by the public, neglected by manufacturers and legislative bodies as well as under-researched by the medical professions. One safety aspect that is of growing importance is that of herb-drug interactions. With the increasing level of consumer acceptance of herbal medicines for diverse reasons, there is a high possibility of interactions between herbal and synthetic drugs. This is because users of herbal medicines tend to believe that these botanicals are inherently safe and are thus likely to

concomitantly use self-prescribed herbal and prescribed synthetic drugs.

Possible interactions between conventional and herbal medicinal products

Considerable and significant inputs in the area of herb -drug interactions have been made by Edzard Ernst (1-4) and very few other researches (5-10). A recent systematic review by this author (Table 1) summarizes the indirect published evidence on the theoretical potentials of herbal medicines to cause interactions.

Such possibilities of interactions are usually derived from an understanding of the mode of action of herbal medicines. However, because such indirect evidences are not conclusive, it is necessary to carry out further systematic reviews and overviews, which will list published case reports of suspected interactions. An attempt to summarize anecdotal and experimental evidence of some herb-drug interactions has similarly been made and is presented in Table 2.

Table 1: Possible Herb-Drug Interactions (Adapted from E. Ernst[2])

Herbal Remedy	Usage of pharmacological effect	Possible interactions
Aloe vera (Aleo barbadensis)	Various	With chronic use potentiation cardiac glycosides or anti-arrhythmic drug due to loss of potassium
Broom (cystitisus scoparius)	Anti-arrhythmic, diuretic	Increases effects of anti-depressants and beta-blockers and cardiac glycosides, circulatory collapse with quinidine, haloperidol or moclobemide
Capsicum (capsicum anuum L)	Appetite stimulant	May interfere with antihypertensives and MAO inhibitors; can stimulate the hepatic metabolism of drugs
Charparral (Larrea tridentate)	Bronchitis, colds	Increases hepatotoxicity of other drugs (pyrrolizidine)
Cinochona (Cinchonae cortex)	Dyspepsia	Increases effect of anticoagulants
Cola (Kola nitida)	Antidepressant, CNS stimulant	Increases risk of adverse effects (tremor, tachycardia) with antibacterial quinolones, may increase half-life of analgetics and antipyretics
Coriander (Coriandrum sativm)	Anthelmintic, antiarthritic	Enhances effects of hypoglycaemics
Cranberry (Vaccinum macrocarpon)	Urinary tract infections	May enhance elimination of some drugs normally excreted in urine. Increased effects of some antibiotics in urinary tract
Cucumber	Diuretic	May potentiate effects of other

(Cucumis sativus)		diuretics
Dandelion (Taraxatum officinale)	Laxative, diuretic	Increases effects of antihypertensive, diuretics and hypogltcaemics
Eucalyptus (Eucalyptus)	Catarrh, rheumatism	Increases hepatic microsomal enzymes and therefore alters metabolism of other drugs
Fenugreek (Trigonella foenumgraecum)	Hypocholesterinaemic	Increases the effects of anticoagulants and hypoglycaemics, may decrease absorption of other drugs.
Flax (Linum uasitatissimum)	Anti-constipation	May diminish absorption of other oral dugs
Garlic (Allium sativm)	Hypocholesterolaemic	Increases the effects of anticoagulants and anti-platelet drugs
Ginger (Zingiber officinalis)	Anti-emetic	Increases the effects of anticoagulants
Ginseng, Siberian (Eleutherococcus senticosus)	Stimulant	May inhibit metabolism of hexobarbital, can increase excretion of vitamins B_1, B_2 and C_2, may interact with cardiac, hypo-and hypertensives as well as with anti-hypoglycaemics
Goldenseal (Hydrastis Canadensis)	Anti-inflammatory, anti-microbial	Increases effects of antihypertensive, calcium channel blockers and digoxin, may decrease anticoagulant effects, many herbalists believe that goldenseal generally enhances the activity of other drugs
Ground ivy (Glechoma hedercea)	Ear nose and throat disorders	Interaction with antiepileptics, may increase risk of seizure
Guarana (Paullinia cupana)	CNS stimulant	High caffeine content may inhibit clearance of lithium, decrease iron absorption, can enhance CNS effects of theophylline
Ilex (L. paraguarensis)	Diuretic, analgetic	Increases risk of adverse effects (tremor, tachycardia) with antibacterial quinolones, may counteract CNS depressants; can increase effects of diuretics, hepatic microsomal enzyme inhibitors. May decrease clearance and cause toxicity
Kava (Piper	Anxiolytic	Potentiation with other anxiolytics, can increase Parkinson-symptoms

methlsticum)		with levadopa
Khat (Catha edulis)	CNS stimulant	Increases effects of antihypertensives, antiarrhythmics, beta-blockers, decongestants, MAO inhibitors and other sympathomimetics
Licorice (Glycrrhizia glaba)	Corticosteroid activity, gastric irritation	Potassium loss, e.g. with thiazide diuretics, water and sodium rentation, increases effects of corticosteroids, cardiac glycosides, and antihypertensive, not recommended with MAO inhibitors
Lily of the cally (Convallaria majalis)	Congestive heart failure	Increases (side) effects of quinodine, calcium, salureties, laxatives, glucosteroids, beta-blockers, calcium channel blockers and digitalis
Lobelia (Lobelia inflata)	Nicotine-like	Increases effects of anticholinergic drugs
Male fern (Dryopteris filixmas)	Anthelmintic	Antacids and pronto pump inhibitors inactivate the herb
Mistletoe (Visum album)	Anti-cancer drug	Increases effects of CNS depressants, antihypertensives and cardiac drugs
MugWort (Artemesia vulgaris)	Analgetic antibacterial	May potentiate effects of anticoagulants
Myrrh (Commiphora molmol)	Anti-inflammatory	Interference with drugs used for hypo-or hyperthyroidism, can increase effects of insulin and suifonylureas
Niauli oil (Melaleuca viridiflora)	Catarrh	Induction of liver enzymes
Nutmeg (Myristica fragrans)	Anti-diarrheal	Decreases effects of haldol, thiothixene, olanzapine, clozapine
Oak bark (Quercus robur)	Astringent	Absorption of alkaline drugs may be reduced
Onion (Allium cepa)	Antihyperglycaemic	Increases the effects of other such drugs
Paullinia (Paullinia cupana)	Coffee-like	Increases risk of adverse effects (tremor, tachycadia) with antibacterial quinolones
Pill-bearing spurge (Euphorbia pilulifera)	Analgesic, antipyretic	Increases the effects of ACE inhibitors, anti coagulants, decreases effects of anticholinergics
Pineapple	Constripation, jaundice,	Over-anticoagulation through

(Anannas comosius)	obesity, anti-ulcer	coumarin contence, may antagonise effects on bradykinin with ACE inhibitors (Bromelain)
Piper longum	Ayurvedic medicine, various indications	Increases bioavailability of theophylline, phenytoin, propranolol, rifampicin, suphadiazine ettracyclin
Piper nigrum	Ayurvedic medicine, various indications	Increases bioavailability of theophylline, phenytoin, propranolol, rifampicin, suphadiazine ettracyclin
Plautains or psyllium (plantago lanceolata)	Bulk laxative	Can delay absorption of other drugs (e.g. lithium), increases effects of digitalis-like medicines
Pokeweed (Phytolacea Americana)	Anti-inflammatory, diuretic	Additive effects with CNS depressants, may increase effects of fertility drugs, may interfere with oral contraceptives
Pupkin seed (Curcubita)	Anthelmintic, diuretic	Can increase effects of diuretics
Reichi (Ganoderma Lucidum	Tonic, liver-protective	Increases effects of anticoagulants, synergism with cefazolin
Rue (Ruta gravelens)	Spasmolytic, antimicrobial	Increased vasodilatation with antihypertensives, increased isorpic effect with digoxin and dobutamine, counteraction with fertility agents
Sarsaparilla (S. aristochiifolia)	Diuretic, psoriasis	Increases absoption of digitalis, glycosides, bismuth; accelerates elimination of hypnotics
Sassairas (S. albidum)	Tonic	May potentiate toxicity of drugs metabolised by hepatic microsomal enzymes systems
Schisandra (Schisandra chinesis)	Tonic, liver-protection	May potentiate drugs metabolised in the liver due to liver enzyme induction
Scotch broom (cysticus scoparius)	Circulatory diseases	Contains tyramine – hypertensives crisis with MAO inhibitors
Senna (Cassia)	Laxative	Loss of potassium with chronic use; potentiation of cardiac glycosides or antiarrhythmic drugs; calcium channel blockers, clamodium antagonists and indomentacine may decrease effects of senna preparations
Sheperd's purse (Capsella	Bleeding disorders	Can enhance effects of hypertensives, beta-blockers, digoxin and calcium

bursapastoris)		channel blockers as well as sedative or hypnotic drugs
Sorrel (Rumex acetosella)	Antiseptic, diuretic	Increases effects of other diuretics, increases hepatotoxicity of other medications
Squill (Urginea maritime)	Heart failure	Increases (side) effects of quinidine, calsium, saluretis, laxatives, glucocorticoids, antiarrhythmics, beta-blockers, calcium channel blockers, digoxin, CNS stimulants
St. John's Wort (Hypericum perforatum)	Anti-depressant	Increases effects of digoxin MAO-inhibitors or serotonin uptake inhibitors, decreses effects of anticonvulsants and anti-diabetic drugs, increases photosensitivity with other such drugs, prolongs narcotic induced sleeping time, probably is a hepatic enzyme inducer thereby reducing plasma levels of drugs metabolised in the liver

Table 2. Case reports of suspected interactions between herbal medicines and prescribed drugs.

Type of herbal remedy	Use of herbal remedy	Interaction with	Clinical effect	Possible mechanism
Danshen	Chinese herb with various uses	Warfarin	Over-anticoagulation	Danshen has anti-platelet activity
Dong quai	Pre-menstrual symptom's	Warfarin	Over-anticoagulation	Not known
Garlic	To lower cholesterol	Warfarin	Over-anticoagulation	Garlic has anti-platelet activity
Papaya extracts	Indigestion	Warfarin	Over-anticoagulation	Not known
Ginkgo biloba	Enhance memory and circulation	Warfarin	Over-anticoagulation	Ginkgo-biloba has anti-platelet activity

Ginkgo biloba	Enhance memory and circulation	Aspirin	Over-anticoagulation	Ginkgo-biloba has anti-platelet activity
Devil's claw	Arthritis	Warfarin	Over-anticoagulation	Not known
Panax ginseng	Various indications	Phenelzine	Mania, headache, hallucinations, insomnia	Not known
Kava	Anxiolysis	Alprazolam	Coma	Synergism of action
St. John's wort	Anti-depressant	Theophylline, cyclosporine, warfarin, ethinyloestradiol	Decrease plasma levels of concomitantly administered drugs	Hepatic enzymes induction
St. John's wort	Anti-depressant	Loperamide	Delirium	Potentiation of MAO inhibition
St. John's wort	Anti-depressant	Paroxetine sera tine nefazodone	Serotonin syndrome: dizziness, weakness, confusion nausea/vomiting	Synergistic serotonin uptake inhibition
Shankhapushpi	Ayurvedic remedy with various indications	Phenytoin	Loss of seizure control	Not known
Evening primrose oil	Eczema, pre-menstrual syndrome	Phenytoin	Loss of seizure control	Not known
Ispaghula husk	Laxative	Lithium salt	None	Lowering of lithum level due to reduced intestinal

				absorption
Betel nut	Various indications	Procylidine	Extrapyramidal syndrome	Antagonism
Liquorice	In many Chinese herbal mixtures	Anti-hypertensive drugs	Hypocalcaemia	Aldostrone effects
Ginkgo biloba	Enhance memory and circulation	Thiazide diuretics	Hypertension	Not known

There are also numerous case reports revealing serious and harzadous interactions of herbal medicines with anti-coagulants. Case report of interactions between *Panax ginseng* and phenelzine , the popular herbal anxiolytic, *kava (Piper methysticum*) and alprazolam, *St. John's Wort (Hypericum perforatum)* and theophylline,

sertraline and oral anti- contraceptives containing ethinyloestradiol, *shankhapushpi* (an Ayurvedic Indian herbal medicine) and phenytoin, *ispaghula husk* (a bulk laxative) and lithium salt, betel nuts and some neuroleptics, liquorice (*Glycyrrha glabra*) and anti- hypertensives etc have been documented. Several clinical trials have also demonstrated evidences of clinically relevant and significant herb-drug interactions.

Clinical trials demonstrating herb-drug interactions

In a crossover study of healthy volunteers, a Chinese herb containing glycyrrhizin affected prednisolone pharmacokinetics in a non-uniform fashion. It was suggested that glycyrrhizin, which is a major constituent of liquorice acts on unknown enzyme modifiers as inhibitors or promoters of metabolism. In another crossover study carried out on eight healthy volunteers, it was demonstrated that *khat (Catha edulis)* chewing significantly reduced the bioavailability of orally administered ampicillin. The possible mechanisms for these interactions are unknown.

However, it is postulated that since ampicillin combines with tannins (one of the alkaloids found in khat leaves) to form insoluble and poorly absorbed complexes, bioavailability impairment may be as a result of reduced gastrointestinal absorption of ampicillin induced by the tannin content of the khat leaves. A decrease of absorption of lovastatin was observed in patients who took this lipid-lowering agent concomitantly with *pectin* or *oat bran*; this resulted to an increase in LDL (low density lipoprotein) levels. The interaction between St. John's Wort extract and digoxin was investigated in a single blinded placebo controlled parallel group study. The 10-day co-medication of St. John's Wort extract resulted in a significant decrease of digoxin bioavailability. This interaction was postulated to be due to an induction of drug transporters or metabolizing enzymes caused by St. John's Wort extract.

Herb-drug interactions involving African ethnomedicinal agents

Several empirical *in-vitro* and *in vivo* studies have been carried out which demonstrate herb-drug interactions (or potential for such) with African ethnomedicinal agents.

In-vitro evidences of herb-drug interactions involving selected African ethnomedicinal agents

Using the agar diffusion assay, the ethanol extract of *Garcinia kola* seed has been shown to inhibit the antimicrobial properties of several antibiotics including gentamycin, tetracycline, co-trimoxazole, ciprofloxacin, ofloxacin, amoxicillin-clavulanic acid (Augmentin^{R}) and penicillin G. It is postulated that the flavonoids and metallic contents of the extract may be connected with the observed herb-drug interactions. This is because metals are known to form various complexes with various antibiotics that may result in their inactivation or reduced activity. Also, the penicillins, aminoglycosides, tetracyclines and fluoroquinolones, which were shown to interact with *G. kola*, do possess characteristic properties (such as specific electron withdrawing or electron donating groups; possession of C=O group or acidic hydrogen atoms) that may make them capable of forming intermolecular complexes with flavonoids. Adsorption of drugs to *G. kola* was also found to be a possible mechanism for herb-drug interactions involving *G .kola* and some synthetic drugs. Based on the high adsorptive potentials of *G. kola*, we proposed based on *in vitro* experimental evidence that *G. kola* could serve as an alternative antidote in the management of ciprofloxacin poisoning.

Contrary to the effect of *G. kola* against flouroquinolones, the seed of another indigenous cola- *Kola nitida* was shown to enhance the antimicrobial properties of three fluoroquinolone antibiotics (ciprofloxacin, pefloxacin and levofloxacin) against a strain of *E. coli*. It is possible that the high content of xanthine alkaloids (for instance, caffeine) in *K. nitida* seed could have potentiated the intracellular concentration of the fluoroquinolones and thus enhance their antimicrobial activities against the test Gram negative bacteria. Interactions of caffeine with diverse drugs have been shown to increase their uptake.

Interaction of the leaf extracts of *Dissotis theifolia* with several disc antibiotics (including ofloxacin, gentamycin, nitrofurantoin, ceftriaxone, cotrimoxazole, cefotaxime, tetracycline, cefuroxime and chloramphenicol) produced mostly antagonistic effects while interactions of same drugs with the most active column fraction of the plant extract produced indifferent effects. Summarily, this suggests that *D. theifolia* has the potential of reducing the antimicrobial properties of these antibiotics.

Herb-drug interaction between extracts of tea (*Camellia sinensis*) and Penicillin G has been shown to be additive, showing that the concormitant administration of tea and Penicillin G may not impair the antimicrobial properties of the latter. However, the interaction between tea and some fluoroquinolones such as ciprofloxacin, ofloxacin and norfloxacin has been shown to be antagonistic.

The interaction between chloroform extracts of *Chromolaena odorata* and lincomycin and itraconazole, studied using a modified checkerboard technique showed varying effects ranging from synergism to additivity, antagonism and indifference depending on the combination ratio of drug and extract. Generally,

interactions of the extract with itraconazole were either synergistic or indifferent; only two combination ratios of the extract and lincomycin were antagonistic. This study reveals that with herb-drug interactions (as in any drug-drug interaction), the combination ratio of herb and drug determines the outcome of the interaction to a large extent. Since it is practically impossible to determine the ratio of drug to herb consumed at any time, it is very difficult to predict the outcome of herb-drug interactions with great certainty.

Constituents of several African medicinal plants (especially starches) have been shown to act as drug adsorbents. Starch from *Gladiolus natalensis* and *Gladiolus actinomorphanthus*, which grow abundantly in the Eastern region of Nigeria have been shown to have a higher adsorptive capacity for chloroquine than the conventional standard adsorbent, activated charcoal. The starches also adsorb aspirin, although to a lower extent than activated charcoal. Also, the sclerotium of Pleurotus tuber-regium has been shown to strongly adsorb pyridoxine hydrochloride.

In-vivo evidences of herb-drug interactions involving selected african ethnomedicinal agents

Several evidences of herb-drug interactions in animal and human models have been reported in the scientific literatures. We shall attempt to describe a few of these involving mostly African ethnomedicinal agents.

The bioavailability and antimicrobial activity of ciprofloxacin in rabbits has been found to be reduced by *Garcinia kola* and by the pulp of unripe *Musa paradisiaca*. Although the precise mechanism of the herb-drug interaction was not elucidated in these studies, the study nevertheless provided preliminary evidences of a potentially non-beneficial herb-drug interaction involving either *G. kola* or *M. paradisiaca* with ciprofloxacin.

The bioavailability and *in-vivo* antibacterial activity of levofloxacin has been shown to be enhanced after concomitant administration with tea, *Camellia sinensis* . Although no mechanistic appraisal of the herb-drug interaction was carried out, it is possible that the inhibitory effect of tea on P-glycoprotein could have resulted in the observed enhanced bioavailability. Levofloxacin is a substrate for P-glycoprotein, which is also expressed in rabbit intestines. Therefore, inhibition of P-gp by tea could potentially enhance bioavailability of drugs that are substrates for P-gp. Recently also, another P-gp inhibitor (ginger) has been shown to enhance the bioavailability of metronidazole in rabbits. Given that ginger is a common spice in many Nigerian diets, the potential for herb-drug interaction involving ginger and metronidazole (and indeed a great deal of other drugs) cannot be over-emphasized.

Nwafor et al showed that the concurrent administration of aqueous leaf extract of *Azadirachta indica* and chloroquine sulphate in rabbits caused a significant reduction in the serum concentration, slower absorption and elimination as well as longer half life of chloroquine sulphate. It is a common practice for patients on antimalarial therapy in the tropics to combine herbal and orthodox medicine. Where these involve the concormitant administration of chloroquine sulphate and *A. indica*, this preliminary study signals a potential antagonistic interaction.

Mustapha and Yakassai earlier reported that *Pamarindus indica* (the major constituent of a local drink commonly consumed in the Northern part of Nigeria) significantly reduced the

bioavailability of aspirin in healthy human volunteers.

The bioavailability of ofloxacin in healthy human volunteers has been shown to be reduced after concomitant administration with *Garcinia kola* seed.

Various fluroquinolones, including pefloxacin, norfloxacine, ciprofloxacine and ofloxacine have shown various degrees of reduced bioavailabilities after concomitant administration with various phytoadaptogens.

Conclusion:

The data presented so far scantly suggest that interactions between two synthetic medicines or between herbal medicines and prescribed drugs exist. A herbal medicine could have similar pharmacological effects as conventional drugs. Consequently, concomitant use of both might result in an addition of the two single effects. For instance, the use of dandelion *(Taraxatum officinale),* a herbal diuretic, together with other conventional diuretics could lead to a potentiated or additive diuretic effect. A herbal medicine can also have the opposite effects of conventional drugs. Parallel usage might thus diminish the expected clinical effect of the latter. An example could be the administration of the hypotensive herbal medicine, Parsley (*Petreselinum crispum*) together with conventional antihypertensives. Other herbal medicines seem to interfere with the intestinal absorption of conventional medicines. In other cases, a herbal medicine might increase the bioavailability of synthetic drugs. An example might be the concomitant use of *Piper longum* and phenytoin.

The implications of drug-drug and herb-drug interactions are multi-dimensional. On the one hand, since there is evidence that clinically relevant interactions exists, health care professionals should appropriately counsel their patients about using non-prescribed OTC drugs together with prescribed drugs and should no longer ignore their patients' use of herbal medications. Physicians should realize that a large proportion of their patients regularly use herbal remedies in addition to prescribed medicines without informing their doctor. Physicians therefore ought to be aware about possible herb-drug interactions and regularly ask their patients about the use of herbal remedies. Patients should also be adequately informed about the possibility of herb-drug interactions.

On the other hand, manufacturers of herbal products should be obliged to take responsibility on informing the public about herb-drug interactions involving their products. Also, regulating bodies should reconsider their stand that herbal remedies can be classified as food supplements.

References

Adikwu, M.U. (1993). *Acta Pharmaceutica* 43: 201-207.

Ernst, E. (2000). *Eur. J. Clin. Pharmacol*. 56: 523 – 524.

Ernst, E. (2000). *Meyler's Side Effects of Drugs,* 14th edition. M. N. G. Dukes, and J. K. Aronson, (eds), Elsevier Science B. V., Amsterdam.

Ernst, E. (2000). *Perfusion*. 13: 4 – 15.

Ernst, E. (2000). *Perfusion*. 13: 60 – 70.

Esimone, C.O., Adikwu, M.U., Ibezim, E.C., Nworu, C.S., Odimegwu, D.C. and Ezugwu, C.O. (2007). *Sci. Res. Essays* 2(11): 482-485.

Esimone, C.O., Adikwu, M.U., Ibezim, E.C., Ofoefule, S.I., Nwafor, S.V. and Onuoha, O.M. (2002) *Acta Pharmaceutica* 52: 219-226.

Esimone, C.O., Adikwu, M.U., Ndu, O.O., Udeogaranya, P.O., Ezeugwu, C.O. and Obonga, W (2003). *Journal of Pharmaceutical & Allied Sciences* 2: 114-120.

Esimone, C.O., Ezeabasili, S.I., Muko, K.N., Ohiri, F.C. and Adikwu, M.U. (2001). *Bolletino Chimico Farmaceutico* 140: 351-353.

Esimone, C.O., Iroha, I.R., Ibezim, E.C., Okeh, C.O. and Okpana, E.M. (2006). *African Journal of Biotechnology.* 5: 1082-1086.

Esimone, C.O., Nwafor, S.V., Okoli, C.O., Chah, K.F., Uzuegbu, D.B., Chibundu, C., Eche, M.A. and Adikwu, M.U. (2002) *Am J Therapeutics* 9: 275-280.

Esimone, C.O., Okoli, C.O. and Ayogu, C.O. (2007). *Int. J. Trop.Med.* 2: 63-67.

Esimone, C.O., Uzuegbu, D.B., Egbu, N.L., Adikwu, M.U., Dibua, U.E. and Iroha, I.R. (2006). *J. Med. Pharm Sci* 2**:**66-73.

Ibezim, E.C., Esimone, C.O., Nnamani, P.O., Onyishi, I.V., Brown, S.A. and Obodo, C.E. (2006). *African Journal of Biotechnology*. 5: 1781-1784.

Mustafa, A. and Yakasai, I.A .(1986) *Eur. J. Drug Metab. Pharmacokinet.* 21: 223-226.

Niebergal, P.J., Husar, D.A., Grossman, W.A., Sugita, E.T. and Doluisio, J.T. (1996). *J. Pharm. Pharmacol* 18:729-736.

Nwafor, S.V., Akah, P.A., Okoli, C.O., Onyirioha, A.C. and Nworu, C.S. (2003). *Acta Pharm* 53: 305-311.

Nwafor, S.V., Esimone, C.O., Amadi, C.A. and Nworu, C.S. (2003) *Eur. J. Drug Metab. Pharmacokinet* 28:253–258.

Ofokansi, K.C., Adikwu, M.U., Esimone, C.O. and Nwodo, M. (2004). *Indian J. Pharm. Sci.* 66: 659-664.

Okonta, J.M., Uboh, M. and Obonga, W.O. (2007). J. Pharm. Res (In Press).

Okore, V. C. and Osuji, A. C. (2001). *Acta Pharm.* 51: 139 – 145.

Revning, R. H. and Levy, G. (1968). *J. Pharm. Sci.* 57: 1342 – 1346.

Vincent, C. and Furnham, A. (1997). *Complementary Medicine. A Research Perspective.* Wiley, Chicester, pp. 97 – 117.