Underestimating the Toxicological Challenges Associated with the Use of Herbal Medicinal Products in Developing Countries

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1. Introduction

With the burst in the use of herbal medicinal products (HMPs) globally, either for primary treatment or as complementary and alternative medicine, safety and efficacy of herbal medicine have become a public health concern. Till date, it has been difficult to make reliable estimates of ill health caused by herbal products particularly because (i) the perception that “natural” equates to “safe” and therefore herbal medicine users would not realise that a herbal remedy may be responsible for adverse symptoms they have experienced; (ii) the lack of communication between patients and medical practitioners regarding the use of herbal medicine; (iii) the presence of low-grade herbal products on the market, and (iv) the supply of counterfeit products.

The World Health Organisation (WHO) estimates that 80% of Asian and African populations rely on traditional medicine as the primary method for health care needs. The scenario in developed countries is very similar with 70% to 80% of the population using some form of complementary and alternative medicine [1]. Commonly used single herbs and polyherbal formulations in developing nations are described in Tables 1 and 2. Whilst conventional medical science has powerful methodologies for proving efficacy, ensuring quality, standardising good manufacturing practices, testing for safety, and conducting postmarketing surveillance for adverse effects, similar guidelines are lacking for herbal products; the same has not been extended to traditional herbal medicines despite these having been embraced by different cultures and regions. It must, however, be acknowledged that a number of protocols documents on safety and toxicity testing of HMPs have been put forward by the Union of Pure and Applied Chemistry [2], the European Medicines Agency (EMEA) [3], and the European Food Safety Authority [4] though they are not followed by all countries. In addition, with the rising demand of medicinal plants from developed countries, international trade particularly via the Internet has soared. However international trade in medicinal plants is
| Country          | Family       | Scientific name of plant            | Vernacular name                      | Parts used | Local medicinal uses                                      | Reported literature |
|------------------|--------------|-------------------------------------|--------------------------------------|------------|----------------------------------------------------------|---------------------|
| Mauritius        | Rutaceae     | Aegle marmelos                      | Bael                                 | Fruit      | Gastrointestinal disorder                                | [7–10]              |
| Mauritius        | Erythroxylaceae | Erythroxylum laurifolium            | Bois de ronde                        | Leaf       | Diuretic, used against renal stores                      | [11, 12]            |
| Ebenaceae        | Diospyros neraudii, Diospyros revaughani, Diospyros tessellera, Diospyros melanida | Ebène                                | Stem bark                            |            | Antibacterial, antifungal, antiviral, anthelminthic, antiprotozoal, and antimalarial | [11–13]              |
| Reunion Island   | Aphloiaceae  | Aphloia theiformis                  | Changeecorce, Goyave marron          | Leaf       | Treat fever and antimalarial properties                  | [14]                |
| Reunion Island   | Asteraceae   | Eupatorium triplinerve              | Ayapana                              | Aerial parts |                                                                       |                     |
| Madagascar       | Acanthaceae  | Justicia gendarussa                 | Ayapana marron                       | Aerial parts |                                                                       | [15]                |
| Madagascar       | Buddlejaceae | Nuxia sp.                           | Vlier                                | Leaf       |                                                                       |                     |
| Madagascar       | Asteraceae   | Psiadia sp.                         | Arina/lary                           | Aerial parts |                                                                       |                     |
| South Africa     | Podocarpaeae | Podorcarpus sp.                     | Fern pine                            | Leaf       | Fevers, asthma, cough, cholera, arthritis, rheumatism, painful joints | [16]                |
| South Africa     | Apocynaceae  | Carissa edulis                      | Conkerberry                          | Root       | Diarrhoea                                                  | [17]                |
| East Africa      | Rutaceae     | Toddalia asiatica                  | Nyalwet-kwach/Kaule/Mdaka komba      | Root, bark, leaf, fruit | Malaria, cough, chest pain, sore throat                  | [18]                |
| East Africa      | Annonaceae   | Uvaria scheffleri                  | Mguma                                | Root Leaf  |                                                                       | [19]                |
| North Africa     | Apiaceae     | Carum carvi                         | El-qarwiya (Caraway)                 | Seed       | Diabetes and hypertension                                  | [20]                |
| North Africa     | Compositae   | Artemisia herba-alba                | Chih (White mugwort)                 | Leaf, root |                                                                       |                     |
| West Africa      | Annonaceae   | Annickia chlorantha                 | Yellow Moambe                        | Stem Bark  |                                                                       | [21]                |
| West Africa      | Annonaceae   | Anonidium mannii                    | Eborne Afan                          | Stem Bark  |                                                                       |                     |
| Northeast India  | Acanthaceae  | Justicia adhatoda                  | Nongmangkha angouba                  | Leaf       | Asthma                                                     | [22]                |
| Northeast India  | Acoraceae    | Acorus calamus                      | Ok hidak                             | Fruit      | Haemorrhoids                                               |                     |
| Northeast India  | Meliaceae    | Aphanamixis polystachya            | Heirangkhoi                          | Root Leaf  | Asthma                                                     |                     |
| South India      | Euphorbiaceae| Acalpyha indica                     | Kuppaimei                            | Leaf       | Bronchitis                                                 | [23]                |
| South India      | Amaranthaceae| Aerva lanata                        | Sirukanpeelai                        | Root       | Diabetes                                                   |                     |
| South India      | Acanthaceae  | Asystasia gangetica                | Medday keerai                        | Whole plant| Rheumatism                                                 |                     |
| China            | Rosaceae     | Agrimonia pilosa                    | Xian he cao                          | Whole plant| Anti-inflammatory, against worms, inflammation, high blood pressure, and headache | [24]                |
| China            | Asteraceae   | Erigeron breviscapus                | Dengzhanxixin                        | Whole plant| Gastrointestinal disorders                                |                     |
| China            | Geraniaceae  | Geranium strictipes                 | Geshanxiao                           | Root       |                                                                       |                     |
proteomics, and metabonomics, can make a significant
ular the “-omic-” technology comprising transcriptomics,
alytical techniques and molecular technology, in partic-
development of herbal medicines and advancements of
studies for herbal products. The demand for and consequently the necessity of toxicological
regarding side effects of herbal medicine, has highlighted the
herbal drugs are still being unveiled, increasing evidence,
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demand for and consequently the necessity of toxicological
studies for herbal products.

With the increased discussion on safety assessment
of herbs, toxicology constitutes an essential role in the
development of herbal medicines and advancements of
analytical techniques and molecular technology, in partic-
lar the “-omic-” technology comprising transcriptomics,
proteomics, and metabolomics, can make a significant
contribution to the predictive and preclinical toxicology
assessment of herbal medicine [28, 29].

Apart from the toxicity of the intended herb(s) itself,
the lack of a stringent and harmonised quality control and
effective monitoring system imposed on herbal medications
may lead to contamination or adulteration that could prove
harmful to humans. Possible contaminants/adulterants such
as heavy metals, pesticides, toxic herbs, and conventional
drugs are commonly encountered toxicological concerns
in herbal preparations. Nevertheless, strategies in devising
suitable toxicological examination protocols to deal with the
wide panoply of components in herbal drugs stand as a
challenge to toxicologists.

Heavy metal contaminants like cadmium (Cd), arsenic
(As), and lead (Pb) can be a risk factor in contributing to the
toxicity of these herbal products [30]. The WHO maximum
permissible limits of As, Cd, and Pb are 1.0, 0.3, and 10 ppm,
respectively [31], with agricultural practices and industrial
emissions being accounted as indirect contributors [32, 33].
Hence, a recent study by Affum et al. [34] showed the level
of arsenic in ready-to-use aqueous-based antimalaria herbal
medicine in Ghana to be above the WHO permissible levels.
Plant material may also be contaminated with pesticides and
subsequent poor manufacturing practices may lead to con-
tamination with bacteria, fungi, and other microorganisms.
In addition, an increasing number of herbal supplements
have been found to be adulterated with active pharmaceutical
products [35].

Case reports have played a crucial role in alerting the
scientific community on the adverse effects of therapeutic
interventions [36, 37]. This is particularly true for herbal
medicines, many of which have a long traditional use but

| Country | Polyherbal formulation | Herbal composition | Vernacular name | Parts used | Medicinal purpose | Reported literature |
|---------|------------------------|--------------------|-----------------|------------|-------------------|-------------------|
| India   | Polyherbal hepatoprotective formulation (PHF) | *Emblica officinalis* | Aamla | Fruits | Hepatic disease | [25] |
|         |                        | *Terminalia chebula* | Haritaki | Fruits |                   |                   |
|         |                        | *Terminalia bellirica* | Vibhitaka | Fruits |                   |                   |
|         |                        | *Picrorhiza kurroa* | Kutki | Stem |                   |                   |
|         |                        | *Tinospora cordifolia* | Guduchi | Rhizomes |                   |                   |
|         |                        | *Swertia chirata* | Felworts | Entire herb |                   |                   |
|         |                        | *Azadirachta indica* | Neem | Bark |                   |                   |
|         |                        | *Adhatoda vasica* | Adusa | Stem bark |                   |                   |
| China   | Wu-Zi-Yan-Zong | *Cuscuta chinensis* | Strangleweed | Fruit | Neuroinflammatory disease | [26] |
|         |                        | *Lycium barbarum* | Chinese wolfberry | Fruit |                   |                   |
|         |                        | *Rubus chingii* | Raspberries | Fruit |                   |                   |
|         |                        | *Schisandra chinensis* | Pinyin | Fruit |                   |                   |
|         |                        | *Plantago asiatica* | Chinese plantain | Fruit |                   |                   |
|         |                        | *Epimedium brevicornum* | Yin Yang huo | Herb |                   |                   |
| Pakistan | PHOE (Polyherbal oil extract) | *Linum usitatissimum* | Alsi, Tuke Katan | Seeds | Antinociceptive and anti-inflammatory | [27] |
|         |                        | *Trachyspermum ammi* | Ajwain Desi | Seeds |                   |                   |
|         |                        | *Myristica fragrans* | Jawatri | Seeds |                   |                   |
|         |                        | *Syzygium aromaticum* | Long | Flower buds |                   |                   |
|         |                        | *Colchicum luteum* | Suranjan Talkh | Roots or tuber |                   |                   |
|         |                        | *Celastrus paniculata* | Mal Kangni | Seeds |                   |                   |
|         |                        | *Pinus roxburghii* | Behroza | Oleo-resin |                   |                   |

not well regulated, with limited data available on the product
identity, on the true demand and supply, and on the price
of the unprocessed raw materials and the processed HMPs
[5]. Although there exists the WHO certification scheme
to regulate the quality of HMPs in international commerce,
noncompliance with this certification further accentuates the
problems of adverse reactions [6].

Adverse health effects associated with herbal products
exist since time immemorial though and could be attributed
to both the inherent toxic effects of herbal medicine and
toxicities induced by adulterants/contaminants. The low inci-
dence of adverse reports associated with HMPs in developing
countries may be explained by the fact that consumers
generally regard them as safe and therefore believe their
symptoms are not attributable to the use of those products.
In addition, the reluctance to indicate the concomitant use
of HMPs to health care professionals, the impression that

| Country | Polyherbal formulation | Herbal composition | Vernacular name | Parts used | Medicinal purpose | Reported literature |
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|         |                        | *Terminalia chebula* | Haritaki | Fruits |                   |                   |
|         |                        | *Terminalia bellirica* | Vibhitaka | Fruits |                   |                   |
|         |                        | *Picrorhiza kurroa* | Kutki | Stem |                   |                   |
|         |                        | *Tinospora cordifolia* | Guduchi | Rhizomes |                   |                   |
|         |                        | *Swertia chirata* | Felworts | Entire herb |                   |                   |
|         |                        | *Azadirachta indica* | Neem | Bark |                   |                   |
|         |                        | *Adhatoda vasica* | Adusa | Stem bark |                   |                   |
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|         |                        | *Rubus chingii* | Raspberries | Fruit |                   |                   |
|         |                        | *Schisandra chinensis* | Pinyin | Fruit |                   |                   |
|         |                        | *Plantago asiatica* | Chinese plantain | Fruit |                   |                   |
|         |                        | *Epimedium brevicornum* | Yin Yang huo | Herb |                   |                   |
| Pakistan | PHOE (Polyherbal oil extract) | *Linum usitatissimum* | Alsi, Tuke Katan | Seeds | Antinociceptive and anti-inflammatory | [27] |
|         |                        | *Trachyspermum ammi* | Ajwain Desi | Seeds |                   |                   |
|         |                        | *Myristica fragrans* | Jawatri | Seeds |                   |                   |
|         |                        | *Syzygium aromaticum* | Long | Flower buds |                   |                   |
|         |                        | *Colchicum luteum* | Suranjan Talkh | Roots or tuber |                   |                   |
|         |                        | *Celastrus paniculata* | Mal Kangni | Seeds |                   |                   |
|         |                        | *Pinus roxburghii* | Behroza | Oleo-resin |                   |                   |
without ever having been submitted to formal tests of safety compared to conventional medicines. Moreover, despite their importance, case reports are often of poor quality, a fact that can seriously limit their value [38]. Hence, many of the case reports in the developing countries are not properly recorded, limiting appropriate conclusion thereby contributing to increasing adverse clinical effects of herbal remedies.

2. Evidence-Based Herbal Drug Toxicity

Toxicological problems associated with the use of herbal medicines are complex but have been regularly associated with serious adverse fatalities ranging from cardiovascular problems to psychiatric to neurological effects to liver toxicity or malfunction to hematologic and renal toxicity [39–41]. The diagnoses of herbal toxicity are usually made after consideration of the temporal relationship between exposure to the herb and the occurrence of the adverse event and by excluding other causes. However, causality assessment using appropriate tools for ascertaining herbal toxicity in a number of cases has failed to show any causal effects or has indicated only weak causal relationship [42,43]. For instance, the report of toxic liver injury due to consumption of the herb Greater Celandine (Chelidonium majus L.) in patients from various European countries has been a matter of concern. Teschke et al. [43] provided evidence of the existence of Greater Celandine hepatotoxicity as a distinct form of herb-induced liver injury in 22 spontaneous cases in Germany, but due to poor data quality the causal association between the herb usage and liver injury was less strong than hitherto assumed.

Moreover, although weak or no causality of herbal toxicity could be shown in many instances, a number of studies still have reported the potentially toxic nature of herbal drugs. In 1992, in Belgium, consumers of a herbal weight-loss preparation containing Aristolochia spp. exhibited severe renal disease manifested by interstitial fibrosis, which rapidly progressed to renal failure [44]. Moreover, Aristolochia spp. also used as an aphrodisiac, as an anticonvulsant, as an immune stimulant, and to treat arthritis, gout, rheumatism, eczema, wound treatment, allergic gastrointestinal colic, and gallbladder colic have been subsequently reported to impair renal function due to the presence of aristolochic acid [45,46]. In 1995, in Southern Taiwan and Japan, the use of Sauropus androgynus in weight control was associated with an outbreak of Sauropus androgynus-related obstructive lung disease [47]. Jones and Lawson [48] reported that the use of blue cohosh herbal medication was associated with profound neonatal congestive heart failure. The effect could be attributed to the presence of vasoactive glycosides and to an alkaloid known to produce toxic effects on the myocardium. Furthermore, blue cohosh has sympathomimetic and direct cardiotoxic effects, which can cause coronary vasoconstriction and decrease oxygen flow to the heart, thereby leading to morbidity and mortality in the foetus or in newborn infant exposed via maternal ingestion [48]. Similarly, cardiac glycosides have been linked with hyperkalaemia, a side effect observed in a patient taking a long list of herbal medicinal drugs [49].

Similarly, in 2005, clinical problems arising from the use of herbal medicines were reported in Hong Kong and Aristolochia species was found responsible for acute renal failure (n = 1), with aconite roots causing aconitine poisoning (n = 2), the Datura species causing anticholinergic poisoning (n = 1), and “yulan” (Stephania sinica) causing tetrahydropralmatine poisoning (n = 3) [50]. Likewise, in 2007, a systematic survey in Swiss hospitals indicated 10 cases implicating Herbalife, a herbal product sold for promoting “wellness” and weight reduction, as a possible cause of potentially severe hepatotoxicity. However it should be noted that the causality assessment in these cases was conducted by the WHO global introspection method, which is not liver-specific and therefore not a reliable tool to ascertain causality in presumed hepatotoxicity cases. Causality assessment of hepatotoxicity cases requires the Council for International Organisations of Medical Sciences (CIOMS) methods. Thus, for the 10 cases, a number of parameters for a valid causality assessment were not reported and there was also a case of hepatitis E explaining the presence of liver disease [51].

The diagnosis of herbal-drug induced hepatotoxicity continues to be a challenge despite the availability of causality assessment tests. There are only limited number of clinical studies with HMPs reported in the literature despite the fact that they have been used for centuries. Thus post-market pharmacovigilance providing interesting source of safety information and causality assessment indicates a link between an observed adverse event to a suspected HMP [52]. Although there is no universally accepted method for causality assessment, the existing methods rely on algorithmic, probability-based, and expert analyses as well as on the quality of adverse reactions reports. Unless causality is established, narrative reports remain less convincing of any herbal adverse reactions.

Cases with severe intoxications in humans have also been reported after consumption of essential oil rich in thujaone. Thujone or thuione-containing products have been reported to cause central nervous system disturbances which can lead to convulsions and ultimately to unconsciousness and death [53]. Similarly, licorice (Glycyrrhiza glabra) commonly used for inflammation of the upper respiratory tract and gastric and duodenal ulcers has been reported to cause suppression of the renin-aldosterone system, resulting in sodium and water retention, hypokalemia, hypertension, cardiac arrhythmias, and myopathy in cases of prolonged use [54,55]. Also, 10 deaths and 13 permanent disabilities from Ephedra-containing herbal drugs were reported to the FDA and the effects with ascribed to its sympathomimetic effects [41,56]. Overall, it is seen that while, on one hand, the toxic effects of herbs have been widely reported in developed countries, the same has not received an equivalent depth of scrutiny in developing countries.

The toxicity of herbs may also result from the generation of reactive intermediates through metabolic activation of herbal constituents via phases I and II reactions within the human body. The resultant reactive intermediates can bind covalently to DNA and proteins, leading to organ toxicity, mutagenicity, and even carcinogenicity. For instance, aristolochic acids in Aristolochia spp. used in a number of
Chinese traditional medicine undergo reduction of the nitro group by hepatic CYP1A1/2 or peroxidases in extrahepatic tissues generating highly reactive cinitrium ions. The latter can react with DNA to form promutagenic DNA adducts such as 7-(deoxyadenosin-N6-yl) aristolactam I and 7-(deoxyguanosin-N2-yl) aristolactam I as well as protein, resulting in activation of H-ras and myc oncogenes and gene mutation in renal cells and finally carcinogenesis of the kidneys [57, 58]. In vitro studies have also indicated the role of herbal reactive intermediates in irreversibly inhibiting various cytochrome enzymes (CYPs). However, the discrepancy of effects between in vitro, animal, and human studies reflects the significance of herbal dosing in the modulation of CYPs [58].

Other factors compromising safety may result from herbs harvested from polluted sites or poor farming practices, medicinal plant products contaminated with pesticides and microbial contaminants, heavy metals, toxic substances, and adulterants which can be toxic to the consumer.

3. Evidence-Based Drug Herbal Interactions

The contemporary use of herbal medicine is widespread but the challenge that society faces with its use is whether a patient will divulge to his or her medical practitioner the concurrent use of herbal products with conventional drugs is mainly based on case reports and human studies reflects the significance of herbal dosing in the modulation of CYPs [58].

Other factors compromising safety may result from herbs harvested from polluted sites or poor farming practices, medicinal plant products contaminated with pesticides and microbial contaminants, heavy metals, toxic substances, and adulterants which can be toxic to the consumer.

Common examples of herb-drug interactions have been found when cardiovascular medications with a narrow therapeutic index, such as digoxin and warfarin, are coadministered with herbs. For instance, concomitant use of warfarin with St. John’s Wort decreases prothrombin time, which may result in reduced anticoagulant effect and need for increased warfarin dose [61]. Other examples of interactions include St. John’s Wort with cyclosporine [62] and grapefruit juice with felodipine and lovastatin [63].

The current evidence that herbal medicine may interact with conventional drugs is mainly based on case reports of patients, case series, and a limited number of clinical studies. Drug-herbal interactions are difficult to evaluate because of the lack of compositional reliability of the herbal products though a number of interactions, amongst which are drug-metabolizing enzymes and drug transporter systems, as well as pharmacodynamic interactions can be involved. However since the pharmacokinetic and pharmacodynamic characteristics of most herbal medicine or supplements are not completely recognized, potential interactions cannot be predicted.

In a clinical study involving 313 patients, Jeong et al. [64] concluded that herbal drugs used alone were relatively safe, but the risk for adverse reactions may increase when herbal and conventional drugs are taken concurrently. The results indicated a 2.3% incidence of liver injury in the combined group of Korean patients. Concomitantly, Zhu et al. [65] reported that rutaecarpine, an alkaloid found in Eudokia rutacecarpa traditionally used in combination with Chinese traditional medicine, had profound effects on the hepatic drug processing enzyme gene expression, CYP enzyme genes and UDP-glucuronosyltransferase, and increased the expression of hepatic uptake and efflux transporters. The authors speculated that all these effects could play an integrated role in rutaecarpine-increased metabolism and elimination of caffeine [66], theophylline [67], and acetaminophen [68].

From evidence-based herb-drug interaction in cancer chemotherapy, Cheng et al. [59] concluded that most of the available information, both positive and negative, came from basic in vitro experiments or trials testing the use of a single herb along with chemotherapy drug when in practice most of the herbs are used in mixtures. The latter argued that “it is not reasonable to discard the potential usefulness of the traditional wisdom of herbal medicine, which has the backing of thousands of years of clinical experience.” However, this statement should be taken with some level of skepticism particularly since clinically relevant pharmacokinetic interactions between anticancer drugs and CAM have already been reported between the frequently used St. John’s Wort and the anticancer drugs irinotecan [69] and imatinib [70]. This justifies the need for clinical studies for confirmation and assessment of the clinical relevance of CAM-drug interactions obtained in vitro and emphasized recently by Goey et al. [71].

4. The Way Forward For Developing Countries

Due to the wide use and easy availability of herbal medicines, herbal toxicity and herb-drug interactions have become an issue of global concern. While HMPs provide opportunities for complementing the armoury of existing drugs, for their purportedly preventive and therapeutic purposes, the major problem with the use of herbal-based treatments is the lack of definite and complete information about the composition of extracts, resulting mainly from the trade secrecy of a number of herbal practitioners. Despite the fundamental role that traditional medical practitioners play in the provision of health services in developing countries, trade secrecy has been observed and is currently encroaching on the proper assessment of local herbal drugs. The lack of Good Manufacturing Practices, Good Agricultural Practices, Good
Laboratory Practices, and metabolic, pharmacokinetic, and toxicologic characteristics further characterized the dangers of HMPs in developing countries.

Hence, in many developing countries involved with the active production and use of HMPs, regulations distinct from the one for food and drugs are warranted. The existence of such regulation can emphasise a premarket system, which provides market authorisation for each HMP based on evidence that the product is safe under the recommended conditions of use without a prescription, effective for the proposed claims, and of high quality, and is mandatory. In addition, a licence issued on the basis of evidence of compliance with Good Manufacturing Practices to importers, manufacturers, packagers, and labellers of HMPs will certainly aid in reducing health-related risks. Such an effort should be in concert with WHO International Regulatory Cooperation for Herbal Medicines (IRCH), established in 2005 to protect and promote public health and safety [72].

There is also a strong need for scientific evidence of the pharmacological qualities and safety of herb-derived remedies employed for centuries as traditional medicines in these countries. This is particularly because sound knowledge of the mechanisms of actions and interactions is essential for a clinical risk assessment. In addition, the design of an appropriate postmarket pharmacovigilance system will help address the fatalities of herbal drugs. Surveillance for HMP-related adverse responses should consist mainly of prompting voluntary reporting from consumers and health care practitioners. It should be noted that even if the interactions between medicinal herbal products and drugs may be clinically insignificant, susceptibility to them may be enhanced by a wide variety of patient-related factors, such as the presence of multiple diseases, other pharmacotheapies, or genetic predisposition.

At the same time, it would be helpful to set up a national and/or regional accessible database to document the use of herbal medicines. Concurrently, efforts should be made to educate both healthcare professionals and patients about the use of herbal medicine. It should also be emphasised that besides its role in primary healthcare, traditional medicines have been and continue to be a strategic option in drug discovery [73].

The previously mentioned long-term strategies could certainly help to address the toxicological concern of herbal drugs in developing countries. But more immediate actions are also warranted and should be geared towards (1) greater communication between patients and physicians about the use of herbal medicine, (2) health care professional should be aware of herb-drug interactions and encourage patients to discuss herbal medicine use, (3) physicians should question patients about their use of herbal medicines, and (4) surveillance of HMP-related adverse responses should be
monitored. In the meantime, preclinical and clinical studies should be conducted to ascertain herb-drug interactions and government regulatory authority should put more efforts into natural health product regulations.

Conflict of Interests
The author declares that there is no conflict of interests.

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