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Review

Drug interactions in African herbal remedies

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Abstract

Herbal usage remains popular as an alternative or complementary form of treatment, especially in Africa. However, the misconception that herbal remedies are safe due to their "natural" origins jeopardizes human safety, as many different interactions can occur with concomitant use with other pharmaceuticals on top of potential inherent toxicity. Cytochrome P450 enzymes are highly polymorphic, and pose a problem for pharmaceutical drug tailoring to meet an individual's specific metabolic activity. The influence of herbal remedies further complicates this. The plants included in this review have been mainly researched for determining their effect on cytochrome P450 enzymes and P-glycoprotein drug transporters. Usage of herbal remedies, such as *Hypoxis hemerocallidea*, *Sutherlandia frutescens* and *Harpagophytum procumbens* is popular in Africa. The literature suggests that there is a potential for drug-herb interactions, which could occur through alterations in metabolism and transportation of drugs. Research has primarily been conducted in vitro, whereas in vivo data are lacking. Research concerning the effect of African herbals on drug metabolism should also be approached, as specific plants are especially popular in conjunction with certain treatments. Although these interactions can be beneficial, the harm they pose is just as great.

Keywords: African herbals; African potato; cytochrome P450; Devil's claw; herb-drug interactions; *Sutherlandia*.

Introduction

Traditional remedies are used by approximately 80% of the population in developing countries and are becoming increasingly common practice in developed areas (1). Owing to increased popularity the herbal remedy market is growing to a multimillion dollar industry (2, 3). Being one of the oldest known forms of therapy, each culture or country has created its own pharmacy of locally grown medicinal plants. Herbal medicinal products are easily accessible and can be found at informal markets, pharmacies, health-food stores or bought online (3). Even though the use of herbal remedies generally targets well-being there is an increased demand for immune and energy boosters, as well as detoxifiers (4). Herbal remedies are also used to treat various ailments (such as immune disorders, multidrug resistant microbial infections and carcinomas) due to the local abundance, cultural significance and inexpensive procurement, when compared to Western pharmaceuticals (5). As herbal remedies are considered "pure and natural" there is a belief that they are also "safe and harmless" (6, 7). This misconception does not mean they are non-toxic or even efficacious.

Herbal usage is often combined concomitantly with Western pharmaceuticals without regard for any interaction between the medications. This could lead to decreased efficacy or increased toxicity (7, 8). Owing to the complex matrix of phytochemical constituents the probability of affecting the pharmacodynamic and/or pharmacokinetic profile of a concomitant drug is high, therefore caution should be employed in dual usage (8). Although research is available concerning the interactions of some herbal preparations, it is limited and not always well-defined, and even less so for indigenous African herbal remedies. In this review paper, all relevant literature pertaining to herb-drug interactions on the African continent together with their mechanisms of action will be addressed.

Methods

The literature was obtained through use of Scopus, Medline and PubMed databases using the following search parameters, or combinations thereof: 'drug-herb', 'interaction', 'CYP', 'metabolism', 'adverse reaction', 'African', 'plant', 'extract', 'herbal' and 'remedy'. This included all articles published to date.

Results

Pharmacotherapy in Africa

The continent of Africa is burdened by a variety of diseases, such as HIV/AIDS, tuberculosis and malaria, among others (9, 10). Owing to this it is of utmost importance that African populations are made aware of and have access to benchmark treatments (11). As there is a definite correlation between the burden of disease and decreased economy, this further affects the population

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(9). Unfortunately owing to socioeconomic factors and others it is often not possible to achieve access to medication, and thus alternative or complementary treatment is necessary (9, 10). Surveys conducted in Dar es Salaam (Tanzania) (12) and South Africa (13) reported that 21% and 60% of the population consult traditional healers, respectively. Research concerning these remedies is generally limited to in vitro experimentation, and poses the possible risk of exposing the population to a burden of adverse events, more so when it is combined with pharmaceutical treatment (14). Although in vivo studies are sometimes performed, short- and long-term effects on interactions are not always clearly defined. Seeing as the therapeutic index of a drug is always strived in pharmacotherapy to limit toxicity and increase efficacy, the effect of interactions is extremely important for medications with narrow indices, such as most antiretroviral drugs (ARVs) (15, 16).

The use of traditional healers and medicines, as valuable as it might be, is questionable due to lack of scientific data supporting efficacy and safety of treatments, absence of guidelines for manufacturing, possible adulteration and misidentification of plants, lack of standardizing active ingredients and inappropriate packaging of products (10, 17, 18).

Drug-herb interactions

Pharmaceuticals, when in the presence of other compounds, can undergo a change in pharmacodynamic and/or pharmacokinetic profiles which influences their physiological response. Owing to the large quantity of compounds, present in a herbal preparation which is often unidentified, the likelihood of an interaction is much greater than that of single active ingredients (19–21). One cannot guarantee the concentrations, efficacy, safety or even the authenticity of these herbal remedies due to poor regulatory guidelines surrounding them (17, 21). Furthermore, patients tend not to disclose the use of complementary medicines to their healthcare providers (20).

Pharmacokinetic interactions By altering the absorption, distribution, metabolism or elimination of a drug the plasma concentration can be shifted outside of therapeutic limits, leading to possible subtherapeutic activity or toxicity (17, 22, 23).

Absorption and distribution Changes in the absorptive environment, such as pH, motility, induction/inhibition of drug transporters or addition of complexing factors could alter the absorption of a drug, affecting bioavailability and efficacy (24, 25). P-Glycoprotein, which actively pumps drugs out of cells through efflux, is found in various tissues, such as the kidney, liver, gut, blood-brain barrier and placenta (25–27). Efflux of drugs from the apical cells will result in changes in the bioavailability of a compound, by limiting absorption by the gut or decreasing biliary and/or renal clearance (15–17, 26, 28, 29). Approximately 50% of drugs are substrates for P-glycoprotein, as well as food additives and various toxins (16, 30, 31) and might function as modulators of xenobiotic (compounds usually foreign to body, such as pharmaceuticals) exposure to metabolizing enzymes (24).

Metabolism Interactions with enzymes could result in biotransformation, altering its ability to interact with a drug. One of the major metabolizing enzyme families of various classes of compounds (sterols, fatty acids, eicosanoids, vitamins) and xenobiotics is the human cytochrome P450 (CYP) family, consisting of 57 enzymes (32, 33). These enzymes evolved through copy number variation and mutation to assist in the metabolism of various endogenous and exogenous compounds, primarily increasing hydrophilicity for renal elimination (34). Approximately 90% of drug metabolism is due to CYP enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 (32), where subfamily CYP3A is thought to contribute 50%, and CYP2D6 approximately 20%–30% of all CYP-mediated xenobiotic metabolism (35–37). Metabolism of these drugs can either activate or deactivate the compound through derivatization, for example, oxidative, peroxidative or reductive processes (32, 34). Some procarcinogens and promutagens are also substrates, converting them to an active carcinogen/mutagen (38). The CYP3A subfamily contributes approximately 30% to CYP enzyme content of the liver and is widely spread in the intestinal tract, lung, kidney, breast and leukocytes (36, 39–43). Although induction of enzymes is generally a long-term process, inhibition can occur rapidly after exposure (24). By binding to a response element on promoter regions the preganane X receptor (PXR) and constitutive androstane/activated receptor, CAR, is able to modulate expression of CYP3A4 and P-glycoprotein (16, 44).

Although the CYP enzymes are considered the major drug metabolizers, other enzymes include uridine dinucleotide phosphate (UDP) glucoronosyl transferases and esterases, flavin-containing monooxygenases (FMO) and phase II enzymes leading to conjugation and hydrolysis (32, 45). The literature suggests that drug-induced FMO expression does not happen often; however, CYP induction or suppression is highly affected by a variety of compounds (8, 33, 45–47).

Elimination Alterations in the clearance of drugs will influence bioavailability and efficacy, such as the increased hydrophilicity and renal elimination (34). Factors affecting tubular secretion and absorption of drugs, or act as competition for these processes, will alter concentrations (24). Induction or inhibition of P-glycoprotein affects the speed at which drugs can be cleared through the biliary and renal systems (26, 28).

Pharmacodynamic interactions Potentiation (additive or synergistic effects) or antagonization of compounds can occur with the addition of a herbal remedy, increasing or decreasing the potency of the physiological effect, respectively (17, 23).

Genetic variation

Although the levels of CYP enzymes involved in normal physiological metabolism are generally stable, xenobiotic-metabolizing enzymes can differ greatly due to interindividual genetic variation. This leads to different metabolic

classes, ranging from poor to ultra-rapid metabolic activity (extensive metabolism being normal function) influencing the physiological effect of a drug (32, 48). Information regarding CYP alleles and their activity in vitro or in vivo has been compiled by the Human Cytochrome P450 Allele Nomenclature Committee and is available on its online database (49). Although a wide variety of reviews and studies describing the genetic variability of different populations are available, only certain groups will be focused on, based on their relevance to Africa.

It is expected that African populations might have a larger genetic diversity than other populations as a result of their extended evolutionary run, large effective population size and environmental influences, such as exposure to indigenous toxins (50, 51). In light of phenotype-genotype discordance observed in African-American populations, it is suggested that African pharmacogenomic studies could benefit African ancestries present in different countries, such as the USA (51).

CYP2C9 alleles *CYP2C9*2*, *CYP2C9*3*, *CYP2C9*5* and *CYP2C9*11* all result in a decreased enzymatic function. The Southern African population is untouched by these alleles, but they increase somewhat from Middle Africa, Western Africa and Eastern Africa. Defective alleles appear at a frequency of 25% in Northern Africa (11). Whereas *CYP2C9*2* are common to most populations, the *CYP2C9*3* allele is uncommon or absent in Africans and Caucasians (37).

Two alleles of *CYP2C19*2* and *CYP2C19*3* result in inactivation of the enzyme. Whereas these alleles were not detected in Middle Africa, they appear almost equally (11%–16%) in Western, Eastern and Northern Africa. Inactive alleles appear in almost a quarter of Southern African populations (11). *CYP2C19*3* is generally found in Caucasian populations, but rarely in Africans. Conversely, the *CYP2C19*8* and *CYP2C19*9* alleles are almost exclusive to African populations, although the effects remain unknown (37). *CYP2C19* alleles (reduced activity) are present in 3% of Caucasians and 20% in Asians (48). *CYP2C19*17*, an allele responsible for increased expression, was originally found in the Swedish population and Ethiopians (52), but has since been found at high frequency in many different populations including the Xhosa and Colored South Africans (53). These alleles have significant importance with regard to increased enzyme function.

Close to 80 different alleles exist for *CYP2D6*, where Caucasian populations present with approximately 7% defective *CYP2D6* genes, and 50% in Asians (48). High levels of polymorphisms are found in *CYP2D6*, and result in either inactivity (*CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*6* and *CYP2D6*4xN*), decreased (*CYP2D6*9*, *CYP2D6*10*, *CYP2D6*17*, *CYP2D6*29* and *CYP2D6*41*) or increased (*CYP2D6*1xN*, *CYP2D6*2xN*, *CYP2D6*10xN* and *CYP2D6*41xN*) activity. These latter alleles are spread at various frequencies across the continent. Inactivity is found highest in Western, Southern and Northern Africa, with lower frequencies occurring in Middle and Eastern populations. Decreased activity is highest in Eastern and Western populations. Increased activity is greatest in Northern Africa, whereas decreased activity is found in Eastern, Southern and Middle Africa. Western Africa contains low frequencies attributed to increased activity (11). Furthermore, *CYP2D6*4* and *CYP2D6*41* occurs at higher frequencies in Caucasian populations, whereas *CYP2D6*17* and *CYP2D6*29* is higher in Africans (37, 54). Although *CYP2D6*10* is uncommon to Africans and Caucasians, *CYP2D6*2* is more common (normal activity); whereas alleles *CYP2D6*4* and *CYP2D6*41* occur at a higher frequency in Caucasians than Africans (37). *CYP2D6*5* occurs in particularly high frequency in the Colored South African population (55, 56).

CYP3A4 and P-glycoprotein variation was found to be comparable between Caucasians, African-Americans, Chinese, Hispanic, Indian and Malaysian ethnicities (57). *CYP3A5* frequency is greater in African-American (60%) populations than in Caucasian and Asian groups (10%–30%), where the latter express *CYP3A5*3* at high rates (34). Homozygous CYP3A5*3 individuals express low-levels of *CYP3A5*, resulting in reduced clearance of substrate drugs (36, 58). Half of African-American populations express high-levels of *CYP3A5*1* alleles (36, 59). *CYP3A5*11* alleles are a rare mutation in Caucasians and result in significantly decreased catabolic activity of enzymes (36). Zimbabwean populations express *CYP3A5*3*, *CYP3A5*6* and *CYP3A5*7* alleles, although not *CYP3A5*1B*, *CYP3A5*1C*, *CYP3A5*2* and *CYP3A5*5* (60).

Caucasian populations are more prone to have dysfunctional *NAT1*4* alleles than Africans. *TPMT*3A* occurs more in Caucasians, whereas *TPMP*3C* are more commonly found in Africans (37). Transporter *SLCO1B1* (reduced function) is found to a greater extent in Caucasians, while having the lowest frequency in Africans, although the latter contain high frequencies of *SLCO1B1*9*. *SLCO1B2* occurs more frequently in Africans than Caucasians (37).

As reported, CYP enzymes are highly polymorphic and already pose problems for pharmaceutical drug tailoring to meet an individual's specific metabolic activity. The influence of herbal remedies further complicates this, as various examples are indicated in Table 1.

African herbals

***Hypoxis hemerocallidea* Firch.Mey. et Avé-Lall. (African potato, family Hypoxidaceae)** Contrary to its name, *H. hemerocallidea* (also referred to as *H. rooperi*) corms do not resemble a potato (74). It is found in South Africa, South America, Australia and Asia as perennial herbs with yellow star-shaped flowers, tuberous corms and multi-branched root systems. It generally grows in grasslands, meanders and mountain regions and survives well in high-stress environments (74, 75). It is a popular medicinal herb used to treat hypertension, diabetes, urinary tract infections, prostate hypertrophy and HIV/AIDS, among others (74, 76). In terms of phytochemicals the main constituent is hypoxoside, a norlignan diglucoside, which is often considered pharmacologically inactive due to its conversion in the gastrointestinal tract to the aglycone rooperol through bacterial β-glucosidase activity (28, 74). Rooperol exhibits anti-inflammatory and anticancer activity (28, 74). Sterols and

Table 1 Drugs substrate of CYP enzymes affected by African herbals.

CYP enzyme	Location	Drug substrate	Plants	References
17	Gonads, liver, adrenal cortex	Steroids	*A. linearis* (*Al*), *S. frutescens* (*Sf*)	(61–63)
19	Ovaries, placenta, brain, adipose	Androgens	*H. hemerocallidea* (*Hh*)	(28, 64)
21	Adrenal cortex	Steroids	*Al*, *Sf*	(61, 62, 65, 66)
11B1	Adrenal cortex	Steroids	*Sf*	(61, 67)
1A2	Liver	Acetaminophen, caffeine, estradiol, imipramine, ondansetron, procarcinogens, theophylline, warfarin	*Al*, *A. vera* (*Av*), *B. carteri* (*Bc*), *B. frereana* (*Bf*), *C. intermedia* (*Ci*), *C. sinensis* (*Cs*), *H. procumbens* (*Hp*)	(38, 48, 68–73)
2C8	Liver, kidney	Retinoids, taxol, docetaxol, fluvastatin, paclitaxel, warfarin, tolbutamide	*Bc*, *Bf*, *Hp*	(48, 68, 72, 73)
2C9	Liver	Diclofenac, flurbiprofen, non-nucleoside reverse transcriptase inhibitors, losartan, phenytoin, piroxicam, protease inhibitors, tolbutamide, torsemide, (S)-warfarin	*A. nilotica* (*An*), *A. robusta* (*Ar*), *A. salicifolia* (*As*), *Av*, *Bc*	(15, 16, 19, 48, 71–73)
2C19	Liver, heart	Diazepam, non-nucleoside reverse transcriptase inhibitors, (S)-mephenytoin, omeprazole, pentamidine, protease inhibitors, propranolol, (R)-warfarin	*An*, *Ar*, *As*, *Bc*, *Bf*, *C. anisata (Ca)*, *C. hildebrandtii (Ch)*, *E. buchananii (Eb)*, *J. multifa (Jm)*, *P. aquilinum (Pta)*, *S. birrea (Sb)*, *Spirostachys africana (Spa)*, *Sterculia africana (Sta)*, *T. holstii (Th)*	(15, 16, 19, 48, 72, 73)
2D6	Liver, brain, heart	Clozapine, codeine, desipramine, dextromethorphan, encainide, fluoxetine, haloperidol, imipramine, non-nucleoside reverse transcriptase inhibitors, nortriptyline, paroxetine, protease inhibitors, propafenone, propranolol, timolol	*An*, *Ar*, *As*, *Av*, *Bc*, *Bf*, *Ca*, *Ch*, *C. roseus* (*Cr*), *Eb*, *Hp*, *Jm*, *Pta*, *Sb*	(15, 16, 19, 47, 48, 68, 71–73)
2E1	Liver, lung, brain, endothelium, heart, bone marrow	Acetaminophen, carbamazepine, chlorozoxazone, clarithromycin, codeine, cyclosporin, dapsone, diazepam, enflurane, erythromycin, ethanol, felodipine, indinavir, lovastatin, midazolam, nifedipine, nitrosamine, tacrolimus	*Av*	(48, 71, 73)
3A4	Liver, GIT, kidney, lung, brain, endothelium, placenta, lymphocytes	Acetaminophen, carbamazepine, clarithromycin, cyclosporin, dapsone, diazepam, erythromycin, felodipine, indinavir, lidocaine, losartan, lovastatin, midazolam, nifedipine, quinidine, tacrolimus, taxol, verapamil	*A. cuspidatum* (*Ac*), *A. melegueta* (*Am*), *An*, *Ar*, *As*, *Av*, *Bc*, *Bf*, *Ca*, *Ch*, *Eb*, *H. abyssinica* (*Ha*), *Hh*, *Hp*, *J. curcas* (*Jc*), *Jm*, *L. multiflora* (*Lm*), *O. abyssinica* (*Oa*), *P. amarus* (*Pha*), *P. americana* (*Pea*), *Pta*, *P. gueneense* (*Pig*), *Sb*, *Sf*, *Spa*	(14, 19, 48, 68, 70, 72, 73)
3A5	Liver, GIT, kidney, lung, brain, endothelium, placenta, lymphocytes	Similar to 3A4	*Ac*, *Am*, *Ha*, *Hh*, *Jc*, *Lm*, *Oa*, *Pha*, *Pea*, *Pig*	(14, 28, 48, 73)
3A7	Fetus, placenta, liver	Similar to 3A4	*Ac*, *Am*, *C. olitorius* (*Co*), *Ha*, *Jc*, *Lm*, *M. lucida (Ml)*, *Oa*, *Pha*, *Pea*, *Pig*, *S. macrocarpon* (*Sm*), *T. triangulare* (*Tt*)	(14, 48, 73)

GIT: Gastrointestinal tract.

stanols, such as stigmasterol, stigmastanol and β-sitosterol are also present, although their medicinal importance within the extracts is not proven (74, 77). Pharmacological extracts have been shown to exhibit antinociceptive, anti-inflammatory, antidiabetic and antioxidant activity (74, 76). African potato extracts are considered safe for human consumption, as a phase I study did not find any significant clinical or physiological parameter changes and only minor gastrointestinal side effects in one individual (78). Bone marrow suppression has been reported, although it has been argued that this was due to extraction via toxic solvents (79, 80).

H. hemerocallidea extracts as well as commercial formulations containing the African potato and main constituents were subjected to CYP3A4, CYP3A5 and CYP19, as well as P-glycoprotein activity. Although hypoxoside did not significantly inhibit CYP enzymes, hypoxoside-containing extracts and formulations did result in inhibition. The influence of hypoxoside was thought to be unrelated. Rooperol showed potent inhibition, although its absence in extracts makes its direct effect unlikely (28, 74). In terms of sterols, only stigmasterol (the others being β-sitosterol and stigmastanol) inhibited CYP activity, as well as a formulation containing it. However, the presence of garlic in the latter formula could not be excluded as an inhibitory factor (28, 81, 82). Hypoxoside was a potent inducer of P-glycoprotein, as well as extracts and formulations containing it. Rooperol, however, did not have any noticeable effect (28).

Aqueous and ethanolic extracts have been shown to inhibit CYP3A4 activity (33%–86%) and activate PXR (two-fold) at concentrations of 100 mg/mL. Contrary to the above study it resulted in moderate (42%–51% relative to verapamil) P-glycoprotein inhibition (16).

Extracts (prepared according to ethnomedicinal guidelines) were found to decrease nevirapine efflux from Caco-2 intestinal cells in the basolateral-apical direction, indicating a possible increased bioavailability (29). These results concur with the inhibition of P-glycoprotein transporters reported above. Owing to its usage as complementary medicine to ARVs it could increase the adverse effect profiles.

***Sutherlandia frutescens* (L.) R.Br. (Cancer bush, family Fabaceae)** *S. frutescens* is a shrub found in South Africa with red flowers and bulbous pods that is well known for its variety of medicinal properties. Ethnomedicinally it is used for indigestion, colds, heart failure, urinary tract infections, cancer, HIV/AIDS and as an immunomodulater (61, 75, 83). *S. frutescens* contains a variety of biologically active compounds, such as L-canavanine, pinitol, γ-aminobutyric acid, flavonoids and triterpenoid glucosides (65, 75). Pharmacological extracts possess the ability to decrease HIV viral activity and decrease inflammation (61, 65, 84). Chronic use is well-tolerated and few adverse effects have been reported, which includes teratogenicity and abortions when ingested during pregnancy (75). *S. frutescens* treatment (as high as nine-fold the normal dosage) was found to be non-toxic in male vervet monkeys (85).

S. frutescens ethanolic and aqueous extracts were able to decrease CYP3A4 (64%–96%) and P-glycoprotein (19%–31%) activity, while activating PXR (2.2-fold) at 100 mg/mL (16). Extracts of *S. frutescens* (aqueous, methanolic and chloroform) inhibited CYP17, CYP21 and CYP11B1 to various degrees thereby affecting adrenal steroidogenesis, and resulting in decreased binding and conversion of progesterone and pregnenolone (65). Chloroform extracts resulted in the greatest inhibition indicating an influence on hydrophobic components, whereas hydrophilic compounds were not able to influence pregnenolone binding significantly (61).

L-Canavanine was able to significantly decrease P-glycoprotein efflux of nevirapine in Caco-2 intestinal cells, although the extract itself did not cause significant inhibition (even though a trend was seen) (29).

***Harpagophytum procumbens* DC (Devil's claw, Pedaliceae)** Devil's claw is a herb found in South Africa, Namibia and Botswana and is called so because of the claw-like hooks found on the fruits. Owing to the nature of its secondary roots, the plant is able to survive in unfriendly environments. Medicinally it is generally used to treat inflammatory conditions, bruises, malaria and indigestion (27, 86, 87). The main active constituents appear to be the iridoid glycosides (such as harpagoside), but appreciable levels of carbohydrates, aromatic acids, phytosterols (β-sitosterol and stigmasterol), flavonoids (kaempferol), triterpene and harpagoquinones are present in the plant (86–88). Pharmacologically it has been shown that Devil's claw is beneficial as an analgesic and anti-inflammatory for diseases, such as rheumatoid arthritis, although contradictory evidence does exist (87). Short- and long-term usage appears to be safe and well-tolerated, although mild gastrointestinal symptoms are sometimes reported. Drug-herb interactions with rheumatoid arthritis medication have not been reported, although the possibility does exist for other therapies (87).

Commercial preparations of *H. procumbens* not only inhibit P-glycoprotein efflux of calcein-AM from HK-2 proximal tubule cells but also decrease esterase activity. These effects were reported to be independent of harpagoside, the phytosterols β-sitosterol and stigmasterol (27, 28). However, flavonoids, such as kaempferol which has been shown to result in potent inhibition, could be involved. *H. procumbens* and harpagoside have been found to increase expression of P-glycoprotein transporters (27, 28). *H. procumbens* is a weak inhibitor of CYP1A2 and CYP2D6, but shows moderate inhibition of CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (68). Purpura and increased anticoagulant effect has been reported with concurrent anticoagulant use (89).

Herbal teas Teas are products of plant material soaked in boiling water and widely consumed. Many different types are present, but those specifically popular in Africa are Rooibos tea [*Aspalathus linearis* (Brum.f) Dahlg., family Fabaceae], Honeybush (*Cyclopia intermedia* Vent, family Fabaceae), black tea [*Camellia sinensis* (L.) Kuntze, Fabaceae] and bush tea (*Athrixia phylicoides* DC, family Asteraceae); this

popularity is not necessarily for medicinal value but also for enjoyment (90–92).

Polyphenolic compounds are known to decrease non-heme iron absorption due to the formation of insoluble complexes in the gut lumen (93). Although black tea has been shown to decrease iron absorption and Rooibos tea did not, this is controversial (90, 94). Polyphenolic compounds from *C. sinensis* have been reported to increase the biological activity of antimicrobial compounds, such as β-lactams and carbapenems (95, 96).

Although not established through experimentation it is theorized that the antimutagenic activity of Rooibos and Honeybush tea could be due to inhibition of CYP enzymes, decreasing the conversion of procarcinogens and promutagens to their more active forms (38). Similarly, green, black and Rooibos tea have been found to decrease mutagenicity of promutagens in V79 Chinese hamster lung fibroblasts (expressing rat CYP1A2 and sulfotransferase), indicating a possible inhibitory action on converting enzymes (69). Rooibos tea acts as an inhibitor of CYP21 and CYP17 activity, where the hydrophobic fraction induces a more potent effect than hydrophilic components (62). Honeybush tea stabilizes and interacts with CYP, decreasing mutagenic effects (97).

Rooibos and Honeybush teas were found to enhance the activity of cytosolic glutathione S-transferase-α and microsomal UDP-glucoronosyl transferase in male Fischer 344 rats, which could affect the metabolism of drugs and promutagens (98). A two week ingestion of *A. linearis* in male Sprague-Dawley rats significantly decreased plasma concentrations of oral midazolam and also increased intestinal CYP3A expression significantly. Intestinal and hepatic CYP3A activity was increased, although not to a significant degree. Flavonoids are thought to contribute to the activity, especially quercetin, although these could not be verified. As reported effects present with short-term usage, long-term use should be taken into account (99). Rooibos tea supplements have also been found to decrease CYP2C11 expression in male Sprague-Dawley rats (100).

***Aloe* genus (Aloe, Asphodelaceae)** *Aloe* includes more than 500 species of succulent plants, of which 160 are found in South Africa, such as *Aloe vera* (L.) Burm. f. and *Aloe ferox* Miller (101–104). Its uses include anti-inflammatory, diabetes, wound-healing and as a laxative (70). Active constituents include anthraquinones, carbohydrates, polysaccharides (such as acemannan), lipids, amino acids and sterol (104).

A. vera juice has been reported to promote expression of CYP1A2, CYP3A4 and multidrug resistant protein 1 (MDR1, P-glycoprotein), but has no significant effect on the P-glycoprotein transport of digoxin in vitro (70, 105). The anthraquinone, rhein, is an inhibitor of CYP2E1, CYP3A, CYP2C9, CYP1A2 and CYP2D6 in order of decreasing potency, and a substrate for MDR1 (71, 106).

A. vera extracts have been reported to increase the time vitamins C and E spend in the bloodstream by delaying the absorptive rate, possibly through protection by forming complexes with polyphenols (103). A component of *Aloe*, dihydrocoumarin, is able to bind to human serum albumin, one of the most prolific proteins found in the body and binder of various drugs (107, 108). This binding might release protein-bound drugs, increasing the bioavailability and effect. Research concerning the hydrogel formation of *Aloe* polysaccharides suggests that they could be used effectively as therapeutic releasing agents, for example, in chemotherapy (109). A single case report of intraoperative bleeding suggests *A. vera* has a herb-drug interaction with sevoflurane (110).

Other examples As research concerning African herbal remedies with potential drug-herb interactions is limited, negligible information is available for most plant species. The plants described below are included due to their effects on P-glycoprotein and CYP enzymes which could lead to possible drug-herb interactivity.

Deferme et al. (25) screened 43 Tanzanian plants for P-glycoprotein inhibitory activity in Caco-2 cells, reporting only two, *Annickia kummeriae* Engl. et Diels (Annonaceae) and *Acacia nilotica* (L.) Del. (Mimosaceae), with significant inhibitory effects, which thus has the potential to lead to herb-drug interactions. van den Bout-van den Beukel et al. (19) investigated the CYP inhibitory activity of 12 Tanzanian plants used for pneumonia and topical applications. All extracts inhibited CYP2C9 and CYP2C19, although only nine inhibited CYP2D6. *Sterculia africana* (Lour) Fiori (Sterculiaceae) was the only extract not able to inhibit CYP3A4 activity (substrate 7-benzyloxyquinolone), neither were *S. africana* and *Turraea holstii* Gurk. (Meliaceae) able to affect the same enzyme with substrate dibenzylfluorescein. *Cyphostemma hildebrandtii* (Gilg) Desc. (Vitaceae) was the most potent inhibiter of CYP3A4 with both substrates. PXR induction was noted for *S. africana*, *C. hildebrandtii*, *Sclerocarya birrea* Sond (Anacardiaceae), *Pteridium aquillinum* (L.) Kuhn (Dennsstraediaceae), *Clausena anisata* Oliv. (Rutaceae), *T. holstii*, *Elaeondendron buchannannii* Loes (Celastraceae), *Jatropha multifida* L. (Euphorbiaceae) and *Aguaria salicifolia* Oliv. (Ericaceae). Of these nine extracts, only *A. salicifolia*, *T. holstii* and *S. africana* significantly induced CYP3A4 mRNA production. Most of these plants are used for topical applications and should thus not pose any significant threat, although the in vivo use might result in significant changes in metabolism of CYP-metabolized drugs. The inhibition of CYP enzymes are expected to result in increased plasma concentrations, whereas the induction of PXR and CYP3A4 mRNA could increase drug metabolism and lead to subtherapeutic levels (19).

CYP3A subfamily activity was determined in 14 Western African plants (14). *Aframomum cuspidatum* Gagnep. (Zingiberaceae), *Aframomum melegueta* Roskoe (Zingiberaceae) and *Piper gueneense* Linn (Piperaceae) are used as adjuvants to increase flavor and effectiveness of herbal treatments; *Corchorus olitorius* Linn (Tiliaceae), *Solanum macrocarpon* Linn (Solanaceae) and *Talinum triangulare* (Jacq.) Willd (Portulacaceae) are food plants; and the rest are used medicinally to treat various ailments. Except for the food plants and *Morinda lucida* Benth (Rubiaceae), the rest inhibited CYP3A4 and CYP3A5 activity. *Harrisonia abyssinica* Oliv. (Simaroubaceae) and the adjuvants (for both

enzymes) and *Persea amarus* Mill (Lauraceae) (for CYP3A4) had the highest activity (14). All plants inhibited CYP3A7 activity, an enzyme expressed primarily in the fetus (slight expression found in certain adult individuals), to varying degrees (14, 111). The potent inhibition resulting from the adjuvants support their usage as a complementary plant in traditional medicine as the activity might increase the efficacy of other compounds. The poor activity found in the food plants, however, indicates good selection in dietary needs, as little interaction is expected. The inhibitory activity on CYP3A7 does, however, pose a threat for intake of these plants during pregnancy as affected metabolism might result in adverse effects (14).

The alkaloid, (–)-roemerine, isolated from *Annona senegalensis* Pers. (Annonaceae) increases toxicity of vinblastine possibly through the inhibition of substrate binding in P-glycoprotein, decreasing cellular efflux of the anticancer agent (112). Gum arabic from *Acacia senegal* Willd. (Fabaceae) has been reported to decrease the absorption of amoxicillin, possibly due to interactions with the fiber content (113, 114).

Catharanthus roseus (L.) G. Don (Apocynaceae), a potent inhibitor of CYP2D6, contains the active constituents vindoline, ajmalicine and serpentine (47). Vindoline and serpentine have been found to inhibit CYP3A4-mediated metabolism (115). Ajmalicine is a reversible inhibitor of CYP2D6, whereas serpentine is irreversible and mechanism-based (115–117). Frankincense (oleo gum-resin) from *Boswellia carteri* Birdw. (Burseraceae) and *Boswellia frereana* Birdw. (Burseraceae) is a potent inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (72).

Khat (*Catha edulis* Forsk., Celastraceae) is traditionally chewed to remedy fatigue and appetite (118). Three case reports surrounding individuals who had chewed khat more than 4 h before surgery reported that although no perioperative interactions occurred, effects were noted. One patient had delayed recovery from the anesthesia, one presented with perioperative sleepiness under spinal anesthesia and another required a relatively larger dosage to induce anesthesia. A greater reaction is expected should chewing occur <4 h before anesthesia (118). Khat reacts significantly with smoking to induce genotoxicity and is associated with increased blood pressure (119, 120). Khat chewing has also been found to decrease the bioavailability of amoxicillin and ampicillin (121).

Dietary supplements Dietary supplements include vitamins, herbal remedies and health tonics. Male Sprague-Dawley rats administered with 116 different supplements were assayed for CYP expression: 75% of the supplements affected at least one enzyme, whereas the remaining 25% left enzymes unaffected (100). CYP2C11 was inhibited by 51% of the supplements, whereas CYP1A2 was the most induced (21%). CYP2E1 and CYP3A1 (CYP3A4 in humans) were also moderately induced, by approximately 8%. CYP1A2, CYP2D1 (CYP2D6 in humans), as well as CYP2E1 and CYP3A1 were the least inhibited, whereas no induction was seen in CYP2C11 and CYP2D1 (100).

Herbal supplements and remedies not specific to Africa, but often used The African population is exposed to a variety of remedies and supplements, some which are not specific or even indigenous to their country, thus it is important to take their possible interactions into account. Former Health Minister of South Africa was an advocate for the use of beetroot, garlic, olive oil and lemon (among *H. hemerocallidea* and *S. frutescens*) as HIV/AIDS treatment (122). Although this was highly scrutinized their use still remains popular among rural populations, and thus the possible herb-drug interactions should be investigated. Herbal supplements, such as garlic, St. John's Wort and grapefruit elicit a wide variety of effects on drug metabolism which have been extensively reviewed (20, 21, 24, 26, 114).

Discussion and conclusions

Traditional remedies have been proven in the past to be effective treatments of ailments. Furthermore, the isolation and modification of various phytochemicals has led to the formation of our modern pharmacopeia (123). The misconception that herbal remedies are safe due to their "natural" origins jeopardizes human safety, as many different interactions can occur with concomitant use with other pharmaceuticals on top of potential inherent toxicity. Furthermore, poor regulatory guidelines concerning the manufacturing of remedies cannot guarantee the safety, efficacy and consistency of products. The lack of clinical data poses a bigger problem, as in vitro research does not necessarily reflect in vivo results. The investigation of extract concentrations that are physiologically improbable further intensifies this. It does appear, however, that many African plants used in traditional medicine have the potential of altering pharmacodynamic and pharmacokinetic properties of compounds, leading to questionable safety and efficacy. Although most research was carried out concerning ARV use in HIV/AIDS treatment, it can be extrapolated to other drug classes acting on the same CYP enzymes (Table 1).

Although the potential for adverse drug-herb interactions does exist and has been shown to occur with many supplements and remedies, the alternative is to exploit these interactions to decrease the amount of drugs needed to elicit effect. Through the use of pharmacokinetic and pharmacodynamic interactions one should be able to achieve the same clinical effect with a lower dose of a compound, thus also decreasing the patient cost (124). The three Tanzanian adjuvants assayed were shown to have great in vitro potential for drug-herb interactions (14). Although this does support their use as efficacy enhancers, one can only speculate to what extent it will enhance compounds in vivo. Also *A. vera* products could increase the bioavailability and plasma concentrations of vitamins (103). Exploitation of drug-herb interactions does require drug tailoring specific to each individual's genetic variability and interaction to herbals.

In conclusion, excluding certain herbal remedies (such as *H. hemerocallidea*, *S. frutescens* and *H. procumbens*) very few studies have been conducted to ascertain drug-herb

interaction potential in vitro or in vivo, with even less research in humans. Research concerning the effect of African herbals on specific drug metabolism should also be approached, as certain plants are especially popular in conjunction with certain treatments (such as African potato with ARV). Although these interactions can be beneficial, the harm they pose is just as great. Africa supports the use of traditional medicine to treat diseases and in a country burdened by various afflictions treated with numerous different compounds, it is imperative that further studies be done to limit the possibility of adverse reactions.

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