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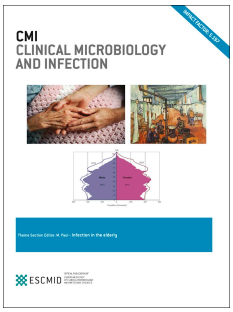

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Interactions between antiretroviral therapy and complementary and alternative medicine: A narrative review

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Abstract

Background: The use of complementary and alternative medicine including herbal medicine (phytotherapy), vitamins, minerals and food supplements is frequent among people living with HIV/AIDS (PLWHAs) who take antiretroviral (ARV) drugs, but often not known by their prescribing physicians. Some drug–supplement combinations may result in clinically meaningful interactions.

Objectives: In this literature review, we aimed to investigate the evidence for complementary and alternative medicine interactions with ARVs.

Sources: A bibliographic search of all *in vitro*, human studies and case reports of the PubMed database was performed to assess the risk of interactions between complementary and alternative self-medication products and ARVs. The "HIV drug interaction" (https://www.hiv-druginteractions.org) and "Natural medicines comprehensive database" (https://naturalmedicines.therapeuticresearch.com) interaction checkers were also analyzed.

Content: St John's wort, some forms of garlic, grapefruit and red rice yeast are known to have significant interaction and thus should not be co-administered, or should be used with caution with certain ARV classes. Data on other plant-based supplements come from *in vitro* studies or very small size *in vivo* studies and are thus insufficient to conclude the real *in vivo* impact in case of concomitant administration with ARVs. Some polyvalent minerals such as calcium, magnesium, and iron salts can reduce the absorption of integrase inhibitors by chelation. Potential interactions with vitamin C and quercetin with some ARVs should be noted and efficacy and tolerance of the treatment should be monitored.

Implications: This review shows the importance of screening all PLWHAs for complementary and alternative medicine use to prevent treatment failure or adverse effects related to an interaction with ARVs. Further human studies are warranted to describe the clinical

significance of *in vitro* interactions between numerous complementary and alternative medicine and ARVs.

Keywords: antiretroviral therapy; complementary medicine; alternative medicine; HIV

1. Introduction

Self-medication is an old and universal practice defined as the over-the-counter use of medicinal products that have received marketing authorization, with or without advice from the pharmacist. Wellness substances or food supplements (e.g. vitamins, minerals, trace elements, creatinine, amino acids, etc.) can also be considered as self-medication. People living with HIV/AIDS (PLWHAs) may practice self-medication because of the adverse effects of antiretroviral drugs (ARVs), to improve their well-being or to treat mild symptoms [1–3]. In case of interaction, the use of a self-medication products may alter ARVs' efficacy or increase their toxicity. Physicians usually underestimate this practice because patients rarely declare their self-medication, especially in case of complementary and alternative medicine. Between 50 to 80% of PLWHAs do not report their self-medication to their physicians and about 80% are self-medicating with at least one product [1,4,5].

The most commonly used therapeutic classes are non-steroidal analgesics/anti-inflammatory drugs (94.2%), drugs indicated for gastrointestinal disorders or used in ear-nose-throat disorders (63.5%), dietary supplements (54%), drugs indicated in skin disorders (31.8%), herbal medicine (20.2%) and anti-allergic drugs (20.2%) [6–8]. Main reasons given for self-medication are strengthening the body, boosting immunity to fight HIV, supplementing ARV therapy, delaying disease progression, relieving symptoms and countering adverse effects of ARVs [7–9]. Overall, 61-81% of users found a benefit in self-medication, particularly for improving quality of life [6–8]. In the USA, 35–75% of PLWHAs use complementary and alternative medicine to treat HIV-related symptoms [1,10–12] and utilization rates are likely to be even higher amongst some subgroups as Latino PLWHA [13].

Several studies have tried to establish a correlation between PLWHAs' use of self-medication and different socio-demographic, cultural and clinical-biological factors, with contradictory results. The main factors associated with self-medication use are female gender

[6,14–16], high educational background [7,9,14,15,17–19], high income [18], presence of adverse effects due to prescribed treatments [9,15], anxiety and depression [19] and pain [19]. However, no link between self-medication and health status has been observed [15] and it thus seems that there is no typical profile of PLWHAs using self-medication products. Therefore, it is necessary to systematically and thoroughly question each patient about self-medication and to be able to detect the presence of potential interactions. In this literature review, we focused on the risks of interactions between ARVs and so-called complementary and alternative self-medication products: herbal medicine (i.e. phytotherapy), vitamins, minerals and food supplements.

2. Methods

A literature review was conducted to assess the risk of interactions between complementary and alternative self-medication products and ARVs using both a bibliographic search in the PubMed database (including the terms "antiretroviral therapy" AND herb-drug interaction" OR "self-medication", "alternative therapies", "complementary therapies", "dietary supplements", "herbal medicines", "homeopathy") and the "HIV drug interaction" (https://www.hiv-druginteractions.org) and "Natural medicines comprehensive database" (https://naturalmedicines.therapeuticresearch.com) checkers. All *in vitro*, human studies and case reports published from 2000 through September 2019 were included. Only studies published in English were considered relevant for this review.

Interaction tables were developed based on the information collected and classified into four situations: (i) "contra-indicated"; (ii) "use with caution" (i.e. situations in which recommendations to adjust dosage or time administration have been made); (iii) "to be noted" (i.e. potential interactions without associated recommendations or based on *in vitro* data only) and (iv) "no interaction" (according to the available studies).

3. Interactions between ARVs and herbal medicine

Cytochromes P450 (CYP) are ubiquitous enzymes involved in the metabolism of diverse substrates and especially drugs. They are divided into families (CYP 1-2-3) and sub-families (CYP 1A - 2C - 2D - 3A). Drug metabolism is mostly hepatic and often involves several CYP. CYP3A4 is the most important in humans representing 30% to 50% of the liver content of CYP450, and also being present at the intestinal level (enterocytes). About half of the drugs metabolized are processed through CYP3A4 [20]. The intestinal absorption of certain drugs is regulated in enterocytes by CYP3A4 coupled with an efflux transporter, P-glycoprotein (P-gp). CYP3A4 directly metabolizes these drugs, while P-gp promotes their release into the intestinal lumen. P-gp, which belongs to the superfamily of ABC carriers (ATP-binding cassette), is one of the most important transporters involved in the bioavailability of xenobiotics in humans and promotes drug elimination in the urine and bile [21].

Although interactions with some plants such as St. John's wort (*Hypericum perforatum*) are well known [22], there are very few *in vivo* data on drug interactions with other plants. Furthermore, results from *in vitro* and *in vivo* studies are often conflicting [23] possibly due to lower *in vivo* plasma concentrations than those studied in *in vitro* assays because of poor bioavailability or significant clearance. *In vitro* studies may also not target the plant's active compounds or metabolites. Finally, for the same plant, interactions can be different depending on the variety, the concentration of active ingredients, the time of harvest or the part used.

Thus, study results are not always representative of real life. As a result, it is sometimes difficult to draw recommendations for clinical practice. **Table 1** summarizes the risk of interactions between herbal medicines and ARVs.

3.1. Plants with a known significant interaction with ARVs

3.1.1. St. John's wort (Hypericum perforatum)

St. John's wort is one of the first plants for which a drug interaction has been documented. It is a potent enzyme inducer, including CYP3A4 and P-glycoprotein (P-gp) [23], reducing plasma concentrations and thus the efficacy of many drugs [22].

The effect of St John's wort on CYP3A4 and P-gp has been described with indinavir with a 57% decrease in its area under the concentration time curve (AUC) and a 81% decrease in its extrapolated concentration eight hours after the administration [24]. An increase in drug clearance will decrease AUC.

A significant decrease in nevirapine exposure due to a 35% increase in its clearance has also been described in five patients with simultaneous use of St. John's wort [25]. For this reason, the use of this plant is contraindicated with protease inhibitors (PIs), non-nucleoside reverse transcriptase (RT) inhibitors (NNRTIs), dolutegravir, bictegravir, maraviroc and ritonavir- or cobicistat-boosted ARV therapy [22]. It should be noted that this effect may continue at least two weeks after St. John's wort is stopped [22].

3.1.2. Garlic (Allium sativum)

The garlic bulb, of which allicin is the main active component, has properties that are favourable for blood circulation and cardiovascular risk, in particular through a cholesterol-lowering effect [26]. Its use is not recommended in patients treated with PIs. Garlic, in capsules containing powdered bulb extract of garlic (600 mg) two times daily (1200 mg), has been shown to reduce saquinavir AUC by 51% and maximum (Cmax) and minimum (Cmin) plasma concentrations by approximately 50% in ten healthy volunteers. AUC and Cmax of saquinavir reached only 60 and 70% of baseline values respectively ten days after stopping garlic intake, underlining a lasting residual effect [26].

The mechanism of interaction is not fully elucidated but it is thought to be related to a decrease in the bioavailability of saquinavir. Data suggest that garlic increases saquinavir efflux via the induction of intestinal P-gp [27]. A potential inducing effect on intestinal CYP3A4 has also been suggested and then refuted [27]. Garlic is also a CYP3A4 inhibitor [23,28]. An *in vitro* study showed an increase in the efflux of darunavir and saquinavir from the enterocytes to the intestinal lumen when combined with garlic, even in the presence of ritonavir [29]. Therapeutic failure has been reported in a man treated with boosted atazanavir consuming about six cloves of fried garlic three times a week. The plasma concentration of atazanavir was sub-therapeutic despite good adherence to treatment and remained below normal ten days after the end of garlic consumption [30].

Garlic should therefore be used with caution in patients treated with PIs, maraviroc, NNRTIs, integrase inhibitors (INIs), abacavir and tenofovir.

3.1.3. Red rice yeast (Monascus purpureus)

Monascus purpureus is a purplish-red mold species that ferments on rice. In its form of red rice yeast, it is used for medical purposes because of its cholesterol-lowering action. This property is due to monacolines, that include a statin called monacolin K or lovastatin [31]. This statin is metabolized by CYP3A4 and is a substrate for P-gp. Its use is contraindicated in combination with CYP3A4 and P-gp inhibitors due to the risk of lovastatin overdose which may lead to rhabdomyolysis [32–34]. Between 2009 and 2013, 24 cases of nutrivigilance attributable to red rice yeast were reported to the National Agency for Food, Environmental and Occupational Health Safety (ANSES). These were mainly cases of myotoxicity and hepatotoxicity [31]. Its use is thus contra-indicated in combination with PIs or elvitegravir/cobicistat and not recommended when using other hepatotoxic ARVs, especially first-generation NNRTIs (nevirapine, efavirenz).

3.1.4. Grapefruit and citrus fruits (Citrus species)

Drug interactions with grapefruit are among the most studied. There is now evidence that grapefruit contains inhibitors of CYP3A4, P-gp and other transporters such as organic-anion-transporting polypeptides (OATPs) which form a family of influx transporters expressed in various tissues upon treatment with drugs and other xenobiotics [23]. Furanocoumarins, mainly bergamotine, are responsible for CYP inhibition [23,35]. They degrade CYP3A4, requiring its *de novo* synthesis to regain metabolic activity, which can take 24 hours [23]. Furanocoumarins act mainly on the intestinal isoenzyme of CYP3A4. Inhibition of CYP3A4 in the liver occurs after repeated doses or a single high-dose of grapefruit [23]. The pharmacokinetic profile of CYP3A4 substrates including PIs, NNRTIs, INIs with partial CYP3A4 metabolism (elvitegravir, bictegravir, dolutegravir) and maraviroc is therefore affected by grapefruit. Kupferschmidt *et al.* showed a 100% increase in the bioavailability of saquinavir when administered in combination with grapefruit juice but no effect on its clearance which is consistent with the inhibition of intestinal CYP3A4 by grapefruit juice [36]. A mouse model showed an increase in the bioavailability of lopinavir when administered with grapefruit. The effect of grapefruit was comparable to that obtained with ritonavir [37]. Conversely, indinavir is a poor substrate for intestinal CYP3A4 and is therefore unaffected [35]. The impact of grapefruit-mediated inhibition on the influx and efflux transporters is less known than for CYP3A4.

Notably, most of the studies were performed with grapefruit juice. The potential effect of grapefruit-based herbal medicine products (especially seed extract) on CYP3A4 substrates depends on the presence or absence of furanocoumarins and therefore on the manufacturing process. The inhibitory effect is variable according to different parameters, in particular the grapefruit variety [23]. The varying quantities of furanocoumarins (or variants) present in the different citrus fruits determines their ability to alter pharmacokinetic profiles of susceptible

drugs. Thus, *Citrus* species with low furanocoumarin content, including *C. sinensis*, *C. limon*, *C. aurantifolia* and *C. reticulata* do not inhibit the activity of CYP3A4. In addition to grapefruit (*C. paradisi*), Seville orange (*C. aurantium*) and pomelo (*C. grandis*) have been shown to inhibit intestinal CYP and increase the bioavailability of several CYP3A substrates. The clinical impact of the grapefruit interaction with ARVs is not known, but their association may alter ARV kinetics and lead to unpredictable and undesirable plasma concentrations. The clinical impact of the grapefruit interaction has been demonstrated with other molecules such as antihypertensive drugs [38]. Patients under ARVs should avoid grapefruit consumption and, if they do not, they should be monitored for biological and/or clinical adverse events.

Products from the Seville, or bitter, orange tree (*Citrus aurantium*) are mainly used for digestive disorders, and can be a source of drug interactions. Indeed, like grapefruit, bitter orange contains bergamotine, which inhibits intestinal CYP3A4. A study conducted in healthy volunteers found a similar effect of bitter orange juice and grapefruit juice on dextromethorphan kinetics. This study concluded that, like grapefruit, Seville orange inhibited CYP3A4 and intestinal P-gp [39]. In another study, co-administration of Seville orange juice caused a significant delay in reaching indinavir Cmax but did not alter other PK parameters [40]. This interaction was therefore not clinically significant. However, unlike other PIs, indinavir is a weak substrate for intestinal CYP3A4. As with grapefruit, other PIs, NNRTIs and maraviroc may be affected by bitter orange with a potential increase in their plasma concentrations.

Orange peel from the sweet orange tree (*Citrus sinensis*) is sometimes used to stimulate the appetite. Studies suggest that orange juice interacts with certain carriers. It contains hesperidin, which inhibits OATP1A2 *in vitro*. Since this transporter allows intestinal absorption of substrate drugs, their concomitant administration could decrease the plasma concentration of the substrate with a loss of therapeutic efficacy. This inhibition has a time-

limited effect, thus a four-hour interval between doses would be sufficient to avoid it [41]. An *in vivo* study also found a decrease in the bioavailability of fexofenadine, a substrate for OATP transporters, in the presence of orange juice. AUC and Cmax were decreased by 30% and 40%, respectively [42]. As a precautionary measure, the interaction should be considered with ARV substrates of this transporter (mainly saquinavir, lopinavir and darunavir). A four-hour delay between orange and ARVs consumption should therefore be recommended.

3.2. Plants with potential but insufficiently documented interaction with ARVs

Most data come from *in vitro* studies or very small size *in vivo* studies. These data, summarized in **Table 1,** are therefore insufficient to conclude the real *in vivo* impact in case of concomitant administration with ARVs. These associations should therefore "be noted" and the control of both efficacy and tolerance indicated.

3.2.1. *Ginkgo biloba*

Ginkgo biloba is widely used to improve concentration and memory and for the treatment of peripheral vascular pathologies such as venolymphatic insufficiency, hemorrhoidal attacks, dementia and depression. It is also known to modulate the activity of several CYPs and P-gp. However, studies differ as to whether it has an inducing or inhibitory effect. A few *in vitro* studies suggest an inhibitory effect on CYP3A4, 2D6, 2C9 and P-gp [43,44]. An *in vivo* study investigating the impact of *Ginkgo biloba* on raltegravir found no significant pharmacokinetic interaction [45]. In another *in vivo* study, an extract of *Ginkgo biloba* decreased midazolam AUC and Cmax by 34% and 31%, respectively, showing evidence for induction of CYP3A4. However, induction was not found when *Ginkgo biloba* was combined with ritonavir-boosted lopinavir, probably due to the potent inhibition of ritonavir [46]. It is therefore unlikely that ritonavir-boosted PIs are affected by the induction of CYP3A4. However, the risk of interaction with unboosted CYP3A4 substrate ARVs (maraviroc, NNRTIs, PIs) is plausible. Indeed, cases of interaction with efavirenz can be found in the literature. The first case

concerns a patient in virological failure with a resistance mutation following the introduction of *Ginkgo biloba*, despite having been stable for two years on the combination of efavirenz, emtricitabine and tenofovir. A decrease in efavirenz plasma concentration was observed yet the patient was compliant with their treatment. Induction of CYP3A4 and P-gp by terpenes contained in *Ginkgo biloba* was suspected [47]. In the second case, the patient had an undetectable viral load for ten years on the combination of zidovudine, lamivudine and efavirenz. Two months after the introduction of *Ginkgo biloba*, the viral load became detectable at 1350 copies/ml. One month after discontinuation of *Ginkgo biloba*, viral load returned to undetectable levels [48]. It is therefore not recommended to use *Ginkgo biloba* in patients treated with efavirenz. No clinical interactions with other ARVs have been reported. However, because of the potential for interaction, the combination should be used with caution and plasma concentrations should be monitored if possible.

3.2.2. *Echinacea*

Echinacea has immunostimulant properties, which are used in the treatment and prevention of upper respiratory tract infections. A study demonstrated *Echinacea* activity inhibiting intestinal CYP3A4 and CYP1A2 but inducing hepatic CYP3A4 [49]. Its effect on the substrate molecules depends on their relative extraction at the intestinal and hepatic levels. Although there are no clinical cases of interaction reported, caution is required when combining with drugs that are substrates for these enzymes (maraviroc, rilpivirine in particular). However, due to the inhibitory effect of ritonavir, the risk of significant interaction appears to be low with boosted PIs, as has been shown when combining *Echinacea* with boosted lopinavir or darunavir [50,51]. Another study demonstrated no change in the pharmacokinetic parameters of etravirine taken concomitantly with *Echinacea* [52].

Nevertheless, even in the absence of a described clinically significant interaction with ARVs, the European product monograph indicates that the use of *Echinacea* is not recommended for PLWHAs [53].

3.2.3. Ginseng (*Panax sp.*)

Ginseng root is used as a tonic to combat asthenia and improve alertness. It has also useful properties against hyperlipidemia, mellitus diabetes and high blood pressure. Finally, ginseng has immunostimulant properties, notably by increasing circulating T-cells.

It can induce CYP3A4, reducing midazolam exposure by 34% when taken concomitantly [54]. These data suggest that ginseng may decrease plasma concentrations and thus the efficacy of drugs metabolized by this cytochrome. However, other studies contradict this finding by showing either inhibition of CYP3A4 [55] or no effect [56,57]. These conflicting results may be due to the variability in the gensenoside composition of the different preparations studied. No changes in the pharmacokinetic parameters of unboosted indinavir were observed when combined with American ginseng (*Panax quinquefolius*) [58]. The pharmacokinetic parameters of lopinavir and ritonavir are also unaffected by the combination with *Panax ginseng* [59]. An interaction between ginseng and a ritonavir-boosted PI therefore seems unlikely. However, in the absence of data, ginseng should be used with caution with other CYP3A4-metabolized and unboosted ARVs such as maraviroc and NNRTIs.

There are no studies on the impact of ginseng on UGTs. Calderon et al. suggest that since the transcription of UGTs and CY3A4 is regulated by a common nuclear receptor, it is possible that ginseng modulates the metabolism of drugs that are substrates for UGTs [59]. One case of hepatic cytolysis with jaundice in an HCV co-infected HIV-positive patient has been reported. This was attributed to an interaction between raltegravir and self-medicated ginseng

started 39 days earlier. The mechanism of this interaction has not been elucidated and the patient had many associated risk factors [60].

3.2.4. Goldenseal (*Hydrastis canadensis*)

The active compounds in goldenseal are alkaloids called berberine and hydrastine. *In vitro*, goldenseal has inhibitory activity against CYP3A4, 2C9 and 2D6 [61,62]. Significant inhibition (approximately 40%) of CYP2D6 and 3A was also demonstrated in a study in healthy volunteers [63]. However, co-administration of hydrastine did not show a significant impact on the pharmacokinetics of indinavir, despite a dose approaching the maximum dose and standard levels of hydrastine and berberine. The authors concluded that hepatic CYP3A4 substrate drugs were unlikely to be affected by hydrastin. However, since indinavir is a poor substrate for intestinal CYP3A4, a risk of interaction at this level could not be excluded for other molecules [64]. In contrast, the pharmacokinetics of midazolam, a CYP3A4 substrate drug, is altered by goldenseal with increased AUC and delayed clearance [65]. Caution should therefore be exercised when combining goldenseal with ARVs that are substrates for these cytochromes.

4. Interactions between ARVs and vitamins

Only two interactions have been reported with vitamins. A significant change in coagulation parameters with an increase in bleeding effects has been observed upon concomitant administration of vitamin E and tipranavir in rats [66]. In patients treated with tipranavir capsules, any vitamin E supplementation should be used with caution and should not exceed a daily dose of 1200 IU of vitamin E. Moreover, since tipranavir oral solution already contains vitamin E as an excipient, no vitamin E supplementation should be combined with this formulation [67].

It has also been suggested that high doses of vitamin C could induce some cytochromes including CYP3A. A study conducted in seven healthy volunteers showed that concomitant administration of 1000 mg of vitamin C per day for seven days significantly reduced the Cmax of unboosted indinavir by 20% [68]. The clinical implications of this interaction and the possible effect of the addition of a low dose of ritonavir remain to be determined.

Other vitamins appear to be free of drug interactions. However, the use of multivitamins should be performed cautiously as they often contain minerals that can interact with ARVs.

5. Interactions between ARVs and minerals

Interactions between ARVs and minerals are summarized in **Table 2**. Some polyvalent minerals such as calcium, magnesium, and iron salts can reduce the absorption of INIs by chelation. To prevent the transfer of viral DNA into the genome of host cells, INIs bind to the magnesium ion present at the active integrase site. However, the active site of INIs may also bind any other polyvalent cation. Chelation prevents their penetration into target cells and their action against integrase. This results in a significant decrease in AUC and Cmax of INIs. However, the interaction and recommendations depend on the dose of the supplementation and the INI drug administered. Plasma dolutegravir AUC (o-∞), C_{max} and C_{24} were reduced by 39%, 37% and 39% respectively when co-administered with 1200 mg calcium carbonate (containing 480 mg elemental calcium) under fasting conditions and by 54%, 57% and 56% respectively when co-administered with 324 mg of ferrous fumarate (containing 107 mg elemental iron) under fasting conditions [69]. In this work, Song *et al* assumed that the different effect by iron *vs*. calcium supplements was due to solubility difference in the dolutegravir-iron chelation complex *vs*. the dolutegravir-calcium chelation complex. Another possible explanation could be a higher affinity of iron for the dolutegravir binding site. Moreover, in this study, co-administration of dolutegravir with a moderate-fat meal and

calcium carbonate or ferrous fumarate counteracted the interaction and provided plasma exposures comparable to dolutegravir alone under fasting conditions. Indeed, a moderate-fat meal increased dolutegravir AUC by 41% in the absence of added supplement without negative impact on safety [69] whereas it increased AUC by 78% in the presence of calcium carbonate and by 114% in the presence of ferrous fumarate [70]. Similarly, dolutegravir administered under fasting conditions two hours prior to administration of a single dose of calcium carbonate or ferrous fumarate resulted in plasma exposures comparable to dolutegravir alone [70]. Thus, calcium, magnesium, iron, zinc or multivitamin supplements should be co-administered with dolutegravir and food [70,71]. If they are not co-administered with a meal, they should be taken at least six hours before or two hours after taking dolutegravir [71], at least four hours before or after elvitegravir [72] or raltegravir [73–75], and two hours before or after bictegravir [76].

Patel *et al*. showed that co-administration of dolutegravir and a multivitamin supplement (162 mg of elemental calcium and 100 mg of magnesium per day, in addition to iron, zinc and copper) induced a modest effect on pharmacocinetic parameters [77]. Thus, they assumed that a clinically significant interaction was unlikely and dolutegravir could be co-administered with multivitamin supplements without therapeutic adaptation. These results are supported by Buchanan *et al*. who showed that the pharmacokinetic parameters of dolutegravir were not altered when it was dissolved in highly mineralized water [78]. However, case reports by Kang-Birken *et al*, showed that the combination of elvitegravir with a low dose of calcium (8 mg of elemental calcium per day) resulted in a decrease in plasma concentration with acquisition of resistance and virological failure in two patients [79] and Roberts *et al.* described another patient who experienced virological failure while receiving a raltegravir containing antiretroviral regimen with concomitant calcium administration [45]. A retrospective study of 152 patients treated with INIs (all molecules combined) and

simultaneously receiving polyvalent cations and/or multivitamin supplements showed that virological failure was observed in 46 (13%) patients, 15%, 11% and 18% respectively with dolutegravir, elvitegravir and raltegravir [80]. Patients taking polyvalent cation had 2.3 times the risk of treatment failure compared to patients without supplementation with any cation or multivitamin supplements [80]. To our knowledge, there is no described interaction between minerals and other ARV classes.

To mitigate the interaction between some INIs and minerals, it may be recommended that they be administered simultaneously with food as described above for dolutegravir and calcium, magnesium, iron, zinc or multivitamin supplements [70,71]. Bictegravir and supplements containing calcium or iron should be taken together with food [47]. Indeed, routine administration of bictegravir under fasting conditions simultaneously with, or two hours after, supplements containing calcium or iron is not recommended [47]. However, this is not necessary for all INIs. The bioavailability of elvitegravir is significantly increased when taken with a meal. However, low doses of calcium caused virological failure even when taken with meal [79]. So it can be assumed that taking it with a meal is not sufficient to overcome the interaction. Moreover, raltegravir taken with a meal alters the pharmacokinetics in a variable and unpredictable way [81].

It is important to note differences between raltegravir and high-dose raltegravir with respect to calcium interactions. Thus, coadministration of 1200 mg raltegravir once a day concomitantly with a calcium carbonate antacid (1000 mg) resulted in decreased raltegravir Cmax, AUC, C_{24} of 74%, 72%, 48%, respectively [82]. When calcium carbonate was administered 12 hours after raltegravir, a decrease in Cmax, AUC and C_{24} of 2%, 10% and 57%, respectively, was observed. This may be explained by the fact that the majority of the dose of raltegravir is absorbed more than 12 hours after administration. A less soluble raltegravir complex forms with calcium and is therefore not absorbed. Thus, administration of 400 mg of raltegravir

twice daily in the presence of calcium did not show any clinically significant interaction. Therefore, coadministration of calcium with high-dose raltegravir is not recommended.

6. Interactions between ARVs and various food supplements

The risks of interaction between various compounds present in food supplements and ARVs are poorly documented. To our knowledge, only quercetin has been shown to be a source of interaction. It can inhibit the activity of different cytochromes including CYP 2C9, 2D6, 3A and P-gp in patients receiving saquinavir 1200 mg three times daily (in 200 mg capsules) with food on days 1-11, and quercetin 500 mg (in capsules) three times daily on days 4-11 [83]. However, no clinical interactions have been reported between quercetin and ARVs. One study did not find any change in the pharmacokinetic parameters of saquinavir in ten patients [83]. However, since PIs are generally used with potent CYP3A4 inhibitors to boost them, a clinically significant effect of quercetin is unlikely with this ARV class.

These associations between quercetin and ARV substrates of cytochromes should therefore be noted and the control of ARV efficacy and tolerance are indicated in concerned patients.

7. Interactions between ARVs and protein supplements for muscle building

Products concerned are generally concentrated protein mixtures with varying levels of purification and concentration. Whey protein, one of the most popular, is a protein derived from bovine whey. Supplements used in the context of muscle building usually contain at least 80% protein and may contain corticosteroids, creatine and multivitamins. These types of supplements can be hepatotoxic [84] and should be avoided in patients with liver disease or treated with hepatotoxic ARVs (e.g. efavirenz, nevirapine, tipranavir, ritonavir, indinavir, atazanavir, didanosine, stavudine). The impact of protein supplements on renal function has always been controversial but does not appear to negatively affect kidney function in healthy adults [85]. Finally, a potential interaction with nephrotoxic ARVs such as tenofovir could be

suspected in people taking creatine with a history of kidney disease or those taking nephrotoxic drugs, due to an increased risk of renal dysfunction [86]. This association should be avoided or the renal function should be monitored to reduce potential adverse effects.

8. Conclusion

ARVs have progressed significantly with simplified treatment regimens and a better safety profile. However, the combination of several ARV molecules remains the most common treatment regimen, which increases the risk of interaction in the event of associated self-medication. Drug interactions with a significant clinical impact, i.e. likely to cause or increase adverse reactions or reduce the effectiveness of treatments, should be taken into account. Knowledge of the pharmacology and pharmacokinetics of the different ARV molecules allows anticipation of the risk of interactions.

Many pharmacokinetic interactions involve enzymes and metabolism transporters. However, for the same drug combination, several enzymes may be involved and it is often difficult to predict the effect of an interaction. In addition, genetic polymorphism that influences the expression of enzymes and transporters adds inter-individual variability in sensitivity to drug interactions [87].

While the marketing authorization dossier for self-medication medicinal products provides information on their enzymatic profile and interaction potential, there is a lack of *in vivo* data on the use of herbal medicine products and food supplements in combination with ARVs. PLWHAs should be systematically warned about the risks of self-medication and asked about their practice of self-medication, including herbal medicine, vitamins, minerals and other dietary supplements on a regular basis. This could be performed during medical follow-up consultation or by the pharmacist to avoid loss of ARV efficacy or an increase in adverse events that could lead to poor medication adherence or even discontinuation of treatment.

9. Author Contributions

JMM, IR and AS designed the project. CB, GLB, AS and PL wrote the manuscript. DL, HF and JPL reviewed the manuscript.

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11. Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables

Table 1 – Description of potential interactions between antiretroviral drugs and herbal medicine

Plants	ARVs	Interaction mechanisms	Recommendations	Nature of interaction	References
Bitter orange (*Citrus aurantium*)	NNRTIs, elvitegravir	Inhibition of intestinal CYP3A4	Risk of increasing the bioavailability of drugs. Patients should be monitored for adverse effects.	Use with caution	[88]
	abacavir, tenofovir, indinavir, raltegravir	Inhibition of P-gp			
	PIs, efavirenz, dolutegravir, bictegravir maraviroc	Inhibition of CYP3A4 and P-gp			
Borage (*Borago officinalis*)	Efavirenz, etravirine, nevirapine, fosamprenavir, tipranavir	Hepatotoxicity of borage metabolites increased in combination with CYP3A4 inducers	Liver function should be monitored.	Use with caution	[89]
Cancer bush (*Lessertia frutescens* or *Sutherlandia frutescens*)	Atazanavir	Inhibition of CYP3A4, 3A5 and P-gp	Risk of reducing the absorption and bioavailability of ARVs. Patients should be monitored for plasma concentration and viral load.	To be noted	[90]
Cat's claw (*Uncaria guianensis, U. tomentosa*)	PIs, delavirdine, efavirenz, etravirine, nevirapine, elvitegravir,	Inhibition of CYP3A4	Risk of increasing the levels of ARVs. Patients should be	To be noted	[91,92]

	dolutegravir		monitored for adverse effects.		
Cranberry (*Vaccinium macrocarpon*)	Nevirapine, rilpivirine, doravirine, elvitegravir	Inhibition of CYP3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[93]
	Abacavir, tenofovir, raltegravir	Inhibition of P-gp			
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Inhibition of CYP3A4 and P-gp			
	Etravirine	Inhibition of CYP 3A4 and 2C9			
Echinacea (*Echinacea purpurea*)	PIs, efavirenz, nevirapine, rilpivirine, doravirine, dolutegravir, elvitegravir, bictegravir, maraviroc	Inhibition of CP3A4 in the intestine and induction in the liver.	Unpredictable effect on ARV plasma levels and risk of increasing viral load. Patients should be monitored for viral load and adverse effects.	To be noted	[94]
		Marginal effect in the presence of a booster.			[51,95]
		No clinically significant interaction with etravirine			[96]
Evening primrose oil	PIs, delavirdine, efavirenz, etravirine, nevirapine, elvitegravir, dolutegravir	Inhibition of CYP3A4 and CYP2D6	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[92,97]

Garlic (*Allium sativum)*	Abacavir, tenofovir, INSTIs, NNRTIs, PIs, maraviroc	Induction of intestinal P-gp and CYP 3A4	Risk of reducing the absorption and bioavailability of ARVs. Patients should be monitored for plasma concentration and viral load.	Use with caution	[26–30]
Ginkgo *(Ginkgo biloba)*	Nevirapine, rilpivirine, doravirine, elvitegravir,	Effect on CYP3A4 (induction or inhibition)	Unpredictable effect on ARV plasma levels. Patients should be monitored for plasma concentration of ARVs and adverse effects.	Use with caution with Efavirenz To be noted for other ARVs	[43] [98] [46] [99] [100]
	Abacavir, Tenofovir	Effect on P-gp No *in vivo* effect on raltegravir			
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Effect on CYP3A4 and P-gp (inhibition or induction). Metabolism-inducing effect leading to virological failure showed with efavirenz in two clinical cases			
	Indinavir	Effect on CYP 3A4 and inhibition of CYP 2D6			
	Etravirine	Effect on CYP 3A4 and inhibition of CYP 2C9			
Ginseng (*Panax ginseng*)	PIs used without booster, NNRTIs, maraviroc, dolutegravir, elvitegravir, bictegravir	Inductive or inhibitory effect on CYP3A4 depending on the composition of gensenosides. Marginal effect without impact on the kinetics of antiretrovirals in the presence of a booster	Unpredictable effect on ARV plasma levels. Patients should be monitored to prevent treatment failure or adverse effects.	To be noted	[101] [102] [103] [104]

Goji (*Lycium barbarum*, *L. chinense*)	Etravirine	Inhibition of CYP2C9	Risk of increasing the levels of ARV. Patients should be monitored for adverse effects.	To be noted	[105]
Goldenseal (*Hydrastis canadensis*)	NNRTIs, PIs (except indinavir), dolutegravir, elvitegravir, bictegravir, maraviroc	Inhibition of intestinal CYP3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[106] [107] [63] [108] [109]
	Cobicistat, ritonavir, indinavir	Inhibition of CYP 3A4 and 2D6			
	Etravirine	Inhibition of CYP 3A4 and 2C9			
Grapefruit *(Citrus pardis, citrus maxima)*	PIs, NNRTIs, elvitegravir, bictegravir, dolutegravir, maraviroc	Inhibition of CYP 3A4 and P-gp	Risk of increasing the absorption and bioavailability of ARVs. Patients should reduce or avoid the consumption of grapefruit and be monitored for adverse effects	Use with caution	[36,37,40,110]
Green tea (*Camellia sinensis*)	NNRTIs, PIs, dolutegravir, elvitegravir, bictegravir, maraviroc	Inhibition of CYP3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[111] [112]
	Efavirenz, nevirapine	Inhibition of CYP 3A4 and 2B6			

Harpagophyton (*Harpagophytum procumbens*)	Nevirapine, rilpivirine, doravirine, elvitegravir	Inhibition of CYP3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[113] [114]
	Abacavir, tenofovir, raltegravir	Inhibition of P-gp			
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Inhibition of CYP3A4 and P-gp			
	Ritonavir, cobicistat, indinavir	Inhibition of CYP 3A4 and 2D6			
	Etravirine	Inhibition of CYP 3A4, 2C9 and 2C19			
Horse chestnut (*Aesculus hippocastanum*)	NNRTIs, elvitegravir	Inhibition of CYP3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[98]
	Abacavir, tenofovir, indinavir, raltegravir	Inhibition of P-gp			
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Inhibition of CYP3A4 and P-gp			
Horsetail (*Equisetum arvense*)	Lamivudine, zidovudine, efavirenz, emtricitabine, tenofovir,	Inhibition of CYP1A2 and CYP2D6	Risk of increasing viral load. Patients should be monitored for viral load.	To be noted	[115]
Moringa (*Moringa oleifera*)	Nevirapine, efavirenz	Inhibition of CYP3A4, 1A2, 2D6	Risk of increasing the levels of antiretroviral. Patients should be monitored for plasma	To be noted	[116]

			concentration of ARVs and adverse effects.		
Milk thistle (*Silybum marianum*)	Etravirine	Inhibition of CYP2C9	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[117]
Red rice yeast *(Monascus purpureus)*	PIs, elvitegravir/cobicistat	CYP3A4 and P-gp inhibitors increase myotoxicity and hepatotoxicity of red rice yeast	Do not combine due to the risk of myotoxicity and hepatotoxicity	Contra-indicated	[31–34]
	Efavirenz, nevirapine	Cumulative hepatotoxicity	Liver function should be monitored.	Use with caution	
Red vine (*Vitis vinifera)*	PIs, NNRTIs, dolutegravir, elvitegravir, bictegravir, maraviroc	Inhibition of CYP 2C9, 2D6 and 3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[102]
Saw palmetto (*Serenoa repens*)	NNRTIs, PIs, dolutegravir, elvitegravir, bictegravir, maraviroc	Inhibition of CYP3A4	Risk of increasing the levels of ARVs. Patients should be monitored for adverse effects.	To be noted	[23] [43]
	Cobicistat, ritonavir, indinavir	Inhibition of CYP 3A4 and 2D6			
	Etravirine	Inhibition des CYP 3A4 and 2C9			
Spirulina (*Arthrospira*	Etravirine	Inhibition of CYP2C9	Risk of increasing the level of ARVs. Patients	To be noted	[118]

platensis)			should be monitored for adverse effects.		
St. John's wort *(Hypericum perforatum)*	PI, NNRTIs, dolutegravir, bictegravir, elvitegravir/cobicistat, ritonavir, maraviroc	Induction of CYP 3A4 and P-gp	Do not combine due to risk of reducing plasma concentration with treatment failure.	Contra-indicated	[22,24,25,110]
Sweet orange (*Citrus sinensis*)	Saquinavir, lopinavir, darunavir	Inhibition of the OATP1A2 transporter allowing intestinal absorption of substrate drugs for four hours	Risk of decreased ARV uptake. Patients should be monitored for plasma concentration and viral load/CD4.	Use with caution	[41] [42]
Turmeric (*Curcuma longa*)	Indinavir, ritonavir, cobicistat	Concentration dependent inhibition of CYP2D6	Risk of increasing the level of ARVs. Patients should be monitored for adverse effects.	To be noted	[119]
	NNRTIs, PIs (except indinavir), dolutegravir, elvitegravir, bictegravir, cobicistat	Inhibition of intestinal CYP3A4			[120]
Valerian (*Valeriana officinalis*)	NNRTIs, elvitegravir	Inhibition of CYP3A4	Risk of increasing the level of ARVs. Patients should be monitored for adverse effects.	To be noted	[121]
	abacavir, tenofovir, raltegravir	Inhibition of P-gp			
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Inhibition of CYP3A4 and P-gp			
Wintergreen	Tenofovir	Cumulative renal toxicity with	Renal function should	To be noted	[122]

(*Gaultheria procumbens*)	salicylated derivatives due to their non-steroidal anti-inflammatory action	be monitored.

ARVs, antiretroviral drugs; NNRTIs, *non-nucleoside reverse transcriptase inhibitors;* PIs, protease inhibitors; INIs, integrase inhibitors.

Table 2 – Interactions between antiretroviral drugs and minerals

	INIs				
	Bictegravir	Dolutegravir	Elvitegravir	Raltegravir	Raltegravir HD
Calcium	Should be co-administered with a meal for calcium and iron Under fasted conditions, should be taken at least, two hours before or after bictegravir [76].	Should be co-administered with a meal [42]. Under fasted conditions, should be taken at least six hours before or two hours after taking dolutegravir [71].	Under fasted conditions, should be taken at least four hours before or after elvitegravir [72].	Under fasted conditions, should be taken at least four hours before or after raltegravir [73–75].	Not recommended
Iron					
Magnesium					
Manganese					
Zinc					

☐ No interaction ■ Use with caution INIs, Integrase inhibitors; HD : High Dose