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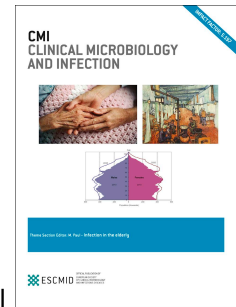
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1 **Interactions between antiretroviral therapy and complementary and**
2 **alternative medicine: A narrative review**

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31 **Abstract**

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

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

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

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

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

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

57

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

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Journal Pre-proof

60 **1. Introduction**

61 Self-medication is an old and universal practice defined as the over-the-counter use of
62 medicinal products that have received marketing authorization, with or without advice from
63 the pharmacist. Wellness substances or food supplements (e.g. vitamins, minerals, trace
64 elements, creatinine, amino acids, etc.) can also be considered as self-medication. People
65 living with HIV/AIDS (PLWHAs) may practice self-medication because of the adverse
66 effects of antiretroviral drugs (ARVs), to improve their well-being or to treat mild symptoms
67 [1–3]. In case of interaction, the use of a self-medication products may alter ARVs' efficacy
68 or increase their toxicity. Physicians usually underestimate this practice because patients
69 rarely declare their self-medication, especially in case of complementary and alternative
70 medicine. Between 50 to 80% of PLWHAs do not report their self-medication to their
71 physicians and about 80% are self-medicating with at least one product [1,4,5].

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

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

85 [6,14–16], high educational background [7,9,14,15,17–19], high income [18], presence of
86 adverse effects due to prescribed treatments [9,15], anxiety and depression [19] and pain [19].
87 However, no link between self-medication and health status has been observed [15] and it
88 thus seems that there is no typical profile of PLWHAs using self-medication products.
89 Therefore, it is necessary to systematically and thoroughly question each patient about self-
90 medication and to be able to detect the presence of potential interactions. In this literature
91 review, we focused on the risks of interactions between ARVs and so-called complementary
92 and alternative self-medication products: herbal medicine (i.e. phytotherapy), vitamins,
93 minerals and food supplements.

94

95 2. Methods

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

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

110 3. Interactions between ARVs and herbal medicine

111 Cytochromes P450 (CYP) are ubiquitous enzymes involved in the metabolism of diverse
112 substrates and especially drugs. They are divided into families (CYP 1-2-3) and sub-families
113 (CYP 1A - 2C - 2D - 3A). Drug metabolism is mostly hepatic and often involves several
114 CYP. CYP3A4 is the most important in humans representing 30% to 50% of the liver content
115 of CYP450, and also being present at the intestinal level (enterocytes). About half of the
116 drugs metabolized are processed through CYP3A4 [20]. The intestinal absorption of certain
117 drugs is regulated in enterocytes by CYP3A4 coupled with an efflux transporter, P-
118 glycoprotein (P-gp). CYP3A4 directly metabolizes these drugs, while P-gp promotes their
119 release into the intestinal lumen. P-gp, which belongs to the superfamily of ABC carriers
120 (ATP-binding cassette), is one of the most important transporters involved in the
121 bioavailability of xenobiotics in humans and promotes drug elimination in the urine and bile
122 [21].

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

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

133

134 3.1. Plants with a known significant interaction with ARVs

135 3.1.1. *St. John's wort (Hypericum perforatum)*

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

139 The effect of St John's wort on CYP3A4 and P-gp has been described with indinavir with a
140 57% decrease in its area under the concentration time curve (AUC) and a 81% decrease in its
141 extrapolated concentration eight hours after the administration [24]. An increase in drug
142 clearance will decrease AUC.

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

149 3.1.2. *Garlic (Allium sativum)*

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

158 The mechanism of interaction is not fully elucidated but it is thought to be related to a
159 decrease in the bioavailability of saquinavir. Data suggest that garlic increases saquinavir
160 efflux via the induction of intestinal P-gp [27]. A potential inducing effect on intestinal
161 CYP3A4 has also been suggested and then refuted [27]. Garlic is also a CYP3A4 inhibitor
162 [23,28]. An *in vitro* study showed an increase in the efflux of darunavir and saquinavir from
163 the enterocytes to the intestinal lumen when combined with garlic, even in the presence of
164 ritonavir [29]. Therapeutic failure has been reported in a man treated with boosted atazanavir
165 consuming about six cloves of fried garlic three times a week. The plasma concentration of
166 atazanavir was sub-therapeutic despite good adherence to treatment and remained below
167 normal ten days after the end of garlic consumption [30].
168 Garlic should therefore be used with caution in patients treated with PIs, maraviroc, NNRTIs,
169 integrase inhibitors (INIs), abacavir and tenofovir.

170 3.1.3. Red rice yeast (*Monascus purpureus*)

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

182 3.1.4. Grapefruit and citrus fruits (*Citrus species*)

183 Drug interactions with grapefruit are among the most studied. There is now evidence that
184 grapefruit contains inhibitors of CYP3A4, P-gp and other transporters such as organic-anion-
185 transporting polypeptides (OATPs) which form a family of influx transporters expressed in
186 various tissues upon treatment with drugs and other xenobiotics [23]. Furanocoumarins,
187 mainly bergamotone, are responsible for CYP inhibition [23,35]. They degrade CYP3A4,
188 requiring its *de novo* synthesis to regain metabolic activity, which can take 24 hours [23].
189 Furanocoumarins act mainly on the intestinal isoenzyme of CYP3A4. Inhibition of CYP3A4
190 in the liver occurs after repeated doses or a single high-dose of grapefruit [23]. The
191 pharmacokinetic profile of CYP3A4 substrates including PIs, NNRTIs, INIs with partial
192 CYP3A4 metabolism (elvitegravir, bictegravir, dolutegravir) and maraviroc is therefore
193 affected by grapefruit. Kupferschmidt *et al.* showed a 100% increase in the bioavailability of
194 saquinavir when administered in combination with grapefruit juice but no effect on its
195 clearance which is consistent with the inhibition of intestinal CYP3A4 by grapefruit juice
196 [36]. A mouse model showed an increase in the bioavailability of lopinavir when
197 administered with grapefruit. The effect of grapefruit was comparable to that obtained with
198 ritonavir [37]. Conversely, indinavir is a poor substrate for intestinal CYP3A4 and is therefore
199 unaffected [35]. The impact of grapefruit-mediated inhibition on the influx and efflux
200 transporters is less known than for CYP3A4.

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

207 drugs. Thus, *Citrus* species with low furanocoumarin content, including *C. sinensis*, *C. limon*,
208 *C. aurantifolia* and *C. reticulata* do not inhibit the activity of CYP3A4. In addition to
209 grapefruit (*C. paradisi*), Seville orange (*C. aurantium*) and pomelo (*C. grandis*) have been
210 shown to inhibit intestinal CYP and increase the bioavailability of several CYP3A substrates.
211 The clinical impact of the grapefruit interaction with ARVs is not known, but their association
212 may alter ARV kinetics and lead to unpredictable and undesirable plasma concentrations. The
213 clinical impact of the grapefruit interaction has been demonstrated with other molecules such
214 as antihypertensive drugs [38]. Patients under ARVs should avoid grapefruit consumption
215 and, if they do not, they should be monitored for biological and/or clinical adverse events.
216 Products from the Seville, or bitter, orange tree (*Citrus aurantium*) are mainly used for
217 digestive disorders, and can be a source of drug interactions. Indeed, like grapefruit, bitter
218 orange contains bergamotone, which inhibits intestinal CYP3A4. A study conducted in
219 healthy volunteers found a similar effect of bitter orange juice and grapefruit juice on
220 dextromethorphan kinetics. This study concluded that, like grapefruit, Seville orange inhibited
221 CYP3A4 and intestinal P-gp [39]. In another study, co-administration of Seville orange juice
222 caused a significant delay in reaching indinavir C_{max} but did not alter other PK parameters
223 [40]. This interaction was therefore not clinically significant. However, unlike other PIs,
224 indinavir is a weak substrate for intestinal CYP3A4. As with grapefruit, other PIs, NNRTIs
225 and maraviroc may be affected by bitter orange with a potential increase in their plasma
226 concentrations.

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

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

238 3.2. Plants with potential but insufficiently documented interaction with ARVs

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

243 3.2.1. *Ginkgo biloba*

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

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

269

270 3.2.2. *Echinacea*

271 *Echinacea* has immunostimulant properties, which are used in the treatment and prevention of
272 upper respiratory tract infections. A study demonstrated *Echinacea* activity inhibiting
273 intestinal CYP3A4 and CYP1A2 but inducing hepatic CYP3A4 [49]. Its effect on the
274 substrate molecules depends on their relative extraction at the intestinal and hepatic levels.
275 Although there are no clinical cases of interaction reported, caution is required when
276 combining with drugs that are substrates for these enzymes (maraviroc, rilpivirine in
277 particular). However, due to the inhibitory effect of ritonavir, the risk of significant
278 interaction appears to be low with boosted PIs, as has been shown when combining
279 *Echinacea* with boosted lopinavir or darunavir [50,51]. Another study demonstrated no
280 change in the pharmacokinetic parameters of etravirine taken concomitantly with *Echinacea*
281 [52].

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

285

286 3.2.3. Ginseng (*Panax sp.*)

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

290 It can induce CYP3A4, reducing midazolam exposure by 34% when taken concomitantly
291 [54]. These data suggest that ginseng may decrease plasma concentrations and thus the
292 efficacy of drugs metabolized by this cytochrome. However, other studies contradict this
293 finding by showing either inhibition of CYP3A4 [55] or no effect [56,57]. These conflicting
294 results may be due to the variability in the ginsenoside composition of the different
295 preparations studied. No changes in the pharmacokinetic parameters of unboosted indinavir
296 were observed when combined with American ginseng (*Panax quinquefolius*) [58]. The
297 pharmacokinetic parameters of lopinavir and ritonavir are also unaffected by the combination
298 with *Panax ginseng* [59]. An interaction between ginseng and a ritonavir-boosted PI therefore
299 seems unlikely. However, in the absence of data, ginseng should be used with caution with
300 other CYP3A4-metabolized and unboosted ARVs such as maraviroc and NNRTIs.

301 There are no studies on the impact of ginseng on UGTs. Calderon et al. suggest that since the
302 transcription of UGTs and CYP3A4 is regulated by a common nuclear receptor, it is possible
303 that ginseng modulates the metabolism of drugs that are substrates for UGTs [59]. One case
304 of hepatic cytolysis with jaundice in an HCV co-infected HIV-positive patient has been
305 reported. This was attributed to an interaction between raltegravir and self-medicated ginseng

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

308

309 3.2.4. Goldenseal (*Hydrastis canadensis*)

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

322

323 4. Interactions between ARVs and vitamins

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

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

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

338

339 **5. Interactions between ARVs and minerals**

340 Interactions between ARVs and minerals are summarized in **Table 2**. Some polyvalent
341 minerals such as calcium, magnesium, and iron salts can reduce the absorption of INIs by
342 chelation. To prevent the transfer of viral DNA into the genome of host cells, INIs bind to the
343 magnesium ion present at the active integrase site. However, the active site of INIs may also
344 bind any other polyvalent cation. Chelation prevents their penetration into target cells and
345 their action against integrase. This results in a significant decrease in AUC and C_{max} of INIs.
346 However, the interaction and recommendations depend on the dose of the supplementation
347 and the INI drug administered. Plasma dolutegravir AUC (0-∞), C_{max} and C₂₄ were reduced
348 by 39%, 37% and 39% respectively when co-administered with 1200 mg calcium carbonate
349 (containing 480 mg elemental calcium) under fasting conditions and by 54%, 57% and 56%
350 respectively when co-administered with 324 mg of ferrous fumarate (containing 107 mg
351 elemental iron) under fasting conditions [69]. In this work, Song *et al* assumed that the
352 different effect by iron *vs.* calcium supplements was due to solubility difference in the
353 dolutegravir-iron chelation complex *vs.* the dolutegravir-calcium chelation complex. Another
354 possible explanation could be a higher affinity of iron for the dolutegravir binding site.
355 Moreover, in this study, co-administration of dolutegravir with a moderate-fat meal and

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

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

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

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

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

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

408 **6. Interactions between ARVs and various food supplements**

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

420 **7. Interactions between ARVs and protein supplements for muscle building**

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

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

433

434 **8. Conclusion**

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

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

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

455

456 9. Author Contributions

457 JMM, IR and AS designed the project. CB, GLB, AS and PL wrote the manuscript. DL, HF
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463 11. Conflict of interest

464 The authors declare that the research was conducted in the absence of any commercial or
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466

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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 (<i>Citrus aurantium</i>)	NNRTIs, elvitegravir	Inhibition of intestinal CYP3A4	Risk of increasing the bioavailability of drugs.	Use with caution	[88]
	abacavir, tenofovir, indinavir, raltegravir	Inhibition of P-gp			
	PIs, efavirenz, dolutegravir, bictegravir maraviroc	Inhibition of CYP3A4 and P-gp	Patients should be monitored for adverse effects.		
Borage (<i>Borago officinalis</i>)	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 (<i>Lessertia frutescens</i> or <i>Sutherlandia frutescens</i>)	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 (<i>Uncaria guianensis</i> , <i>U. tomentosa</i>)	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 (<i>Vaccinium macrocarpon</i>)	Nevirapine, rilpivirine, doravirine, elvitegravir	Inhibition of CYP3A4	Risk of increasing the levels of ARVs.	To be noted	[93]
	Abacavir, tenofovir, raltegravir	Inhibition of P-gp	Patients should be monitored for adverse effects.		
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Inhibition of CYP3A4 and P-gp			
	Etravirine	Inhibition of CYP 3A4 and 2C9			
Echinacea (<i>Echinacea purpurea</i>)	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 (<i>Allium sativum</i>)	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 (<i>Ginkgo biloba</i>)	Nevirapine, rilpivirine, doravirine, elvitegravir,	Effect on CYP3A4 (induction or inhibition)	Unpredictable effect on ARV plasma levels.	Use with caution with	[43]
	Abacavir, Tenofovir	Effect on P-gp No <i>in vivo</i> effect on raltegravir	Patients should be monitored for plasma concentration of ARVs and adverse effects.	Efavirenz To be noted for other ARVs	[98] [46] [99]
	PIs, efavirenz, dolutegravir, bicitegravir, maraviroc	Effect on CYP3A4 and P-gp (inhibition or induction). Metabolism-inducing effect leading to virological failure showed with efavirenz in two clinical cases			[100]
	Indinavir	Effect on CYP 3A4 and inhibition of CYP 2D6			
	Etravirine	Effect on CYP 3A4 and inhibition of CYP 2C9			
Ginseng (<i>Panax ginseng</i>)	PIs used without booster, NNRTIs, maraviroc, dolutegravir, elvitegravir, bicitegravir	Inductive or inhibitory effect on CYP3A4 depending on the composition of ginsenosides. 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 (<i>Lycium barbarum</i> , <i>L. chinense</i>)	Etravirine	Inhibition of CYP2C9	Risk of increasing the levels of ARV. Patients should be monitored for adverse effects.	To be noted	[105]
Goldenseal (<i>Hydrastis canadensis</i>)	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 (<i>Citrus pardis</i> , <i>citrus maxima</i>)	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	[36,37,40,10]
Green tea (<i>Camellia sinensis</i>)	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 (<i>Harpagophytum procumbens</i>)	Nevirapine, rilpivirine, doravirine, elvitegravir	Inhibition of CYP3A4	Risk of increasing the levels of ARVs.	To be noted	[113]
	Abacavir, tenofovir, raltegravir	Inhibition of P-gp	Patients should be monitored for adverse effects.		[114]
	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 (<i>Aesculus hippocastanum</i>)	NNRTIs, elvitegravir	Inhibition of CYP3A4	Risk of increasing the levels of ARVs.	To be noted	[98]
	Abacavir, tenofovir, indinavir, raltegravir	Inhibition of P-gp	Patients should be monitored for adverse effects.		
	PIs, efavirenz, dolutegravir, bictegravir, maraviroc	Inhibition of CYP3A4 and P-gp			
Horsetail (<i>Equisetum arvense</i>)	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 (<i>Moringa oleifera</i>)	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 (<i>Silybum marianum</i>)	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 (<i>Monascus purpureus</i>)	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 (<i>Vitis vinifera</i>)	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 (<i>Serenoa repens</i>)	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 (<i>Arthrospira</i>)	Etravirine	Inhibition of CYP2C9	Risk of increasing the level of ARVs. Patients	To be noted	[118]

<i>platensis</i>)			should be monitored for adverse effects.		
St. John's wort (<i>Hypericum perforatum</i>)	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	[22,24,25,10]
Sweet orange (<i>Citrus sinensis</i>)	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 (<i>Curcuma longa</i>)	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 (<i>Valeriana officinalis</i>)	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

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