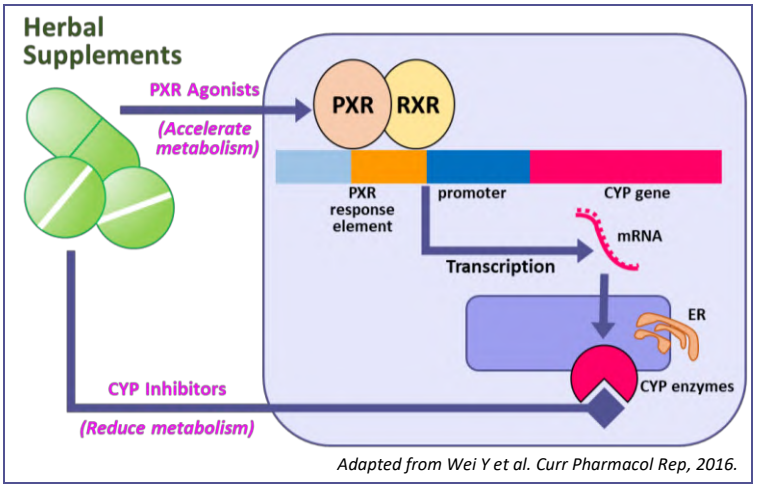
Drug-drug interactions with herbal and mineral supplements

Drug-Drug Interactions with Herbal Supplements

- The main mechanism of drug-drug interactions with herbal supplements is **induction**.
- Several herbal supplements are activators of pregnane X receptor (PXR) whose function is to regulate expression of drug metabolizing enzymes and drug transporters.
- Upon drug binding, PXR heterodimerizes with the retinoic acid receptor (RXR) and translocates in the hepatocyte nucleus to activate transcription of drug metabolizing enzymes or drug transporters. An increase in synthesis results in more enzymes/transporters being available to induce drug metabolism/transport.



Adapted from Wei Y et al. Curr Pharmacol Rep, 2016.

Herbal supplements with inducing properties include:

- African potato
- Garlic
- Gingko biloba (inconsistent data)
- Guggulsterone
- Hops
- Liquorice (modest effect)
- Malabar nut tree
- St John's wort (significant induction with >1 mg/day hyperforin)

Interactions between ARVs and Herbal Supplements

	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV oral	FTR	LEN	MVC	BIC/ F/TAF	CAB oral	CAB/ RPV	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	FTC/ TAF	FTC/ TDF
Herbal Supplements																						
African potato	↔	↔	↔	↔	↔	⇓	↔	↔	↔	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	⇓	↔	⇓	⇓a	↔
Cat's claw	⇑	⇑	⇑	⇑	⇑	⇑	⇑	⇑	⇑	⇑	⇑	⇑	⇑	↔	↔	⇑	↔	⇑	⇑	↔	↔	↔
Cubeb pepper	↔	↔	↔	↔	↔	⇑	↔	↔	↔	⇑	↔	⇑	⇑	↔	↔	⇑	↔	⇑	⇑	↔	⇑a	⇑ a
Echinacea	↔	↔	↔	↔	↔	⇓	↔	↔	↔	⇓	⇓	↔	⇓	⇓	↔	⇓	↔	↔	↔	↔	↔	↔
Garlic	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	⇓	⇓	⇓	↔	⇓a	↔
Ginger	↔	↔	↔	↔	↔	⇑	↔	↔	↔	⇑	↔	↔	⇑	↔	↔	⇑	↔	↔	↔	↔	↔	↔
Gingko biloba	↔	↔	↔	↔	↔	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔	↔	↔
Grapefruit juice	↔	↔	↔	↔	↔	⇑	↔	↔	↔	⇑	↔	↔	⇑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Green tea extracts	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇑	? b	↔	↔	↔	? b	? b	↔	? b	? b
Guggulsterone	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	⇓	↔	⇓	⇓	↔	↔	↔
Hops	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	⇓	⇓	↔	⇓a	↔
Inula racemosa	↔	↔	↔	↔	↔	⇑	↔	↔	↔	⇑	⇑	↔	⇑	↔	↔	⇑	↔	↔	↔	↔	↔	↔
Liquorice	↔	↔	↔	↔	↔	⇓	↔	↔	↔	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	⇑	⇑	↔	⇑a	⇑a
Malabar nut tree	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	⇓	↔	⇓	⇓	⇓	⇓	⇓	↔	↔
Menthol	↔	↔	↔	↔	↔	⇑	↔	↔	↔	⇑	⇑	↔	⇑	↔	↔	⇑	↔	↔	↔	↔	↔	↔
Quercetin	⇑?	⇑?	⇑?	⇑?	⇑?	⇑	⇑?	⇑?	⇑?	⇑	↔	↔	⇑	↔	↔	⇑	↔	↔	↔	↔	↔	↔
Red yeast rice	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔
Seville orange juice	↔	↔	↔	↔	↔	⇑	↔	↔	↔	⇑	↔	↔	⇑	↔	↔	↔	↔	↔	↔	↔	↔	↔
St John's wort	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓c	⇓	⇓c	⇓c	⇓	⇓c,d	↔

No clinically significant interactions expected with Aloe vera, Black cohosh, Eucalyptus globulus, Ginseng, Goldenseal root, Milk thistle, Saw palmetto, Turmeric, Valerian.

Interactions with CAB/RPV long acting injections
Pharmacokinetic interactions shown are mostly with RPV.

Interactions with Lenacapavir
Residual LEN may affect exposure of sensitive CYP3A4 substrates initiated within 9 months after stopping subcutaneous LEN.

Interactions with Ibalizumab
None

Interactions with Abacavir (ABC), Lamivudine (3TC), Tenofovir-DF (TDF) or Zidovudine (ZDV)
ABC: No clinically relevant interactions expected.
3TC: No clinically relevant interactions expected.
TDF: The effect of green tea on tenofovir is unclear (b).
TDF: Caution with Cat's claw and Cubeb pepper as tenofovir systemic concentrations could potentially increase.
ZDV: No clinically relevant interactions expected.

Colour Legend
- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dose adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity. No *a priori* dosage adjustment is recommended.

Text Legend
- ↔ No significant effect
- ↑ Potential increased exposure of the supplement
- ↓ Potential decreased exposure of the supplement
- ⇑ Potential increased exposure of HIV drug
- ⇓ Potential decreased exposure of HIV drug

Notes
a No effect on emtricitabine expected.
b The effect on tenofovir is unclear as green tea extracts appeared to inhibit P-gp in vivo, but a contradictory effect was observed in vivo.
c Coadministration is not recommended in product label. However, a low risk of a clinically relevant pharmacokinetic interaction has been shown with low-hyperforin formulations (<1 mg/day) of St John's Wort (hyperforin is the constituent responsible for induction of CYPs and P-gp). Coadministration may be considered with St John's wort formulations that clearly state the hyperforin content and which have a total daily hyperforin dose of 1 mg or less.
d No effect on emtricitabine is expected, but tenofovir alafenamide concentrations may decrease which may result in loss of therapeutic effect and development of resistance.

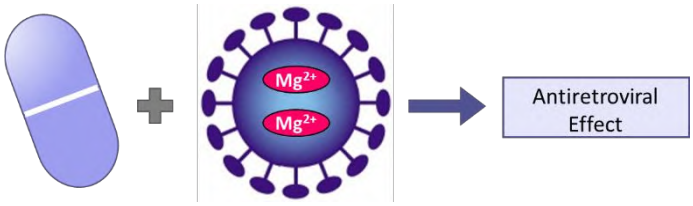
Abbreviations ATV atazanavir DRV darunavir LPV lopinavir /c cobicistat /r ritonavir DOR doravirine EFV efavirenz ETV etravirine NVP nevirapine RPV rilpivirine FTR fostemsavir LEN lenacapavir MVC maraviroc BIC bictegravir CAB cabotegravir DTG dolutegravir EVG elvitegravir RAL raltegravir F or FTC emtricitabine TAF tenofovir alafenamide TDF tenofovir-DF

Drug-drug interactions with herbal and mineral supplements

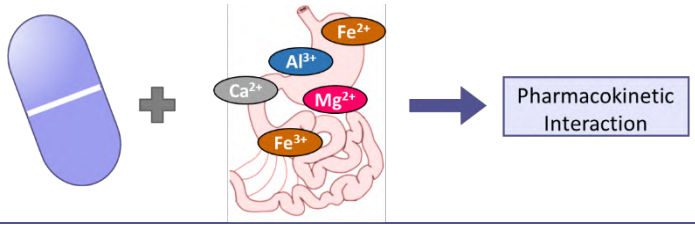
Drug-Drug Interactions with Mineral Supplements

- The main mechanism of drug-drug interactions with mineral supplements is **chelation**.
- Integrase Strand Transfer Inhibitors (INSTI; **bictegravir, cabotegravir, dolutegravir, elvitegravir, raltegravir**) inhibit HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration.
- Mg^{2+} is critical in the integration phase and cation inactivation by chelation causes functional impairment of integrase.
- However, the flip side of INSTI binding to polyvalent cations is potentially clinically significant drug interactions with coadministered cation-containing supplements.

INSTI binds to Mg^{2+} in active site of integrase



INSTI binds to cations in GI tract



There are a few important points to note:

- Oral cation administration is the focus for a potential clinically relevant interaction due to high concentrations in the GI tract.
- Polyvalent cations are present at varying amounts in supplements and multivitamin preparations. If in doubt – check!
- Although different INSTIs have specific recommendations around timing of co-administration and/or dosing with food, in general the recommendation is to ensure the separation of dosing of INSTI from cations.

Interactions between ARVs and Mineral Supplements

	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV oral	FTR	LEN	MVC	BIC/ F/TAF	CAB oral	CAB/ RPV	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	FTC/ TAF	FTC/ TDF
Mineral supplements																						
Ascorbic acid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓a	⇓a	↔	⇓a	⇓a	⇓a	⇓a	↔	↔
Calcium	⇓b	⇓b	↔	↔	↔	↔	↔	↔	↔	⇓b	↔	↔	↔	⇓	⇓	↔	⇓	⇓	⇓	⇓	↔	↔
Ferrous fumarate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓	⇓	↔	⇓	⇓	⇓	⇓	↔	↔
Folic acid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓a	⇓a	↔	⇓a	⇓a	⇓a	⇓a	↔	↔
Iodine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓a	⇓a	↔	⇓a	⇓a	⇓a	⇓a	↔	↔
Iron (infusion/injection)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Iron (oral)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓	⇓	↔	⇓	⇓	⇓	⇓	↔	↔
Magnesium	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓	⇓	↔	⇓	⇓	⇓	⇓	↔	↔
Multivitamins	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓	⇓	↔	⇓	⇓	⇓	⇓	↔	↔
Nicotinamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓a	⇓a	↔	⇓a	⇓a	⇓a	⇓a	↔	↔
Various vitamins	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇓c	⇓c	↔	⇓c	⇓c	⇓c	⇓c	↔	↔

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Colour Legend
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Text Legend
- ↔ No significant effect
- ⇓ Potential decreased exposure of HIV drug

Notes
a Only when used in multivitamin preparations as they can contain mineral supplements.
b Calcium supplements containing calcium carbonate may decrease atazanavir or rilpivirine concentrations due to gastric pH increase.
c Only for vitamin preparations containing divalent cations.

Abbreviations ATV atazanavir, DRV darunavir, LPV lopinavir, /c cobicistat, /r ritonavir, DOR doravirine, EFV efavirenz, ETV etravirine, NVP nevirapine, RPV rilpivirine, FTR fostemsavir, LEN lenacapavir, MVC maraviroc, BIC bictegravir, CAB cabotegravir, DTG dolutegravir, EVG elvitegravir, RAL raltegravir, F or FTC emtricitabine, TAF tenofovir alafenamide, TDF tenofovir-DF