Interactietabel: Complementary and Alternative Herbal Medicines (CAHMs) en geneesmiddelen

CONTACTGEGEVENS

Voor opmerkingen en/of vragen omtrent de inhoud van de interactietabel: gelieve contact op te nemen met het apotheekteam oncologie van UZ Leuven (apo.oncologie@uzleuven.be).

GEBRUIKSVOORWAARDEN

Deze gebruiksvoorwaarden omschrijven de voorwaarden waaronder gebruik gemaakt kan worden van de interactietabel.

- De interactietabel tussen Complementary and Alternative Herbal Medicines (CAHMs) en geneesmiddelen werd met grote zorg opgesteld op basis van vijf referentie bronnen. De tabel is bedoeld voor gebruik door professionals, in het bijzonder voor artsen, apothekers, verpleegkundig specialisten (zoals oncocoaches).
- De tabel beoogt een ondersteunend hulpmiddel te zijn in het afhandelen van CAHM-geneesmiddel interacties en vervangt geen grondige klinische evaluatie. Een niet-limitatieve lijst van criteria die mee in rekening gehouden moeten worden voor de finale beoordeling van interacties omvat o.a. patiënt-specifieke factoren, de therapeutisch-toxische marge van het geneesmiddel en de andere geneesmiddelen die de patiënt neemt.
- Potentiële klinische gevolgen van de interactie werden op een gestandaardiseerde manier geformuleerd voor metabolisme- en transporter-gemedieerde farmacokinetische interacties, zoals inhibitie leidende tot een toegenomen blootstelling met risico op nevenwerkingen en toxiciteit; inductie leidende tot verminderde blootstelling en risico op verminderde efficaciteit. Hierbij dient opgemerkt te worden dat dit niet van toepassing is voor CYP450-geactiveerde prodrugs.
- Om het gebruik van de tabel te vergemakkelijken, werden niet-limitatieve lijsten van geneesmiddelen met bepaalde farmacodynamische eigenschappen toegevoegd. Niet-limitatieve lijsten van substraten, inhibitoren en inducers werden ook toegevoegd op basis van vier referenties (Belgisch Centrum voor Farmacotherapeutische Informatie, UpToDate, MedicinesComplete en de Drug Interaction Flockhart Table™). Deze lijsten zijn terug te vinden als supplementaire tabellen, cf. Appendix I en Appendix II.
- Informatie voor het opstellen van de tabel werd verzameld tussen februari 2022 en december 2022. UZ Leuven zal alles in het werk stellen om deze informatie in de interactietabel op regelmatige basis te updaten en kan dus niet garanderen dat deze op elk ogenblik up-to-date is.
- De finale tabel bevat 12 CAHMs en 124 CAHM-geneesmiddel interacties. De afwezigheid van een geneesmiddel is geen garantie voor de afwezigheid van een interactie. Indien een geneesmiddel ontbreekt, dienen bijkomende bronnen nagekeken te worden.
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Inhoudstafel

CAHMDI TABEL – VERSIE APRIL 2023

Ashwagandha					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Anticonvulsants, barbiturates, benzodiazepines	PD	It was suggested that Ashwagandha may have sedative effects.	additive sedative effects	insufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
Antidiabetics[a]	PD	The mechanism is unclear. Ashwagandha may have blood-glucose-lowering effects.	additive blood-glucose-lowering effects	sufficient	
Digoxin	herb-laboratory	Some withanolides (i.e. major constituents of Ashwagandha) may interfere with digoxin fluorescence polarisation immunoassay methods.	↑ digoxin levels	insufficient	
Thyroid drugs	PD	The mechanism is unclear. Ashwagandha may have additive effects on thyroid serum levels.	↑ thyroid hormone serum levels	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
Antithyroid drugs	PD	The mechanism is unclear. Ashwagandha may have additive effects on thyroid serum levels and may antagonise the antithyroid drug action.	antagonising effects	sufficient	
CYP3A4 substrates	PK	*In vitro*, it was suggested that Ashwagandha may induce CYP3A4.	↓ exposure of CYP3A4 substrates, risk of decreased efficacy	insufficient	

CYP2B6 substrates	PK	*In vitro,* it was suggested that Ashwagandha may inhibit CYP2B6.	↑ exposure to CYP2B6 substrates, ↑ risk of adverse effects	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
Glucosamine					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Statins	PK/PD	Glucosamine did not appear to alter the effects of statins and is unlikely to influence blood levels of cholesterol or triglycerides.	no adverse consequences	sufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
Tetracyclines	PK	The mechanism of the interaction is unknown.	slightly ↑ in tetracycline absorption and serum concentrations	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
Antidiabetics[a]	PD	Endogenous glucosamine exerts a role in glucose metabolism and, therefore, may increase insulin resistance. This could potentially apply to glucosamine supplements as well.	↑ blood glucose levels	sufficient but conflicting	
Antithrombotic agents[b]	PD	It was suggested that glucosamine may increase the risk of bleeding by inhibiting platelet aggregation and having limited anticoagulant activity.	↑ bleeding risk	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
Topoisomerase II inhibitors, anthracyclines	PD	It was suggested that glucosamine may reduce the expression of topoisomerase II and increase the resistance to antineoplastic agents (i.e. doxorubicin and etoposide) *in vitro*.	risk of decreased efficacy	insufficient	**Combination is contraindicated and should be avoided.**

Echinacea					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
CYP2D6 substrates	PK	Echinacea did not affect CYP2D6-mediated metabolism of dextromethorphan and debrisoquine.	no adverse consequences	sufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
P-gp substrates	PK	Echinacea did not affect P-gp-mediated efflux transport of digoxin and fexofenadine.	no adverse consequences	sufficient	
Vitamin K antagonists	PK/PD	Echinacea did not affect the pharmacokinetics and pharmacodynamic effects of warfarin.	no adverse consequences	sufficient	
CYP2C19 substrates	PK	*In vitro*, Echinacea did not affect CYP2C19 activity.	no adverse consequences	insufficient	
CYP2C9 substrates	PK	Echinacea seemed not to inhibit neither induce CYP2C9-mediated metabolism of tolbutamide in a clinically relevant way.	probably no clinically significant interaction unless unexpected adverse events are seen	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
CYP3A4 substrates	PK	The effects of Echinacea on CYP3A4 substrates were unclear. Both inducing, inhibiting, as well as no effects were observed.	clinically relevant effects are difficult to predict due to discrepant findings	sufficient but conflicting	
CYP1A2 substrates	PK	The effects of Echinacea on CYP1A2-mediated metabolism of caffeine appeared to be variable. Inhibiting, as well as no effects were observed.	clinically relevant effects are difficult to predict due to discrepant findings	sufficient but conflicting	**Combination that requires close monitoring or follow-up. Consider advising against use.**

Oseltamivir	PK	*In vitro,* Echinacea appeared to reduce the formation of the active drug of oseltamivir.	↓ exposure to oseltamivir, risk of decreased efficacy	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
Tamoxifen	PK	*In vitro,* Echinacea was found to be a strong inhibitor of CYP450-mediated metabolism of tamoxifen. However, clinical studies with CYP2D6- and CYP3A4 probe drugs could not confirm this.	↓ exposure to endoxifen, risk of decreased efficacy	insufficient	**Combination is contraindicated and should be avoided.**
Immunosuppressants[c]	PD	Echinacea was considered to have immunostimulant effects.	risk of decreased efficacy	sufficient	

Valerian

Drug	Type of CAHMDI	Mechanism	Potential (clinical) consequences	Evidence category (DRIVE)	Risk rating
CYP1A2 substrates	PK	Valerian did not affect CYP1A2-mediated metabolism of caffeine.	no adverse consequences	sufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
CYP2E1 substrates	PK	Valerian did not affect CYP2E1-mediated metabolism of chlorzoxazone.	no adverse consequences	sufficient	
CYP2D6 substrates	PK	Valerian did not affect CYP2D6-mediated metabolism of dextromethorphan.	no adverse consequences	sufficient	
CYP2C19 substrates	PK	*In vitro,* valerian did not affect CYP2C19 activity.	no adverse consequences	insufficient	

CYP2C9 substrates	PK	*In vitro,* valerian did not affect CYP2C9 activity.	no adverse consequences	insufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
CNS depressants	PD	It was suggested that valerian may modulate GABA, resulting in sedative effects.	↑ sedative effects	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
Thiopental, pentobarbital	PD	Valerian could prolong the sleeping time, especially in combination with thiopental or pentobarbital.	↑ sedative effects	insufficient	
CYP3A4 substrates	PK	No significant changes were seen on the pharmacokinetics of midazolam and alprazolam, which were both used as probe drugs for CYP3A4.	no adverse consequences	sufficient	
Stimulating agents[d]	PD	Valerian may theoretically have opposing clinical effects of stimulating agents.	↑ sedative effects	insufficient	
P-gp substrates	PK	*In vitro,* it was suggested that valerian may inhibit P-gp efflux transport.	↑ exposure to P-gp substrates, ↑ risk of adverse effects	insufficient	
UGT substrates	PK	*In vitro,* it was suggested that valerian may inhibit UGT enzymes.	↑ exposure to UGT substrates, ↑ risk of adverse effects	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**

Ginger					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Metronidazole	PK	Based on an animal study, it was suggested that ginger could have spasmolytic effects reducing gastric emptying and gastrointestinal motility. This could potentially lead to increased metronidazole absorption.	↑ metronidazole absorption	insufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
Hypoglycaemia associating agents[a]	PD	The mechanism is unclear. Ginger may have blood glucose-lowering effects.	↑ risk of hypoglycaemia	insufficient	
Antithrombotic agents[b]	PK/PD	Controversial results have been reported regarding the effects of ginger on the INR and bleeding risk. Some studies suggest that ginger may increase the risk of bleeding when used in combination with antiplatelet drugs or anticoagulants. Additionally, ginger may inhibit P-gp which could increase the exposure to dabigatran. Note that all direct oral anticoagulants are P-gp substrates.	↑ bleeding risk, variable effects on INR	sufficient but conflicting	**Combination that requires close monitoring or follow-up. Consider advising against use.**
NSAID	PD	Coadministration of NSAIDs and ginger has not been studied. It was speculated that ginger may inhibit platelet aggregation.	↑ bleeding risk	insufficient	
Thrombolytic agents[b]	PD	Coadministration of ginger and thrombolytic agents has not been studied. It was speculated that ginger may affect platelet aggregation and coagulation.	↑ bleeding risk	insufficient	
CYP3A4 substrates	PK	It was suggested that ginger may inhibit CYP3A4.	↑ exposure to CYP3A4 substrates, ↑ risk of adverse effects	sufficient	
P-gp substrates	PK	It was suggested that ginger may inhibit P-gp efflux transport.	↑ exposure to P-gp substrates, ↑ risk of adverse effects	sufficient	

Cyclosporine	PK	The bioavailability of orally administered cyclosporine was reduced when ginger was administered before or concurrently with cyclosporine. It did not occur when cyclosporine was administered intravenously.	↓ bioavailability of orally administered cyclosporine, risk of decreased efficacy	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use**
Turmeric/curcumin					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Paracetamol, aspirin and NSAIDs	PD	*In vitro,* it was suggested that paracetamol, aspirin and ibuprofen may alter the bioactivity of curcumin.	potential altered bioactivity of curcumin	insufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
Iron compounds	PK	Turmeric did not affect iron absorption.	no adverse consequences	sufficient	
Amphotericin B	PD	By an in-silico-analysis, it was suggested that curcumin could delay red cell lysis, caused by amphotericin B because they could bind on different regions of albumin and form complexes.	delay in red cell lysis	insufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
CYP3A4 substrates	PK	Turmeric appeared to have variable, both inhibitory and no effects on different CYP3A4 substrates.	probably no clinically significant interaction unless unexpected adverse events are seen	sufficient	
Antithrombotic agents[b]	PK/PD	It was suggested that curcumin may have antiplatelet and anticoagulant properties. Another speculated mechanism was inhibition of vitamin K antagonists and DOACs by curcumin via P-gp, CYP2C9, and CYP3A4.	↑ bleeding risk, ↑ INR	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
NSAID	PD	Coadministration of turmeric and NSAIDs has not been studied. It was suggested that curcumin may inhibit platelet aggregation.	↑ bleeding risk	insufficient	

CYP1A2 substrates	PK	It was suggested that curcumin may inhibit CYP1A2-mediated metabolism of caffeine.	↑ exposure to CYP1A2 substrates, ↑ risk of adverse effects	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
CYP2A6 substrates	PK	It was suggested that curcumin may increase expression of CYP2A6, involved in the metabolism of caffeine.	↓ exposure to CYP2A6 substrates, risk of decreased efficacy	sufficient	
CYP2D6 substrates	PK	It was suggested that curcumin may inhibit CYP2D6-mediated metabolism of dextromethorphan.	↑ exposure to CYP2D6 substrates, ↑ risk of adverse effects	sufficient	
P-gp substrates	PK	It was suggested that curcumin may inhibit P-gp efflux transport.	↑ exposure to P-gp substrates, ↑ risk of adverse effects	sufficient	
CYP2C9 substrates	PK	*In vitro,* it was suggested that curcumin may inhibit CYP2C9.	↑ exposure to CYP2C9 substrates, ↑ risk of adverse effects	insufficient	
BCRP substrates	PK	It was suggested that curcumin may inhibit BCRP efflux transport.	↑ exposure to BCRP substrates, ↑ risk of adverse effects	sufficient	
Cladribine	PK	*In vitro,* it was suggested that curcumin may inhibit the ENT1 transporter and therefore, may interfere with ENT1 substrates such as cladribine.	↑ exposure to cladribine, ↑ risk of adverse effects	insufficient	**Combination is contraindicated and should be avoided.**
Paclitaxel	PK/PD	A case report concerned the development of hepatotoxicity, probably due to the combination of a contaminated Chlorella supplement, turmeric and paclitaxel. It was also suggested that curcumin may inhibit CYP3A4-mediated metabolism of paclitaxel.	↑ exposure to paclitaxel, ↑ risk of hepatotoxicity	sufficient	

Antineoplastic agents	PD	*In vitro,* curcumin may inhibit the generation of ROS and the JNK pathway. It was suggested that it may antagonise chemotherapy induced-apoptosis of cancer cells.	risk of decreased efficacy of antineoplastic agents	insufficient	**Combination is contraindicated and should be avoided.**
Milk thistle					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
CYP3A4 substrates	PK	Milk thistle did not affect the pharmacokinetics of CYP3A4 substrates.	no adverse consequences	sufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
CYP1A2 substrates	PK	Milk thistle did not affect CYP1A2-mediated metabolism of caffeine.	no adverse consequences	sufficient	
CYP2E1 substrates	PK	Milk thistle did not affect CYP2E1-mediated metabolism of chlorzoxazone.	no adverse consequences	sufficient	
Nifedipine	PK/PD	It was speculated that milk thistle could slightly decrease the absorption of nifedipine, but did not to appear to affect the metabolism or pharmacodynamics of nifedipine.	no adverse consequences	sufficient	
BCRP substrates	PK	Milk thistle seemed not to affect BCRP efflux transport of rosuvastatin.	no adverse consequences	sufficient	
OATP1B1 substrates	PK	Milk thistle seemed not to affect OATP1B1-mediated transport of rosuvastatin.	no adverse consequences	sufficient	

CYP2C8 substrates	PK	*In vitro,* it was suggested that milk thistle did not affect CYP2C8 activity.	no adverse consequences	insufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
CYP2C19 substrates	PK	*In vitro,* it was suggested that milk thistle did not affect CYP2C19 activity.	no adverse consequences	insufficient	
Metronidazole	PK	The mechanism of the interaction is not yet clarified. Induction of P-gp and CYP3A4 by milk thistle was hypothesized however, this was not demonstrated with probe substrates. The contribution of CYP enzymes or P-gp efflux transport in the pharmacokinetics of metronidazole is also unclear.	↓ exposure to metronidazole	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
P-gp substrates	PK	There was a trend towards a minor reduction in digoxin exposure, but it was suggested that milk thistle would not affect the pharmacokinetics of digoxin in a clinically relevant way.	probably no clinically significant interaction unless unexpected reduced effects are predicted	sufficient	
Sirolimus	PK	It was suggested that milk thistle may inhibit sirolimus clearance in hepatically impaired patients. Sirolimus is a substrate for CYP3A4 and P-gp. Studies with other CYP3A4 substrates could not confirm possible CYP3A4 or P-gp inhibiting effects of milk thistle.	↑ exposure to sirolimus, ↑ risk of sirolimus toxicity	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
CYP2C9 substrates	PK	It was suggested that milk thistle may inhibit CYP2C9 activity.	↑ exposure to CYP2C9 substrates, ↑ risk of adverse effects	sufficient	
Pyrazinamide	PK	In an animal study in rats, it was suggested that milk thistle may decrease hepatobiliary excretion of pyrazinoic acid and inhibit xanthine oxidase. Xanthine oxidase is an enzyme involved in the metabolism of pyrazinamide.	↑ exposure to pyrazinamide, ↑ risk of adverse effects	insufficient	
UGT substrates	PK	It was suggested that milk thistle may inhibit UGT.	↑ exposure to UGT substrates, ↑ risk of adverse effects	insufficient	

Passionflower					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Hypnotics and sedatives	PD	It was suggested that passionflower may have GABA-related effects, which may be additive to anxiolytics, hypnotics and sedatives.	↑ sedative and anxiolytic effects	insufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
Stimulating agents[d]	PD	Passionflower is used for its hypnotic and sedative effects, which may theoretically antagonise the effects of psychostimulating agents.	↓ effects of stimulating agents	insufficient	
Feverfew					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Antithrombotic agents[b]	PD	It was suggested that feverfew may inhibit platelet aggregation.	↑ bleeding risk	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
CYP450 substrates	PK	It was suggested that feverfew may inhibit CYP3A4, CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.	↑ exposure to CYP450 substrates, ↑ risk of adverse effects	sufficient	

Soy					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Artemether + lumefantrine	PK	It was suggested that soy milk may increase the bioavailability of the hydrophobic, lipophilic lumefantrine component, as well as of artemether.	↑ absorption of artemether + lumefantrine	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
CYP3A4 substrates	PK	It was suggested that soy may induce CYP3A4 activity.	↓ exposure to CYP3A4 substrates, risk of decreased efficacy	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
P-gp substrates	PK	It was suggested that soy milk, miso and soy isoflavones may activate P-gp efflux transport.	↓ exposure to P-gp substrates, risk of decreased efficacy	insufficient	
UGT substrates	PK	It was suggested that soy may modulate UGT enzymes by inhibition or induction.	↑ or ↓ decreased exposure	insufficient	
Levothyroxine	PK/PD	It was suggested that soy products may decrease levothyroxine absorption and may interfere with the thyroid function.	potential need for a higher dose of levothyroxine	sufficient	
Caffeine	PK	It was suggested that soy-based formulas for infants may induce CYP1A2-mediated metabolism of caffeine, but the constituent responsible for this effect remains unknown. In contrary, soy isoflavones have been found to increase theophylline levels, by inhibiting CYP1A2.	↓ exposure to caffeine, potential need for higher doses	sufficient but conflicting	

Vitamin K antagonists	PD	Soy-products with a high vitamin K content (e.g. natto) may antagonise the anticoagulant effects of vitamin K antagonists by decreasing the INR. It is currently unclear how the INR is affected by soy products that do not contain vitamin K.	↓ effects of vitamin K antagonists, ↓ INR	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
CYP2C9 substrates	PK	*In vitro* and animal data suggested that soy may inhibit CYP2C9 activity.	↑ exposure to CYP2C9 substrates, ↑ risk of adverse effects	insufficient	
MAO-inhibitors, RIMA	PD	Fermented or preserved soy products contain significant amounts of tyramine, which in combination with non-selective MAO-inhibitors, could induce a hypertensive crisis due to the release of noradrenaline. Effects may persist for up to two weeks after stopping the MAO-inhibitor. The risk is reduced when taking a RIMA.	risk of hypertensive crisis	sufficient	**Combination is contraindicated and should be avoided.**

Soy isoflavones

Drug	Type of CAHMDI	Mechanism	Potential (clinical) consequences	Evidence category (DRIVE)	Risk rating
Antibacterials	PK	It was speculated that antibacterials could potentially impact the metabolism and activity of isoflavones, by altering the colon bacteria responsible for the metabolism of isoflavones.	no adverse consequences	insufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
CYP2A6 substrates	PK	It was suggested that soy isoflavones may slightly inhibit CYP2A6-mediated metabolism of nicotine.	Slightly ↑ exposure to CYP2A6 substrates, adverse effects are less likely	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
P-gp substrates	PK	Both increased expression and inhibition of P-gp efflux transport were reported by preclinical studies.	↑ or ↓ decreased exposure	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**

CYP1A2 substrates	PK	It was suggested that soy isoflavones (geinistein, dadzein and equol) may inhibit CYP1A2-mediated metabolism of theophylline. Contradictorily, it was shown that in infants receiving soy-based infant formulas, higher doses of caffeine (a CYP1A2 substrate) were required.	↑ exposure to CYP1A2 substrates, ↑ risk of adverse effects	sufficient but conflicting	**Combination that requires close monitoring or follow-up. Consider advising against use.**
OATP2B1 substrates	PK	*In vitro,* it was suggested that aglycones of soy isoflavones (especially genistein and biochanin) and S-equol may inhibit OATP2B1 transport.	affected drug uptake	insufficient	
CYP2E1 substrates	PK	*In vitro,* it was suggested that the soy isoflavones, genistein and equol may inhibit CYP2E1 activity.	↑ exposure to CYP2E1 substrates, ↑ risk of adverse effects	insufficient	
CYP3A4 substrates	PK	*In vitro,* it was suggested that soy isoflavones may inhibit CYP3A4 activity.	↑ exposure to CYP3A4 substrates, ↑ risk of adverse effects	insufficient	
Aromatase inhibitors	PD	*In vitro,* it was suggested that genistein may affect the efficacy of aromatase inhibitors by increasing oestrogen-dependent MCF-7 tumour cell growth, breast cancer aromatase expression and activity.	risk of decreased efficacy of aromatase inhibitors	insufficient	**Combination is contraindicated and should be avoided.**
Tamoxifen	PD	The effects of soy isoflavones on the efficacy of tamoxifen are unclear, but decreased efficacy was suggested. Soy isoflavones may interact with oestrogen receptors, possibly leading to antagonistic or beneficial effects in patients with breast cancer.	risk of decreased efficacy of tamoxifen	sufficient but conflicting	

Cannabidiol (CBD)					
Drug	**Type of CAHMDI**	**Mechanism**	**Potential (clinical) consequences**	**Evidence category (DRIVE)**	**Risk rating**
Anti-epileptic drugs (clonazepam, lacosamide, pregabaline, perampanel, vigabatrine, levetiracetam, topiramate)	PK	Cannabidiol did not affect the metabolism of these anti-epileptic drugs. A potential CYP-mediated interaction was suggested for topiramate, but it is not consistent with its metabolic pathway.	no adverse consequences	sufficient	**CAHM-drug combination is allowed. No clinically relevant interaction is expected.**
CYP3A4 substrates	PK	Cannabidiol seemed not to affect the metabolism of CYP3A4 substrates in a clinically relevant way.	probably no clinically significant interaction unless unexpected adverse events are seen	sufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
CNS depressants	PD	Cannabidiol may enhance somnolence and sedation.	↑ sedative effects	sufficient	
Levothyroxine **(CBD as victim)**	PK	It was speculated that levothyroxine may inhibit CYP3A4-mediated metabolism of CBD. However, potential CYP3A4 inhibiting effects of levothyroxine are not yet clarified.	↑ exposure to cannabidiol, ↑ risk of adverse effects	insufficient	
Opioid antagonists	PD	The mechanism of a possible interaction is not yet clarified. It may be related to the close interrelationship between opioid and cannabinoid receptors.	altered (↑ or ↓) effects of cannabinoids	sufficient	

Sympathomimetic agents[e]	PD	Hypertension and tachycardia were observed due to the combination of cannabis (smoking marijuana or tetrahydrocannabinol ingestion) with sympathomimetic agents.	hypertension and tachycardia	insufficient	**CAHM-drug combination is possible, but inform patients or health care professionals about a potential interaction.**
Zonisamide	PK	It was suggested that cannabidiol may inhibit CYP3A4-mediated metabolism of zonisamide. However, cannabidiol has not shown to have CYP3A4 inhibiting effects on midazolam, a probe drug for CYP3A4 activity.	↑ exposure to zonisamide, ↑ risk of adverse effects	sufficient	
Nicotine	PD	It was suggested that the combination of nicotine and cannabis may lead to an increased heart rate and addictive potential.	↑ stimulant effects	sufficient	
NSAID	PD	It was speculated that cannabis may antagonise the effects of NSAIDs and vice versa.	↓ effects of NSAIDs ↓ effects of cannabis	sufficient	
Phencyclidine	PK	The mechanism of the interaction is unknown.	↑ levels of phencyclidine	insufficient	
Tricyclic antidepressants	PD	The combination of tricyclic antidepressants and smoking cannabis may have additive beta-adrenergic and antimuscarinic effects, possibly affecting the heart rate.	risk of tachycardia	sufficient	
P-gp substrates	PK	Cannabidiol may inhibit P-gp efflux transport.	↑ exposure to P-gp substrates, ↑ risk of adverse effects	sufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
CYP2C19 substrates	PK	Cannabidiol may inhibit CYP2C19 activity.	↑ exposure to CYP2C19 substrates, ↑ risk of adverse effects	sufficient	

Strong or moderate CYP2C19 inhibitors (CBD as victim)	PK	Cannabidiol is metabolised by CYP450 isoenzymes, including CYP2C19. CYP2C19 inhibitors may theoretically increase cannabidiol concentrations, although this was not confirmed by a PK study with omeprazole as CYP2C19 inhibitor.	clinically relevant effects are difficult to predict due to discrepant findings	sufficient but conflicting	**Combination that requires close monitoring or follow-up. Consider advising against use.**
CYP2C9 substrates	PK	Cannabidiol may inhibit CYP2C9 activity.	↑ exposure to CYP219 substrates, ↑ risk of adverse effects	sufficient	
CYP1A2 substrates	PK	It has been suggested that cannabidiol may inhibit CYP1A2-mediated metabolism of caffeine. However, when cannabis is smoked, opposing effects may be seen due to the presence of polycyclic hydrocarbons, which are known CYP1A2 inducers.	↑ exposure when taking oral cannabis, ↓ exposure when smoking marijuana	sufficient	
CYP2C19 inducers (CBD as victim)	PK	Cannabidiol is metabolised by CYP450 isoenzymes, including CYP2C19. CYP2C19 inducers may decrease exposure to cannabidiol.	risk of decreased efficacy of CBD	sufficient	
CYP3A4 inducers (CBD as victim)	PK	Cannabidiol is metabolised by CYP450 isoenzymes, including CYP3A4. CYP3A4 inducers may decrease exposure to cannabidiol.	risk of decreased efficacy of CBD	sufficient	
CYP3A4 inhibitors (CBD as victim)	PK	Cannabidiol is metabolised by CYP450 isoenzymes, including CYP3A4. CYP3A4 inhibitors may increase exposure to cannabidiol.	↑ risk of adverse effects of CBD	sufficient	
Opioids	PD	It was suggested that nabiximols (dronabinol and CBD) may enhance the analgesic potency of opioids.	↑ analgesic effects, ↑ sedative effects	sufficient	

Methadone	PK/PD	Different effects of cannabidiol in patients on methadone maintenance treatment were described. It was suggested that cannabidiol may alter methadone concentrations, but no clear explanation was given.	clinically relevant effects are difficult to predict	sufficient but conflicting	**Combination that requires close monitoring or follow-up. Consider advising against use.**
Methylphenidate	PK	It was suggested that cannabidiol may inhibit hepatic carboxylesterase 1, an enzyme involved in the metabolism of methylphenidate.	mild ↑ in methylphenidate exposure,	sufficient	
Buprenorphine	PK	It was suggested that cannabidiol may inhibit CYP3A4-mediated metabolism of buprenorphine, although this could not be demonstrated with CYP3A4 probe drugs. Competition for UGT by cannabidiol and buprenorphine was also suggested as a possible mechanism.	↑ exposure to buprenorphine, altered or enhanced opioid activity	sufficient	
Valproate	PD	Concurrent use of cannabidiol and valproate may increase liver function tests. The mechanism of the interaction is unknown.	↑ liver function tests, ↑ risk of hepatotoxicity	sufficient	
Fluoxetine	PK/PD	The mechanism of the interaction is not yet clarified. One hypothesis suggested a synergistic effect on central serotonergic neurons, while another suggested a CYP2C9-mediated interaction between cannabidiol and fluoxetine in patients with null CYP2D6 activity.	↑ exposure to fluoxetine, ↑ risk of adverse effects	sufficient	
Tamoxifen	PK	It was suggested that cannabidiol may inhibit tamoxifen metabolism via CYP3A4 and CYP2D6. However, no notable effect of cannabidiol could be demonstrated on the pharmacokinetics of midazolam which is a probe drug for CYP3A.	↑ exposure to tamoxifen (↓ endoxifen levels), especially in intermediate or poor CYP2D6 metabolisers	sufficient	
CYP2B6 substrates	PK	It was suggested that cannabidiol may inhibit or induce CYP2B6 activity.	altered (↑ or ↓) exposure to CYP2B6 substrates	insufficient	

UGT1A9 substrates (UGT1A1, UGT1A4, UGT1A6)	PK	It was suggested that cannabidiol may inhibit UGT1A9 at clinically relevant concentrations. Its metabolite, 7-carboxy-cannabidiol was also found to be an inhibitor of UGT1A1, UGT1A4 and UGT1A6 *in vitro*.	↑ exposure to UGT1A9, UGT1A1, UGT1A4 and UGT1A6 substrates, ↑ risk of adverse effects	insufficient	**Combination that requires close monitoring or follow-up. Consider advising against use.**
UGT2B7 substrates	PK	It was suggested that cannabidiol may inhibit UGT2B7-mediated metabolism.	↑ exposure to UGT2B7 substrates, ↑ risk of adverse effects	insufficient	
UGT1A7, UGT1A9 and UGT2B7 inhibitors (CBD as victim)	PK	Cannabidiol is metabolised by CYP450 enzymes and glucuronidated by UGT1A7, UGT1A9 and UGT2B7 isoforms. Coadministration with UGT inhibitors may theoretically increase serum concentrations of cannabidiol.	increased exposure to cannabidiol, ↑ risk of adverse effects	insufficient	
CYP2C8 substrates	PK	It was suggested that cannabidiol may inhibit CYP2C8-mediated metabolism of repaglinide.	↑ exposure to CYP2C8 substrates, ↑ risk of adverse effects	insufficient	
Immunotherapy[f]	PD	Cannabinoids are supposed to have immunomodulating properties, which may interfere with the effects of nivolumab.	↓ response rate	sufficient	**Combination is contraindicated and should be avoided.**

Abbreviations: BCRP: breast cancer resistance protein; CAHM: complementary and alternative medicine; CAHMDI: CAHM-drug interaction; CBD: cannabidiol; CNS: central nervous system; CYP: cytochrome P450; DOAC: direct oral anticoagulant; DRIVE: DRug Interaction eVidence Evaluation; ENT: equilibrative nucleoside transporter; GABA: gamma-aminobutyric acid; INR: International Normalized Ratio; JNK: Jun NH(2)-terminal kinase; MAO-I: monoamine oxidase inhibitor; NSAID: non-steroidal anti-inflammatory drug; OATP: organic anion transporter polypeptide; PD: pharmacodynamic; P-gp: P-glycoprotein; PK: pharmacokinetic; PK/PD: combined pharmacokinetic/pharmacodynamic; RIMA: reversible inhibitor of monoamine oxidase A; ROS: reactive oxygen species; UGT: UDP-glucuronosyltransferase

APPENDIX I: NIET LIMITATIEVE LIJST VAN SUBSTRATEN, INHIBITOREN EN INDUCERS

Cytochrome P450 (CYP)

CYP1A2	**substrates**	Acetaminophen; acebrophylline; agomelatine; alosetron; aminophylline; anagrelide; amitriptyline; apremilast; asenapine; bendamustine; binimetinib; caffein; clomipramine; clozapine; cyclobenzaprine; dacarbazine; deferasirox; doxepin; euloxetine; erlotinib; estradiol; fenfluramine; flecainide; flutamide fluvoxamine; frovatriptan; haloperidol; Imipramine; leflunomide; lidocaine; melatonin; mexiletine; nabumetone; naproxen; olanzapine; ondansetron; phenacetin; pirfenidone pomalidomide; propranolol tamelteon; rasagiline; riluzol; roflumilast; ropinirole; ropivacaine; tacrine; tasimelteon; theophylline tizanidine; triamterene; verapamil; warfarin; zileuton; zolmitriptan
CYP2A6	**substrates**	Unknown
CYP2B6	**substrates**	Artemisinin; bupropion; clobazam; cyclophosphamide; esketamine; fenfluramine; ifosphamide; ketamine; levomethadone; meperidine; methadone; nevirapine; propofol; selegiline; sibutramine; sorafenib; thiotepa; tramadol; velpatasvir
CYP2C8	**substrates**	Amiodaron ; amodiaquine; apalutamide; carbamazepine; cerivastatin; clonazepam; dabrafenib; daprodustat; dasabuvir; desloratadine; enzalutamide; fluvastatine ; ibuprofen; imatinib ; loperamide; montelukast; olodaterol ; ombitasvir; ozanimod; paclitaxel; paritaprevir; pioglitazone; ponatinib; remdesivir; repaglinide; riociguat ; roxadustat; rosiglitazone; selexipag; sorafenib; torsemide; treprostinil; tucatinib; zopiclon
CYP2C9	**substrates**	Abrocitinib; acenocoumarol; amitriptyline; avatrombopag; azilsartan; bosentan; candesartan; capecitabine; carvedilol; celecoxib; chlorpropamide; clopidogrel; co-trimoxazole; diclofenac; doxepin; phenobarbital; phenytoin; fluconazole; fluoxetine; flurbiprofen; fluvastatin; fosphenytoin; flibenclamide; gliclazide ; glimepiride; glipizide; gliquidone; glyburide; ibuprofen; indometacine; irbesartan; lesinurad; lornoxicam; losartan; meloxicam; midostaurine; naproxen; nateglinide; nitisinon; olodaterol; ospemifene; phenindione; phenprocoumon; phenytoin; piroxicam; rosiglitazone; rosuvastatine; ruxolitinib; siponimod; s-naproxen; sulfamethoxazole; suprofen; s-warfarin; tamoxifen; tetrahydrocannabinol; tolbutamide; torasemide; valproic acid; valsartan; venlafaxine ; vismodegib; voriconazole; zafirlukast
CYP2D6	**substrates**	Ajmaline; almotriptan; alprenolol; amitriptyline; amphetamine; aripiprazole; aripiprazole; atomoxetine; brexpiprazole ; bufuralol; cariprazine; carvedilol; chlorpheniramine; chlorpromazine; citalopram; clomipramine; clonidine; clozapine; codeine; dapoxetine; darifenacin; debrisoquine; desipramine; deutetrabenazine; dexfenfluramine; dextroamphetamine; dextromethorphan; dihydrocodeine; diphenhydramine; donepezil; doxepin; doxorubicin; duloxetine; eliglustat; encainide; escitalopram; ethylmorphine; fingolimod; flecainide; fluoxetine; fluvoxamine; galantamine haloperidol; hydrocodone; iboga; ibrutinib; iloperidone; Imipramine; lidocaine; lisdexamfetamine; lofepramine; lofexidine; maprotiline; methamphetamine; methoxyamphetamine; metoclopramide; metoprolol ; mexiletine; mianserine; minaprine ; nebivolol ; nortriptyline; oliceridine; ondansetron; oxycodone; paliperidone; palonosetron; paroxetine; perhexiline; perphenazine; phenacetin; phenformin; pimavanserin; pimozide; pindolol ; pitolisant; pomalidomide; ponatinib; promethazine; propafenone; propranolol ; ranolazine; remdesivir; risperidone; sertindole; sparteine; tamoxifen; tamsulosin; tetrabenazine; thioridazine; timolol; tolterodine; tramadol; trimipramine; umeclidinium; valbenazine; venlafaxine; vilazodone; vortioxetine; yohimbine; zuclopenthixol
CYP2E1	**substrates**	Acetaminophen; aniline; benzene; chlorzoxazone; enflurane; ethanol; halothane; isoflurane; methoxyflurane; n,n-dimethylformamide; sevoflurane; theophylline

CYP2C19	**substrates**	Abrocitinib; acenocoumarol; ambrisentan;amitriptyline; atomoxetine;brivaracetam; cannabidiol; carisoprodol;celecoxib; chloramphenicol; chlorpropamide; cilostazol; citalopram; clobazam;clomipramine; clopidogrel; co-trimoxazol; cyclophosphamide;diazepam; doxepin; escitalopram ;esomeprazole; etravirine; flibanserin; fluconazol;fluvastatin; fosphenytoin; gliclazide; glimepiride; glipizide; gliquidon; glyburide; hexobarbital; imipramine; labetalol; lansoprazol; lesinurad; leflunomide; mavacamten; moclobemide; nelfinavir; nilutamide; omeprazole; ospemifene; pantoprazole; pentamidine; phenindione; phenobarbital;phenobarbitone; phenprocoumon ;phenytoin; pomalidomide; primidone; progesterone; proguanil ; propranolol; rabeprazole;r-mephobarbital ; r-warfarin; sertraline ; s-mephenytoin; siponimod; teniposide; terbinafine; thalidomide; ticlopidine; tofacitinib; tolazamide;tolbutamide; trimethoprim
CYP2C19	**inhibitors**	Armodafinil; cannabidiol; cenobamate;chloramphenicol; cimetidine; citalopram; esomeprazole; etravirine; fedratinib; felbamate; fexinidazole; fluconazole (100 mg daily); fluoxetine; fluvoxamine; givosiran; isoniazid;ketoconazole; luliconazole;moclobemide; modafinil; omeprazole (20 mg daily) ; oral contraceptives; oritavancin; osilodrostat;quercetin; rucaparib; stiripentol;ticlopidine; topiramate ; voriconazole
CYP2C19	**inducers**	Apalutamide; artemisinin; carbamazepine; dasabuvir; dicloxacillin dipyrone; efavirenz; enzalutamide; letermovir; nirmatrelvir and ritonavir; ombitasvir; paritaprevir; prednisone; rifampin; ritonavir; st. john's wort; zanabrutinib

CYP3A4	**substrates**	Abemaciclib; abiraterone; acalabrutinib; adagrasib; alectinib; alfentanil; alfuzosin; algestone; acetophenide; alitretinoin; almotriptan; alosetron ; alpelisib; alprazolam;ambrisentan;amiodarone; amitriptyline; amlodipine; amprenavir; anastrozole; apixaban; apremilast; aprepitant; aripiprazole;artemether and lumefantrine; asciminib; astemizole; asunaprevir;atazanavir;atogepant;atorvastatin; avacopan; avanafil; avatrombopag; axitinib; bedaquiline;benidipine; benzhydrocodone; betamethasone; bexarotene; bictegravir ;boceprevir; bortezomib; bosentan; bosutinib; brentuximab vedotin; brexpiprazole; brigatinib; bromocriptine; bromperidol; brotizolam; budesonide; bupivacaine; buprenorphine; buspirone; cabazitaxel ; cabergoline; cabozantinib; cafergot; caffeine; cannabidiol ; cannabis; capmatinib; carbamazepine; cariprazine; cerinitib; cerivastatin; chloormadinon; chlordiazepoxide; chlormadinone; chlorpheniramine; cilostazol; cinacalcet; cisapride; citalopram; clarithromycin; clindamycine; clobazam;clonazepam; clopidogrel; clozapine;cobicistat; cobimetinib; cocaine; codeine; colchicine ; conivaptan; copanlisib; co-trimoxazol ; crizotinib; cyclophosphamide;cyproterone and ethinyl estradiol; cyclosporine;dabrafenib; daclatasvir; dapoxetine; dapsone; daridorexant; darifenacin; darolutamide; darunavir; dasatinib; deflazacort; delamanid; desfesoterodine; desogestrel; dexamethasone; dextromethorphan; diazepam; dienogest; diënogest; diethylstilbestrol; dihydroergotamine; diltiazem; disopyramide; disulfiram; docetaxel; dofetilide; dolutegravir; domperidone; donepezil; doxepin; doxorubicin; dronabinol; dronedarone; droperidol; drospirenon; dutasteride; duvelisib; ebastine; elacestrant; elagolix; elbasvir/grazoprevir; eletriptan ; elexacaftor; eliglustat; elvitegravir; encorafenib; enfortumab vedotin; elbasvir and grazoprevir; entrectinib; enzalutamide; eplerenone; eravacycline; erdafitinib; ergonovine; ergot derivatives; ergotamine; erlotinib; erythromycin; escitalopram; esketamine; esomeprazole; estradiol ; estradiol and dienogest; estradiol and levonorgestrel; estradiol and norethindrone; estradiol and norgestimate; estradiol enthanate ; estetrol; estriol; estrogens; estrone estropipate; eszopiclone; ethinylestradiol; ethosuximide; ethynodiol diacetate; etizolam; etonogestrel; etoposide; everolimus; exemestane; fedratinib; felodipine; fentanyl; fesoterodine; finasteride; finerenone; fingolimod; flibanserin; flurazepam; fluticasone; fosamprenavir; fosaprepitant; fostamatinib; fostemsavir; galantamine; gefitinib; gestodene; gilteritinib; glasdegib; glecaprevir ; granisetron ; grazoprevir; guanfacine; halofantrine; haloperidol; hydrocodone; hydrocortisone; ibrexafungerp; ibrutinib; idelalisib; ifosfamide; iloperidone; imatinib; imidafenacin; indacaterol; Indinavir; infigratinib; irinotecan; isavuconazole; isradipine; istradefylline; itraconazole; ivabradine; ivacaftor; ivermectine; ivosidenib; ixabepilone ;ixazomib; ketoconazole; kinidine; kinine; lansoprazole; lapatinib; larotrectinib; lidocaine (systemic); lefamulin; lemborexant; leniolisib; lenvatinib; lercanidipine; letermovir; letrozole; leuprolide and norethindrone; levamlodipine; levoketoconazole; levomethadone; levomilnacipran; levonorgestrel ; linagliptin; lomitapide; lonafarnib; loperamide; lopinavir ; loratadine; lorlatinib; lovastatin; lumacaftor and ivacaftor; lumateperone; lumefantrine; lurasidone; lynestrenol; macitentan; manidipine; maraviroc; mavacamten; medroxyprogesterone; mefloquine; memborexant; meperidine; mestranol; methadone; methylergonovine; methylprednisolone; methysergide; midazolam; midostaurin; mifepristone; mirabegron; mirodenafil ; mirtazapine; mitapivat; mobocertinib; modafinil ; mometason; naldemedine; nalfurafine; naloxegol; naloxone; nateglinide;

		nelfinavir;neratinib; netupitant; nevirapine; nicardipine; nifedipine; nilotinib; nimodipine; nirmatrelvir; nisoldipine; nitrendipine;nomegestrol; norelgestromin ;norethindrone; norgestimate;norgestrel; olaparib;oliceridine; omaveloxolone; omeprazole; ondansetron; orelabrutinib; osimertinib ; ospemifene;oxybutynin; oxycodone;paclitaxel; pacritinib ; palbociclib; palovarotene; panobinostat ;pantoprazole; parecoxib; paricalcitol; pazopanib ;pemigatinib; perampanel ; pexidartinib; pibrentasvir; pimavanserin; pimozide; piperaquine; pirtobrutinib; pitolisant;pomalidomide; ponatinib; pralsetinib; praziquantel;prednisolone; prednison ; progesterone; promestriene; propranolol; quetiapine; quinidine;quinine; ramelteon; ranolazine;red yeast rice; reboxetine; regorafenib; remdesivir; repaglinide; ribociclib; rifabutin; rifaximine; rilpivirine;rimegepant; riociguat ; ripretinib; risperidone; ritonavir; rivaroxaban; roflumilast; rolapitant; romidepsin; rupatadine;ruxolitinib;salmeterol; saquinavir; saxagliptin; segesterone acetate; selexipag; selpercatinib; selumetinib;sertindole;sibutramine; sildenafil ;silodosin;simeprevir; simvastatin; siponimod; sirolimus; sitagliptine ; solifenacin; sonidegib; sorafenib; sparsentan; sufentanil; sunitinib; suvorexant; tacrolimus(fk506);tadalafil; tamoxifen;tamsulosin; taxol; tazemetostat; telaprevir; telithromycin; temsirolimus; terbinafine; terfenadine; testosterone; tetrahydrocannabinol; tezacaftor; and ivacaftor; thiotepa; tiagabine; tibolone; ticagrelor ; ticlopidine; tinidazole; tipranavir; tisotumab vedotin; tofacitinib;tolterodine ; tolvaptan; topiramate; toremifene; torisel; trabectedin; tramadol; trastuzumab-emtansine; trazodone;triamcinolone;triazolam;trimethoprim; ubrogepant; udenafil; ulipristal; upadacitinib; valbenazine; vandetanib; vardenafil; velpatasvir; vemurafenib; venetoclax; venlafaxine ; verapamil; vilanterol;vilazodone; vinblastine; vincristine; vindesine; vinflunine; vinorelbine; vismodegib; voclosporin;vorapaxar; voriconazol ; voxilaprevir ; yohimbine;zaleplon; zanubrutinib; ziprasidone; zolpidem; zonisamide; zopiclone
CYP3A4	**inhibitors**	Acalabrutinib;adagrasib; amiodarone; aprepitant; atazanavir;atomoxetine;berotralstat ; boceprevir; ceritinib; chloramphenicol ; cimetidine; ciprofloxacin; clarithromycin; cobicistat; conivaptan;crizotinib; cyclosporine;darunavir; delavirdine; diltiazem; dronedarone; duvelisib; entrectinib; erythromycin; esomeprazole; everolimus;fedratinib; fluconazole; fluoxetine; fluvoxamine; fosamprenavir; fosaprepitant; fosnetupitant; givosiran ;grapefruit juice; idebenon ;idelalisib; imatinib ; indinavir; isavuconazol; itraconazole; ivacaftor; ketoconazole; lapatinib; larotrectinib; lefamulin;lesinurad ; letermovir; levoketoconazole; lomitapide; lonafarnib;lopinavir; mibefradil ;mifepristone; nefazodone; nelfinavir; netupitant (as a single dose);nilotinib ;nirmatrelvir-ritonavir; ombitasvir-paritaprevir-ritonavir; ombitasvir-paritaprevir-ritonavir plus dasabuvir ;omeprazole; osilodrostat; pantoprazole; pazopanib; posaconazole; quercetin ; ranolazine; ribociclib; ritonavir; roxithromycin; rucaparib; saquinavir; schisandra; selpercatinib; simeprevir ; star fruit; stiripentol; telaprevir ; telithromycin; ticagrelor; tipranavir; tofisopam; tucatinib; verapamil; voriconazole
CYP3A4	**inducers**	Aprepitant (effects appear transient); armodafinil;barbiturates; bexarotene; bosentan; brigatinib; carbamazepine ;cenobamate;clobazam; dabrafenib; darolutamide; dexamethasone; dipyrone; efavirenz; elagolix ; enzalutamide; eslicarbazepine; etravirine; fosaprepitant (effects appear transient); fosphenytoin ; glucocorticoids; letermovir ; lorlatinib; lumacaftor-ivacaftor; mitapivat;mitotane; modafinil; nafcillin; nevirapine; oxcarbazepine; pexidartinib; phenobarbital;phenytoin; pioglitazone; pitolisant; primidone; rifabutin; rifampicine; rifapentine ;rufinamide; sotorasib;; St John's wort (Hypericum perforatum); telotristat; topiramate; troglitazone; vandetanib; vemurafenib

Transporters

P-glycoprotein	**substrates**	Acalabrutinib; afatinib; alfentanil; aliskiren; ambrisentan; amisulpride; amitriptyline; apixaban; atazanavir; atorvastatine; azithromycine; barbiturates; berotralstat; bictegravir; bilastine; binimetinib; brentuximab vedotin; brigatinib; budesonide; canagliflozine; carbamazepine; carvedilol; celiprolol; ceritinib; cetirizine; ciclosporine; citalopram; clobazam; clopidogrel; cobimetinib; colchicine; cyclosporine; dabigatran etexilate; dabrafenib; darolutamide; darunavir; dasatinib; daunorubicine; desloratidine; dexamethason; digoxin; diltiazem; docetaxel; dolutegravir; domperidone; doxorubicine; droperidol; edoxaban; efavirenz; elagolix; elbasvir ; eletriptan; eliglustat; emtricitabine ; enzalutamide; erlotinib; erythromycine; eslicarbazepine; estradiol; ethinylestradiol; etoposide; everolimus; fentanyl; fexofenadine; fidaxomicine; fostemsavir;gefitinib ; gilteritinib; glecaprevir; glucocorticoids ; grazoprevirimatinib; indacaterol; irinotecan; itraconazole; lapatinib; Larotrectinib; ledipasvir; Lefamulin; lenvatinib; letermovir ;linagliptine;loperamide; loratadine; lorlatinib;maraviroc; mefloquine methylprednisolone; mirabegron; mitomycine ;modafinil;morfine;naloxone; nevirapine; nilotinib; nintedanib; niraparib: nortriptyline; odevixibat; ondansetron; oseltamivir; osimertinib; oxcarbazepine; paclitaxel; paroxetine; pazopanib; phenobarbital;phenytoin; pibrentasvir; pioglitazone pomalidomide; posaconazol ;pralsetinib; prednisone; raltegravir;ranolazine; relugolix;remdesivir; rifabutin; rifampin; rifaximine; rimegepant; riociguat; risperidone; ritonavir; rivaroxaban ;saquinavir;saxagliptine;sertraline ;silodosin;sirolimus; sitagliptine;sofosbuvir; sorafenib; st. john's wort; sunitinib; tacrolimus; talazoparib; talinolol; telotristat; temsirolimus; tenofovir; tepotinib; ticagrelor ; tipranavir; tolvaptan; topotecan trabectedine; troglitazone; ubrogepant; umeclidinium;velpatasvir; vemurafenib; venetoclax; venlafaxine; verapamil; vilanterol; vinblastine; vincristine; vinorelbine; vismodegib; voxilaprevir
Breast Cancer Resistance Protein (BCRP)	**substrates**	Atorvastatin; fluvastatin; rosuvastatin; sulphasalazine; topotecan
Organic Anion Transporter Polypeptide (OATP) substrates	**OATP1B1 substrates**	Atorvastatin; bosentan; fexofenadine; fluvastatin; rosuvastatin
	OATP2B1 substrates	Atorvastatin, fexofenadine, fluvastatin, rosuvastatin

UDP-glucuronosyltransferases (UGT)

UGT1A9	**substrates**	Fenofibrate; diflunisal
UGT2B7	**substrates**	Gemfibrozil; lamotrigine
UGT1A7, UGT1A9, UGT2B7	**inhibitors**	Mefenamic acid; probenecid

APPENDIX II: NIET LIMITATIEVE LIJST VAN GENEESMIDDELEN MET BEPAALDE FARMACODYNAMISCHE EIGENSCHAPPEN

Agents affecting glucose metabolism[a]	*Antidiabetics:* metformin, glibenclamide, glipizide, gliquidone, gliclazide, glimepiride, acarbose, sitagliptin, vildagliptin, saxagliptin, linagliptin, aldogliptin, pioglitazon, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, dapaglifozin, canaglifozin, empaglifozin, ertuglifozin, repaglinide, Insulin and analogues
	Other hypoglycemia associating agents: chloroquine, disopyramide, hydroxychloroquine, lanreotide, mecasermin, mifepristone, octreotide, quinine, somatostatin acetate, sunitinib, tramadol
Antithrombotic and thrombolytic agents[b]	*Antithrombotic agents:* antitrombine, dalteparine, enoxaparin, nadroparin, danaparoid, warfarin, phenprocoumon, acenocoumarol, clopidogrel, ticlopidine, acetylsalicylic acid, epoprostenol, tirofiban, treprostenil, prasugrel, ticagrelor, bivaluridin, dabigatran etexilate, rivaroxaban, apixaban, edoxaban, fondaparinux, caplacizumab, defibrotide
	Thrombolytic agents: alteplase, tenecteplase, urokinase
	Other drugs with a potential increased bleeding risk: abrocitinib, acalabrutinib, bevacizumab, cabozantinib, caplacizumab, cobimetinib, dasatinib, ibrutinib, obinutuzumab, trastuzumab emtansine, zanabrutinib
Immunosuppressants[c]	abatacept, abrocitinib, adalimumab, alemtuzumab, anakinra, anifrolumab, antithymocyte globulin, azathioprine, baricitinib, basiliximab, belimumab, bimekizumab, brodalumab, canakinumab, certolizumab, cyclosporine, eculizumab, etanercept, filgotinib, fingolimod, golimumab, guselkumab, infliximab, ixekizumab, leflunomide, mycophenolate, natalizumab, ocrelizumab, ozanimod, pegcetacoplan, ponesimod, risankizumab, sarilumab,secukinumab, siponimod, sirolimus, tacrolimus, teriflunomide, tocilizumab, tofacitinib, upadacitinib, ustekinumab, vedolizumab
Stimulating agents[d]	lisdexamfetamine, methylphenidate, modafinil
Sympathomimetic agents[e]	caffeine, dobuamine, dopamine, Doxapram, epherine, epinephrine, etilefrine, fenoterol, formoterol, Guarana, indacaterol, lisdexamfetamine, methylphenidate, modafinil, naphazoline (nasal), norepinephrine, olodaterol, oxymetazoline (nasal), phenylephrine, pseudoephedrine, salmeterol, terbutaline, theophylline, vilanterol, xylometazoline
Immunotherapy[f]	atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab

APPENDIX III: REFERENTIES

Referentiebronnen CAHM-geneesmiddel interacties

- UpToDate: Lexicomp Drug Interactions
- Integrative Medicine: Search About Herbs - Memorial Sloan Kettering Cancer Center (MSKCC)
- MedicinesComplete: Stockley's drug interactions
- Williamson E, Driver S, Baxter K. Stockley's Herbal Medicines Interactions: a guide to the interactions of herbal medicines. Second edition ed. London: Pharmaceutical Press; 2013. ISBN 978-0-85-711026-8
- European Union herbal monographs and assessment reports

Metabolisatie pathways van de bestudeerde *victim drugs*

- FDA labels
- European Public Assessment Reports
- Electronic Medicines Compendium
- General drug information from UpToDate

Lijsten van substraten, inhibitoren en inducers

- BCFI
- MedicinesComplete: Stockley's drug interactions
- UpToDate: Lexicomp Drug Interactions
- Drug Interaction Flockhart Table

APPENDIX IV: EVIDENTIE CLASSIFICATIE

- Gebaseerd op het Drug Interaction eVidence Evaluation Instrument[(1)]

Category	Evidence

Sufficient evidence	*One or more of the following even when items of the insufficient category were present:*
	<u>Direct evidence</u>
	- Systematic review or meta-analysis
	- Clinical PK studies: prospective controlled studies and observational studies
	- Retrospective analysis, including case reports and case series
	- Physiologically based pharmacokinetic model
	<u>Indirect evidence involving related drugs</u>
	- Reasonable extrapolation on the basis of any of the above listed study designs involving drugs with similar pharmacologic properties
	  ○ PK properties (e.g. Echinacea and caffeine → CYP1A2 substrates)
	  ○ PD properties (e.g. Ashwagandha and thyroid drugs → antithyroid drugs)

Insufficient evidence	*One or more of the following without supporting evidence from the "sufficient" category:* - In-silico analysis - Inference on the basis of studies with *in vitro* substrate, inhibitor or inducer data - Hypothesis-generating research methods, including patient surveys (e.g. glucosamine and paracetamol) - Animal data - Unsubstantiated statements in product labelling or drug databases: statements that are unsubstantiated by data or pharmacological properties of the drug (e.g. ginger and hypoglycaemia associating agents)

[(1)]Grizzle AJ, Hines LE, Malone DC, Kravchenko O, Hochheiser H, Boyce RD. Testing the face validity and inter-rater agreement of a simple approach to drug-drug interaction evidence assessment. J Biomed Inform. 2020;101:103355.