



Universiteit Utrecht



HagaZiekenhuis

# The Prevalence of Clinically Relevant Herb-Drug Interactions between Herbal Products and Anti-Cancer Therapy in Older Adults with Cancer

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## Abstract

**Background:** 30-90% of cancer patients use complementary and Alternative Medicine (CAM). About 50-70% of these patients do not inform their physicians concerning CAM. Herbal drug use in cancer patients may interfere with the exposure to anti-cancer medication, which may lead to higher toxicity or treatment failure.

**Objective:** This study aimed to investigate the prevalence of potentially relevant Herb-Drug Interaction (HDI) in older adults (aged 65 years or older) with cancer. Furthermore, the overall use of herbal products in this patient population is also examined.

**Method:** HERDICHEM was a single-centre cross-sectional study, performed at the Haga teaching hospital, the Netherlands. Patients who were  $\geq 65$  years of age and were prescribed an intravenous or oral pharmacological treatment for cancer were recruited from the departments of internal medicine – oncology, hematology, and pulmonology.

The primary endpoint was the percentage of potentially relevant HDI in older patients ( $\geq 65$  years) with cancer. The secondary endpoint was the percentage of herbal product use in older adults ( $\geq 65$  years) with cancer. Another secondary endpoint was the association between the prevalences of the occurrence of an HDI and the overall use of herbal products with patient characteristics; gender, age, oncological specialism, number of regular systemic drugs, or level of education.

**Results:** A total of 125 patients were included in this study, 66 of which were male and 59 were female with a mean age of 74 years old. The use of herbal products was found in 8.3% of patients and 2.3% of herbal drug use showed a potentially relevant HDI. There was no significant association between the use of herbal products and age, gender, oncological specialism, level of education or number of systemic drugs. This also applies to the occurrence of HDI and age, gender, oncological specialism, level of education or number of systemic drugs.

**Discussion:** Due to the lack of power, no conclusion can be made about the associations between herbal drug use and the occurrence of HDI with regards to age, gender, oncological specialism, level of education, or number of systemic drugs.

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# Introduction

The prevalence of potential drug-drug interactions is 80% in the elderly population (aged 65 years or older). This is due to an increased number of comorbidities, which lead to a larger number of prescribed drugs<sup>[1],[2]</sup>. Approximately 4% of all deaths in cancer patients are caused by drug-drug interactions<sup>[3]</sup>. Considering most oncolytic are metabolized by the liver, they are more potent for drug-drug interactions<sup>[4]</sup>.

The use of dietary supplements by elderly cancer patients has increased<sup>[4]</sup>. Cancer patients sometimes combine herbal products with their anti-cancer therapy to help treat cancer symptoms, reduce side effects caused by anti-cancer therapy, and improving quality of life<sup>[5]</sup>. However, there may be a potential risk of interference between the herb and the anti-cancer therapy. The prevalence of complementary and alternative medicines (CAM) among cancer patients is 30 to 90%<sup>[1],[4],[6]</sup>. CAM refers to a broad set of health care practices that do not fall under the conventional healthcare system guidelines, as defined by the World Health Organization (WHO) (e.g., herbal product treatment)<sup>[7]</sup>. Herbal products are some of the most popular CAM among cancer patients and can be easily purchased at e.g. drugstores<sup>[8]</sup>. Most patients do not seek advice or guidance from the physician regarding the use of CAM<sup>[9]</sup>. About 50-70% of these patients do not inform their physicians<sup>[9],[10]</sup>. Hence, the physicians are oftentimes unaware of potential herb-drug interactions (HDIs).

HDIs become relevant when the herbal product modifies exposure to prescribed medication (e.g., enzyme and/or transporter induction/inhibition). Anti-cancer drugs have a narrow therapeutic window, therefore any alteration in anti-cancer drug exposure can lead to toxicity or treatment failure<sup>[11]</sup>. Moreover, some anticancer agents such as ifosfamide and cyclophosphamide are prodrugs meaning they only become activated after the biotransformation by cytochrome P450 (CYP) enzymes. Therefore, they are more likely to be affected by CYP enzyme interactions<sup>[11]</sup>.

The prevalence of potentially relevant HDIs at the Haga teaching hospital is unknown. It is, therefore necessary to study the prevalence of potentially relevant HDIs. All things considered, this prospective cross-sectional study aims to investigate the prevalence of potentially relevant HDI in older adults (aged 65 years or older) with cancer. Thereby, the overall use of herbal products in this patient population is also examined.

# Method

## Study design

HERDICHEM was a single-centre cross-sectional study, performed at the Haga teaching hospital, the Netherlands. Patients  $\geq 65$  years who had an intravenous or oral pharmacological treatment for cancer were recruited from the departments of internal medicine – oncology, hematology, and pulmonology. This study was an 'investigation not subject to the WMO' (Medical Research Involving Human Subjects Act), examined by The Medical Ethics Review Committee (METC). All study participants provided written Informed Consent (IC). The questionnaires (Appendix I HERDICHEM questionnaire) were filled in by interview either in person or via the phone.

## Patients

Eligible patients were  $\geq 65$  years of age, who received an active oral or intravenous pharmacological cancer treatment between March 1, 2021 and, July 1, 2021 at the Haga teaching hospital. Monoclonal antibody cancer treatments were excluded from this study.

## Endpoints

The primary endpoint was the percentage of potentially relevant HDI in older patients ( $\geq 65$  years) with cancer. A HDI was potentially relevant if the combination of the herbal product and the anti-cancer drug was contraindicated or if the patient should be warned that a significant interaction or adverse outcome could occur<sup>[12]</sup>.

The secondary endpoint was the percentage of overall use of herbal products (defined as; medicines derived from plants, which are used as supplements to improve health and well-being, and may be used for other therapeutic purposes<sup>[13]</sup>) in older adults ( $\geq 65$  years) with cancer. Another secondary endpoint was the association between the prevalences of the occurrence of a HDI and the overall use of herbal products with patient characteristics; gender, age, oncological specialism, number of regular systemic drugs or level of education.

## Procedure

A questionnaire (see Appendix I HERDICHEM questionnaire) was prepared. This questionnaire was completed by patients  $\geq 65$  years who received active pharmacological treatment for cancer. The questionnaire consisted of a few general questions about the use of herbal supplements and two sections to identify which of thirteen herbal supplements with potential HDIs to prescription medication was in use. Herbal products mentioned in the questionnaire were: st. Jonh's Wort, red yeast rice, ginseng, red sage, curcumin, cannabis, ginkgo biloba, green tea, garlic, milk thistle, valerian, echinacea, and black cohosh. These herbal products are commonly used herbs, as mentioned in the published list of the College ter beoordeling van Geneesmiddelen (CBG) as commonly used herbs. Open questions on the questionnaire allowed patients to document the use of any herbal products not mentioned above. The results of the questionnaire were compared to the oncological treatment to identify potentially relevant HDI.

The prescribed cancer treatments were extracted from the electronic hospital's medical record, Hix. The clinical relevance of any potential HDI was assessed independently by a pharmacist and pharmacist-clinical pharmacologist and was discussed until consensus was reached. If no consensus was reached, a third pharmacist was involved for a final decision. The oncologist/patients, as appropriate, was informed and received regarding the management of any potentially relevant HDI identified.

The oncological specialty and number of regular systemic drugs were extracted from the electronic hospital's medical record, Hix. A drug was considered a regular systemic drug if it was applied systemically, if it was taken continuously or as needed and if it was not part of or directly related to the cancer treatment, such as anti-emetics, granulocyte colony stimulating factor (G-CSF), or drugs for bone metastases. The patients gender, age and level of education were collected with the questionnaire.

### Statistical analysis

The prevalence of the number of older patients with potentially relevant HDIs outcomes and the overall use of herbal products were described using descriptive statistics. The association between the categorical variables (oncological specialism, gender, and level of education) and the occurrence of an HDI and overall use of herbal products were analysed with the Chi-square test. When more than 20% of the cells contained an expected cell count lower than five or when the smallest count was lower than one, the Likelihood ratio was used. If the Omnibus Tests of Model of Coefficients was significant, Binary Logistic Regression was used to determine the association between the continuous variables and the occurrence of an HDI and overall use of herbal products. For insignificant results, the independent samples T-test and nonparametric Mann Whitney U test were used.

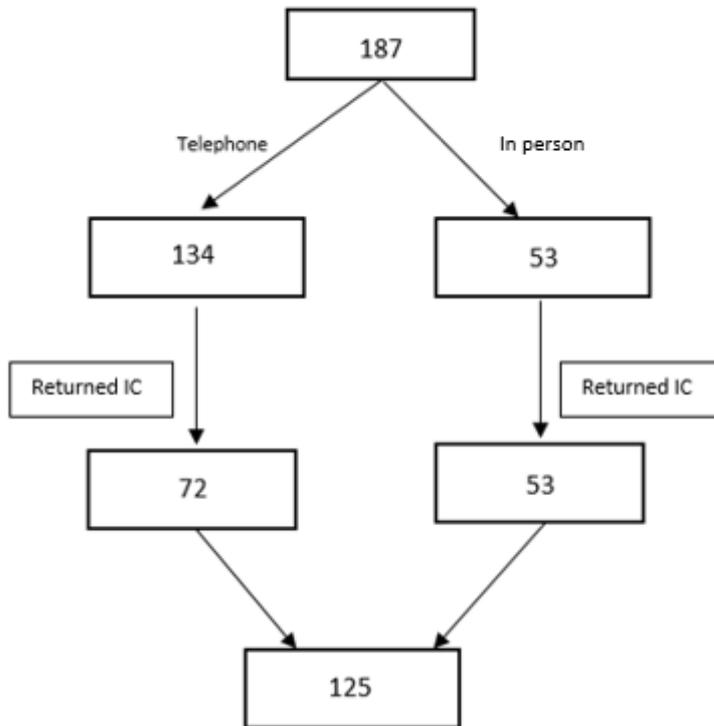
The association between the continuous variables (age or number of regular drugs) occurrence of HDI and of overall use of herbal products were analysed with independent samples T-test and nonparametric Mann Whitney U test. The independent samples T-test was used for normally distributed continuous variables and the Mann Whitney U test was used for the not normally distributed continuous variables. In all analyses,  $p < 0.05$  was considered statistically significant and all analyses were performed in SPSS version 24.

# Results

## Patient population

The study was conducted between February 8, 2021, to July 1, 2021. A total of 187 patients were approached, 134 of which by telephone and 53 in person. A total of 134 Patient Information Folders (PIF's) and ICs were sent out to the patients approached by telephone. Of these only 72 were returned.

**Figure 1** Overview of included patients.



Overall, 125 (66,8%) patients with pharmacological treatment of cancer at the Haga Teaching hospital were included. Baseline patient characteristics are summarized in Table 1.

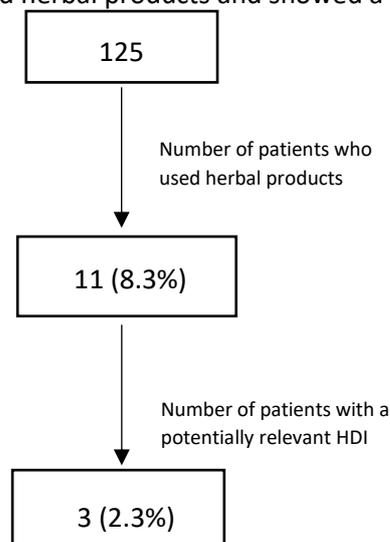
**Table 1** Summary of baseline patient characteristics.

Characteristic	N=125	
<b>Age, years</b>		
Mean (SD)	74 (6,6)	
<b>Gender, (N(%))</b>		
Male	66 (52.8)	
Female	59 (47.2)	
<b>Education level, (N(%))</b>		
No education	1 (0.8)	
Primary education	21 (16.8)	
Secondary School	66 (52.8)	
College	32 (23.5)	
University	5 (3.6)	
<b>Oncological specialism, (N(%))</b>		
Internal medicine	70 (56.0)	
Hematology	41 (32.8)	
Pulmonology	14 (11.2)	
<b>Number of systemic drugs*(N(%))</b>		
0-5, n	51 (40.8)	*Drugs which were applied systemically and if it was not part of the cancer treatment or supportive therapy related to the cancer treatment.
6-10, n	53 (42.4)	
11-15, n	12 (9.6)	
16-20,n	9 (7.2)	

### Endpoints

Out of the 125 patients, 11 patients (8.3%) used herbal products during their cancer treatment. Three patients appeared to have potentially relevant HDI, see Figure 2. Each of these patients showed two potentially relevant HDIs, thus a total of six potentially relevant HDIs, see Table 2.

**Figure 2** Overview of patients who used herbal products and showed a potentially relevant HDI.



**Table 2** This table describes the potentially relevant HDIs found.

	PATIENT 1	PATIENT 2	PATIENT 3
<b>HDI</b>	Curcuma longa and paclitaxel	Red yeast rice and olaparib	Allium sativum (garlic) and enzalutamide
<b>ADVICE</b>	Continue use	Continue use	Continue use
<b>HDI</b>	Echinacea and paclitaxel	Echinacea and olaparib	Echinacea and enzalutamide
<b>ADVICE</b>	Discontinue use	Discontinue use	Continue use

Patient one:

The first patient showed two potentially relevant HDIs, see Table 2. Paclitaxel is metabolised by CYP2C8 and to a lesser extent by CYP3A4. Curcuma is a possible inhibitor of CYP3A4. However since a smaller proportion of paclitaxel is metabolized by CYP3A4 and the evidence is weak, this interaction was unlikely to be clinically relevant. Echinacea can induce hepatic CYP3A4 (and inhibit intestinal CYP3A4) and thereby accelerate the metabolism of paclitaxel. The relevance of this interaction was questionable, but because the effect of paclitaxel is not directly measurable and the indication is compelling, the advice to the patient was to discontinue the herbal preparation containing echinacea.

Patient two:

The second patient was treated with olaparib and used red yeast rice. Olaparib is a weak inhibitor of CYP3A4 and red yeast rice contains lovastatin, a substrate for CYP3A4. Olaparib may increase the level of lovastatin slightly. However, because olaparib is a weak CYP3A4 inhibitor and the lovastatin dose is low, this interaction was considered irrelevant. The effect of echinacea during the treatment with olaparib is expected to be limited. Because the effect of olaparib is not directly measurable, the advice to the patient was to discontinue the herbal preparation containing echinacea.

Patient three:

The third patient used allium sativum and Echinacea during enzalutamide treatment. Enzalutamide is a substrate for CYP2C8 and to a much lesser extent for CYP3A4. Dose adjustment is only advised in the Summary of Product Characteristics (SmPC) for combination with strong CYP2C8 inhibitors and is not necessary for CYP3A4 inhibitors or inducers. The possible effect of allicin-containing garlic preparations on intestinal (inducing) and hepatic (inhibiting) CYP3A4 is small. Therefore, there was no relevant interaction between allium sativum and enzalutamide. As for echinacea, there was no relevant interaction between enzalutamide and echinacea.

The association between the use of any herbal products or the occurrence of a potentially relevant HDI and gender, oncological specialism and level of education is shown in Table 3. The overall use of herbal products by patients of the internal medicine was higher compared to hematology and pulmonology, but this difference was not significant, see Table 4.

Out of eleven patients who used herbal products, three patients showed a potentially relevant HDI. Two patients with a potentially relevant HDI were female and one male. Although the associations cannot be justified with a total of three HDIs, it was still examined. Patients with a bachelor's degree showed a higher overall use of herbal products in comparison with other degrees of education levels.

**Table 3** The associations between the use of any herbal products and the occurrence of a potentially relevant HDI and gender, oncological specialism and level of education.

N=125	Number of use of any herbal products	Number of no use of herbal products	Number of potentially relevant HDI of patients who used herbal products
<b>Gender (N(%))</b>			
▪ Male	6 (4.8%)	60 (48%)	1 (0.8%)
▪ Female	5 (4%)	54 (43.2%)	2 (1.6%)
<b>Oncological Specialism (N(%))</b>			
▪ Internal Medicine	8 (6.4%)	62 (49.6%)	3 (2.4%)
▪ Hematology	3 (2.4%)	38 (30.4%)	0 (0.0%)
▪ Pulmonology	0 (0.0%)	14 (11.2%)	0 (0.0%)
<b>Level Of Education (N(%))</b>			
▪ No Education	0 (0.0%)	1 (0.8%)	0 (0.0%)
▪ Primary Education	1 (0.8%)	20 (16%)	1 (0.8%)
▪ Secondary School	4 (3.2%)	62 (49.6%)	2 (1.6%)
▪ College	6 (4.8%)	26 (20.8%)	0 (0.0%)
▪ University	0 (0.0%)	5 (4%)	0 (0.0%)

There was no significant association between the overall use of herbal products and level of education, see Table 4. Also, there was no significant association between the use of any herbal products and the occurrence of HDI with age or number of regular drugs, see Table 4. Although, the use of any herbal products did show a trend with the number of regular drugs.

**Table 4** P-values of the associations of use of any herbal products and occurrence of HDI with the different variables; age, gender, oncological specialism, level of education and number of regular drugs.

	Age	Gender	Oncological specialism	Level of education	Number of regular drugs
<b>Use of any herbal products</b>	0.487	0.903	0.197	0.497	0.068
<b>Occurrence of HDI</b>	0.550	0.385	0.129	0.062	0.630

# Discussion

The prevalence of overall use of herbal products in older adults ( $\geq 65$  years) with cancer was 8.3% (11 patients), from which 2.3% (3 patients) showed a potentially relevant HDI at the Haga teaching hospital. All three patients had two potentially relevant HDIs. The first patient had one potentially relevant HDI. As a follow-up, the physician and patient will be consulted to discuss the consequence of the use of the herbal product during the anti-cancer treatment, and advice to discontinue the herbal product will be given. Also, the advice of the second patient with one potentially relevant HDI was to discontinue the use of the herbal product, because the effect of the oncolytic was not measurable and the indication was compelling. For the third patient, the HDIs were deemed not relevant and thus the patient could continue to use the herbal product.

A secondary endpoint was the association between the prevalences of the occurrence of an HDI and the overall use of herbal products with patient characteristics. There was no association found between the use of herbal products and age, gender, oncological specialism, level of education or number of systemic drugs. The occurrence of HDI was also not associated with age, gender, oncological specialism, level of education, or number of systemic drugs.

The fact that none of the variables showed an association with the outcomes could be due to the number of patients included. Originally 250 patients were planned to be enrolled in this study however, only 125 patients were included. The reason was, a delay in the approval of the METC and the science office of the Haga teaching hospital. An increase in power may have yielded statistically significant results.

In addition, the cancer patients in the Haga teaching hospital are closely monitored. For example, during the intake interview patients are already asked about herbal products. The use of herbal products is also discouraged by the oncologist / haematologist, which explains the lower prevalence in our population than the 30 to 90% mentioned in the literature<sup>[1],[4],[6]</sup>.

Future research should involve several hospitals and a larger study population, because the literature shows that cancer patients have a lot of interest in herbal medicines and oftentimes use it without informing their physicians. This may lead to increased toxicity or decreased treatment effectiveness. However, our current study could not confirm this. Hence, the probability found that the increase in toxicity or decrease in treatment effectiveness due to the use of herbal products in this population was small.

When performing the analysis in SPSS, a syntax was kept. This file could be used for future research. Also, the used questionnaire (Appendix I HERDICHEM questionnaire) could be reused in the future as it is a short, not time-consuming questionnaire for the patients.

# References

1. Clairet AL, Boiteux-Jurain M, Curtit E, Jeannin M, Gérard B, Nerich V, et al. Interaction between phytotherapy and oral anticancer agents: prospective study and literature review [Internet]. *Medical Oncology* 2019 [cited 2021 Jun 18];36(5). Available from: <https://pubmed.ncbi.nlm.nih.gov/30993543/>
2. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly [Internet]. *Expert Opinion on Drug Safety* 2014 [cited 2021 Jun 18];13(1):57–65. Available from: <https://pubmed.ncbi.nlm.nih.gov/24073682/>
3. van Leeuwen RWF, Brundel DHS, Neef C, van Gelder T, Mathijssen RHJ, Burger DM, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs [Internet]. *British Journal of Cancer* 2013 [cited 2021 Jun 18];108(5):1071–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/23412102/>
4. Riechelmann RP, del Giglio A. Drug interactions in oncology: How common are they? [Internet]. *Annals of Oncology* 2009 [cited 2021 Jun 18];20(12):1907–12. Available from: <https://pubmed.ncbi.nlm.nih.gov/19713244/>
5. Hardy ML. Dietary Supplement Use in Cancer Care: Help or Harm [Internet]. *Hematology/Oncology Clinics of North America* 2008 [cited 2021 Jun 18];22(4):581–617. Available from: <https://pubmed.ncbi.nlm.nih.gov/18638690/>
6. Fasinu PS, Rapp GK. Herbal Interaction With Chemotherapeutic Drugs—A Focus on Clinically Significant Findings [Internet]. *Frontiers in Oncology* 2019 [cited 2021 Jun 18];9. Available from: <https://pubmed.ncbi.nlm.nih.gov/31850232/>
7. Traditional, Complementary and Integrative Medicine [Internet]. [cited 2021 Jun 18]; Available from: [https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab\\_1](https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab_1)
8. Goey AKL, Mooiman KD, Beijnen JH, Schellens JHM, Meijerman I. Relevance of in vitro and clinical data for predicting CYP3A4-mediated herb-drug interactions in cancer patients [Internet]. *Cancer Treatment Reviews* 2013 [cited 2021 Jun 18];39(7):773–83. Available from: <https://pubmed.ncbi.nlm.nih.gov/23394826/>
9. Gupta D, Lis CG, Birdsall TC, Grutsch JF. The use of dietary supplements in a community hospital comprehensive cancer center: Implications for conventional cancer care [Internet]. *Supportive Care in Cancer* 2005 [cited 2021 Jun 18];13(11):912–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/15856334/>
10. Haefeli WE, Carls A. Drug interactions with phytotherapeutics in oncology [Internet]. *Expert Opinion on Drug Metabolism and Toxicology* 2014 [cited 2021 Jun 18];10(3):359–77. Available from: <https://pubmed.ncbi.nlm.nih.gov/24387348/>
11. Choi MK, Song IS. Interactions of ginseng with therapeutic drugs [Internet]. *Archives of Pharmacal Research* 2019 [cited 2021 Jun 18];42(10):862–78. Available from: <https://pubmed.ncbi.nlm.nih.gov/31493264/>
12. Natural Medicines [Internet]. [cited 2021 July 12]; Available from: <https://naturalmedicines.therapeuticresearch.com/tools/stop-light-rating-system.aspx>
13. Drugs [Internet]. [cited 2021 July 12]; Available from: <https://www.drugs.com/drug-class/herbal-products.html>

# Appendix

## I HERDICHEM questionnaire



### HERDICHEM vragenlijst

Vragenlijst bij de HERDICHEM-studie voor het onderzoek naar de wisselwerking tussen kruidenpreparaten en chemotherapie.

#### Gegevens deelnemer

Geslacht man / vrouw

Leeftijd ..... jaar

Hoogst voltooide opleiding

- |  |  |
|--|--|
| <input type="checkbox"/> Geen diploma                      | <input type="checkbox"/> Bachelor (HBO/WO) |
| <input type="checkbox"/> Basisonderwijs                    | <input type="checkbox"/> Master (HBO/WO)   |
| <input type="checkbox"/> VMBO, HAVO/VWO<br>onderbouw, MBO1 | <input type="checkbox"/> Doctor, PhD       |
| <input type="checkbox"/> HAVO, VWO, MBO 2-4                |  |

#### In te vullen door de onderzoeker

PID

Enquête FTF / zelf / videocall / telefoon / post

Afgenomen door

Datum

Paraaf

#### Onderdeel A

Algemene vragen over het gebruik van kruidenpreparaten

- Ik wist dat sommige kruidenpreparaten een effect kunnen hebben op de behandeling tegen kanker.  
 Ja  
 Nee
- Ik gebruik kruidenpreparaten in de periode dat ik voor kanker behandeld word.  
 Ja → ga verder met de vragenlijst  
 Nee → u bent klaar met de vragenlijst
- Mijn oncoloog weet dat ik kruidenpreparaten gebruik.  
 Ja  
 Nee  
 Weet ik niet
- Ik zou stoppen met het gebruik van kruidenpreparaten als mijn oncoloog zegt dat dat beter is.  
 Ja  
 Nee  
 Weet ik (nog) niet
- Ik gebruik kruidenpreparaten  
 Op eigen initiatief  
 Op advies van anderen zoals familie, kennis, vrienden, burens  
 Op advies van een alternatieve genezer  
 Anders, namelijk .....

## Onderdeel B

Vink aan als u één of meer van onderstaande kruiden of kruidenpreparaten gebruikt.

- |   |   |
|---|---|
| <input type="checkbox"/> Sint-janskruid ( <i>Hypericum perforatum</i> )       | <input type="checkbox"/> Japanse notenboom of ginkgo ( <i>Ginkgo biloba</i> ) |
| <input type="checkbox"/> Rode gist rijst                                      | <input type="checkbox"/> Groene thee* ( <i>Camellia sinensis</i> )            |
| <input type="checkbox"/> Amerikaanse Ginseng ( <i>Panax quinquefolius</i> )   | <input type="checkbox"/> Knoflook* ( <i>Allium sativum</i> )                  |
| <input type="checkbox"/> Danshen of rode salie ( <i>Salvia miltiorrhiza</i> ) | <input type="checkbox"/> Mariadistel ( <i>Silybum marianum</i> )              |
| <input type="checkbox"/> Geelwortel of kurkuma* ( <i>Curcuma longa</i> )      | <input type="checkbox"/> Valeriaan ( <i>Valeriana officinalis</i> )           |
| <input type="checkbox"/> Cannabis. Zo ja, met welke actieve stoffen:          | <input type="checkbox"/> Rode zonnehoed ( <i>Echinacea</i> )                  |
| <input type="radio"/> Alleen of voornamelijk CBD                              | <input type="checkbox"/> Zilverkaars ( <i>Cimicifuga</i> )                    |
| <input type="radio"/> Alleen of voornamelijk THC                              |   |
| <input type="radio"/> THC + CBD   |   |
| <input type="radio"/> Onbekend  |   |

- Ik gebruik geen (van bovenstaande) kruidenpreparaten

\*Kurkuma, groene thee en knoflook alleen wanneer die in gebruik zijn als kruidensupplement. Groene thee als drank of kurkuma en knoflook bij het bereiden van een maaltijd niet aankruisen.

## Onderdeel C

Als u andere kruidenpreparaten gebruikt, kunt u die hieronder invullen.

Hartelijk bedankt voor het invullen van deze vragenlijst!

Het onderzoeksteam.