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ORIGINAL RESEARCH

# Cytochrome *P*-450-mediated herb and food—drug interactions can be identified in cancer patients through patient self-reporting with a tablet application: results of a prospective observational study

**P. Gougis[1,2,3*], A. Géraud[4], M. Hilmi[5], A. Vozy[3], L. Campedel[3], B. Abbar[3], C. Allio[2,3], S. De Chatillon[2,3], A. Portalier[6], F. Lapray[3], S. Choquet[6], J.-P. Spano[3], F. Reyal[1,7,8], O. Mir[9], C. Funck-Brentano[2] & A.-S. Hamy[1,10]**

[1]Residual Tumor & Response to Tre atment Laboratory, RT2Lab, INSERM, U932 Immunity and Cancer, Institut Curie, Université Paris, Paris; [2]Sorbonne Université, Institut national de la santé et de la recherche médicale (INSERM), Assistance Publique—Hôpitaux de Paris (AP-HP), Clinical Investigation Center (CIC-1901), Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris; [3]Department of Medical Oncology, Assistance Publique—Hôpitaux de Paris (AP-HP), Pitié-Salpêtrière Hospital, Paris; [4]Department of Drug Development, Gustave Roussy Cancer Center, Villejuif; [5]Medical Oncology Department, Curie Institute, Versailles Saint-Quentin University (UVQ), Paris Saclay University, Saint-Cloud; [6]Clinical Hematology Unit, Groupe Hospitalier Pitié-Salpêtrière, AP-HP Sorbonne Université, Paris; [7]Department of Breast, Gynecological and Reconstructive Surgery, Institut Curie, Université Paris, Paris; [8]Department of Surgical Oncology, Institut Godinot, Reims; [9]Department of Ambulatory Care, Gustave Roussy Cancer Campus, Villejuif; [10]Department of Medical Oncology, Institut Curie, Université Paris, Paris, France

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**Background:** Consumption of herbs, food used as medicine and dietary supplements (HFDSs) is common in cancer patients. Herbs and food-drug interactions (HFDIs) can lead to serious adverse effects and can be prevented. We previously reviewed cytochrome *P*-450 (CYP)-mediated HFDI for 261 HFDSs and we classified the risk of CYP inhibition and induction on a level of evidence scale from 1 (high evidence, supported by several clinical studies) to 5 (low evidence, only limited preclinical data).

**Patients and methods:** We conducted a prospective, non-interventional study (NCT04128865) to assess whether self-assessment of patients could detect HFDI classified as 'probable' (i.e. level 1, 2 or 3 of the scale) in a population of cancer patients. Patients were invited through a tablet application to report their consumption of herbs, regular CYP-interacting food consumption and dietary supplements, as well as some clinical data and cancer treatments. The patient's completion of the survey could be supervised by a health care professional or not. A prespecified threshold of 5% of HFDIs classified as 'probable' detected with the application was deemed relevant.

**Results:** Between 29 March 2018 and 22 June 2018, 143 patients completed the survey. Ninety-five patients (66%) reported at least one current systemic cancer treatment and were included in the analyses. Seventy-four patients reported an intake of at least one HFDS (77.9%), while 21 patients reported no HFDS (22.1%). Twenty-two HFDIs classified as 'probable' were found in 16 patients (16.8%) with the application, which was significantly superior to the prespecified threshold ($P = 0.02$). The interactions were reported with food ($n = 19$, 86%) more frequently than with herbs ($n = 3$, 14%) or with dietary supplements (no interaction reported).

**Conclusions:** Self-assessment of HFDS interaction with cancer treatment with an application is feasible and should be considered in daily routine. Prospective interventional studies should be conducted to better assess the clinical benefits of this approach.

**Abbreviations:** HFDS: Herbs, Food and Dietary Supplements - HFDI: Herbs and Food and Drug Interactions - PK: PharmacoKinetics

**Key words:** connected devices, patient-reported measures, herb—drug interaction, food—drug interaction, anticancer drugs, cytochromes

## INTRODUCTION

The use of herbs, food used as medicine and dietary supplements (HFDSs) is increasing in Western countries. HFDSs also represent the core of medical treatments in Asia, Africa and South America where access to pharmaceutical drugs is limited. Between 1997 and 2015, the prevalence of herbal medicine use increased from 12% to

*Correspondence to: Dr Paul Gougis, Institut Curie, 26 rue d'Ulm, 75005 Paris, France. Tel: +33-(0)-1-56-24-55-00

E-mail: paul.gougis@curie.fr (P. Gougis).

one-third of the population in the United States,[1] and an estimated proportion of 40%-60% of cancer patients are taking HFDSs.[1-3] HFDSs are also used in phase I trials[4,5] where up to 93% of patients report the use of a pharmacologically active substance, mostly vitamins and mineral preparations.

HFDSs contain xenobiotics that are absorbed to exert biological activity. Herbs and food-drug interactions (HFDIs) share the same mechanisms as drug—drug interactions, which have been extensively described in oncology.[6-8] Two main types of drug interactions exist: (i) pharmacokinetic (PK) interactions, where one of the substances affects the concentration of others; and (ii) pharmacodynamic (PD) interactions when the drugs have an additive, synergistic or antagonistic effect or have the same target or pathway. Some HFDIs have been extensively described, such as the induction of cytochrome *P*-450 (CYP) 3A4 by patients consuming extracts of St. John's wort (*Hypericum perforatum*), or its inhibition by grapefruit juice (*Citrus paradisi*). Bush et al.[9] prospectively investigated potential HFDIs in 804 patients and found that 15% of patients ($n = 122$) were using traditional medicines. Forty-nine patients (40%) were exposed to a potential plant—drug interaction, and eight interactions were actually observed clinically (7% of plant users). While there is growing evidence that HFDI can lead to serious and even fatal adverse effects such as transplant rejection or cardiovascular shock,[10] HFDS may still be perceived as harmless by (cancer) patients, notably because they are non-prescription drugs.

HFDI might lead to more severe adverse effects in cancer patients than in other patients, given the narrow therapeutic index of anticancer treatments. Hence, slight changes in clearance or absorption could have a major impact on efficacy or toxicity.[11] Engdal et al.[12] found 47 potential interactions involving CYPs and P-glycoprotein transport in 42 patients receiving cancer treatments and phytotherapy.

In a preliminary work,[13] we systematically reviewed clinical and preclinical *in vitro* and *in vivo* data for 189 herbal medicines and food and 72 dietary supplements commonly used or likely to be responsible for interactions. We classified the level of evidence of the interaction between the HFDS and cytochromes from 1 (very likely) to 5 (unlikely), and HFDIs classified from 1 to 3 were considered as clinically proven or 'probable' (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100650). Twenty-one HFDSs were found to significantly inhibit or induce CYP3A4, such as grapefruit, pomelo, green tea or cranberry in clinical studies.

Connected devices, with electronically reported outcome platforms or follow-up applications, can increase patients' quality of life and overall survival.[14-16] Different strategies could be used depending on their technical knowledge, equipment and background. So far, such device has not been previously tested as a self-assessment tool to detect HFDI. PRINCESSE (PRevention of INteractions Between Phytotherapies and CancEr Treatments by a SmartphonE/Tablet Automated SurvEy) is a prospective observational study (ClinicalTrials.gov—NCT04128865). The primary objective of this study was to assess the percentage of patients with a probable cytochrome-mediated HFDI classified as level 1-3 (clinical evidence), using self-reporting through a tablet application (Figure 1).

## PATIENTS AND METHODS

### Study design

PRINCESSE is a single-center, prospective, observational study. The study was approved by an institutional review and ethical committee [Comité Local d'éthique pour les publications de l'hôpital Cochin (CLEP), n° AAA-2018-08002]. The database was registered (Commission Nationale Informatique et Liberté, n° Wa12515027K). The trial was registered on ClinicalTrials.gov (NCT04128865). All patients enrolled in the study provided electronic informed consent.

### Study population

Patients with the following characteristics were eligible for inclusion: (i) history of cancer, (ii) age $\geq$18 years at diagnosis, (iii) fluency in French and (iv) ability to provide electronic informed consent. Patients with the following characteristics were excluded: (i) no current systemic anticancer treatment (either chemotherapy, targeted therapy, hormone therapy, immunotherapy or any combination).

### Patients' enrollment

Between 29 March 2018 and 22 June 2018, patients were recruited from three sites of Pitié-Salpêtrière Hospital, Paris: (i) the daycare hospital of the oncology department, (ii) coordinating nurse visits in the hematology department and (iii) the waiting room of the scanner of the radiotherapy department. Patients were either encouraged to fill the questionnaire on a tablet by the receptionist or one of the staff members (site 1), by the nurse care coordinator (site 2) or indirectly through advertisements (site 3).

### Data collection

Three tablets (Galaxy tab S2, Samsung©, Seoul, South Korea) were dedicated to the study. On sites 1 and 3, the tablet was fixed on a stand. Before 16 April, patients on site 1 were supervised to fill out the questionnaire. After this date, on site 1 and on site 3, tablets were used in an unsupervised manner. On site 2, the tablet was proposed by the nurse care coordinator who invited patients to participate and supervised filling of forms. Forms were filled on the 'Kenko' application (Figure 1). The 'Kenko' application was updated on 3 May 2018 to allow auto-completion of a prespecified list of HFDSs and anticancer drugs. This updated version of the application also included specific food questionnaires.

### Form completion

The form included 16 questions, including sociodemographics [age (years), gender]; cancer history (cancer

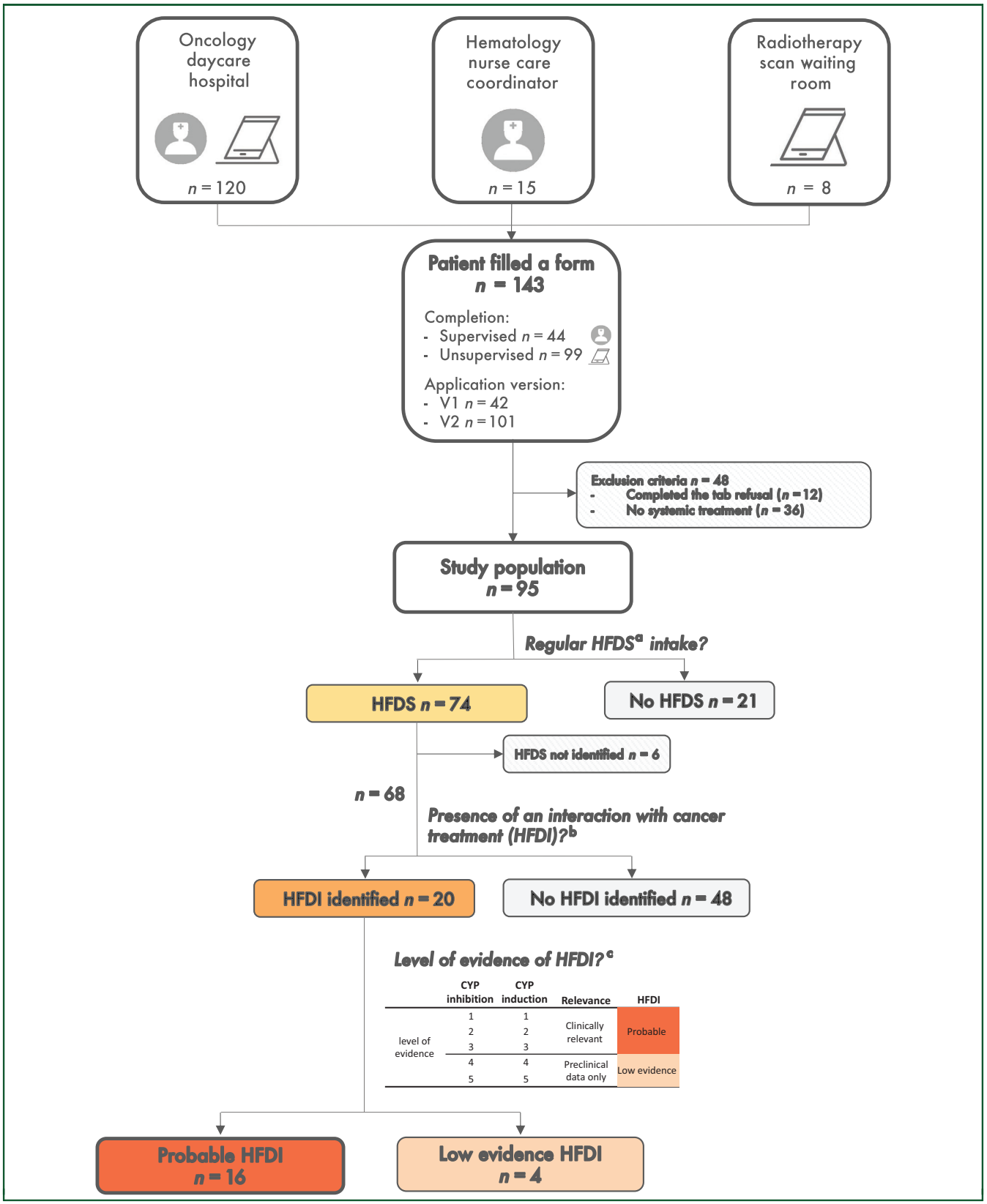


**Figure 1. Principle of data collection and HFDI identification in the study.** Data are collected through the 'Kenko' application completion by patients. Patients could have filled the first version of the app or the second version that included auto-completion and with or without the supervision of a health care professional. The risk of CYP-mediated drug interaction is automatically assessed according to previous published work.[13]
CYP, cytochrome *P*-450; HFDI, herbs and food-drug interaction; HFDS, herb, food and dietary supplements.
[a]HDFS: regular intakes of herb, CYP-interacting food or dietary supplements.
[b]HFDI: herb or food—drug interaction; evaluation based on Gougis et al.[13]
[c]According to literature review.

localization, time since diagnosis), disease stage (metastasis or localized); cancer treatment (surgery, radiotherapy, systemic anticancer treatments).

### HFDS intake

HFDS intake was defined as regular use of phytotherapy, dietary supplements, essential oils taken orally, infusions or consumption of over 3 times a week of CYP-interacting food (>2 cups a day for coffee) identified in the previous review.[13]

Data were collected on the use of alternative therapies (general use of oral therapy, phytotherapy, dietary supplements, essential oils, infusions, homeopathy), the specific name of HFDS intakes (free text fields) and use of other alternative medicines. In the second version of the application, auto-completion was added to fill cancer treatments and HFDS intakes. From 3 May 2018, a specific food questionnaire was added, asking for the daily use of each CYP-interacting food: green tea, cranberry (berries or juice), grapefruit, pomelo, bitter orange (Seville orange), licorice, soy (roots or extracts) and coffee (>2 cups a day).

### Definition and classification of HFDIs

The definition and classification of HFDIs were based on a preliminary work in which we systematically reviewed clinical and preclinical *in vitro* and *in vivo* data for 189 herbal medicines and food and 72 dietary supplements commonly used or likely to be responsible for interactions.[13] HFDS—drug interactions where the HFDS was the victim were not considered.

The level of evidence was classified based on (i) the type of evidence of CYP-mediated HFDI (based on clinical trials versus based on *in vitro* or preclinical data); (ii) the similarity of the CYP metabolizing anticancer treatment and HFDS (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100650).

HFDI was defined as regular intake of an HFDS interacting with a CYP involved in the metabolism of one of the current anticancer treatments, based on the review mentioned previously.

HFDI was further classified as: (i) 'probable' in case of clinical evidence of HFDS interaction with a cytochrome involved in anticancer treatment (i.e. level 1-3 of the classification); (ii) 'low evidence' when the evidence of interaction was based on *in vitro* or preclinical data (i.e. level 4 or 5 of the classification).

### Study objectives

The main endpoint was the proportion of HFDIs classified as 'probable'. We aimed to show that self-reports from a tablet application could identify at least 5% of patients with a probable HFDI in the study population.

### Power consideration and data analysis

The prespecified hypothesis was that we could detect 5% of probable HFDIs in the population. The number of probable interactions existing in the population has been estimated at 10%.[9] For an $\alpha$ risk of 0.05 and a $1-\beta$ power of 80%, we estimated that a population of 150 individuals was needed (one-sided test) using an exact binomial test. Since this study was set for hypothesis generating purposes, no Bonferroni adjustment was made as per exploratory analysis. Standard quality controls include basic descriptive statistics (including mean, median and range) and outliers will be studied for coherence.

The population with an identified probable HFDI was compared to the population without any interaction. Proportions were compared using Fisher's exact test, and quantitative variables with a Wilcoxon test. Statistical analyses were carried out with R software version 4.1.2 (R Core Team - Alcatel-Lucent, NJ).

## RESULTS

### Patients' characteristics and treatments

One hundred and forty-three patients completed the form. Twelve patients declined participation through the 'refusal tab' of the application. Thirty-six patients did not fill any systemic treatment and were not included in the analysis (exclusion criteria) leaving 95 patients for the analysis (Figure 1). Most patients were recruited from the oncology department ($n = 82$), while a minority was recruited in the hematology ($n = 12$) or in the radiotherapy department ($n = 1$). Thirty-four patients (36%) were supervised by a health care professional during the application completion. The population for which data acquisition was unsupervised was different regarding cancer types with more patients having breast cancer (34% versus 21%) and less patients with hematologic diseases (3% versus 35%) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100650).

The study population is detailed in Table 1. The median age was 57 years, and gender was well balanced (women/men 55%/45%, respectively). The repartition of cancer by localization was as follows: breast cancer ($n = 28$, 30%), lung cancer ($n = 16$, 17%), hematologic cancer ($n = 14$, 15%) and gynecological cancer ($n = 10$, 10%). Half of the patients ($n = 49$) had no surgery or no planned surgery. Thirty-five patients (37%) had no radiotherapy or no planned radiotherapy. Eighteen percent of patients were all tobacco smokers, and 3% were cannabis users. The repartition of patient's characteristics and cancer localizations were compatible with the local distribution of patients in daycare hospital and the hematology department.

### HFDS intakes

Overall, 74 patients ($n = 74/95$, 77.9%) reported at least one chronic intake of HFDS, and a total of 148 HFDSs were reported (Figure 2) (phytotherapy $n = 40$, 27%; CYP-interacting food $n = 78$, 53%; dietary supplement $n = 8$, 5%). Twenty-two HFDSs were reported but could not be automatically identified or mapped (15%, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.

**Table 1. Population characteristics of patients with one or more herb, CYP-interacting food or dietary supplement (HFDS group) and patients with no HFDS intakes**

| | | | HFDS | | |
|---|---|---|---|---|---|
| | n | Overall 95 | No 21 (22.1) | Yes 74 (77.9) | P value |
| Population characteristics | | | | | |
| Age (years) | Median (IQR) | 55.8 (16.1) | 54.2 (19.6) | 56.1 (15.5) | 0.704 |
| Gender | Female | 43 (55.1) | 8 (66.7) | 35 (53.0) | 0.531 |
| | Male | 35 (44.9) | 4 (33.3) | 31 (47.0) | |
| Data collection modalities | | | | | |
| Supervision of a health care professional | Supervised | 34 (35.8) | 11 (32.4) | 23 (67.6) | 0.12 |
| | Unsupervised | 61 (64.2) | 10 (16.4) | 51 (83.6) | |
| Version of the application | Version 1 | 26 (27.4) | 11 (42.3) | 15 (57.7) | 0.006 |
| | Version 2 | 69 (72.6) | 10 (14.5) | 59 (85.5) | |
| Site | 1—Oncology—daycare hospital | 82 (86.3) | 20 (24.4) | 62 (75.6) | 0.445 |
| | 2—Hematology—nurse | 12 (12.6) | 1 (8.3) | 11 (91.7) | |
| | 3—Radiotherapy—scanner | 1 (1.1) | 0 (0) | 1 (100) | |
| Cancer and treatments | | | | | |
| Number of anticancer treatments | Median (IQR) | 1.8 (1.0) | 2.0 (1.0) | 1.8 (1.0) | 0.420 |
| Systemic cancer treatments | Chemotherapy | 58 (61.1) | 12 (20.7) | 46 (79.3) | 0.801 |
| | IV targeted therapy | 30 (31.6) | 8 (26.7) | 22 (73.3) | 0.595 |
| | Oral targeted therapy | 12 (12.6) | 0 (0) | 12 (100) | 0.062 |
| | Hormone therapy | 6 (6.3) | 2 (33.3) | 4 (66.7) | 0.611 |
| | Immunotherapy | 8 (8.4) | 3 (37.5) | 5 (62.5) | 0.369 |
| | Not identified | 12 (12.6) | 2 (16.7) | 10 (83.3) | 1 |
| Cancer type | Breast | 28 (29.5) | 8 (28.6) | 20 (71.4) | 0.67 |
| | Gastrointestinal | 6 (6.3) | 2 (33.3) | 4 (66.7) | |
| | Gynecological | 10 (10.5) | 1 (10) | 9 (90) | |
| | Hematologic | 14 (14.7) | 1 (7.1) | 13 (92.9) | |
| | Head and neck | 8 (8.4) | 3 (37.5) | 5 (62.5) | |
| | Lung | 16 (16.8) | 3 (18.8) | 13 (81.2) | |
| | Urological | 4 (4.2) | 1 (25) | 3 (75) | |
| | Other | 8 (8.4) | 2 (25) | 6 (75) | |
| | Unknown | 1 (1.1) | 0 (0) | 1 (100) | |
| Stage | Localized cancer | 28 (34.6) | 8 (28.6) | 20 (71.4) | 0.115 |
| | Metastasized cancer | 48 (59.3) | 9 (18.8) | 39 (81.2) | |
| | Patient does not know | 5 (6.2) | 3 (60) | 2 (40) | |
| Time since diagnosis | <6 months | 13 (20.0) | 1 (7.7) | 12 (92.3) | 0.806 |
| | 6 months to 1 year | 15 (23.1) | 3 (20) | 12 (80) | |
| | 1 to 2 years | 11 (16.9) | 2 (18.2) | 9 (81.8) | |
| | 2 to 5 years | 14 (21.5) | 1 (7.1) | 13 (92.9) | |
| | >5 years | 12 (18.5) | 2 (16.7) | 10 (83.3) | |
| Surgery | No | 49 (51.6) | 10 (20.4) | 39 (79.6) | 0.91 |
| | Planned | 6 (6.3) | 1 (16.7) | 5 (83.3) | |
| | Yes (<1 year) | 19 (20.0) | 4 (21.1) | 15 (78.9) | |
| | Yes (>1 year) | 9 (9.5) | 3 (33.3) | 6 (66.7) | |
| | Patient does not know | 12 (12.6) | 3 (25) | 9 (75) | |
| Radiotherapy | No | 35 (36.8) | 9 (25.7) | 26 (74.3) | 0.813 |
| | Ongoing | 6 (6.3) | 0 (0) | 6 (100) | |
| | Planned | 12 (12.6) | 3 (25) | 9 (75) | |
| | Yes (<1 year) | 23 (24.2) | 4 (17.4) | 19 (82.6) | |
| | Yes (>1 year) | 8 (8.4) | 2 (25) | 6 (75) | |
| | Patient does not know | 11 (11.6) | 3 (27.3) | 8 (72.7) | |
| Smoking habits | Tobacco | 14 (18.2) | 2 (14.3) | 12 (85.7) | 1 |
| | Cannabis | 2 (2.8) | 0 | 2 (100) | 1 |
| HFDS and alternative medicines | | | | | |
| Oral alternative medicine | Phytotherapy—herb extracts | 19 (20.4) | 0 | 19 (100) | — |
| | Infusions | 20 (33.9) | 0 | 20 (100) | — |
| | Essential oil (aromatherapy) | 6 (6.5) | 0 | 6 (100) | — |
| | Dietary supplements | 22 (23.7) | 0 | 22 (100) | — |
| | Homeopathy | 12 (12.9) | 1 (8.3) | 11 (91.7) | 0.448 |
| Other alternative medicine | Acupuncture | 8 (66.7) | 0 | 8 (100) | 0.091 |
| | Hypnose | 1 (8.3) | 0 | 1 (100) | |
| | Qi gong | 1 (8.3) | 1 (100) | 0 | |
| | Reiki | 2 (16.7) | 1 (50.0) | 1 (50.0) | |
| Food habits | Green tea | 17 (26.6) | 0 | 17 (100) | — |
| | Coffee (>2 cups a day) | 39 (60.9) | 0 | 39 (100) | — |
| | Licorice (roots or sweets) | 1 (1.6) | 0 | 1 (100) | — |
| | Soy | 3 (4.7) | 0 | 3 (100) | — |
| | Grapefruit | 5 (7.8) | 0 | 5 (100) | — |
| | Pomelo | 3 (4.7) | 0 | 3 (100) | — |

*Continued*

**Table 1. Continued**

| | n | Overall 95 | HFDS No 21 (22.1) | HFDS Yes 74 (77.9) | P value |
|---|---|---|---|---|---|
| | Bitter orange (Seville orange) | 10 (15.6) | 0 | 10 (100) | — |
| | Cranberry | 3 (4.7) | 0 | 3 (100) | — |
| Patient reported at least | Yes | 74 (77.9) | 0 | 74 (100) | — |
| one HFDS | No | 21 (22.1) | 21 (100) | 0 | |
| Probable HFDI identified | Yes | 16 (16.8) | 0 | 16 (100) | — |
| | No | 79 (83.2) | 21 (26.6) | 58 (73.4) | |

The population with HFDS was compared with the population without HFDS using Wilcoxon test for quantitative variables and Fisher's exact test for categorical variables. Missing values (total n = 95): supervised: 0; version: 0; center: 0; age: 18; gender: 27; cancer type: 0; time since diagnosis: 30; stage: 14; surgery: 0; radiotherapy: 0; tobacco: 18; cannabis: 24; phytotherapy: 2; dietary supplements: 2; aromatherapy: 2; homeopathy: 2; infusions: 36; food habits: 31.
*P*-values under 0.05 are in red and *P*-values between 0.05 and 0.1 are bold.
HFDS, herb, food and dietary supplements; HFDI, herb and food—drug interaction; IQR, interquartile range; IV, intravenous.

2022.100650). The most frequently reported HFDS was coffee with 39 patients reporting daily use of over two cups. All 39 patients reported at least one other HFDS. Twelve patients reported the use of other alternative therapies (8/12 acupuncture). Four patients reported the use of 5 or more HFDSs, and one patient reported 10.

No significant differences in characteristics were found between the groups of patients reporting HFDS intake and patients who did not (Table 1), except for a higher proportion of patients reporting HFDS intake with version 2 of the application than those with no HFDS reported (80% versus 48%, $P = 0.006$). Among the 26 patients who filled version 1 of the application, only 15 patients had an HFDS (58%) compared to 59 (86%, $P = 0.006$) with version 2 (Table 1). Patients and tumor characteristics according to the version of the application are detailed in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100650.

### *HFDI identification*

Among 74 patients who reported at least one HFDS, 6 patients reported only HFDS that could not be identified on the prespecified list (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100650), leaving 68 patients with potential HFDS—cancer treatment interactions for analysis.

Among 31 HFDIs reported, 22 were classified as probable and 9 had a low level of evidence (Table 2). Sixteen patients (16/95, 16.8%) had at least one HFDI classified as probable, which was significantly superior to the 5% prespecified threshold ($P = 0.02$). This result remains significant in the

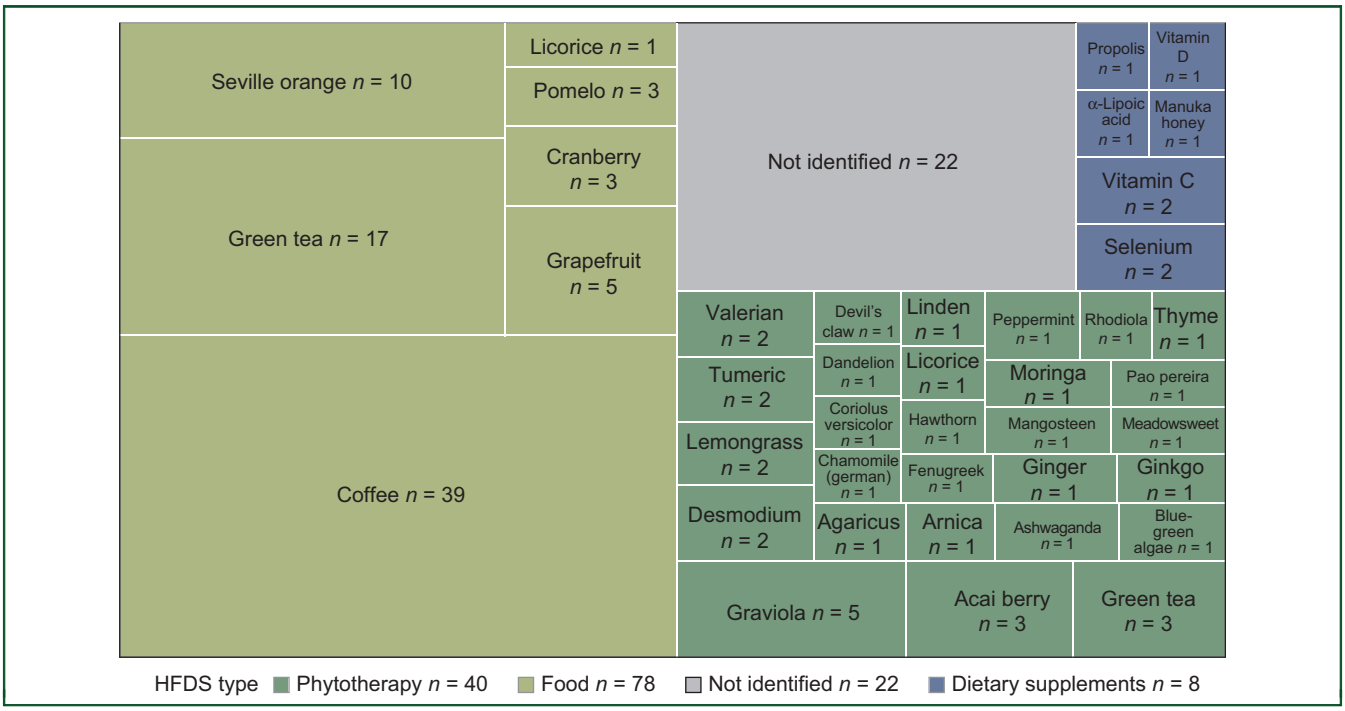


**Figure 2. Treemap plot of the 148 HFDSs reported among the 95 patients of the study.** Green tea and licorice could have been used as a phytotherapy (intake of herb/root extract) or as food (infusion or roots) through the specific food questionnaire. Phytotherapies are represented in green, food in olive green and dietary supplements in blue.
HFDS, herbs, food and dietary supplements.

**Table 2. Interaction between HFDS and anticancer treatments found in the study with the application**

| Patient's study number | HFDS | Cancer treatment | CYP involved | CYP modification | Level | Supervised | Auto-implementation | Food questionnaire | HFDS type | HFDI category |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | Green tea | Vinorelbine | CYP3A | Inhibition | 3 | Yes | No | No | Herb | Probable |
| 30 | Green tea | Paclitaxel | CYP3A | Inhibition | 3 | No | Yes | Yes | Food | Probable |
| | Licorice | Paclitaxel | CYP3A | Induction | 1 | No | Yes | Yes | Food | Probable |
| 36 | Green tea | Letrozole | CYP3A | Inhibition | 3 | No | Yes | Yes | Food | Probable |
| 38 | Cranberry | Paclitaxel | CYP3A | Inhibition | 2 | No | Yes | Yes | Food | Probable |
| | Grapefruit | Paclitaxel | CYP3A | Inhibition | 1 | No | Yes | Yes | Food | Probable |
| 40 | Coffee | Cyclophosphamide | CYP1A2 | Inhibition | 2 | No | Yes | Yes | Food | Probable |
| 44 | Green tea | Trastuzumab-emtansine | CYP3A | Inhibition | 3 | No | Yes | Yes | Food | Probable |
| 46 | Green tea | Paclitaxel | CYP3A | Inhibition | 3 | No | Yes | Yes | Food | Probable |
| 55 | Coffee | Cyclophosphamide | CYP1A2 | Inhibition | 2 | No | Yes | Yes | Food | Probable |
| 60 | Peppermint | Lenvatinib | CYP3A | Inhibition | 2 | No | Yes | No | Herb | Probable |
| | Green tea | Lenvatinib | CYP3A | Inhibition | 2 | No | Yes | Yes | Food | Probable |
| 71 | Grapefruit | Dexamethasone | CYP3A | Inhibition | 1 | Yes | Yes | Yes | Food | Probable |
| 73 | Cranberry | Lapatinib | CYP3A | Inhibition | 2 | No | Yes | Yes | Food | Probable |
| 78 | Green tea | Ibrutinib | CYP3A | Inhibition | 3 | Yes | Yes | Yes | Food | Probable |
| 79 | Green tea | Vinblastine | CYP3A | Inhibition | 3 | Yes | Yes | Yes | Food | Probable |
| | Pomelo | Vinblastine | CYP3A | Inhibition | 3 | Yes | Yes | Yes | Food | Probable |
| 85 | Coffee | Cyclophosphamide | CYP1A2 | Inhibition | 2 | Yes | Yes | Yes | Food | Probable |
| 87 | Green tea | Vinblastine | CYP3A | Inhibition | 3 | No | Yes | Yes | Food | Probable |
| | Pomelo | Vinblastine | CYP3A | Inhibition | 3 | No | Yes | Yes | Food | Probable |
| | Grapefruit | Vinblastine | CYP3A | Inhibition | 1 | No | Yes | Yes | Food | Probable |
| 89 | Coffee | Cyclophosphamide | CYP1A2 | Inhibition | 2 | No | Yes | Yes | Food | Probable |

The scale for the HFDS level of evidence of interaction with cytochromes is available in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100650, and has been reported in a previous study.[13] Version 2 of the application allowed both auto-implementation and the acquisition of CYP-interacting food through a specific food questionnaire. In version 2 of the application, food—drug interactions could be detected either through the general questionnaire or the specific food questionnaire.
CYP, cytochrome P-450; HFDI, herb and food—drug interaction; HFDS, herb, food and dietary supplements.

unsupervised population (11/61 patients, 18.0%, $P = 0.04$). Most HFDI classified as probable were identified as related to food products (20/22). Two herbs were identified as interacting: green tea (*Camellia sinensis*) and peppermint (*Mentha piperita*). No HFDIs classified as probable were found with dietary supplements. Green tea through the food questionnaire was identified within eight interactions. One patient had three interactions (green tea, pomelo and grapefruit). Four interactions were level 1, 8 were level 2 and 10 interactions were level 3. Six of the 22 food interactions concerned oral drugs [lenvatinib (×2), lapatinib, ibrutinib, dexamethasone and letrozole]. Eighteen of 22 probable interactions were mediated through CYP3A4. Only one cytochrome induction leading to probable HFDI was found (CYP3A4 induction by licorice).

### *Differences in the population with an interaction*

For most variables tested (Table 3), no significant difference was found between HFDIs classified as probable and those of lower certainty. However, the proportion of patients from the hematology department (10% versus 25%) was higher in the probable HFDI group. Fourteen of the 16 patients with probable HFDI had a breast/gynecological cancer or a hematologic cancer (14/16 versus 38/79, $P = 0.005$). No significant difference was found between patients who were supervised for the completion (37%, 29/79) and those with no supervision (31%, 5/16, $P = 0.9$).

## DISCUSSION

In the present study, we showed that a tablet application helped identify interactions between herbs, dietary supplements or food and cancer treatment in the routine care of cancer patients.

Our study gives several insights into the field of oral alternative medicine and cancer care.

Firstly, we found that 77.9% (74/95) of patients reported a regular intake of HFDS. Among these patients 148 HFDSs were identified, mainly CYP-interacting food ($n = 78/148$, 53%). This proportion is higher than in previous reported studies in cancer patients. Out of 1739 patients with cancer in the US, Rashrash and colleagues[1] reported that 43% were using herbal medicine. In the early breast cancer prospective cohort CANTO,[3] among 5237 women, 23.0% reported oral alternative medicines, mostly homeopathy (65.4%). Finally, in another cohort from phase I trials, out of 212 patients, 72 (34%) were taking herbs or dietary supplements. As clinically relevant herb—drug or food—drug interactions can occur, leading to increased toxicity or decreased efficacy, identifying such intakes is critical for good care.

Secondly, among 74 patients who reported HFDS intakes, we identified 22 HFDIs classified as probable, i.e. likely to be clinically significant, within 16 patient reports ($n = 16/95$, 16.8%). In a previous study in 804 patients, Bush et al.[9] found that 122 patients (15%) were using traditional medicines, 49 of whom (6% of all patients) had a potential herb—drug interaction. We found a higher rate of HFDI in our study which could be explained by the specific food questionnaire that we used. However, the clinical impact of HFDI we found in our study, even classified as 'probable', could in fact be low. We found four patients with an HFDI involving cyclophosphamide and coffee. Cyclophosphamide is an oxazaphosphorine derivative that has a complex

**Table 3. Population characteristics of patients with and without one or more identified herb–drug or food–drug interaction (HFDI) classified as probable**

| | | | HFDI classified as 'probable' | | |
|---|---|---|---|---|---|
| | n | Overall 95 | No 79 (83.2) | Yes 16 (16.8) | P value |
| Population characteristics | | | | | |
| Age | Median (IQR) | 55.8 (16.1) | 56.3 (16.8) | 53.9 (13.5) | 0.606 |
| Gender | Female | 43 (55.1) | 32 (74.4) | 11 (25.6) | 0.344 |
| | Male | 35 (44.9) | 30 (85.7) | 5 (14.3) | |
| Data collection modalities | | | | | |
| Supervision of a health care professional | Supervised | 34 (35.8) | 29 (85.3) | 5 (14.7) | 0.897 |
| | Unsupervised | 61 (64.2) | 50 (82) | 11 (18) | |
| Version of the application | Version 1 | 26 (27.4) | 25 (96.2) | 1 (3.8) | 0.077 |
| | Version 2 | 69 (72.6) | 54 (78.3) | 15 (21.7) | |
| Site | 1—Oncology—daycare hospital | 82 (86.3) | 71 (86.6) | 11 (13.4) | 0.019 |
| | 2—Hematology—nurse | 12 (12.6) | 8 (66.7) | 4 (33.3) | |
| | 3—Radiotherapy—scanner | 1 (1.1) | 0 (0) | 1 (100) | |
| Cancer and treatments | | | | | |
| Number of anticancer treatments | Median (IQR) | 1.8 (1.0) | 1.7 (0.9) | 2.1 (1.1) | 0.144 |
| Systemic cancer treatments | Chemotherapy | 58 (61.1) | 48 (82.8) | 10 (17.2) | |
| | IV targeted therapy | 30 (31.6) | 24 (80) | 6 (20) | |
| | Oral targeted therapy | 12 (12.6) | 8 (66.7) | 4 (33.3) | |
| | Hormone therapy | 6 (6.3) | 5 (83.3) | 1 (16.7) | |
| | Immunotherapy | 8 (8.4) | 8 (100) | 0 (0) | |
| | Not identified | 12 (12.6) | 11 (91.7) | 1 (8.3) | |
| Cancer type | Breast | 28 (29.5) | 23 (82.1) | 5 (17.9) | 0.103 |
| | Gastrointestinal | 6 (6.3) | 6 (100) | 0 (0) | |
| | Gynecological | 10 (10.5) | 7 (70) | 3 (30) | |
| | Hematologic | 14 (14.7) | 8 (57.1) | 6 (42.9) | |
| | Head and neck | 8 (8.4) | 8 (100) | 0 (0) | |
| | Lung | 16 (16.8) | 15 (93.8) | 1 (6.2) | |
| | Urological | 4 (4.2) | 4 (100) | 0 (0) | |
| | Other | 8 (8.4) | 7 (87.5) | 1 (12.5) | |
| | Unknown | 1 (1.1) | 1 (100) | 0 (0) | |
| Stage | Localized cancer | 28 (34.6) | 24 (85.7) | 4 (14.3) | 0.669 |
| | Metastasized cancer | 48 (59.3) | 42 (87.5) | 6 (12.5) | |
| | Patient does not know | 5 (6.2) | 5 (100) | 0 (0) | |
| Time since diagnosis | <6 months | 13 (20.0) | 9 (69.2) | 4 (30.8) | 0.545 |
| | 6 months to 1 year | 15 (23.1) | 11 (73.3) | 4 (26.7) | |
| | 1 to 2 years | 11 (16.9) | 10 (90.9) | 1 (9.1) | |
| | 2 to 5 years | 14 (21.5) | 12 (85.7) | 2 (14.3) | |
| | >5 years | 12 (18.5) | 8 (66.7) | 4 (33.3) | |
| Surgery | No | 49 (51.6) | 41 (83.7) | 8 (16.3) | 0.249 |
| | Planned | 6 (6.3) | 5 (83.3) | 1 (16.7) | |
| | Yes (<1 year) | 19 (20.0) | 13 (68.4) | 6 (31.6) | |
| | Yes (>1 year) | 9 (9.5) | 9 (100) | 0 (0) | |
| | Patient does not know | 12 (12.6) | 11 (91.7) | 1 (8.3) | |
| Radiotherapy | No | 35 (36.8) | 29 (82.9) | 6 (17.1) | 0.355 |
| | Ongoing | 6 (6.3) | 4 (66.7) | 2 (33.3) | |
| | Planned | 12 (12.6) | 11 (91.7) | 1 (8.3) | |
| | Yes (<1 year) | 23 (24.2) | 17 (73.9) | 6 (26.1) | |
| | Yes (>1 year) | 8 (8.4) | 7 (87.5) | 1 (12.5) | |
| | Patient does not know | 11 (11.6) | 11 (100) | 0 (0) | |
| Smoking habits | Tobacco | 14 (18.2) | 11 (78.6) | 3 (21.4) | 1 |
| | Cannabis | 2 (2.8) | 1 (50.0) | 1 (50.0) | 0.38 |
| HFDS and alternative medicines | | | | | |
| Oral alternative medicine | Phytotherapy—herb extracts | 19 (20.4) | 14 (73.7) | 5 (26.3) | 0.306 |
| | Infusions | 20 (33.9) | 16 (80) | 4 (20.0) | 0.424 |
| | Essential oil (aromatherapy) | 6 (6.5) | 3 (50.0) | 3 (50.0) | 0.061 |
| | Dietary supplements | 22 (23.7) | 18 (81.8) | 4 (18.2) | 1 |
| | Homeopathy | 12 (12.9) | 11 (91.7) | 1 (8.3) | 0.684 |
| Other alternative medicine | Acupuncture | 8 (66.7) | 6 (75) | 2 (25) | 0.721 |
| | Hypnose | 1 (8.3) | 1 (100) | 0 (0) | |
| | Qi gong | 1 (8.3) | 1 (100) | 0 (0) | |
| | Reiki | 2 (16.7) | 1 (50) | 1 (50) | |
| Food habits | Green tea | 17 (26.6) | 9 (52.9) | 8 (47.1) | 0.016 |
| | Coffee (>2 cups a day) | 39 (60.9) | 32 (82.1) | 7 (17.9) | 0.235 |
| | Licorice (roots or sweets) | 1 (1.6) | 0 | 1 (100) | 0.234 |
| | Soy | 3 (4.7) | 3 (100) | 0 | 1 |
| | Grapefruit | 5 (7.8) | 2 (40.0) | 3 (60.0) | 0.079 |
| | Pomelo | 3 (4.7) | 1 (33.3) | 2 (66.7) | 0.134 |
| | Bitter orange (Seville orange) | 10 (15.6) | 10 (100) | 0 | 0.1 |

*Continued*

**Table 3. Continued**

| | | | HFDI classified as 'probable' | | |
|---|---|---|---|---|---|
| | n | Overall 95 | No 79 (83.2) | Yes 16 (16.8) | P value |
| | Cranberry | 3 (4.7) | 1 (33.3) | 2 (66.7) | 0.134 |
| Patient reported at least one HFDS | Yes | 74 (77.9) | 58 (78.4) | 16 (21.6) | 0.045 |
| | No | 21 (22.1) | 21 (100) | 0 (0) | |
| Probable HFDI identified | Yes | 16 (16.8) | 0 (0) | 16 (100) | — |
| | No | 79 (83.2) | 79 (100) | 0 (0) | |

The population with an HFDI classified as probable was compared to the population without an HFDI using Wilcoxon test for quantitative values and Fisher's exact test for categorical variables. Missing values (total n = 95): supervised: 0; version: 0; center: 0; age: 18; gender: 27; cancer type: 0; time since diagnosis: 30; stage: 14; surgery: 0; radiotherapy: 0; tobacco: 18; cannabis: 24; phytotherapy: 2; dietary supplements: 2; aromatherapy: 2; homeopathy: 2; infusions: 36; food habits: 31.
*P*-values under 0.05 are in red and *P*-values between 0.05 and 0.1 are bold.
HFDI, herb and food—drug interaction; HFDS, herb, food and dietary supplements; IQR, interquartile range; IV, intravenous.

pharmacology. It is a prodrug which needs to be activated by several cytochromes, including CYP3A, CYP2B6 and CYP1A2[13] to exert its activity. Coffee inhibits CYP1A2 and can lead to a clinically significant rise in concentrations of drugs metabolized through this CYP.[17] Although the interaction of coffee with CYP1A2 is clinically proven, the role of CYP1A2 in the activation of cyclophosphamide is unlikely to result in a decreased efficacy since most of this activation occurs via CYP3A and CYP2B.[18] Similarly, CYP modifications due to HFDS consumption are often mild (<25%). The relevance of these interactions for treatments with large therapeutic indexes, such as letrozole, may be irrelevant. Our study did not take into account the volume, frequency and schedule of HFDSs taken by the patient, although it modifies the intensity of the interaction.[13] Subsequent studies should be able to quantify HFDS consumption as well as time between drug and herb intake to better assess HFDI relevance.

Thirdly, we found that most interactions were food-mediated rather than herb-mediated. Most published studies focused on oral alternative interactions rather than food—drug interactions.[9,12] Though frequent, food—drug interactions are rarely reported or considered, and they may be the tip of the iceberg of HFDI. Some of these interactions may increase the risk of anticancer drug toxicity or inefficacy. Grapefruit is a strong CYP3A4 inhibitor that could be responsible for severe toxicity by decreasing the bioavailability of anticancer drugs metabolized by CYP3A4.[13]

Finally, we found that a tablet application could successfully be used to collect both HFDS and cancer treatments and ultimately detect HFDI. This finding remains in the population that filled the questionnaire without the presence of a health care professional. This is particularly noteworthy because collecting the use of HFDS is time-consuming with up to 10 HFDSs for a single patient in our cohort. Also, few health care professionals are trained in the field of herb—drug and food—drug interactions and identifying them requires pharmacological expertise. Our work demonstrates that the acquisition of data does not need to be supervised by a health care professional to be relevant when auto-completion and precise questionnaires are provided. An extensive analysis of HFDS to identify probable HFDI could therefore be, at least partially, automated. The collection of these self-reported data is doable in routine care, and the use of such device and applications is expected to grow in oncology in the near future. However, we showed a major role of active encouragement by the staff to fill out the application questionnaire. In the radiotherapy department where simple passive advertising was used, only one patient completed the questionnaire and was included in our study within 3 months. After the end of the data acquisition phase of the study, the tablet was stolen from the stand, despite appropriate locking measures. Passive enrollment failed to contribute to our study and should not be considered as an appropriate option.

Our study has several strengths. To our knowledge, no study to date has examined how self-reported HFDS intakes could identify potential drug interactions. Our work is thus the first to demonstrate the feasibility of such an approach. Of note, we cannot exclude that some interactions failed to be identified, either because patients failed to accurately report data, or because these HFDIs have not been published or identified in the literature review we relied on.[13]

Our study opens several perspectives. We confirmed the high frequency of HFDS intakes and showed that a substantial proportion of HFDSs interact with anticancer treatment. An automated questionnaire could highlight potential herb—drug and food—drug interaction and help clinicians and clinical pharmacists to detect them and prevent them when relevant.[19]

Clinically significant PK herb—drug or food—drug interaction could have several consequences. When relevant cytochromes are inhibited, the interaction could lead to a decrease in drug clearance and increased mean plasma concentration of the anticancer drug, thus increasing the risk of drug-induced toxicity.[11] One patient with daily grapefruit juice intake, a CYP3A4 inhibitor, had a doubling in docetaxel plasma.[20] In this case, the docetaxel dose was low (40 mg/m$^2$), but a doubling of docetaxel exposure could have dramatic consequences with a higher dose.[21] In contrast, the induction of cytochromes involved in anticancer drugs' metabolism could increase drug clearance and decrease drug exposure, leading to reduced efficacy. CYP3A4 induction properties of piperine (with curcumin)

have been observed to decrease everolimus $C_{trough}$ concentration below drug level targets with clinical consequences[22] and likely led to a decreased anticancer efficacy.

Similar questionnaires could also be implemented on a smartphone device. In a breast cancer survivor population, over 70% of the population had access to a smartphone.[23] A smartphone application could allow the implementation of patient-oriented questionnaires on a large scale and provide prospective data for future studies. In this proof-of-concept study, we demonstrated that a tablet application could identify and help prevent herb—drug and food—drug interactions. The clinical benefit of such an approach to decrease anticancer drug toxicity or inefficacy remains unknown and should be explored on a larger-scale study focusing on clinical outcomes.

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## DISCLOSURE

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