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DRUG INTERACTIONS

Adverse events associated with interactions with dietary and herbal supplements among inpatients

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AIMS

Dietary and herbal supplements (DHS) are commonly used among inpatients and may cause interactions with drugs or other DHS. This study explored whether adverse events were actually associated with such interactions and examined specific characteristics among inpatient DHS users prone to such adverse events.

METHODS

This was a cross-sectional study of 947 patients hospitalized in 12 departments of a tertiary academic medical centre in Haifa, Israel. It evaluated the rate of DHS use among inpatients, the potential for interactions, and actual adverse events during hospitalization associated with DHS use. It also assessed whether DHS consumption was documented in patients' medical files. Statistical analysis was used to delineate DHS users at risk for adverse events associated with interactions with conventional drugs or other DHS.

RESULTS

In 17 (3.7%) of the 458 DHS users, an adverse event may have been caused by DHS–drug–DHS interactions. According to the Drug Interaction Probability Scale, 14 interactions 'probably' caused the adverse events, and 11 'possibly' caused them. Interactions occurred more frequently in older patients ($P = 0.025$, 95% CI: 2.26–19.7), patients born outside Israel ($P = 0.025$, 95% CI: 0.03–0.42), those with ophthalmologic ($P = 0.032$, 95% CI: 0.02–0.37) or gastrointestinal ($P = 0.008$, 95% CI: 0.05–0.46) comorbidities, and those using higher numbers of DHS ($P < 0.0001$, 95% CI: 0.52–2.48) or drugs ($P = 0.027$, 95% CI: 0.23–3.77).

CONCLUSIONS

Approximately one in 55 hospitalizations in this study may have been caused by adverse events associated with DHS–drug–DHS interactions. To minimize the actual occurrence of adverse events, medical staff education regarding DHS should be improved.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dietary and herbal supplements (DHS) are widely used by inpatients.
- Potential DHS–drug interactions have been described, including during hospitalization.
- Physicians tend not to ask their patients about DHS use.

WHAT THIS STUDY ADDS

- One in 55 hospitalizations seems to be associated with interactions with DHS.
- Most of these interaction-adverse event associations are 'at least possible'.
- Medical staff members are generally not aware of these safety issues.

Tables of Links

TARGETS	
Transporters [2]	**Enzymes** [3]
OATP	CYP2C9
	CYP2D6
	CYP3A4

LIGANDS	
Aspirin	Omega-3
Clopidogrel	Simvastatin
Cyclosporine A	Turmeric
Digoxin	Vitamin C
Enoxaparin	Vitamin D
Levothyroxine	Warfarin
Methadone	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Introduction

Dietary and herbal supplements (DHS) have recently attracted attention due to their widespread use, particularly in developed countries. The rate of DHS consumption has been increasing in the general population in Western countries, including during hospitalization [4–8]. However, DHS consumption is largely under-reported to medical staff [7, 8]. In 1994, the Dietary Supplements Health and Education Act (DSHEA) defined DHS as products other than tobacco that are taken by mouth. Unlike regular medications, DHS are not regulated by the United States (US) Food and Drug Administration (FDA), although the DSHEA imposed some rules for their commercialization [9].

Despite increasing DHS consumption among hospitalized patients, under-disclosure of DHS use may have dangerous consequences resulting from potential DHS side effects and possible DHS–drug and DHS–DHS (DHS–drug–DHS) interactions. Most reports of such interactions are based on *in vitro* or animal research or on case reports. Bleeding induced by the interaction between omega-3 fish oil and antithrombotic drugs due to their additive antiplatelet effects is one example of a DHS–drug interaction described in humans [10]. Another example of a potentially dangerous DHS–drug interaction is the case of St John's wort, which has recently been banned for sale by the French Ministry of Health [11] due to its serotonin effects and its dangerous interactions with some antidepressants, which may lead to potentially fatal serotonin syndromes [12]. Furthermore, a pharmacokinetic interaction between this herbal supplement and cyclosporine has been described. The interaction potentially decreases the cyclosporine blood level, with increased risk of transplant rejection [13–15]. Some of these DHS–drug interactions have been studied in sub-populations of outpatients, inpatients or people with specific comorbidities [16–20].

Only a few studies have assessed the actual occurrence of adverse events caused by such interactions. For example, an analysis of potential DHS–drug interactions in ambulatory care found that in four primary care practices, 15% of patients consumed DHS [16]. Fourteen percent of these cases involved potentially dangerous interactions between DHS and the patients' prescription drugs, although no increased rate of adverse events was found among these cases compared to non-DHS users. Another study conducted in the outpatient setting at the Mayo Clinic in 2002–2003 revealed that 40% of patients used DHS (not including vitamins or minerals). Thirty-four percent of these cases involved DHS–drug interactions, though no actual adverse events resulted from these interactions [21]. Finally, a study conducted in the internal medicine departments of two public health hospitals in Israel in 2006 found potential DHS–drug interactions among 7% of DHS users [7]. Of these cases, one involved a potentially dangerous chamomile-cyclosporine interaction due to chamomile-induced cytochrome P450 (CYP) 3A4 inhibition.

The Naranjo algorithm is a useful way of determining the causal relationship between an adverse reaction and a single drug [22]. For drug–drug interactions, the recently constructed Drug Interaction Probability Scale (DIPS) uses a short questionnaire to assess the causal relationship between interactions and the actual occurrence of adverse events [23]. However, these tools have not been validated

in DHS-related adverse events. In addition, no study has systematically tested whether potential DHS–drug–DHS interactions have actual deleterious consequences for hospitalized patients.

In this study, we explored whether adverse events associated with DHS–drug–DHS interactions actually occurred among inpatients, and we looked for the specific characteristics of inpatient DHS users who might be prone to such adverse events.

Methods

This prospective cross-sectional study was conducted on a cohort of patients hospitalized in a public academic medical centre in Israel from 2009 to 2014. The study, part of an overarching study on various aspects of DHS use among hospitalized patients, was reviewed and approved by the Institutional Ethics Committee of Bnai-Zion Medical Centre in accordance with the Helsinki Declaration. The research database was used for diverse research goals, and some data overlapped between the different studies [8, 24–27]. Figure 1 shows the flowchart of the present research methodology.

Determination of DHS users

A questionnaire in Hebrew was constructed in a stepwise manner by a multidisciplinary team of researchers trained in integrative medicine. The questionnaire was validated by three focus groups, as previously published [24]. Fourth-year college students studying naturopathy conducted the survey after receiving eight hours of training. The survey was directed at patients aged 18 years and above who were able to communicate and provide verbal informed consent. Twelve internal medicine and surgical departments participated in this study. Surveyors approached hospitalized patients to assess their eligibility and willingness to participate in the study. The interview began with a general question: 'During the past year, have you used dietary supplements or herbs for health issues?' When patients responded negatively to the initial question, the surveyor rephrased the question using predetermined keywords, such as natural substances and remedies, folk/traditional herbs picked in the wild, and vitamins. Thus, the identification of hospitalized DHS users was highly reliable.

Characterization of DHS users

Additional data were collected from DHS users regarding their sociodemographic characteristics (year of birth, gender, residence type, country of birth, education). Medical files were assessed for cause of hospitalization, presence of comorbidities and concomitant medications, and physicians' mention of DHS. Physician notes during hospitalization, laboratory results and additional evaluations (imaging, etc.) were also extracted from medical records. Comorbidities were classified into 13 categories.

Assessment and classification of interactions

The pharmacokinetics and half-lives of DHS have not been well studied. We assumed that one week was a reasonable cut-off for their continuing effects. We therefore took into account only DHS used within the week prior to hospitalization. Adverse events associated with DHS–drug–DHS interactions were examined in the following way:

Step I: We selected patients hospitalized on an 'emergency' (not elective) basis as we were interested in assessing the actual cause of their hospitalization. For these patients, we checked the Natural Medicine database [28] for theoretical interactions between DHS and other DHS and/or drugs taken within the week preceding hospitalization.

Step II: If this type of interaction was found, we checked the medical records for the actual occurrence of adverse events that may have been caused by the interaction (bleeding, hypotension, laboratory changes, etc.).

Step III: We adapted the Drug Interaction Probability Scale (DIPS) to DHS–drug–DHS interactions (Table 1) and used it to assess the causality between actual adverse events and the described interactions.

Step IV: Since the DIPS has not been validated in the context of interactions with DHS, cases were presented to three specialists in clinical pharmacology. Each of them evaluated the causality of every described adverse event with potential DHS–drug–DHS interactions using a Likert scale of 1–5 (definitely not, probably not, possibly, probably, definitely).

Sample size calculation

Based upon a two-tailed hypothesis, we calculated the minimal sample size using Raosoft software. The rate of DHS use in hospitalization in Israel has been estimated at 55% [8]. To achieve a sample that would reflect that 55% with 95% confidence and 80% power, we needed a minimum of 374 inpatients in order to screen approximately 200 hospitalized DHS users. Since no rate of actual adverse events associated with interactions with DHS has yet been assessed in the literature, we estimated it at 1% of hospitalizations. Thus, we assumed that the 374 screened patients would lead to the identification of approximately four patients with adverse events due to interactions with DHS.

Statistical analysis

All results were entered into an Excel table. The data were evaluated using the SPSS software program (version 21). Descriptive statistics in terms of mean ± SD, median and ranges were calculated for all parameters in the study. The Pearson χ^2 test and the Fisher exact test were used to detect differences in the prevalence of categorical variables between DHS users with detected actual adverse events and DHS users without such adverse events. In addition, a *t*-test was conducted to determine whether there were any differences in the continuous variables between the two groups. Confidence intervals (CI) of 95% were calculated for the difference in the means of age, the difference in the medians of the number of DHS and drugs used, and the difference in the proportions of the remaining variables.

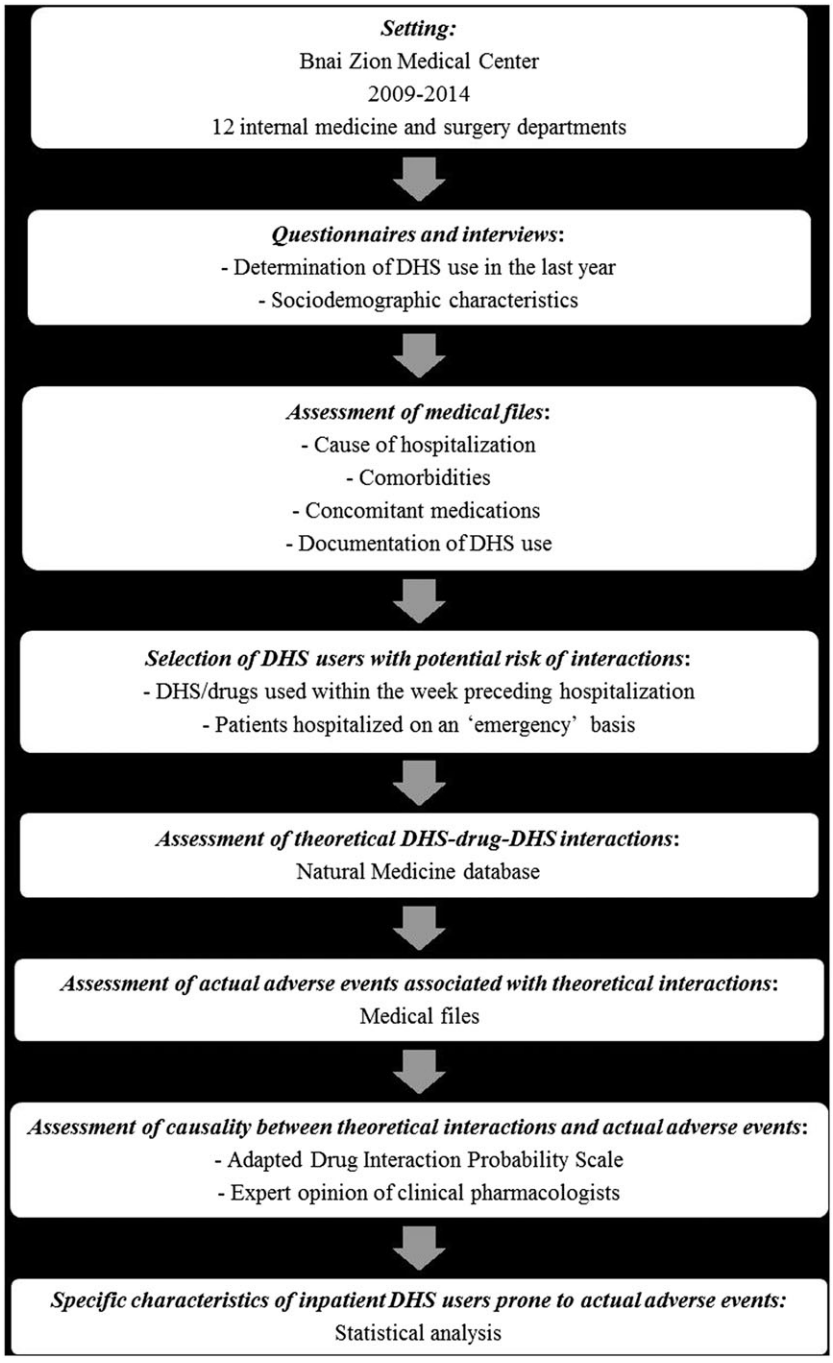

Figure 1
Flowchart of research methodology

Results

Study population

In the current study, 1020 hospitalized adult patients were approached. Among them, 927 agreed to answer the questionnaire (91% response rate). Of the 927, 526 participants were hospitalized in surgical departments and 401 in internal medicine departments. Among the 927 interviewees, 458 (49%) reported using 89 different DHS in the past year, totalling 946 DHS used (mean: 2.1 DHS per patient). Table 2 shows the commonly used DHS. The majority of DHS users were women (67%), and their mean age was 61.3 years. Most DHS users lived in urban areas (75%), were born in Israel (51%) and had at least a high school education (81%). Main comorbidities included metabolic (53%), cardiovascular (52%), endocrine (29%) and haemato-oncologic (21%) conditions (Table 3).

Table 1

Adaptation of the Drug Interaction Probability Scale (DIPS)

Questions	Yes	No	Unknown/ non-applicable
1. Are there previous credible reports of this interaction in humans?	+1	−1	0
2. Is the observed interaction consistent with the known interactive properties of DHS 1?	+1	−1	0
3. Is the observed interaction consistent with the known interactive properties of the drug/DHS 2?	+1	−1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	−1	0
5. Did the interaction remit upon de-challenge of the DHS 1 with no change in the drug/DHS 2?	+1	−2	0
6. Did the interaction reappear when the DHS 1 was re-administered in the presence of continued use of the drug/DHS 2?	+2	−1	0
7. Are there reasonable alternative causes for the event?	−1	+1	0
8. Was the drug/DHS 2 detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the drug/DHS 2 (other than drug concentrations from previous question)?	+1	0	0
10. Was the interaction greater when the DHS 1 dose was increased or less when the DHS 1 dose was decreased?	+1	−1	0

Total score: >8 = highly probable; 5–8 = probable; 2–4 = possible; <2 = doubtful

Table 2

Twenty most commonly used Dietary and Herbal Supplements (DHS)

DHS	DHS users, *n* (%)
Vitamin D	95 (21%)
Vitamin B12	82 (18%)
Multivitamin	78 (17%)
Omega-3 fish oil	72 (16%)
Calcium	64 (14%)
Iron	61 (13%)
Sage	41 (8.9%)
Folic acid	39 (8.5%)
Peppermint	38 (8.3%)
Vitamin C	29 (6.3%)
Vitamin E	22 (4.8%)
Chamomile	21 (4.6%)
Hyssop	17 (3.7%)
Green tea	16 (3.5%)
Triple vitamin (B1, B6, B12)	14 (3.1%)
Coenzyme Q10	12 (2.6%)
Cranberry	11 (2.4%)
Glucosamine	10 (2.2%)
Lemon verbena	9 (2%)
Rosemary	9 (2%)

Description of actual adverse events

Among the 458 DHS users, 25 interactions associated with adverse events during hospitalization were identified in 17 (3.7%) patients, including 22 DHS–drug interactions and three DHS–DHS interactions. In other words, among the 927 study participants constituting a representative sample of inpatients (DHS users or non-users), 1.8% of hospitalizations were possibly or probably caused by DHS–drug–DHS interactions (Table 4).

The presumably most severe adverse event involved a patient intubated due to CO_2 narcosis that was apparently associated with an interaction between sage and methadone. Indeed, according to *in vitro* studies, sage may inhibit the metabolism of CYP2D6, which metabolizes methadone. Thus, the concomitant use of sage and methadone may have led to an increased level of methadone and its side effects, including respiratory failure with severe hypercapnia. This is what seemed to have occurred in a 62-year-old patient who was admitted with respiratory distress with a pCO_2 of 162 mmHg and who had to be intubated and mechanically ventilated. Although the patient was a former drug addict with chronic obstructive pulmonary disease (COPD), no specific cause of respiratory failure was identified during the present hospitalization. A side effect of methadone augmented by the consumption of sage, although not confirmed, should have been considered in the differential diagnosis of severe hypercapnic respiratory failure.

The patient who had the greatest number of interactions that may have led to hospitalization was a 33-year-old man with a history of recurrent venous thromboembolism treated with warfarin. This patient concomitantly used five DHS in the week preceding hospitalization. He had one potential DHS–DHS interaction (between flaxseed and omega-3 fish oil) and four potential DHS–drug interactions (interactions

Table 3

Comparison of DHS users with and without actual adverse events

Characteristics	Total DHS users (n = 458)	Actual adverse event(n = 17)	No actual adverse event(n = 441)	P-value	95% CI[b]
Average age (years)	61.3 ± 19.4	72 ± 18	61 ± 19	***0.025***	***2.26; 19.7***
Gender					
Male	152 (33%)	8 (47%)	144 (33%)	0.29	−0.04; 0.40
Female	306 (67%)	9 (53%)	297 (67%)		
Country of birth					
Israel	235 (51%)	4 (24%)	231 (52%)	***0.025***	***0.03; 0.42***
Other	223 (49%)	13 (76%)	210 (48%)		
Residence					
Urban	342 (75%)	15 (88%)	327 (74%)	0.26	−0.07; 0.25
Rural	116 (25%)	2 (12%)	114 (26%)		
Education					
≤ Elementary	88 (19%)	3 (18%)	85 (19%)	1.00	−0.22; 0.13
≥ High School	370 (81%)	14 (82%)	356 (81%)		
Number of DHS[a]	2 [1–3]	3 [1.25–4.75]	2 [1–2]	***<0.0001***	***0.52; 2.48***
Number of drugs[a]	2 [0–6]	4 [3–7]	2 [0–6]	***0.027***	***0.23; 3.77***
Comorbidities					
Metabolic	243 (53%)	12 (75%)	231 (52%)	0.08	−0.05; 0.36
Cardiovascular	237 (52%)	11 (69%)	226 (51%)	0.21	−0.09; 0.33
Endocrine	132 (29%)	6 (38%)	126 (29%)	0.41	−0.11; 0.31
Haemato-oncologic	95 (21%)	6 (38%)	89 (20%)	0.11	−0.03; 0.39
Gastrointestinal	39 (8.5%)	5 (31%)	34 (8%)	***0.008***	***0.05; 0.46***
Respiratory	39 (8.5%)	1 (6%)	38 (9%)	1.00	−0.19; 0.08
Neurologic	38 (8%)	0	38 (9%)	0.38	−0.10; 0.11
Renal	37 (8%)	1 (6%)	36 (8%)	1.00	−0.19; 0.08
Rheumatologic	37 (8%)	1 (6%)	36 (8%)	1.00	−0.19; 0.08
Pregnancy	30 (7%)	0	30 (10%)	0.61	−0.12; 0.09
Psychiatric	29 (6%)	1 (6%)	28 (6%)	1.00	−0.21; 0.06
Ophthalmologic	21 (5%)	3 (19%)	18 (4%)	***0.032***	***0.02; 0.37***
Urologic	17 (4%)	0	17 (4%)	1.00	−0.15; 0.06
Hepatobiliary	10 (2%)	0	10 (2%)	1.00	−0.16; 0.04
Report in medical files	51 (11%)	0	51 (12%)	0.24	−0.07; 0.15

[a]Median [25th–75th percentiles]
[b]Confidence intervals (CI) of 95% calculated for the difference in the means of age, the difference in the medians of the number of used DHS and drugs, and the difference in the proportions of the remaining variable.

between warfarin and flaxseed, omega-3 fish oil, chamomile and sage). All these interactions could potentially lead to bleeding and/or prolonged INR. While flaxseed, omega-3 fish oil and chamomile have been shown to have antiplatelet properties that may cause bleeding when associated with antithrombotic drugs, sage is apparently an inhibitor of CYP2C9 that metabolizes warfarin. Thus, their concomitant use can potentially prolong INR and increase bleeding. This specific patient was admitted for gastrointestinal bleeding manifested by melena with uncontrolled INR (4.18). When the patient was admitted, warfarin treatment was suspended. However, his medical records made no mention of DHS consumption, and he probably continued taking DHS with warfarin after discharge.

Table 4

Description of interactions with DHS

Patient number	DHS–drug–DHS interaction	Outcome of interaction	Possible mechanism of action of interaction [Ref]	DIPS causality rating	Median Likert scale scores of expert opinion
1	Green tea / Digoxin	**Lowered digoxin level**	OATP inhibition [33]	3 (Possible)	4 (Probable)
2	Turmeric / Clopidogrel	**Gastrointestinal bleeding**	Antiplatelet effect,CYP 3A4 inhibition [34]	5 (Probable)	4 (Probable)
3	Sage / Methadone	**CO_2 narcosis - Respiratory failure**	CYP 2D6 inhibition [35]	3 (Possible)	4 (Probable)
4	Sage / Simvastatin	**Rhabdomyolysis→ Suspended simvastatin**	CYP 3A4 inhibition [35, 36]	3 (Possible)	3 (Possible)
	Peppermint oil / Simvastatin			3 (Possible)	3 (Possible)
5	Coenzyme-Q10 / 2 antihypertensive drugs	**Syncope**	Antihypertensive effects [37]	5 (Probable)	3 (Possible)
6	Vitamin D / Lercanidipine	**Uncontrolled hypertension**	CYP 3A4 induction [38]	3 (Possible)	3 (Possible)
7	Vitamin D / Warfarin	**Portal vein thrombosis**	CYP 2C9 induction [39]	4 (Possible)	3 (Possible)
8	Omega-3 fish oil / Casein	**Hypotension**	Antihypertensive effects [40, 41]	3 (Possible)	2 (Probably not)
9	Calcium / Levothyroxine	**Uncontrolled hypothyroidism**	Reduced absorption [42, 43]	6 (Probable)	4 (Probable)
	Iron / Levothyroxine			6 (Probable)	4 (Probable)
10	Flaxseed / Aspirin	**Anaemia - Rectal bleeding**	Antiplatelet effect [44]	5 (Probable)	4 (Probable)
11	Omega-3 fish oil / 3 antihypertensive drugs	**Orthostatic hypotension**	Antihypertensive effects [40, 45]	5 (Probable)	3 (Possible)
	Blond Psyllium / 3 antihypertensive drugs			3 (Possible)	3 (Possible)
	Omega-3 fish oil / Blond Psyllium			3 (Possible)	3 (Possible)
12	Omega-3 fish oil / 2 antithrombotic drugs	**Postoperative haemoglobin drop**	Antithrombotic effect [10]	5 (Probable)	4 (Probable)
13	Omega-3 fish oil / Aspirin	**Gastrointestinal bleeding**	Antiplatelet effect [10]	5 (Probable)	4 (Probable)
14	Flaxseed / Omega-3 fish oil	**Melena - INR 4.18**	Antiplatelet effect [10, 44]	3 (Possible)	3 (Possible)
	Omega-3 fish oil / Warfarin		Antiplatelet effect [10]	6 (Probable)	3 (Possible)
	Flaxseed / Warfarin		Antiplatelet effect [44]	6 (Probable)	3 (Possible)
	Chamomile / Warfarin		Antiplatelet effect [46]	3 (Possible)	3 (Possible)
	Sage / Warfarin		CYP 2C9 inhibition [47]	6 (Probable)	4 (Probable)
15	Omega-3 fish oil / Enoxaparin	**Postoperative haemoglobin drop**	Antiplatelet effect [10]	5 (Probable)	3 (Possible)
16	Omega-3 fish oil / Warfarin	**Bleeding - Haemoglobin 5.7**	Antiplatelet effect [10]	6 (Probable)	3 (Possible)
17	Omega-3 fish oil / Enoxaparin	**Surgical bleeding (mild)**	Antiplatelet effect [10]	5 (Probable)	3 (Possible)

CYP, cytochrome P450; DIPS, drug interaction probability scale; OATP, organic anion transporting polypeptide; Ref, reference

Causality evaluation

According to the Drug Interaction Probability Scale, 14 (56%) of the 25 described interactions were 'probably' the cause of the associated adverse events (six of them rated '6' and eight rated '5'), while the remaining 11 (44%) 'possibly' caused the associated events (one rated '4' and 10 rated '3'). Likewise, our clinical pharmacology experts rated most interactions as being 'at least possible' (Table 4). When they were asked about missing data that hampered their evaluation, they mentioned the lack of data concerning the duration of drug and DHS use (25 interactions) and regarding DHS dosage (six interactions). They specifically pointed to the potential interactions between calcium and iron with levothyroxine (two interactions), asking whether the ingestion of these was concomitant and therefore clinically significant.

Potential risk factors

The mentioned adverse events were found to occur more frequently in older patients (72 ± 18 *vs.* 61 ± 19 years, $P = 0.025$, 95% CI: 2.26–19.7) and in patients born outside Israel (13 (76%) *vs.* 210 (48%), $P = 0.025$, 95% CI: 0.03–0.42). Concerning medical conditions, ophthalmologic (3 (19%) *vs.* 18 (4%), $P = 0.032$, 95% CI: 0.02–0.37) and

gastrointestinal comorbidities (5 (31%) *vs.* 34 (8%), $P = 0.008$, 95% CI: 0.05–0.46) were more commonly found in patients with actual adverse events. Finally, patients using greater numbers of DHS (3 [1.25–4.75] *vs.* 2 [1–2], $P < 0.0001$, 95% CI: 0.52–2.48) or concomitant medications (4 [3–7] *vs.* 2 [0–6], $P = 0.027$, 95% CI: 0.23–3.77) were more involved in actual adverse events associated with DHS–drug–DHS interactions (Table 3).

While DHS use was documented in the medical files of 11% of DHS users (Table 3), no DHS use involved in interactions associated with actual adverse events was reported in the patients' medical files.

Discussion

Our results point to the possibility that the consumption of DHS in various DHS–drug–DHS interactions may be associated with hospitalization or the worsening of existing medical conditions during hospitalization. Based on our findings, we can say that in populations similar to those in our study, one in every 55 hospitalizations (1.8%) may be associated with an adverse event related to such interactions. Most of these seem to have an 'at least possible' causal relationship, according to pharmacologic scales (DIPS) and expert opinions, although causality could not be confirmed by our study design. In spite of these serious ramifications, DHS are still under-reported in medical files. Moreover, as we considered only interactions reported in the Natural Medicine database, the actual incidence of DHS-related adverse events may be even higher and include effects that have yet to be recognized.

These findings should motivate the medical establishment to require physicians to ask their patients explicitly about their DHS use and to enter this information into patients' medical files. If a DHS–drug–DHS interaction is confirmed as causing an adverse event or is highly suspected of causing such an event, it should be further reported to local and international pharmacovigilance programs [29].

The use of keywords that address sociocultural diversities [24] can facilitate careful history taking about DHS use. Moreover, promoting access to outpatient medical files and encouraging physicians and herbal practitioners to report on the use of supplements [30] can help hospitals collect accurate information about DHS use. Medical staff members should be made more aware of DHS use, and medical education should emphasize collecting information on DHS use when taking patients' medical histories and when documenting this information in patients' medical files.

Once DHS consumption is confirmed by a carefully taken medical history, the next step in the diagnostic assessment of actual adverse events is to consider DHS–drug–DHS interactions as a possible cause of acute medical conditions. Hospital physicians should adopt a low threshold of suspicion regarding DHS and should always consider DHS–drug–DHS interactions in the differential diagnosis of acute illness. To facilitate patient workup and to keep medical staff updated, educational interventions should be instituted that specifically provide physicians with a systematic approach to DHS interactions. Indeed, a pilot study involving 86 physicians and nurses recently showed that a 90-minute educational intervention improved knowledge about the safety of DHS consumption and reduced apprehension among medical staff members regarding their ability to use DHS safety databases [31]. Furthermore, the assessment of DHS-related issues can be facilitated by promoting integrative medicine and clinical pharmacology consultations in the hospital setting.

When physicians suspect a DHS–drug–DHS interaction as a cause of an adverse event, they must determine the likelihood of whether the adverse reaction was actually caused by the specific interaction. Pharmacological algorithms such as the DIPS [11] are generally used to assess the causality of drug–drug interactions. These algorithms are not completely adapted to DHS–drug–DHS interactions as some aspects of medications do not apply to DHS. For example, the pharmacokinetics and half-lives of DHS have not been studied sufficiently [29]. Moreover, DHS dosages are not precise enough to evaluate the effect of their modification on the adverse reaction, and it is generally not practical to check a DHS plasma level to assess the causality of DHS–DHS interactions. To facilitate DHS evaluation, the DIPS was adapted to DHS–warfarin interactions [32]. Nevertheless, this modified DIPS was based on expert opinions and did not consider the issues mentioned here. For these reasons, the DIPS should be reassessed and adapted to DHS–drug–DHS interactions in order to improve physicians' diagnostic skills in this domain.

Strengths and limitations

Our study had good external validity as it regrouped a large population of inpatients who had various socioeconomic and cultural backgrounds, had a wide spectrum of comorbidities, were treated with diverse medications and used numerous and varied DHS. Internal validity was provided by our methodology, which was based on (a) a multicultural questionnaire created by experts from diverse backgrounds, (b) a search for interactions that was reproducible and relied on evidence-based data, and (c) an assessment of the causality of the described adverse events that was based on the adapted DIPS combined with expert opinions. Furthermore, we had a good response rate, which minimized the sampling bias. Nevertheless, the generalizability of our findings might be limited as our study was conducted at only one medical centre in Israel. In addition, in this study, relatively few inpatients were determined to have experienced an actual adverse event associated with DHS interactions. This small number limited the statistical analyses, even though we did attain the number of patients required by our minimal sample calculation. Given that our study was based on interviews and questionnaire completion, we cannot rule out the possibility of some recall bias, although this was minimized by considering only DHS taken within a week preceding hospitalization. Causality could not be deduced from our cross-sectional study design. We did not actually assess new symptoms and signs and trace them back to DHS–drug–DHS interactions. Furthermore, we did not study drug concentrations to verify potential DHS inhibitory/inducing effects on drug metabolism. Rather, we considered theoretical interactions and further monitored them in medical files. Longitudinal or interventional studies should be used to confirm a causal relationship between DHS–drug–DHS interactions and the actual

occurrence of adverse events. Moreover, we may have overestimated DHS–drug–DHS interactions as most of them relied on case reports or on *in vitro* or animal studies. On the other hand, we may have overlooked adverse events that were not described in the Natural Medicine database. Larger clinical trials are needed for a further assessment of DHS–drug–DHS interactions in humans. Since most data about the pharmacokinetics of DHS have not been well studied, we cannot verify that our cut-off of one week for the influences of DHS on hospitalization was appropriate. Finally, some of the DIPS questions could not be answered as it was not possible to de-challenge, re-administer or change DHS dosage retrospectively. DHS dosage should be prospectively assessed in future studies to confirm causality.

Conclusion

In conclusion, previously described theoretical DHS–drug–DHS interactions might actually occur, thus confirming one of the hazards of DHS and medication combinations, specifically among patients with multiple comorbidities. Nevertheless, these findings should not be over-interpreted. Indeed, the causal relationship between DHS–drug–DHS interactions and the actual occurrence of adverse events is yet to be confirmed.

Competing Interests

There are no competing interests to declare.

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