CHAPTER 6

Potential Safety Issues With Combined Use of Dietary Supplements and Medication – Focus on Interactions

Marit Waaseth[1], *Silje Brækkan Rønning*[2] & *Guri Skeie*[3]

[1]Department of Pharmacy, UiT The Arctic University of Norway, Tromsø, Norway

[2]Vitusapotek Nordstjernen, Bergen, Norway

[3]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

Abstract: The use of dietary supplements (DS) is widespread and tends to increase with age and female gender. DS use can in some situations represent a safety risk for patients. For instance, concomitant use of medication and dietary supplements, particularly herbal remedies, may cause clinically significant pharmacological interactions. The study underlying this chapter aimed to investigate the prevalence of potentially clinically significant DS-medication interactions in a general population of middle-aged women. The study is a questionnaire survey among Norwegian women born between 1943 and 1957. Data were collected from 2002 to 2006 as a part of the Norwegian Women and Cancer study (NOWAC). The participants listed all medications and all DS they had used during the previous week. The reported DS were checked for interaction potential in combination with medication, using the Natural Medicines database. The study population comprised 3,970 women, of whom 1,885 combined medication and dietary supplements. Overall, 630 (16% of the total population) used a DS-medication combination with a potential for at least one clinically significant interaction. Of these, 132 women used herb-medication combinations, 63 used combination(s) that represented more than two interactions, and three used combinations classified as a major health risk. There is considerable

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potential for clinically significant medication-supplement interactions in a general population such as the one described in the study. Although few of the identified interactions represent a major health risk, the findings indicate that health personnel should take supplements into account when assessing the safety of medication use among their patients.

Keywords: Dietary supplements, medication, patient safety, interaction, general population

According to Norwegian legislation, dietary supplements (DS) are nutritional products and substances: 1) intended to supplement the diet; 2) representing concentrated sources of vitamins and minerals or other substances with a nutritional or physiological effect, alone or in combination; and 3) sold in prepacked, dosed form designed for intake of small, measured amounts (*Forskrift om Kosttilskudd [Regulation on Dietary Supplements]*, Lovdata [Norwegian statutes in force], 2004). "Other substances" include herbs and other substances of so-called natural origin, for instance omega-3 fatty acids. This legislation is adopted from European legislation (EU directive, 2002).

Use of DS in Norway increased extensively from 1986 to 2004 (Waaseth et al., 2007). There was a slight decrease from 2006 to 2012 (Norwegian Food Safety Authority, 2013). The biannual NAFCAM surveys from 2012 to 2018 have shown a fairly stable prevalence in the use of natural remedies/herbs in Norway (Bergli, 2020). NAFCAM is Norway's national research center for complementary and alternative medicine.

International reports suggest that women use more DS than men, and most show that prevalence of use increases with increasing age, socioeconomic status and healthy lifestyle (Bailey et al., 2013; Kofoed et al., 2015; Li et al., 2010; Park et al., 2009; Touvier et al., 2006). A previous publication from the Norwegian Women and Cancer study (NOWAC) showed that in a general population of middle-aged women, 71% used some type of DS and the use was associated with socioeconomic, lifestyle and health-related factors, including medication use (Waaseth et al., 2019).

DS do not undergo the same detailed approval processes as medications. Thus, use of DS may be unsafe for many reasons. One can experience side effects from substances in the product or interactions can occur

between such substances and medications through combined use (Ronis et al., 2018). Similar effects can occur from non-declared content or contamination. For instance, heavy metal contamination may interact with medication (Anwar-Mohamed et al., 2009). Other reasons that use of DS may be unsafe include the risk of toxic reactions due to overdose, impact on diagnostic and perioperative procedures (Abe et al., 2014), and lack of necessary treatment due to some patients replacing medication with supplements. The last one is rare, however. Commonly, DS are used complimentary to evidence-based treatment, and mostly to improve overall health (Astin, 1998; Bailey et al., 2013; Salamonsen, 2013). Finally, it is difficult for both health personnel and DS users to find easily available and reliable information about DS safety (Owens et al., 2014; Risvoll et al., 2021).

Some patient groups are particularly vulnerable to unsafe use of dietary supplements. This is exemplified by persons with dementia who, in addition to the direct risks mentioned above, are affected indirectly due to cognitive decline (Risvoll et al., 2017). Risvoll et al. shows how this patient group receives far less assistance with their dietary supplements use compared with medication use, and that health personnel are uncertain regarding who should take responsibility for safeguarding such use (Risvoll et al., 2019; Risvoll et al., 2021).

High quality DS do not pose a large health risk when used alone, according to recommended dosage, and by healthy individuals. However, concomitant use of medication and DS, particularly herbal remedies, may cause clinically significant pharmacokinetic or pharmacodynamic interactions (Boullata, 2005; Reddy et al., 2021; Ronis et al., 2018; Tarirai et al., 2010). Pharmacokinetic interactions occur when a substance A (from medication or herb) changes the absorption, protein binding, distribution, metabolism or excretion of a substance B, thereby causing a changed concentration of substance B in the body. St. John's wort (*hypericum perforatum)* is an herb particularly known for its influence on the metabolism of medical substances through induction of liver enzymes (Tarirai et al., 2010). In Norway, legal sales of products containing St. John's wort are restricted to pharmacies because of the need for guidance in relation to the herb's interaction

potential. Pharmacodynamic interactions occur when substance A, directly or indirectly, interferes with substance B on its action site, thereby influencing the effect, but not the body concentration of substance B.

Through experiences from pharmacy practice and from the work on the previously mentioned publication from NOWAC (Waaseth et al., 2019), we have seen worrying cases of DS use. This can for instance be the use of two or even three different omega-3-supplements, representing a risk of over dosage of fat-soluble vitamins, or concomitant use of herbs and medication, which represents a possible interaction. Such cases indicate a potential health risk. They also suggest a lack of knowledge among the general population when it comes to what such supplements contain. The NOWAC study found concomitant use of DS and medication among 48% of the population, suggesting a potential for medication-DS interaction.

Compared with pharmaceuticals, the safety of DS is rarely investigated through traditional evidence-based research methods. Randomized controlled trials are resource demanding, and not a prerequisite for legal distribution of DS (Waaseth et al., 2007). Even products with marketing authorization as herbal medicines are not checked for safety beyond documentation of "long-established use" according to the EU directive (EU directive, 2004). Observational studies, using data from surveys and registries, therefore play an important role in describing DS use, and identifying safety issues related to this use, although such research also has its challenges (Arab, 2000). So far, most of the research on this subject has focused on prevalence of use and user characteristics (Li et al., 2010), or potential interaction mechanisms related to certain herbs and/or medications (Mouly et al., 2017; Tarirai et al., 2010). Few have attempted to quantify DS-medication interactions, and mainly among specific patient groups (Bush et al., 2007; Dergal et al., 2002; Firkins et al., 2018; Peng et al., 2004; Risvoll et al., 2017).

The study underlying this chapter aims to describe the prevalence of potentially clinically significant interactions between DS and medication use in a general population of middle-aged women, using data from the NOWAC study.

Material and Methods

This is a cross-sectional study among Norwegian women born between 1943 and 1957. Data were collected from 2002 to 2006 as a part of NOWAC.

Study Population

The Norwegian Women and Cancer study (NOWAC) is a nationwide, population-based cohort study with participants randomly sampled from the National Population Register, held by Statistics Norway (Lund et al., 2007). Since 1991, approximately 172,000 women have answered questionnaires on health, lifestyle and socio-demography.

From 2002 to 2006 approximately 50,000 women participated in the blood sample collection for the NOWAC biobank (overall response rate 71%). Participants (born 1943–1957) reported their use of medication and DS during the week preceding the blood donation and accompanying questionnaire. The women were invited in groups of 500. Data from eleven groups (5,500 invitees), randomly chosen, were electronically available at the time of analysis and comprise the basis of our study sample of 3,970 women (response rate 72%).

Use of Medication and Dietary Supplements

The participants listed all medication and all DS they had used during the previous week. In addition to the general question on DS use, the questionnaire included three specific questions on use of soy, cod liver oil and other omega-3 supplements. Information on dosage was not included as it was not collected for all participants, nor all products, due to slight differences in questionnaires for the various waves of data collection.

DS were mapped according to content based on manufacturer information, if available. Some were classified according to the reported product title (for instance, “calcium”, “antioxidant supplement”, etc.).

Medications were coded according to WHO’s ATC-classification (*ATC/DDD Index*. The WHO Collaborating Centre for Drug Statistics Methodology), and further categorized into groups relevant to different

types of interaction. A category either represents the mechanism by which the included substances interact: cytochrome P450 enzymes (CYPs)(Anwar-Mohamed et al., 2009; *Drug Interactions Flockhart Table*™; Zanger & Schwab, 2013); P-glycoprotein (*P-glycoprotein*; Wang et al., 2005); narcotics (*List of Narcotic Analgesics*); organic anion transporting polypeptides (OATPs)(Niemi, 2007; Shitara et al., 2013; Stieger & Hagenbuch, 2014); photosensitizing substances (Zhang & Elmets, 2020); QT-prolonging substances (*QTDrug Lists*); seizure threshold lowering substances (Buchanan, 2001; Hitchings, 2016; Nestor et al., 2010); CNS depressants (*Prescription CNS Depressants DrugFacts*) or stimulants (*List of CNS stimulants*); hepatotoxic substances (Björnsson, 2016); glucuronidation substrates (Kiang et al., 2005); or it represents a medication class, for instance antiepileptics or opioids (*ATC/DDD Index*. The WHO Collaborating Centre for Drug Statistics Methodology). The medication categories were not mutually exclusive as some substances occur in several categories.

Identifying Interactions

The registered content/substances from all reported, decipherable DS were checked for interaction potential in combination with medication, using the Natural Medicines database (Natural Medicines, accessed 2020) professional monographs. Natural Medicines is a not-for-profit database, primarily focused on the safety and effectiveness of natural products of all kinds. It is systematically updated, and potential literature sources are critically evaluated for relevance and validity. Interactions are classified according to a stop-light rating system, combining severity and likelihood of occurrence (Natural Medicines). In addition, the interactions are classified according to level of evidence: A) high-quality RCT/meta-analysis; B) non-randomized/observational studies; C) consensus/expert opinion; and D) anecdotal/animal/in vitro/theoretical evidence.

In our study, we defined clinically significant interactions as interactions of moderate to high severity and of possible, probable, or likely occurrence (Figure 1). These were labelled "potential" interactions, as they were based on self-reported use and the data material did not provide

information about clinical evidence of an actual interaction occurring. In addition, classification C or D in level of evidence was considered low-grade documentation.

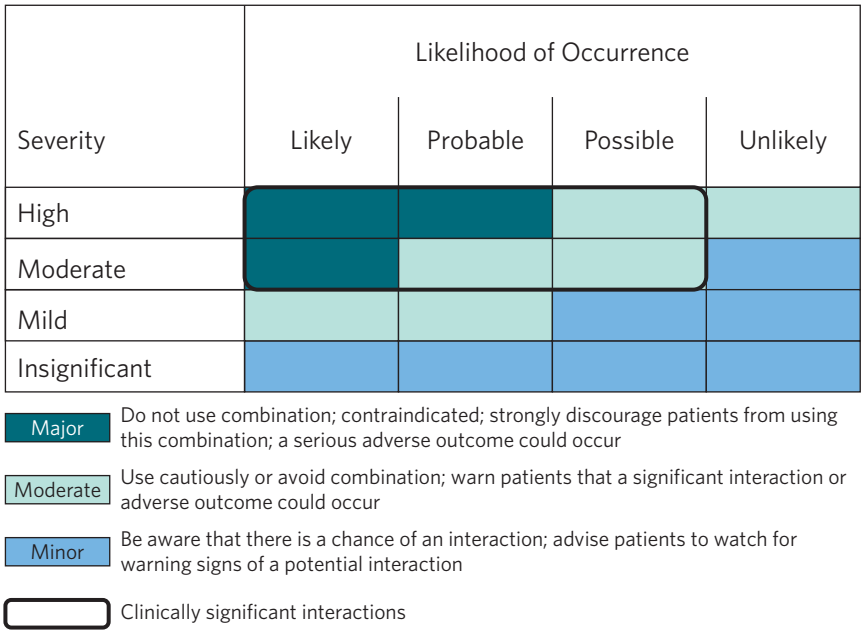

Figure 1. Classification of Clinically Significant Interactions
The figure is modified from the stop-light system for interaction severity and likelihood of occurrence (Natural Medicines). Reproduced with permission from Therapeutic Research Center, November 2021

We created a variable for each DS-medication or medication category combination with interaction potential identified by Natural Medicines. Interactions were further classified as potentially clinically significant or not (Figure 1). We counted the number of interactions and calculated the proportion of participants with a potential interaction. We also categorized the participants according to number of interactions identified (1, 2 and >2). One DS-medication combination may give rise to more than one interaction: a DS may interact through several interaction mechanisms due to mixed content, and a medication may belong to more than one medication group, it may for instance be both an OATP and a CYP3A4 substrate.

Analysis

Descriptive statistics (counts and percentage) were used to describe the number of potential interactions and proportion of participants with one or more identified interactions. We used IBM SPSS Statistics version 26 for the statistical analyses.

Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. NOWAC is approved by the Regional Committee for Medical and Health Research Ethics in North Norway (141/2008). Storage of data comply with the rules of the Norwegian Data Inspectorate and has an approved Data Protection Impact Assessment (DPIA) from UiT the Arctic University of Norway (ref. 743201, 16.11.2021). Written informed consent was obtained from all participants.

Results

The study population comprised 3,970 women, of whom 2,577 (65%) used medication, 1,824 (71%) used DS and 1,885 (47%) combined medication and DS use. Most of the women were postmenopausal (Table 1). The women reported a total of 463 different DS products. The content of 22 of these were not decipherable, and 64 participants used one (n = 59) or two such DS (n = 5).

Irrespective of documentation grade, the prevalence of potentially clinically significant DS-medication interactions was 44% (n = 823), that is the proportion of DS-medication users with at least one interaction identified (Table 2). When excluding interactions with low-grade documentation, the proportion was 33% (n = 630), which represents 16% of the total study population. Among these, 132 women (7%) used herb-medication combinations, and 63 (3%) used combination(s) that represented more than two interactions.

Altogether, 1,857 DS-medication interactions were identified, 591 of these were herb-medication interactions. The corresponding number of interactions after exclusion of those with low-grade documentation was 960 and 173 respectively. As shown in Table 3, herb-medication interactions are more

Table 1. Characteristics of the Study Population Overall and According to Use of Medication and Dietary Supplements (DS)*

	Total		No medication, no DS		DS, no medication		Medication, no DS		Medication and DS	
	N = 3970		N = 454 (11.4%)		N = 939 (23.7%)		N = 692 (17.4%)		N = 1885 (47.5%)	
Age, mean years (SD)	55.0	(3.9)	54.1	(4.1)	54.6	(4.0)	54.7	(3.9)	55.6	(3.8)
BMI, mean kg/m^2 (SD)	25.7	(4.4)	25.3	(3.7)	24.8	(3.7)	26.8	(5.0)	25.8	(4.4)
Number of medications, median (range)	1.0	(0–20)	0.0		0.0		2.0	(1–12)	2.0	(1–20)
Number of DS, median (range)	1.0	(0–12)	0.0		2.0	(1–12)	0.0		2.0	(1–9)
Smoking, n (%)	829	(20.9)	116	(25.6)	180	(19.2)	168	(24.3)	365	(19.4)
Menstrual status, n (%)										
Regular	487	(12.3)	84	(18.5)	146	(15.5)	85	(12.3)	172	(9.1)
Irregular	318	(8.0)	47	(10.4)	75	(8.0)	52	(7.5)	144	(7.6)
No menstruation	3126	(78.7)	313	(68.9)	711	(75.7)	547	(79.0)	1555	(82.5)

*Missing information was defined as non-use. 18 did not answer the question about medication use and 16 did not answer the questions about dietary supplement use.

Table 2. Number (%)* of Participants with Identified Potentially Clinically Significant Interactions Related to Dietary Supplements (DS) Use Among Participants Combining Medication and DS (n = 1885)

	Total		1 interaction		2 interactions		>2 interactions	
	N	(%)	N	(%)	N	(%)	N	(%)
DS-medication interaction overall#	823	(43.7)	330	(17.5)	243	(12.9)	250	(13.3)
Herb-medication interaction	299	(15.9)	154	(8.2)	83	(4.4)	62	(3.2)
Other DS-medication interaction	654	(34.7)	285	(15.1)	211	(11.2)	157	(8.3)
Excluding interactions with low-grade documentation:								
DS-medication interaction overall#	630	(33.4)	404	(21.4)	163	(8.6)	63	(3.3)
Herb-medication interaction	132	(7.0)	97	(5.1)	29	(1.5)	6	(0.3)
Other DS-medication interaction	547	(29.0)	380	(20.2)	121	(6.4)	46	(2.4)

*The percentages represent the proportion of participants who combine DS and medication, (i.e., 1,885).
#The overall numbers are not the sum (vertically) of participants with herb-medication and other DS-medication interactions. Some participants have both interaction types, and some have one interaction of one type and several interactions of another.

Table 3. Frequency of Potential Dietary Supplements-Medication Interactions, Excluding Interactions with Low-Grade Documentation

Herb	Medication	#	Non-herbal substance	Medication	#
Soy	Antidiabetics	1	Vitamin A	Hepatotoxic med.	68
	Antihypertensives	28	Vitamin B3, niacin	Antihypertensives	1
	Thyroxine	17	Vitamin B9, folate	Methotrexate	1
Fenugreek	Anticoagulants	1	Vitamin B6	Antihypertensives	8
	CYP1A2 substrates	11	Vitamin C	Estrogens	159
Ginkgo biloba	CYP1A2 substrates	2		Statins	42
	CYP3A4 substrates	2		Niacin	2
Ginseng	Antidiabetics	1	Vitamin D	CYP3A4 substrates	297
	CYP2D6 substrates	10		Diltiazem	1
	CYP3A4 substrates	32		Verapamil	1
	QT prolonging med.	8	Vitamin E	Anticoagulants	46
Grapefruit	CYP2C19 substrates	1		Statins	82
	Levothyroxine	2		Niacin	2
	OATP transporters	2*		Warfarin	3
	CYP2E1 substrates	4	Cr	Levothyroxine	9
	CYP3A4 substrates	17	Zn	Antidiabetics	1
Ginger	Anticoagulants	3		Tetracyclines	1
St. John's wort	CYP3A4 substrates	1*	Se	Statins	1
	P-glycoprotein substrates	1*	Mg	Bisphosphonates	2
Cassia	Antidiabetics	1	Ca	Aluminum salts	1
	CYP3A4 substrates	1		Bisphosphonates	5
	Anticoagulants	3		Levothyroxine	30
	Antidiabetics	1		Sotalol	1
Milk thistle	CYP2C9 substrates	3		Tetracyclines	2
Olive leaves	Antihypertensives	1		Tiazides	2
Capsicum annuum	Anticoagulants	3	Fe	Levothyroxine	11
	CYP3A4 substrates	7	Chlorophyll	Photosensitizing medication	8
Echinacea purpurea	CYP1A2 substrates	5			
	CYP3A4 substrates	4			
Total		**173**	**Total**		**787**

*Major risk of adverse outcome.
OATP: Organic Anion Transporting Polypeptides; CYP: Cytochrome P450.

often specifically related to liver metabolism and membrane transport than non-herb-medication interactions. Four of the herb-medication interactions, representing three of the participants (0.02% of 1,885 DS-medication combination users), were classified as major risk of adverse outcome according to the Natural Medicines database (Figure 1) and involved grapefruit and St. John's wort. One participant combined St. John's wort with clarithromycin, which represents a risk of reduced plasma concentration of clarithromycin due to induction of the liver enzyme CYP3A4. She also used a tomato extract, cod liver oil and a soy supplement. Two participants used a herbal mixture which included grapefruit, combined with levothyroxine, an OATP1B1 substrate. Due to the many herbs present in the herbal product as well as use of some other DS products, both women had several additional potentially clinically significant interactions identified, but these were all classified as low-grade documentation.

A complete list of identified DS-medication interactions is available on request.

Discussion

The main study findings are that among a middle-aged population of Norwegian women, 71% used DS and 47% combined DS and medication use. The prevalence of potentially clinically significant DS-medication interactions was 33% among the DS-medication users, 16% in the total study population. DS-medication combinations with a potentially serious interaction outcome were identified, but the prevalence was very low.

Other studies that have reported prevalence of DS-medication interactions, have found a variation from 5% to 40% (Bush et al., 2007; Dergal et al., 2002; Firkins et al., 2018; Peng et al., 2004; Risvoll et al., 2017). There are several plausible reasons for this variation: 1) varying study populations (elderly, particular patient groups (cancer, kidney, dementia)); 2) various countries/geographical regions with differing legislation and culture for DS use; and 3) varying methods and tools used to define DS or herbal use and DS-medication interactions.

The Norwegian study by Risvoll et al. (2017) is particularly interesting as it includes persons with dementia, a patient group who may be excluded from surveys either intentionally, or indirectly due to their cognitive status. Among 151 participants, 46% used DS and 11% had a potentially clinically significant DS-medication interaction. A similar Canadian study conducted at a memory clinic detected potential herb-medication interactions in 5% of the patients (Dergal et al., 2002). A survey among patients attending American outpatient clinics detected a substantial number of potentially adverse herb-medication (prescription) interactions (40% of the herb users), but did not uncover any serious adverse interactions after reviewing the patients' charts (Bush et al., 2007). Another American survey in primary care identified potential DS-medication interactions among 17% of the participants, while 1% had potentially severe interactions (Peng et al., 2004). A German study in oncology clinics found that 16% of the patients risked interaction due to combined use of conventional medication and so-called biologically based CAM (complementary and alternative medicine) (Firkins et al., 2018), but severity was not assessed.

The results from these studies, ours included, may be summed up as follows. There is a noteworthy potential for clinically significant interactions to occur between DS and medications, and the prevalence may be high or low depending on the type and number of medications used in the study population. Also, although there is a risk of seriously compromised health through combining DS-medication, the prevalence of interactions representing a major health risk is generally low.

Strengths and Limitations

The strengths of this study include a fairly large, nation-wide study population, random sampling of participants, and acceptable participation rate. NOWAC has been shown to be representative of middle-aged Norwegian women (Lund et al., 2003). We have used a comprehensive, quality ensured database for information on DS-medication interactions.

All information on medication and DS use was based on self-reporting. Participants were asked to list the products they used, and this may result in some level of underreporting. As we combined the

lists with specific questions on use of soy, cod liver oil and other omega-3 supplements, the risk of underreporting was somewhat reduced. Over-the-counter medication could be underreported, although the questionnaire did not specify prescription medicine. Validation analyses have been performed for frequently used medication groups (antidepressants and hormone therapy), and for vitamin D, all suggesting high validity with plasma concentrations as a reference standard (Brustad et al., 2004; Waaseth et al., 2008; Waaseth et al., 2020).

We have identified *potential* interactions, as we cannot know to which degree DS and medication use happened concurrently, beyond that they were used during the same week. Thus, there may be some overestimation of the prevalence of potential interactions. On the other hand, although unknown products or content comprised a small proportion of the DS use, some degree of missing information on use must be assumed, and consequently an underestimation of interaction prevalence. Neither for medication nor for DS did we know the dosage used or the timing of intake and cannot assess the seriousness of the identified interactions beyond what is stated in the Natural Medicines' professional monograph.

Our focus was on DS-medication interactions, and so we did not check for potential DS-DS interactions. Nor have we looked into interactions involving tobacco or alcohol consumption, although nicotine was included as a medication for those reporting medications used in nicotine dependence (N07BA). However, health personnel should be aware of these possibilities as well, and the professional monographs in Natural Medicines include such information.

Implications for Medication Safety in Municipal Health and Care Services

We identified a noteworthy prevalence of potentially clinically significant DS-medication interactions in a general population sample of middle-aged women. Some of these interactions had the potential to seriously affect the users' health. Health personnel need to be aware of potential problems regarding DS use and apply tools to identify them. Medication reconciliation procedures, as for example, the Integrated Medicines

Management (IMM) model (Scullin et al., 2007), should as a rule include questions regarding DS use, which should be asked actively. Patients tend not to disclose DS use to health personnel unless asked about it (Gardiner et al., 2015; Guzman et al., 2019). Regarding St. John's wort, sales are restricted to pharmacies particularly because of the interaction potential. The fact that we found a case of unsafe combination involving St. John's wort may suggest a lack of guidance from pharmacy personnel or that the product was bought illegally through other sales channels. Also, if the woman was already using St. John's wort when she got the clarithromycin prescription, this should have been detected at the doctor's office or at the pharmacy if health personnel in either setting had asked, "Which dietary supplements do you take?".

We have previously shown that DS use is more frequent among medication users, particularly when the reported medication suggests a chronic disease or condition (Waaseth et al., 2019), and particularly herbal supplements. The latter is noteworthy because herbs are the most worrisome DS due to the potential for pharmacokinetic interactions. The risk of interaction would necessarily increase with an increasing number of products used, both DS and medications, indicating a need to focus on elderly medication users. However, our material also shows that several, even severe, interactions may occur from a combination of just a few products.

The quality of online, public sources of information about DS is variable and generally lack safety information (Owens et al., 2014). Availability of reliable information about DS is also a problem for health personnel (Risvoll, 2021). How to relate to and interpret the detailed content in an otherwise reliable source can also be a challenge. Pharmacists should have a lower threshold for retrieving and interpreting such information, as they are trained in interaction mechanisms for medications in general. However, reliable databases are not readily available in community pharmacies. The regional medication information centers (RELIS) in Norway use Natural Medicines as the main source of information about DS-medication interactions. A subscription to this (or similar) databases and safety monitoring of consequences of DS-medication combination use, should be seen as an investment in quality health care by pharmacy chains, health authorities and policy makers (Skalli & Soulaymani

Bencheikh, 2012). Apart from databases, there are initiatives from clinical researchers in providing algorithms for the identification and management of DS-medication interaction within vulnerable patient groups, particularly cancer patients (Reddy et al., 2021; Ziemann et al., 2019).

According to European legislation (EU directive, 2002), all DS sold in a country shall be registered, or the regulatory food authorities shall have an inventory. As far as we know, it has not been a priority for Norwegian authorities to establish such a registry. Although it would not include information on interactions, it could be a great help in establishing the content of the various DS, which is a prerequisite for assessing the interaction potential of DS-medication combinations.

For pharmacists or other health personnel who feel they need an update on safety regarding DS use in general or DS-medication interaction specifically, there are good reviews to be found (Reddy et al., 2021; Tarirai et al., 2010), as well as digital courses. For instance, the National Institute of Health's National Center for Complementary and Integrative Health provide a course on DS-medication interactions (Gurley, 2014).

Conclusion

Pharmacological interaction with medications is one of several ways in which dietary supplements can adversely affect patients' health. There is considerable potential for clinically significant dietary supplement–medication interactions in a general population of middle-aged women. Whether this poses a serious health threat, could not be unequivocally established by the data material from NOWAC, though the probability of serious health risks seems low in this population segment. However, our findings indicate that health personnel should take supplements into account when assessing health risk and medication use among their patients.

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