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Drug/Natural Products-Related problems in Elderly

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Abstract: Herbal remedies have risen for decades in developed and developing countries. In this systematic review, the herbs such as cannabis, St. John's wort, kava, turmeric, grapefruit, bitter orange, ginger, garlic, and Chinese Herbal tea are discussed to interact with medicines and potentially cause adverse reactions. This study aimed to investigate the occurrence and prevalence of drug/NP interactions in healthy volunteers or patients with comorbidities in elderly populations above 65. A systematic literature review was conducted using PubMed, Google Scholar, Scopus, Cochrane, and MedRxiv databases, from May 2022 until July 2022. Studies investigating drug/NP-related problems (DNRP) in healthy patients or patients with comorbidities were included. The data obtained was then commenced with the quality assessment by the Joanna Briggs Institute (JBI) tool. The inclusion criteria comprised six studies demonstrating that most drug classes associated with DNRP were represented by Selective Serotonin reuptake inhibitors (SSRIs), kinase inhibitors, and anti-neoplastic agents. Factors linked to DNRP are age, the number of medications, gender, five or more prescribed drug, presence of comorbidity, underestimation of potential adverse events, and length of hospitalization. This systematic review has proven that DNRPs may occur due to herb-drug interaction or multi-medication consumption. Limitations such as patients not disclosing their DNRPs to pharmacists may affect the investigation. At the same time, larger sample sizes are required to unfold the real problem in future studies.

Keywords: Drug-related problems; Drug/NP-related problems; herbs; drug-herb interaction; St. John's wort; Turmeric; kava; ginger; Grapefruit

1. Introduction

Drug/NP-related problem is ascribable to physiological changes such as damaged kidney function and aging[1-3]. This is because the kidney would frequently turn smaller due to the reduction in the number of cells. After 30 years old, individuals experience different changes, such as less blood passing through the kidney and, consequently, less blood is

filtered, and fewer waste products are eliminated. Similarly, this also applies to the liver. The liver enzymes function less efficiently to help the body process and remove drugs and other substances. Changes in every cell and organ lead to changes in the function and appearance of an individual's body as they age. Fortunately, compared to most parts of the body, the digestive system is only slightly affected by age. For example, food movement in the esophagus is not affected; however, the esophagus muscles will be more relaxed. Then, the stomach cannot grasp a large quantity of food, and the content is removed less quickly due to reduced elasticity; stomach emptying is delayed, and proteolysis is inhibited[4]. However, these changes are often unrecognized by the majority of people. In addition, food passing through the large intestine are also slightly slower. There is also a decrease in intestinal blood flow, which tends to delay or restrict drug absorption. Perhaps there is a decrease in the number of absorbing cells in the intestine, resulting in a loss of absorbing surface in the elderly; this could explain the reported reduction of passive diffusion in the elderly. All of these variables point to decreased medication absorption in the elderly. Fortunately, the absorption decrease is followed by a decline in metabolism and excretion. As a result, medication absorption from the intestine is balanced by delayed excretion[5]. Differently, Blood vessels become stiffer, which results in high blood pressure because the blood fills in the organs at a slower pace, and the arteries have a reduced tendency to dilate[6]. Notably, the two leading causes of arterial stiffness are age and high blood pressure. Due to wave reflections, big arteries harden, and systolic and pulse pressures rise in elderly with hypertension. In conclusion, studies show that aortic stiffness was connected with insulin resistance syndrome risk variables such as increased common carotid intima-media thickness, heart rate, and decreased physical activity measured several years earlier[4, 5].

1.1 The Growing use of Herb

Herbs are often utilized as a traditional way to treat illnesses of all ages instead of using them for supporting healthy conditions or acting as prophylaxis against diseases, which is essential for the elderly. The main reasons for the consumption of herbs over conventional treatment are that people would prefer herbal medicine as an initial prior treatment, family tradition or traditional practice, pleasing experience from previous use, excellent outcomes achieved, or disappointment from taking conventional medications[6]. Despite that, herbs are often considered as effective as medicines because they look like medicines in terms of dosage form administered, such as tablets or capsules[7]. In decades prior to modern medicine, herbal medicine was the most common form of healthcare in developing and developed countries[8, 9]. Currently, approximately eighty percent of the population worldwide still depends on herbal medications as their essential treatments, particularly in developing countries. As stated by World Health Organization (WHO), an estimated seventy to eighty percent of the population globally depends on herbal medications, and natural products, for essential healthcare needs. However, there are complications and disadvantages to consuming herbal medications. The adage "Herbal products are safe because they are natural"

isn't always accurate. Although herbal therapies are considered natural, many can interact with other medications, resulting in decreased effectiveness and potentially harmful side effects[9-11, 14]. Additionally, the fact that millions of people use herbal therapies concomitantly with prescription and non-prescription medications would add to the interactions and adverse effects dilemma.

Despite the growing use of herbs worldwide, there is limited data published regarding herb-drug interactions. However, various adverse effects associated with using individual herbal supplements have also been reported worldwide, such as hepatotoxicity and stroke linked with adulterated supplements. Another example demonstrated is the use of St. John's Wort, which seems to cause adverse effects similar to Fluoxetine. Two factors may cause these adverse effects. Firstly, the usage of illegal or poor-quality products containing drug ingredients, and secondly, the concomitant use of several dietary supplements or medicines at the same time or excessive intake, which could lead to severe adverse effects.

1.2 Elderly Drug-Related Problems with Herbal Products

Due to above stated functional changes, the elderly are more important to consider due to the higher risk of polypharmacy as being well documented, more sensitivity to certain medications, and the organs that process many drugs simultaneously have decreased functional capacity with increasing age. In addition, adverse effects responses happen 2 to 3 times more commonly in elderly over 65, making older people more sensitive to their effects. This can be explained by lower hepatic drug clearance, altered body water and fat compositions, decreased renal drug elimination, and age-related changes in pharmacodynamics, which increase the chance of adverse medication responses in older people. Notably, compared to 1% of younger people, 3 to 4% of older people taking nonsteroidal anti-inflammatory drugs (NSAIDs) have gastrointestinal bleeding[. These elements increase the probability that harmful drug-drug and drug-herb combinations will occur as patients may take more medications, leading to polypharmacy. Another issue is that it is generally acknowledged that roughly 50% of herbal product consumers do not disclose their usage to a healthcare professional, which theoretically increases the risk of harmful Complementary/Alternative Products and Conventional Medicines (CAM)-drug interactions[16]. According to a recent nationwide study of non-institutionalized US adults, more than 90% of those 65 and older utilized at least one medicine weekly, while more than 40% of adults used at least five and 12% at least ten or more variety of medications each week. In a geriatric clinic, approximately 73% of patients were using anticoagulants prescribed, while 46% of patients were consuming anticoagulant supplements without suspecting the possible interactions. In another study, it was found that 1 in 6 adults using

conventional prescribed medicines was recorded with associated usage of more than 1 CAM product within the prior week[17]. The primary use of drugs by the senior population shows that substantial numbers of older people are impacted, even though most medication mistakes do not cause injury[18]. In order to decrease the chance of adverse events linked with herbal medicines, the World health organization (WHO) has committed to developing new guidelines on safety and quality assurance for these products, as well as updating existing technical papers[19].

2. Materials and Methods

Electronic databases utilized to conduct this review were PubMed, Google Scholar, Scopus, Cochrane, and preprint platforms such as MedRxiv database of Systematic Reviews. The compilation of articles was initiated from May 2022 until July 2022. These terms were used along with Boolean operators "AND" and "OR" in the 'advanced search' category. The search terms utilized in the databases to obtain the results can be demonstrated in **Supplementary Table 1**.

There were 321 results obtained from PubMed, 60 from Google Scholar, 43 from Cochrane Library, 40 from MedRxiv, and 227 from Scopus. The following results were transferred to Endnote, referred to as a citation tool to cite references and remove any duplication found. After duplication had been removed, the gathered remaining results were screened twice. Based on the title and abstract, non-relevant results were eliminated during the first screening. The second screening was then conducted to evaluate if the studies were eligible to be included in this review. The results must satisfy the inclusion and exclusion criteria.

The inclusion criteria may be as follow:

1. Articles were obtained from books, documents, clinical trials, conference papers, randomized controlled trials, and research papers.
2. Articles involve interaction(s) between the herbs listed and the prescribed medication or the side effects of consuming the herbs alone.
3. Human studies
4. Studies that use English Language only
5. Drug/NP-related problems in elderly

The exclusion criteria may be as follow:

1. Literature includes meta-analysis, clinical trial, systematic review, review, case study, and case report.
2. Studies involving pharmacokinetics and not related to the drug/NP-related problem
3. Studies that do not cover the specified herbs and do not disclose any side effects from the interactions
4. Studies that highlight the side effects but do not name specific herbs or prescribed medications

Screening of publications on studies related to Drug-Related Problems due to consuming herbs was performed. Any appropriate literature was retrieved and reviewed if they were to meet the criteria of the review.

2.1 Quality Assessments

The included studies were independently critically appraised for the systematic review by the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data tool. This formerly verified tool utilizes four straightforward responses: "Yes," "No," "Unclear," and "Not applicable," as demonstrated in **Table 3**.

3. Results

The PRISMA flow diagram, **Figure 1,** demonstrates the search strategy that has been used. As a result, 550 studies were screened, and 41 were excluded from this review as duplicates were removed before the screening. Only six papers were retrieved and included in this study after 544 studies were removed for not fulfilling the established inclusion criteria. The results of the studies included in this review, Author, year And Country, Study Design, the aim of the study, Patient details, Condition, Herbs used, Drugs involved, Drug/NP-Related Problem, and Percentage of the population affected or statistical significance are summarized in **Table 1**.

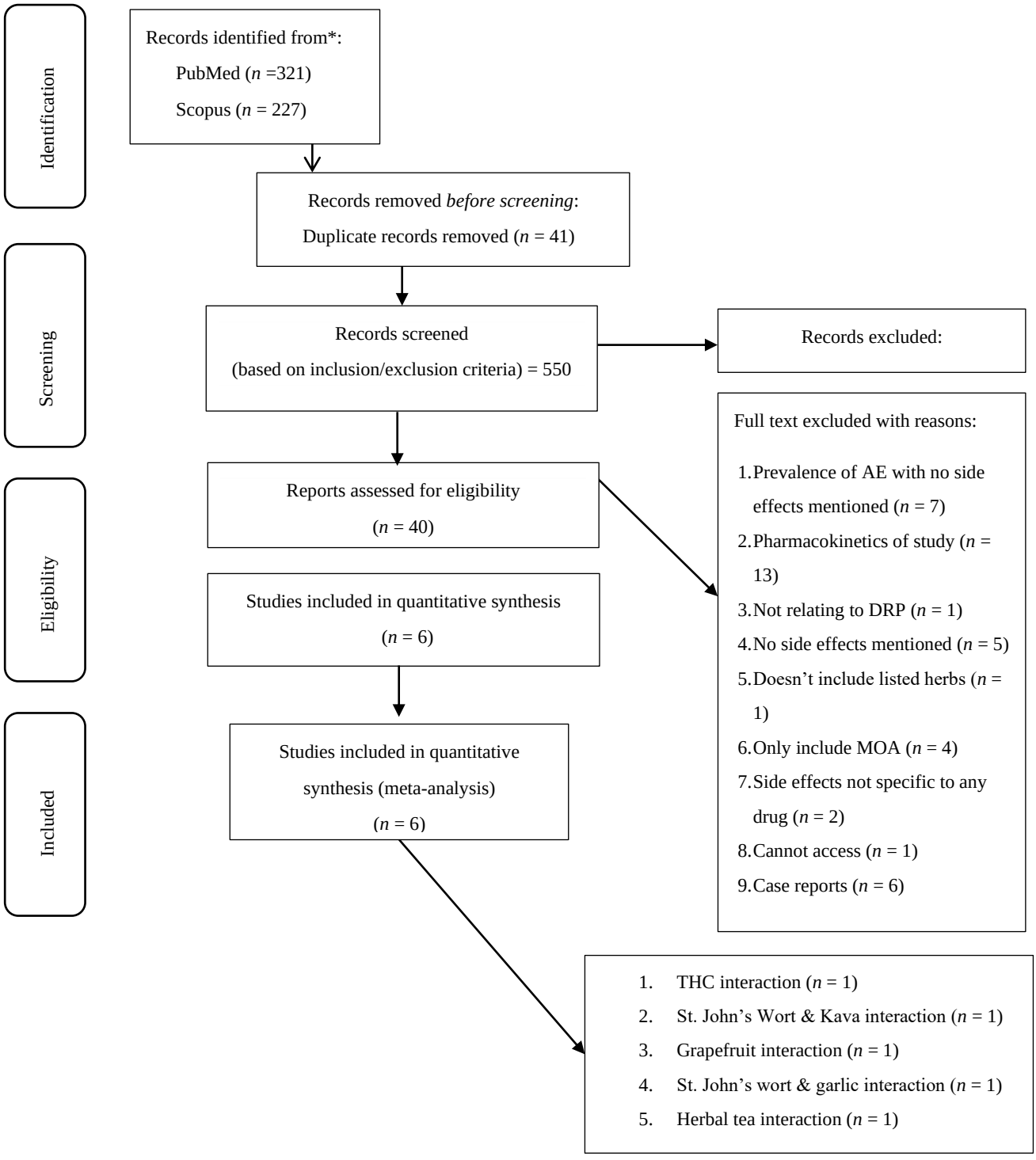

Figure 1. PRISMA flow diagram.

3.1 Quality Assessment

The six studies were overall of an excellent standard; however, only four had sufficient sample size to provide a reliable prevalence estimation, as seen in **Table 2**. The

unsuitable sampling frame was observed in 2 studies. Further analysis was required in 2 of the studies.

3.2 Study Design

There were a variety of studies as each was comprised of a Double-blind, placebo-controlled, Crossover, prospective cohort study, Cross-referenced self-reported, Two-phase Cross-sectional, and Retrospective analysis. Two studies were found common in undergoing a crossover study. One of the studies was a two-phase cross-sectional, which performed implementation of active surveillance in community pharmacies and data collection through patient interviews in the first phase, followed by assessing the AE causality and laboratory analysis where necessary, as seen in the table of evidence in **Table 1**.

3.3 Prevalence of DNRP Due to Herb Use

In the six studies, the prevalence of Drug-Related Problems due to herb use ranged between 5.8% to 89.4%. Two studies did not state the percentages of prevalence in DNRP. Prely et al. found 89.4% of Drug-drug interaction (DDI) and 23.1% of Herb-drug interaction (HDI), and 21.7% of both DDI and HDI. Moreover, one of the studies found that 60.8% of patients had a minimum of one high-risk DDI for oral anti-cancer drugs for 179 patients. For instance, the interaction between amiodarone and escitalopram, amiodarone and hydroxyzine, as well as escitalopram and pentamidine, may lead to a higher risk of cardiac rhythm disorder. However, the interaction between azithromycin and colchicine derived from *Colchicum autumnale* may cause increased serum concentrations of colchicine due to the inhibition of P-glycoprotein. In addition, 76.5% of DDI between the association of alprazolam and oxycodone may result in the central nervous system, and the interaction between hydroxyzine and sulfamethoxazole or trimethoprim may cause prolongation of QT interval. Regarding HDI, this study found 56.7% pharmacokinetic interactions in connection with oral anti-cancer drugs with grapefruit or bitter orange, which results in drug metabolism by inhibition of CYP3A4, as seen in **Table 3**. Furthermore, the interaction of turmeric and gamma-linolenic acid in blackcurrant leaf extract may lead to a higher risk of bleeding[21].

In another study, 45% of 89 patients had a potential for drug–dietary supplement interactions investigated from a total of 197 recently consuming a minimum of 1 dietary supplement given with prescription medications. From this, there were 6% of possible severe interactions of drug-dietary supplements and 3% for patients coincidentally using medications and dietary supplements. It was also reported that among patients consuming supplements, 7% of patients from Pittsburgh and 12% of patients from Los Angeles encountered a minimum of 3 possible interactions between a drug and dietary supplement[22].

3.4 Risk Factors

Risk factors were conducted in the six included studies. The patient's age was the most similar associated factor in the event of Drug/NP-Related Problems in the six studies. Subsequently, the number of medications and gender were shared in the five studies, followed by the patient's condition, five or more prescribed drugs, and the physician's quantity of medications that were common in the four studies. The presence of comorbidity and underestimation of potential adverse events were common in the three studies. Lastly, the length of hospitalization was typical in the two studies. Other risk factors are stated in **Table 4**.

3.5 Method of Identifying DNRPs

There are multiple methods of identifying the DNRPs in the studies. Most of the methods are based on electronic platforms such as Drugs.com, MEDLINE, and Thériaque®, as well as a combination of both paper and electronic platforms to assess the DNRPs, as seen in **Table 3**.

3.6 Most Common Drug Involves in DNRPs

The included studies listed several drugs that have been linked to DNRPs. In order to accomplish a particular aim, several studies concentrated on specific drugs or drug classes. Each study investigated various drugs, some of which have similar classes. The majority of the drug classes associated with Drug/NP-Related Problems were represented by Selective Serotonin reuptake inhibitors (SSRIs), kinase inhibitors, and anti-neoplastic agents in this review. All of the drugs mentioned in the studies may interact with certain herbs, such as the interaction between garlic and warfarin may increase the likelihood of bleeding, and the interaction between St John's wort and paroxetine could result in higher serotonin levels. Additionally, one study found that 49% of combinations of potential interactions of garlic or ginkgo with conventional drugs could lead to bleeding risks, as seen in **Table 3**[23].

Table of Evidence

Table 1. The summary of Drug/NP-Related Problems

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender)		Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
			Intervention	Control					
[24]	Double-blind, placebo-controlled, crossover	"To examine the safety and efficacy of a potential treatment medication, modafinil, in combination with oral delta-9-tetrahydro-cannabinol (THC)"	-	- 18 to 55 years old - Cannabis use more than once in last 2 months and more than 10 times in lifetime - Positive urine sample for detection of cannabis - Participants received medication followed by a light meal - The sessions started at 8:00 am and lasted for	Cannabis addiction	delta-9-tetrahydrocannabinol (THC) oral form of THC (Marinol®)	Four treatment conditions which included: 1. placebo+placebo 2. modafinil (400 mg)+ placebo 3. THC (15 mg)+placebo, or 4. modafinil (400 mg)+ THC (15 mg) Modafinil (Provigil®)	- Increased heart rate - Feeling of "high" - Sedated - Euphoria - Increased participants ratings on the ARCI subscales of PCAG (sedation), LSD (dysphoria) and M (marijuana) - 400 mg modafinil increased participants' heart rate and systolic and	- 12 male and female occasional cannabis users - THC increased heart rate ([F (1, 461) = 18.6; $p < 0.0001$]) and lowered systolic blood pressure ([F (1, 461) = 4.6; $p < 0.05$]), compared to placebo. - THC increased subjective ratings of feeling high ([F (1, 460) = 6.7 p b 0.05]), sedative ([F (1,

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender)		Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
			Intervention	Control					
				approximately 7 hours				diastolic blood pressure	460) = 5.5; p b 0.05]), compared to placebo.
[25]	Crossover	"Report the randomized controlled trial (RCT) using a combination of St. John's wort (SJW) and Kava for the treatment of Major Depressive Disorder (MDD) with comorbid anxiety"	- Treated during the active phase with SJW flowering tops extract (*Hypericum Perforatum*) 1 x 1.8 g tablet 3 times per day - Kava rhizome aqueous extract (*P. methysticum*) 1 x 2.66 g tablet, 3 times per day. - SJW tablets were formulated from pressed, dried,	- 18 to 65 y/o - Unipolar depression - Score of at least 10 on the Beck Anxiety Inventory	Major Depressive Disorder (MDD) and comorbid anxiety	St. John's wort & kava	-	- Gastrointestinal upset - Slightly raised liver enzyme - Reduction in self-reported depression	- 28 adults - 2 cases of gastrointestinal upset (1 placebo & 1 active) - 1 case of slightly raised liver enzyme (placebo) - 15 were allocated to PA and 13 to AP - Average age of 42.9 years (SD ¼ 12.4; range ¼ 18–60), and 12.9 years of education (SD ¼ 2.4: 8, 29%, and only one

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender)		Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
			Intervention	Control					
			ethanol extract and was standardised to 990 mcg of hypericin, and 1500 mcg of flavone glycosides. - Kava tablets formulated from pressed, dried aqueous extract, standardised to 50 mg of kavalactones. – Placebo tablets formulated using a colour-film coat identical in appearance to herbal tablets – The excipients were calcium hydrogen phosphate, micro-crystalline cellulose, sodium starch glycolate and magnesium stearate						had less than high school). - 6 (21%) were currently unemployed and 3 (11%) had history of a suicide attempt - 64% completed the study - Marginal improvement from 2 to 6 weeks across conditions ($F_{1,25} = 3.03$, $p = 0.094$)

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender)		Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
			Intervention	Control					
[21] between 2017 and 2019 in a 1038-bed university hospital at Hospices Civils de Lyon (France)	Prospective cohort study	"To assess DDI and HDI in outpatients taking oral anti-cancer drug"		-67 years old (55-79)		Turmeric + gamma-linolenic acid present in blackcurrant grapefruit (*Citrus maxima*), bitter orange (*Citrus x auriantum*), turmeric (*Curcuma longa*), aloe vera (*Aloe vera*), ginseng (*Panax ginseng*), and ginger (*Zingiber offficinale*)		Risk of bleeding - Risk of bleeding (9.7%), - Central depression (7.7%) - Cardiovascular disorders (6.8%)	- 55% of patients used a minimum of 1 CAM - A minimum of 1 interaction found for 267 patients (90.8%)
						Turmeric	Crizotinib	Hematologic toxicity upon CYP 3A4 inhibition	
						Grapefruit (Citrus maxima)	Exemestane	Inhibition of CYP 3A4 & ↑ toxicity of exemestane	
						Turmeric (*Curcuma longa*)	Ibrutinib	Hematologic toxicity & CYP 3A4 inhibition	
						Ginger (*Zingiber officinale*)	Ibrutinib	CYP 3A4 inhibition & ↑ toxicity of ibrutinib	
						Turmeric (*Curcuma longa*)	Lenalidomide	Hematologic toxicity	
						Turmeric (*Curcuma longa*)	Pomalidomide	Hematologic toxicity & High blood pressure at initiation of turmeric	

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender) Intervention	Control	Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
						Garlic	Warfarin	- Lowered platelet aggregation; - Increased risk of bleeding	- 458 veteran outpatients - 53% of Pittsburgh and 56% of Los Angeles were taking 1 or 2 supplements - 41% of of Pittsburgh and 39% of Los Angeles were taking 3 to 6 supplements - 6% of of Pittsburgh and 5% of Los Angeles were taking more than 6 supplements per day - 43% were tak- ing at least 1
[22]	Cross-referenced selfreported	"To explore the incidence and severity of potential interactions between prescription medications and dietary supplements"				St John's wort	Paroxetine	Increased serotonin levels	

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender)		Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
			Intervention	Control					type of dietary supplement
[26]	Two-phase Cross-sectional Phase I: implementation of active surveillance in community pharmacies and data collection through patient interviews Phase II: AE causality assessment and laboratory analysis where appropriate	"To investigate the rates and causality of adverse event(s) (AE) associated with natural health product (NHP) use, prescription drug use and concurrent NHP-drug use through active surveillance in community pharmacies"		- 10 community pharmacies - Pharmacy staff screened consecutive patients, or agents of patients, who were dropping or picking up prescription medications. - 8.5 year-old Chinese female		Chinese herbal tea	- Sertraline - Polyethylene glycol - Metoclopramide - Mineral Oil - Fluticasone - Propionate inhalation aerosol	Cardiac arrest	54 patients reported an AE representing 1.2% (95% CI 0.51% to 2.9%), 2.7% (95% CI 0.4% to 16.9%) and 7.3% (95% CI 5.6% to 9.6%) of each population 1 patient identified
[23]	Retrospective analysis	"To determine the prevalence of CAM product use concurrent with conventional medications, prescription and non-prescription, in a Medicare population and assess the		Adults aged 65 years and older	- Coronary heart disease - Stroke	Ginger	Aspirin	Bleeding	- 2 patients prevalence (1.20%)
						Garlic	NSAIDs	Bleeding	- 73 patients prevalence (1.10%)
						Garlic	Gemfribozil	Bleeding	- 4 patients Prevalence (0.02%)

Reference	Study Design (hospital/ community etc)	Aim of the study	Patient details (number, age, gender)		Disease /condition	Herbs used (formulation, dose, frequency, duration)	Drugs involved (formulation, dose, frequency, duration)	Drug/NP-Related Problem	Percentage of population effected/statistical significance
			Intervention	Control					
		risk for adverse interactions"							

Table 2. Quality assessment of the included studies.

Studies Assessment	Q1: Was the sample frame appropriate to address the target population?	Q2: Were study participants sampled appropriately?	Q3: Was the sample size adequate?	Q4: Were the study subjects and the setting described in detail?	Q5: Was the data analysis conducted with sufficient coverage of the identified sample?	Q6: Were valid methods used for the identification of the condition?	Q7: Was the condition measured in a standard, reliable way for all participants?	Q8: Was there an appropriate statistical analysis?	Q9: Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall appraisal
[24]	Y	N	Y	Y	N	Y	Y	N	N	I
[25]	N	N	N	Y	N	Y	Y	Y	Y	I
[21]	N	Y	Y	Y	N	Y	Y	Y	Y	I
[22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
[26]	Y	Y	Y	N	Y	Y	Y	Y	Y	I
[23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I

Abbreviations:
Y: Yes; **N**: No; **U**: Unclear; **NA**: Not Applicable; **I**: Include; **E**: Exclude; **S**: Seek Further Information

Table 3. Drug/NP-Related Problem characteristics in the included studies.

Studies Assessment	Overall prevalence	Method of detecting DNRPs	Most common drugs
[24]	-	• Drug Effects Questionnaire (DEQ) • The Addiction Research Center Inventory-Short Form (ARCI) • The Profile of Mood States (POMS)	• Modafinil • Marinol®
[25]	-	• Composite International Diagnostic Interview • Beck Depression Inventory-II • Beck Anxiety Inventory • WHO Quality of Life Survey • Liver function tests	• SJW flowering tops extract • Kava rhizome aqueous extract
[21]	• 89.4% of DDI • 23.1% of HDI • 21.7% both DDI and HDI • 60.8% DDI leads to an increased likelihood of cardiac rhythm disorder, and possible risk of increased serum concentrations of colchicine due to inhibition of P-glycoprotein • 76.5% DDI leads to central nervous system depression and prolongs QT interval • 56.7% HDI caused inhibition of CYP3A4	• Thériaque ® • Drugs.com • Hédrine® • Memorial Sloan Kettering Cancer Center (MSKCC)	• Lenalidomide • Ibrutinib • Amiodarone • Escitalopram • Hydroxyzine • Escitalopram • Pentamidine • Crizotinib • Exemestane • Pomalidomide
[22]	• 48% of 99 Pittsburgh patients and 44% of 98 Los Angeles patients had potential interactions of drug and dietary supplements (severe or not severe)	• Web pages • MEDLINE	• Warfarin • Paroxetine

Studies Assessment	Overall prevalence	Method of detecting DNRPs	Most common drugs
	• 89 (45%) had a potential interactions for drug and dietary supplement • 7% of Pittsburgh patients and 12% Los Angeles patients having more than 3 potential interactions for drug and dietary supplement • 6% (5/89) of potentially severe interactions in drug and dietary supplements • 3% (5/197) interactions of taking coincident dietary supplements and medications		
[26]	7.4% take NHPs and prescription drugs concurrently report an AE	• Clinical NHP expert • Basic science NHP expert • Committee chair (SV) • WHO Causality Assessment Criteria • Naranjo Probability Scale • The Horn Drug Interaction Probability Scale • NHP constituent assessment • Adulteration or contamination assessment • Pharmacy SONAR	• Sertraline
[23]	• 5.8% have a significant risk for an adverse interaction • 49% combinations of potential interactions of garlic or ginkgo with conventional drugs lead to risks of bleeding	• RHM	• Aspirin • Gemfribozil

Table 4. Risk factors for Drug/NP-related problems in the included studies.

Risk factors	[24]	[[25]	[21]	[22]	[26]	[23]	Total
1. Patient's condition		/	/	/		/	4
2. Number of medications	/	/	/	/		/	5
3. Number of prescribed drugs ≥5			/	/	/	/	4
4. Age	/	/	/	/	/	/	6
5. Age <60 years	/						1
6. Gender	/	/		/	/	/	5
7. Length of hospitalization			/			/	2
8. Presence of comorbidity		/		/		/	3
9. Number of drugs requiring dosing adjustments in patients in renal impairment							
10. Prescriber's poor knowledge of medications requiring dosage adjustment							
11. Lack of evidence-based data to guide prescribers on dosage adjustments as well as lack of quantitative data in the available Manufacturer's Instructions		/					1
12. Underestimation of potential adverse events	/	/		/			3
13. Lower serum level of albumin							
14. Vascular disease							
15. Higher serum level of CRP							
16. Physician's quantity of prescriptions	/	/		/		/	4
17. Clinical experience of physicians							
18. Presence of ≥5 comorbidities							
19. Marital status (married)							
Total	7	9	6	9	4	9	44

4. Discussions

4.1 Oral Tetrahydrocannabinol-Related Problems

The first cannabinoid medication to receive United States approval was an oral form of synthetic THC[27]. This was derived from trying to find alternative routes of administration that could produce a consistent amount of absorbed drug, preferably with reduced central nervous system side effects compared to smoked cannabis and without delivering potential carcinogens[28]. Tetrahydrocannabinol (THC) acts as a muscle relaxant and analgesic to treat muscle spasticity, however, minor psychological reaction from consuming THC involves euphoria, sedation, relaxation, anxiety, paranoia, dysphoria, depression, and psychosis[28, 29].

4.2 St. John's Wort and Kava

Hypericum extracts have mild and uncommon side effects. Only 2.4% of individuals using hypericum in a trial with over 3,000 patients had side effects, primarily allergic responses and gastrointestinal upset[30, 31]. The side effects of St. John's wort include gastrointestinal upset, photosensitivity, confusion, dizziness, fatigue, and anxiety. St. John's wort also affects the P-glycoprotein, a transport drug-protein, and the cytochrome P450 system for initiating isozymes 3A4 and 2C9. 0.6% Gastrointestinal irritations, 0.5% allergic responses, 0.4% of fatigue, and 0.3% restlessness were the estimation found on the unfavorable symptoms that were most frequently reported[33].

Moreover, several reports of liver injury have recently raised concerns about the safety of kava products[34]. There was a higher serum aminotransferase and a minimal rise in alkaline phosphatase quantity, with the pattern of enzyme elevations being hepatocellular. Immunoallergic hepatitis may be present in some cases, in addition to eosinophilia, fever, and rash, which are recurrent upon re-exposure. Rarely, kava may cause allergic responses manifested by skin yellowing or scaling, gastrointestinal issues, dilated pupils, and impaired vision[30].

4.3 Garlic and Warfarin

Garlic has not been reported to potentiate the effects of warfarin, but the evidence that is currently available points to the possibility of a significant interaction. It is postulated that garlic ingestion shows anti-thrombotic actions and inhibits platelet aggregation[36]. According to some reports, garlic oil prevents the production of thromboxane A2, which inhibits platelet activity. According to one author, adding essential garlic oil to blood samples

from six healthy subjects reduced in vitro platelet aggregation within five days. Additionally, an elderly patient who consumed about 2 g of garlic each day spontaneously developed an epidural hematoma[37]. However, this interaction was found in patients taking warfarin therapy primarily involving two contradicting probabilities: the likelihood of bleeding due to an aggravation of the anticoagulant effect of the drug and the lack of effectiveness due to a decrease in the drug's effect caused by blood clot stimulation[[38-40].

4.4 St John's Wort and SSRIs

St John's wort interactions with Selective Serotonin Reuptake Inhibitors (SSRI) such as paroxetine caused serotonin syndrome due to the selectively inhibited serotonin and noradrenaline reuptake. In most cases, the serotonin syndrome usually settles 24 hours after the beginning of the treatment and stopping of serotonergic drugs. However, symptoms may continue in some patients taking the medications with long elimination half-lives or active metabolites[41-43]. The effects of St John's wort are attributed mainly to hypericin and hyperforin. In addition to having GABA-A receptor agonist, antiviral, and anti-inflammatory properties, hypericin may also have a serotonin reuptake inhibitory effect. It has also been documented that hypericin interacts with benzodiazepine receptors. Hyperforin, another ingredient in St. John's wort, has various neurochemical properties and may contribute to the drug's antidepressant effects. Hyperforin appears to interact with GABA and glutamate receptors and has been shown to have serotonin, dopamine, and norepinephrine reuptake actions in vitro[44].

4.5 Chinese Herbal Tea-Related Problems

There have been growing issues regarding the safety and possible harmfulness of the Chinese materia medica (CMM), which consists of herbs, animal parts, and minerals, as traditional Chinese medicine (TCM)[45]. The potential harm of certain CMM is well recognized in TCM, and in order to prevent its likelihood, the usage of some herbs has been limited, while others have had their toxicity modified via the development of particular processing techniques. Notably, abusing or misusing Chinese medicine may show various NP-related problems, such as adverse reactions and interactions with other food and drugs taken concomitantly. Despite safety issues, Chinese medicine seems rather safe, with relatively fewer adverse reaction reports than all drugs[46,47]. Certain Chinese Medicinal Herbs include *Angelica sinensis* or Don quai, *Lycopodium serratum* or Jin bu huan, Thunder god vine or lei gong teng or *Tripterygium wilfordii Hook F* and *Erycibe henryi prain* or Ting kung teng was found to be linked with heart toxicity reports[47].

4.6 Turmeric-Related Problems

The potential of abnormal bleeding can't be excluded entirely while consuming turmeric, especially when blood-thinning medications are involved and under specific conditions, such as the higher vulnerability of consumers and increased consumption. Subjects taking this herb must take care while using turmeric or curcumin alone or in association with anti-platelet drugs[48]. The majority of these effects of curcumin, including its anti-platelet properties, have been attributed to the inhibition of prostaglandin and thromboxane production and the promotion of hydrocortisone release. Therefore, it's probable that turmeric and NSAIDs interact pharmacologically in an additive way, and using these medications together may result in coagulation issues and an increased risk of bleeding[49].

4.7 Grapefruit (Citrus maxima), Bitter Orange (Citrus auriantum), and Ginger (Zingiber officinale) Related Problems

Grapefruit may result in severe adverse reactions with certain medications, such as gastrointestinal bleeding, torsade de pointes, nephrotoxicity, myelotoxicity, respiratory depression, and rhabdomyolysis[50]. The usage of *C. aurantium*-containing products has been investigated due to the potential adverse reactions of *C. aurantium* on the cardiovascular system, mainly due to the presence of p-synephrine. The authors demonstrated potential cardiovascular damage along with an anti-obesity effect from the administration of *C. aurantium*. It was utilized in traditional medicines to reduce body fat, but the National Collegiate Athletic Association (NCAA) has outlawed it because alkaloid extracts may harm the cardiovascular system. Most research, however, has refuted the cardiovascular effects of p-synephrine. In addition, neroli oil is an evaporative oil extracted from the flowers of *Citrus aurantium*, and it is used to alleviate the digestive system, lower heart rate, palpitations, and promote sleep. Nevertheless, the consumption of this plant is allowed for Olympic athletes, as recently stated by the World Anti-Doping Agency (WADA)[51].

The United States Food and Drug Administration (FDA) views ginger root with a maximum of 4 g daily as safe[52]. Gastrointestinal discomfort, hypersensitivity, prolonged pre-existing bleeding, arrhythmia, and central nervous system depression are all possible side effects obtained at larger dosages. According to some studies, consuming a minimum of 6 grams of ginger root might cause gastrointestinal problems, including gastric reflux, diarrhea, and heartburn[53]. It may also worsen the toxicity of warfarin and its anticoagulant effects, which might result in bleeding. It has been demonstrated to induce irregular heartbeat in a limited number of cases and can lower blood pressure[54].

4.8 Grapefruit (Citrus maxima) and Exemestane

Furanocoumarins, present in grapefruit, are the compounds involved in the interaction of grapefruit with the anti-breast cancer exemestane. CYP3A4 metabolizes furanocoumarins to reactive intermediates that form a covalent connection with the enzyme's active site, rendering the enzyme permanently inactive (mechanism-based inhibition). Additionally, all grapefruit products, such as frozen concentrate, freshly squeezed juice, and whole fruit, may possibly decrease CYP3A4 activity since the fruit naturally contains these compounds. It would take one entire grapefruit or approximately 200 mL of grapefruit juice to raise the systemic concentration of the drug and the subsequent adverse reactions. Some interactions between grapefruit or *Citrus maxima* and exemestane may cause Torsade de Pointes, nephrotoxicity, rhabdomyolysis, and breast cancer[50,55]. Furthermore, ingesting grapefruit juice raises the drug concentrations, brought about by the inhibitory action of cytochrome P450 isozyme CYP3A4 in the small intestine wall. These effects may lead to reduced first-pass metabolism with increased bioavailability and maximal plasma concentration (C_{max}) of the substrate[56]. Therefore, this inhibition of the CYP3A4 may lead to a rise in the toxicity of exemestane.

4.9 Garlic and NSAIDs

Interview data from the Cardiovascular Health Study from 1994, 1995, 1997, and 1999 were analyzed retrospectively. The frequency of concurrent use of CAM products and prescription medications was tallied. The adverse interaction risks were classified as theoretical, significant, and unknown[16]. The majority of 379 participants involved a potential bleeding risk from taking ginseng, ginkgo, or garlic with aspirin, warfarin, ticlopidine, or pentoxifylline. Garlic or ginkgo combinations with medications that alter blood coagulation, such as aspirin, totaled 5.8% of the participants, and 294 of the individuals using these combinations were considered to have a significant risk of an unfavorable interaction, making up more than 95% of the list of substantial interactions. Moreover, it has been proven that the majority of garlic compounds, especially alliin, block the production and the release of chemical mediators such as thromboxane. The inhibition or blocking of cyclooxygenase (COX) and fibrinogen receptors on membranes containing platelet by certain compounds present in garlic have been proposed as one of the underlying effects. These effects are thought to be caused by various garlic phytochemicals that can result in inhibiting platelet aggregation and enhancing bleeding[57]. In a separate case study, postoperative bleeding and the appearance of a sudden spinal epidural hematoma were detected after an elderly consumed a significant amount of garlic. According to the results of

two further studies, garlic increases the anti-platelet and anticoagulant effects of NSAIDs, such as aspirin and other blood-thinning drugs, especially warfarin, which is associated with a higher risk of bleeding[48].

5. Conclusion

In conclusion, this systematic review has proven the occurrence of DNRPs due to the consumption of herbs, DDI, and HDI. This systematic review highlighted the adverse effects of improper herbal product consumption and significant drug-herb interactions. This systematic review also found a moderate to high prevalence of DNRPs, but the prevalence percentages vary across studies. It was also found that most drug classes associated with Drug/NP-Related Problems were represented by Selective Serotonin reuptake inhibitors (SSRIs), kinase inhibitors, and anti-neoplastic agents. The patient's age was the most common risk factor obtained from studies. Due to some limitations of the studies, patients do not disclose their experience with DNRPs to their pharmacists or physician, which causes these issues to be under-reported or less recognized. It is urged that all healthcare professionals ask patients about their use of dietary supplements, particularly in light of the growing number of reports of severe morbidity and mortality, with or without concurrent pharmaceutical usage. Additionally, healthcare professionals should consider possible herbs and drug interactions, regardless of how severe they can be, because even slight interactions might impact a patient's quality of life and drug therapy. To validate the impact and evaluate predictions regarding the effects of interactions, larger samples with monitored patient compliance evaluation are required in future studies.

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Supplementary

Supplementary table 1. Search terms conducted in databases.

Database	Search term conducted
PubMed and Google Scholar	1. “Linum usitatissimum” OR Flax* OR Flaxseed OR Linseed 2. “Medicago sativa” OR Alfalfa OR Lucerne 3. “Senna alexandrina” OR Senna OR “Cassia acutifolia*” OR “Cassia alexandrina*” 4. “Taraxacum* officinale” OR Dandelion OR “wandering dandelion” 5. “Vaccinium macrocarpon” OR *Cranberry* OR large cranberry OR American cranberry OR bearberry 6. “Vaccinium myrtillus” OR “European Blueberry” 7. “Zingiber officinale*” OR Ginger 8. “Allium sativum*” OR Garlic 9. “Camellia sinensis*” OR Tea OR "tea plant" OR "tea shrub" OR "tea tree" 10. “Cannabis sativa” OR Marijuana OR ganja OR marihuana 11. “Curcuma longa*” OR *Turmeric* OR “Turmeric oleoresin” OR Zingiberaceae 12. “Glycine* max*” OR Soybean OR Moench 13. “Hypericum perforatum*” OR St* John’s Wort OR “Tipton's weed” OR “Rosin rose” OR goatweed OR chase-devil OR “Klamath weed” 14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 15. "Drug-Related Side Effects and Adverse Reactions" OR Inappropriate Prescribing OR Medication Error* OR Adverse Drug Reaction Reporting Systems OR drug-related problem*[Title/Abstract] OR medicine-related problem*[Title/Abstract] OR medication-related problem*[Title/Abstract] OR adverse drug event*[Title/Abstract] OR adverse drug reaction*[Title/Abstract] medication error*[Title/Abstract] OR inappropriate prescri*[Title/Abstract] OR inappropriate medication*[Title/Abstract] OR drug-related complication*[Title/Abstract] OR medicine-related complication*[Title/Abstract] OR medication-related complication*[Title/Abstract] OR "drug-therapy problem*"[Title/Abstract] OR "drug therapy problem*"[Title/Abstract] OR "ADR"[Title/Abstract] OR "ADE"[Title/Abstract] OR "DRP"[Title/Abstract] OR "MRP"[Title/Abstract] OR “drug?related problem*”[tw] OR “medication* side effect*”[tw] OR “Drug Interactions”[Mesh] OR “Drug?related problem” OR “Pharmaceutical issue”[tw] OR “Pharmaceutical care issue”[tw] OR “Pharmaceutical intervention”[tw] OR “Adverse drug reaction”[tw] OR “Adverse drug event”[tw] OR “Herb-drug interaction*” OR “Plant?Drug interaction*” OR "Medication Systems"[Mesh] OR "Medication Review"[Mesh] OR “Medication Misadventure”[tw] 16. "Aged"[Mesh] OR “old people”[tw] OR “old person”[tw] OR elderly[tw] OR aged[tw] OR “getriat*”[tw] OR “old adult”[tw] 17. #14 AND #15 AND #16
Cochrane Library	“Linum usitatissimum” OR Flax* OR Flaxseed OR Linseed OR “Medicago sativa” OR Alfalfa OR Lucerne OR “Senna alexandrina” OR Senna OR “Cassia acutifolia*” OR “Cassia alexandrina*” OR “Taraxacum* officinale” OR Dandelion OR “wandering dandelion” OR “Vaccinium macrocarpon” OR *Cranberry OR bearberry OR “Vaccinium myrtillus” OR “European Blueberry” OR “Zingiber officinale*” OR Ginger OR “Allium sativum*” OR Garlic OR “Camellia sinensis*” OR Tea OR "tea

Database	Search term conducted
MedRxiv	plant" OR "tea shrub" OR "tea tree" OR “Cannabis sativa” OR Marijuana OR ganja OR marihuana OR “Curcuma longa*” OR *Turmeric* OR “Turmeric oleoresin” OR Zingiberaceae OR “Glycine* max*” OR Soybean OR Moench OR “Hypericum perforatum*” OR (St?John?Wort) OR “Tipton's weed” OR “Rosin rose” OR goatweed OR chase-devil OR “Klamath weed” AND "Drug?Related Side Effect* and Adverse Reaction*" OR “Inappropriate Prescribing” OR Medication Error* OR “Adverse Drug Reaction Reporting System” OR “drug?related problem” OR “medicine?related problem” OR “medication?related problem” OR “adverse drug event” OR “adverse drug reaction” OR “medication error” OR “inappropriate prescri*” OR “inappropriate medication*” OR “drug?related complication*” OR “medicine?related complication*” OR “medication?related complication*” OR "drug?therapy problem*” OR "drug therapy problem*” OR "ADR” OR "ADE” OR "DRP" OR "MRP" OR “drug?related problem*” OR “medication* side?effect*” OR “Drug Interactions” OR “Drug?related problem” OR “Pharmaceutical issue” OR “Pharmaceutical care issue” OR “Pharmaceutical intervention”OR “Adverse drug reaction” OR “Adverse drug event” OR “Herb?drug interaction*” OR “Plant?Drug interaction*” OR "Medication System*" OR "Medication Review" OR “Medication Misadventure” in Title Abstract Keyword AND "Aged" OR “old people” OR “old person” OR elderly OR aged OR “geriat*” OR “old adult” “Linum usitatissimum” OR Flax* OR Flaxseed OR Linseed OR“Medicago sativa” OR Alfalfa OR Lucerne OR “Senna alexandrina” OR Senna OR “Cassia acutifolia*” OR “Cassia alexandrina*” OR “Taraxacum* officinale” OR Dandelion OR “wandering dandelion” OR “Vaccinium macrocarpon” OR *Cranberry* OR large cranberry OR American cranberry OR bearberry OR“Vaccinium myrtillus” OR “European Blueberry” OR “Zingiber officinale*” OR Ginger OR “Allium sativum*” OR Garlic OR “Camellia sinensis*” OR Tea OR "tea plant" OR "tea shrub" OR "tea tree" OR “Cannabis sativa” OR Marijuana OR ganja OR marihuana OR “Curcuma longa*” OR *Turmeric* OR “Turmeric oleoresin” OR Zingiberaceae OR “Glycine* max*” OR Soybean OR Moench OR “Hypericum perforatum*” OR St* John’s Wort OR “Tipton's weed” OR “Rosin rose” OR goatweed OR chase-devil OR “Klamath weed”
Scopus	TITLE-ABS-KEY(“Linum usitatissimum” OR Flax* OR Flaxseed OR Linseed OR “Medicago sativa” OR Alfalfa OR Lucerne OR “Senna alexandrina” OR Senna OR “Cassia acutifolia*” OR “Cassia alexandrina*” OR “Taraxacum* officinale” OR Dandelion OR “wandering dandelion” OR “Vaccinium macrocarpon” OR *Cranberry OR bearberry OR “Vaccinium myrtillus” OR “European Blueberry” OR “Zingiber officinale*” OR Ginger OR “Allium sativum*” OR Garlic OR “Camellia sinensis*” OR Tea OR "tea plant" OR "tea shrub" OR "tea tree" OR “Cannabis sativa” OR Marijuana OR ganja OR marihuana OR “Curcuma longa*” OR *Turmeric* OR

Database	Search term conducted
	“Turmeric oleoresin” OR Zingiberaceae OR “Glycine* max*” OR Soybean OR Moench OR “Hypericum perforatum*” OR (St?John?Wort) OR “Tipton's weed” OR “Rosin rose” OR goatweed OR chase-devil OR “Klamath weed”) AND TITLE-ABS-KEY("Drug?Related Side Effect* and Adverse Reaction*" OR “Inappropriate Prescribing” OR Medication Error* OR “Adverse Drug Reaction Reporting System” OR “drug?related problem” OR “medicine?related problem” OR “medication?related problem” OR “adverse drug event” OR “adverse drug reaction” OR “medication error” OR “inappropriate prescri*” OR “inappropriate medication*” OR “drug?related complication*” OR “medicine?related complication*” OR “medication?related complication*” OR "drug?therapy problem*” OR "drug therapy problem*” OR "ADR” OR "ADE” OR "DRP" OR "MRP" OR “drug?related problem*” OR “medication* side?effect*” OR “Drug Interactions” OR “Drug?related problem” OR “Pharmaceutical issue” OR “Pharmaceutical care issue” OR “Pharmaceutical intervention”OR “Adverse drug reaction” OR “Adverse drug event” OR “Herb?drug interaction*” OR “Plant?Drug interaction*” OR "Medication System*" OR "Medication Review" OR “Medication Misadventure”) AND TITLE-ABS-KEY("Aged" OR “old people” OR “old person” OR elderly OR aged OR “geriat*” OR “old adult”)