Identification of Natural Health Product-Associated Adverse Events and Natural Health Product-Drug Interactions in Adults and Children with Cancer

by

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Abstract

Background: Patients with cancer frequently use natural health products (NHPs) to help treat cancer, reduce side effects, or improve effectiveness of conventional cancer treatment, and improve their quality of life. Often oncology healthcare providers do not inquire about NHP use, leading to low rates of disclosure from patients. NHPs are commonly perceived by patients as helpful and safe, with limited recognition of the potential adverse events (AEs) or NHP-drug interactions. However, patients with cancer are susceptible to clinically important AEs and NHP-drug interactions due to the bioactive compounds that NHPs may contain, the narrow therapeutic index of anticancer medications, and polypharmacy. Serious safety concerns also exist because of variations in the quality control of NHPs. We hypothesize that patients with cancer who take NHPs are at a higher risk of experiencing clinically important AEs, including NHP-drug interactions.

Methods: A two-pronged approach was undertaken. Two systematic reviews were conducted to synthesize the existing clinical evidence on the efficacy and safety of concurrent use of NHPs and anticancer medications. Two anticancer drug categories, immunotherapy and antimicrotubule anticancer agents, and nine clinically relevant NHPs were the focus of these systematic reviews. Findings were presented as a narrative synthesis with summary tables.

Two cross-sectional studies using Study Of Natural health product Adverse Reactions (SONAR) active surveillance methods were conducted to identify and characterize NHP use, and associated AEs. One study focused on adults with cancer and the other on children with cancer. Patients were asked about their use of NHPs, prescription medications and AE(s) experienced. Those reporting NHP use and a serious AE were provided a consent form for a follow-up interview to inform causality assessment.

Results: Available clinical evidence on concurrent use of NHPs and anticancer medications identified in the systematic reviews was heterogeneous and primarily consisted of phase I/II clinical trials and pilot studies with methodological limitations as well as case series/reports. Several AEs associated with NHPs were identified including safety signals with the use of vitamins C, D, and E, milk thistle, and turmeric alongside antimicrotubule agents.

Active surveillance was implemented in Canadian cancer centres as part of routine clinical workflow. Most patients with cancer take NHPs and many take them along with prescription medications. Thirty-seven percent of adults and 31% of children taking at least one prescription medication or NHP reported AE(s). Unexpectedly, the proportion of patients reporting AEs was not significantly different in those taking NHPs and prescription medications concurrently, and those using prescription medications alone. High losses to follow-up occurred prior to causality adjudication.

Conclusion: This work has expanded our understanding on the safety of NHP use in patients with cancer. Contrary to our hypothesis, and to our surprise, active surveillance did not demonstrate that patients with cancer who take NHPs are at a higher risk of experiencing clinically important AEs. Critical considerations of this work include that each NHP may have differing impacts on AEs, and it is not possible to determine NHP causation of harm using these studies alone. NHP-associated AEs and NHP-drug interactions were identified in our systematic reviews. Although these safety signals are hypothesis generating, as opposed to hypothesis-proving, they are a reminder that NHP use cannot be ignored throughout patient care. Until important research gaps are addressed, recommendations on the use of NHPs in patients with cancer must be individualized; given the seriousness of the condition being treated, continued caution about polypharmacy appears prudent.

There is a continued need for clinical research with improved reporting of harms outcomes on the use of NHPs and anticancer medications to support clinicians in shared decision making. Causality assessment is also crucial to improve our understanding of the NHP-associated AEs in this population. There are opportunities for enhancement of our active surveillance method by screening only patients being actively treated with anticancer medications, utilizing an electronic screening form, incorporating validated patient-reported AE measurement systems and additional demographic questions, and linking to healthcare databases. Our active surveillance methods can be adopted more widely to be used as a framework for improved inquiry and documentation of NHP use and AEs in routine oncology practice, and to augment pharmacovigilance of NHPs to enhance safety signal detection through the development of a population-based database.

Preface

This thesis is original work by Morgan Bharadia. The initial Study Of Natural health product Adverse Reactions (SONAR) in oncology protocol development and recruitment was initiated by other members of the SONAR team. Site principal investigators also contributed to this research collaboration. While the data analysis is my original work, biostatistical guidance was provided by the Alberta SPOR SUPPORT Unit. The Specialty SONAR research project, of which my thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Hospital SONAR: specialty clinic NHP-drug data collection", Pro00025387, December 21, 2011. Two second reviewers, Dr. Radhika Singh and Emma Sparks, participated in the systematic reviews of this thesis.

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List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BCG	Bacillus Calmette-Guerin
CAR	Chimeric Antigen Receptor
CENTRAL	Cochrane Central Register of Controlled Trials
CONSORT	Consolidated Standards of Reporting Trials
CYP	Cytochrome P450
DIN-HM	Homeopathic Medicine Number
DIPS	Drug Interaction Probability Scale
EMR	Electronic Medical Records
ITT	Intention To Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	Natural Health Product
NPN	Natural Product Number
NSS	Not Statistically Significant
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PSA	Prostate-Specific Antigen
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
SONAR	Study Of Natural health product Adverse Reactions
WHO-UMC	World Health Organization-The Uppsala Monitoring Centre

CHAPTER 1: Introduction

Natural Health Product Use in Patients with Cancer

Health Canada defines natural health products (NHPs) as "naturally occurring substances" derived from plants, animals, microorganisms, and marine sources.[1] This includes vitamins and minerals, herbal medicines, probiotics, amino acids, essential fatty acids, homeopathic remedies, and traditional medicines.[1] Despite being derived from a plant, cannabis is regulated differently than NHPs by Health Canada, and therefore, was not evaluated in this thesis.[2] In Canada, NHPs are largely sold and purchased in community pharmacies.[3,4] While many see a role for pharmacists in regards to their patients' NHP use,[3–6] pharmacists and other healthcare providers may be ill-equipped to provide this care due to inadequate knowledge and paucity of available information on safety and efficacy that is complicated by the profit-driven retail atmosphere.[3,7–9] Additionally, patients and caregivers often do not disclose NHP use due to healthcare providers' hesitancy to inquire about NHP use, fear of the provider's judgement, or the perception by patients and caregivers that NHPs are risk-free.[9–14] In primary care, it does not appear that the rate of disclosure of NHP use to physicians has improved in the last 15 years.[15] While disclosure has not increased, the use of NHPs by patients with cancer continues to increase considerably.[16]

Adults with cancer

Adults with cancer report a higher use of NHPs as compared to individuals without illness.[17] It appears that the prevalence of NHP use in these patients may be as high as 63%.[18] Those who are women, younger, have higher income, and have more education appear to have higher NHP use.[12,18–20] A large proportion of patients who take NHPs, take them concurrently with conventional therapies, including anticancer medications.[14,21,22] Reported reasons for self-care with NHPs by adults with cancer include treating cancer, reducing side effects or improving effectiveness of conventional cancer treatment, improving their ability to cope with their diagnosis, and improving quality of life.[14,23]

Patient consideration of NHP use appears to start immediately after cancer diagnosis, often in conjunction with feelings of fear and the desire to develop a sense of control.[14,24] A number of sociodemographic, psychological, social and disease-related factors impact the

decision to use NHPs throughout cancer care.[20,23–26] Decision-making about NHP use may be spontaneous, occurring quickly with limited information, or deliberate in a more time-consuming process where information sources are evaluated for credibility.[14,24] Regardless of the style, seeking NHP information is challenging and typically happens outside of the oncology clinic setting.[14] Despite improved discussion about NHPs being identified as necessary between healthcare providers and cancer patients,[10,14,27,28] it has been found that these discussions occur only in a small percent of medical oncology visits and typically last less than one minute.[13,29]

Children with cancer

In children with cancer, the prevalence of use of complementary health approaches may be as high as 91%,[30] with NHPs being the most common approach.[30–32] Personal experiences of parents and "word of mouth" appear to influence NHP use in pediatric patients.[33,34] Additionally, it seems that parents that use complementary approaches for their children have lower satisfaction with their child's primary care.[33] Higher parental education may also be associated with increased NHP use in pediatric patients with cancer.[30] Reasons for use include to help treat the child's cancer, provide symptomatic relief, strengthen their immune system and reduce side effects of conventional treatment.[30,34] Although many children take NHPs with conventional medicine,[32] most parents perceive concurrent use as positive and safe, with limited recognition of the potential adverse events (AEs) or risk of NHP-drug interactions.[33,34] It has been found that less than half of pediatric oncologists routinely ask about NHP use;[35] therefore, disclosure rates of NHP use are quite low.[32,33,36] Instead, caregivers commonly seek NHP advice and information from the internet, their family members or their social networks.[33,37]

Potential NHP Risks in Patients with Cancer

NHPs often contain bioactive compounds, and while this may mean potential for beneficial therapeutic effects and drug discovery, it also means that there are risks of potential AEs.[6,38,39] Patients with cancer are particularly susceptible to clinically important AEs and NHP-drug interactions for a number of reasons.[40–46] First, anticancer medications generally have a very narrow therapeutic index in which small changes in plasma concentrations can result in serious toxicity or therapeutic failure.[40–44] Additionally, anticancer medications have complex and highly variable pharmacokinetics and pharmacodynamics, where both inter- and intra-patient variability often exist.[40,42,44] Polypharmacy is also common in patients with cancer due to multi-drug

anticancer regimens, co-morbidities, and other cancer-associated conditions; this further contributes to the potential for interaction between products and risk of harm.[44–46] In community pharmacies,[47] and more recently at mental health and HIV clinics,[48–50] our research team has found that patients taking NHPs and prescription medications concurrently are more likely to experience an AE compared to those taking prescription medications alone.

The risk of NHP-associated AEs and NHP-drug interactions is further complicated in pediatric patients. Although children with cancer may not have significant comorbidities, supportive care can have a significant impact on polypharmacy; the concurrent use of anticonvulsants, antiemetics, uric acid lowering drugs, acid suppressants, antifungals, antibiotics, antivirals, analgesics, and colony stimulating factors increase the interaction potential with anticancer medications and NHPs.[51] Additionally, the risk is enhanced by developmental differences in the pharmacokinetics and pharmacodynamics of medications.[51,52] Pediatric patients are likely to respond differently to NHPs, medications, or the combination of them, than adults and even other children.[51–53] This is due to age-related developmental differences in body composition and organ function as well as differences in disease state.[51–53]

Both pharmacokinetic and pharmacodynamic NHP-anticancer medication interactions may occur.[39,40,54] Pharmacokinetic interactions occur when an NHP affects the absorption, distribution, metabolism and/or elimination of a medication.[39,54,55] Absorption may be influenced by altering gastrointestinal pH, complexation and chelation, competition at absorption sites and changing gastrointestinal motility.[54] A major mechanism of pharmacokinetic NHP-drug interactions is the induction or inhibition of the cytochrome P450 (CYP) isoenzyme system most frequently found in the liver and intestinal tracts.[39,40,43,54] CYP3A4, in particular, is responsible for metabolizing more than 50% of medications.[39,40,54,55] NHPs may modulate these enzymes which will affect drug bioavailability and/or clearance.[39,54,56–58] This is also problematic for chemotherapeutic agents that are prodrugs and rely on CYP enzymes for activation.[44] Pharmacokinetic phase II conjugation reactions generate metabolites that are highly polar and may be excreted in urine or feces; these pathways can also be altered by NHP-drug interactions.[39,40,54,55] Pharmacokinetic profiles of drugs are heavily influenced by transport and efflux proteins such as the adenosine triphosphate binding cassette drug transporters, the most notable being p-glycoprotein.[39,40,54,55] Either competitive or non-competitive interactions at the level of these transporters may drastically affect the pharmacokinetic profile of a

medication.[39,40,54,55] Renal function may also be altered by NHPs by changing tubular secretion, reabsorption or glomerular filtration.[54] Pharmacodynamics encompasses the mechanism of action of drugs and involves drug receptors that elicit a physiologic response.[55] NHP-drug pharmacodynamic interactions can occur at receptor sites and may be synergistic, additive, or antagonistic.[39,54] For example, some herbal medicines have been shown to reverse immune suppression and impact hormone-sensitive cancers *in vitro* and in animal models.[39,59,60] Several herbs and vitamins also have anticoagulant and antioxidant activities.[39,61–63] Antioxidants, such as vitamin C and E, have been shown to protect cells from oxidative damage, and therefore, a theoretical concern exists regarding their detrimental effect on chemotherapy agents that act by producing free radicals.[39,61–63] When used preventatively, antioxidants have been associated with increased cancer incidence and total mortality.[62,64] Vitamin C was also shown to antagonize the therapeutic efficacy of a number of mechanistically dissimilar anticancer agents *in vitro,*[63] emphasizing that vitamins may have additional unknown mechanisms for NHP-drug interactions and AEs.[39,61–63]

The multitude of available pathways for interactions is not the only aggravating factor for NHP-related AEs. Serious safety concerns have been raised by the adulteration or contamination of NHPs due to variations in the quality control of these products.[65] Adulteration is a fraudulent practice where an NHP is "substituted partially or fully with impure, extraneous, improper or inferior products/substances."[65] Most frequently, NHPs are adulterated with prescription drugs.[65] Undeclared drugs have been found in NHPs promoted for weight loss, erectile dysfunction, insomnia and inflammation.[66] For example, benzodiazepines have been identified in NHPs promoted for sleep problems.[66] Contamination occurs when impurities are added to the product during manufacturing, storage or transport; this may include dust, pollens, parasites, microbes, toxins, pesticides, toxic heavy metals, or other toxic chemicals.[65,67,68] Likewise, lack of standardization in growing, handling, and manufacturing can lead to significant variation in the chemical composition of the product, which could lead to accidental overdose and other health concerns.[39,40,65,68,69]

Synthesizing Existing Clinical Evidence

Information regarding NHP-drug interactions is often inferred from *in vitro* studies.[40,43,44,54] Whereas *in vitro* results are sometimes correlated with *in vivo* behavior, they often do not accurately predict the clinical significance of these effects.[40,43,44,54] The ability of *in*

vitro data to predict clinically relevant interactions also varies between products.[40,43,44,54] There may be a few reasons for this, one of which is the highly variable bioactive content among brands and even within batches of NHPs.[40,43] This means that the ability for an NHP to affect CYP enzymes may also vary.[40,43] Additionally, many of the phytochemical components lack bioavailability due to poor solubility and gastric digestion, and may not reach systemic concentrations high enough to cause an interaction.[40,43] Although *in vitro* data are useful to first detect potential NHP-drug interactions, the clinical importance must be explored in humans.[40,43,44]

A lack of NHP knowledge has been identified among frontline clinicians and may act as a barrier to discussions with patients.[3,9] NHP research is often heterogeneous in design, internal validity, and generalizability.[39,40,65,70–72] Often these publications may also be difficult to locate due to inconsistent indexing.[70,71,73] Pre-appraised evidence syntheses, such as systematic reviews, which synthesize and evaluate the quality of human data on NHP-anticancer medication interactions, are required to enhance the clinical relevance and accessibility of this information for healthcare providers. Additionally, synthesizing available clinical studies on NHP-drug interactions is important to identify current gaps within the literature and to reveal safety signals that require further investigation.

Post-Marketing Surveillance of NHPs

Pre-marketing approval of NHPs varies worldwide, but generally, the pre-marketing requirements are limited, and in some jurisdictions there are none.[74–77] In Canada, depending on the nature of the health claim being made for the NHP, the required level of pre-market efficacy and safety evidence varies to be authorized for sale.[78] For traditional use health claims, the supporting pre-market evidence may include a monograph published in a pharmacopoeia.[78] For modern health claims deemed to be at low risk, textbook references or pilot studies may be sufficient evidence for authorization.[79] Modern health claims deemed to be at high risk, claims for the treatment, prevention or cure of serious health conditions, require higher levels of evidence such as multiple phase III/IV randomized controlled trials and meta-analyses.[79] Although these methods importantly place value on traditional and historical use of a product, it is possible that potential AEs will not be uncovered prior to marketing due to the limitations of the safety evidence required. The weaknesses of the current approval process were further highlighted when a fake homeopathic pediatric product was able to obtain a Health Canada

license.[80] NHPs licensed in Canada are assigned a Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM); since 2004 when the Natural Health Produce Regulations came into effect, over 70,000 NHPs have been authorized for sale.[81] Concerns exist that providing a product license may also convey a false sense of safety, particularly when minimal pre-market evidence was required.[82]

The current pre-marketing NHP regulations highlights the importance of post-marketing surveillance in the detection and understanding of NHP AEs. Passive surveillance, often considered the "mainstay of pharmacovigilance",[83] relies on unsolicited AE reports.[77,83–86] These reports are typically submitted to a national pharmacovigilance agency by healthcare professionals, pharmaceutical companies or patients.[77,83–86] Although passive surveillance, or spontaneous reporting, has the advantage of covering a large number of patients and a broad range of drugs and NHPs in a relatively cost effective way, many limitations also exist.[87] Most notably, this form of post-marketing surveillance is severely hampered by underreporting.[83,85,87] A systematic review by Hazell *et al.* estimated that only approximately 6% of drug AEs are reported through spontaneous reporting systems.[87] Underreporting of AEs appears to be worsened for NHPs; compared to 19% who reported drug-drug interactions, only 1.5% of community pharmacists who had identified a potential NHP-drug interaction reported the AE to a regulatory authority.[88] Likewise, patients also treat AEs related to NHPs differently than conventional medications where nearly 30% would consult their physician or pharmacist for a serious AE experienced with a conventional over-the-counter medication but would not for a similar AE experienced with an NHP.[89] Poor quality reports with incomplete information are also common with passive surveillance.[87] Moreover, the absence of a control group and denominator prevents the quantification of the risk.[87,90–92]

Other pharmacovigilance methods exist, such as active surveillance, a method that addresses several of the limitations of passive approaches.[83,85] Active surveillance uses a continuous pre-organized process to proactively solicit AEs.[74] Existing active post-marketing surveillance systems are scarce.[33,83,85,93] Our research team identified a need for the implementation of active surveillance of AEs associated with NHPs: Study Of Natural health product Adverse Reactions (SONAR). This work has been implemented in community pharmacies, mental health clinics, and HIV clinics.[47–50,94,95] Active surveillance allows for more comprehensive AE data; therefore, causality assessment is also possible.[47,86,94] A causality

adjudication process specific for NHP-associated AEs was developed and implemented by our research team as part of SONAR.[47,94,96] Additionally, a systematic method can increase the rate in which AEs are reported.[47,94,97,98] In the same time period, community pharmacy active surveillance resulted in 54 AE reports per 1,118 patients, compared to the 342 spontaneous reports per 30 million Canadians.[47] Another benefit of SONAR is that it is integrated into clinical workflow and has the potential to increase patient engagement in pharmacovigilance.[99]

Thesis Hypothesis

We hypothesize that patients with cancer who take NHPs are at a higher risk of experiencing clinically important AEs, including NHP-drug interactions.

Thesis Objectives

To improve our understanding of the safety of NHP use in patients with cancer, including concurrent use with anticancer medications, a two-pronged approach was undertaken (Figure 1.1). The first objective of this thesis was to synthesize the existing clinical evidence on the efficacy and safety of concurrent use of NHPs and anticancer medications. A total of eight groups of anticancer agents, categorized by mechanism of action, were determined by our research team through consultation with oncology pharmacists, oncologists, and experts in the field as well as the review of drug databases, chemotherapy protocols and cancer drug benefit programs. To develop an NHP-drug interaction tool for frontline clinicians, a review of existing literature is planned by our research team for each drug category, two of which are the focus of this thesis: immunotherapy and antimicrotubule anticancer agents.

Generally, systematic reviews are adequate to collate what is known on a topic. However, given the suboptimal quality of harms reporting in primary literature,[72,100,101] it is necessary to undertake additional clinical research to identify AEs. Therefore, the second objective of this thesis is to identify and characterize NHP use, and associated AEs experienced by patients with cancer using SONAR active surveillance.

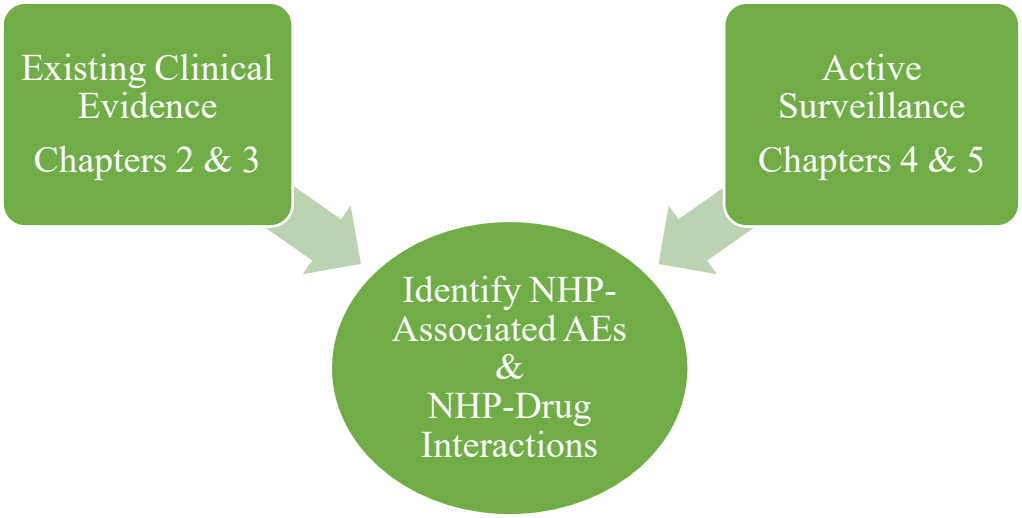


Figure 1.1 The two-pronged approach taken in this thesis to identify NHP-associated AEs and NHP-drug interactions in patients with cancer

Specific Chapter Objectives

Chapter 2: A systematic review to summarize existing clinical evidence on the efficacy and safety of concurrent use of NHPs and anticancer immunotherapy.

Chapter 3: A systematic review to summarize existing clinical evidence on the efficacy and safety of concurrent use of NHPs and antimicrotubule anticancer medications.

Chapter 4: A cross-sectional study that implemented SONAR active surveillance in adult oncology clinics to: 1) determine the prevalence of NHP/drug use; 2) describe common NHPs used; 3) determine the prevalence of AEs in those taking prescription medications alone, NHPs alone or both concurrently; 4) compare the prevalence of AEs between the above groups; 5) describe of the types of AEs reported; 6) determine the likelihood that NHPs caused a serious AE.

Chapter 5: A cross-sectional study that implemented SONAR active surveillance in pediatric oncology clinics to: 1) determine the prevalence of NHP/drug use; 2) describe common NHPs used; 3) determine the prevalence of AEs in those taking prescription medications alone, NHPs alone or both concurrently; 4) compare the prevalence of AEs between the above groups; 5) describe of the types of AEs reported; 6) determine the likelihood that NHPs caused a serious AE.

Chapter 6: An overall summary and the limitations and implications of this thesis.

CHAPTER 2: Natural health product use with anticancer immunotherapy: A systematic review

Introduction

Advances in the prevention, screening and treatment of cancer have resulted in declines in cancer mortality rates in high-resource countries.[102,103] Cancer immunotherapy is one of such treatments that is rapidly evolving and impacting the treatment of patients with cancer.[104–109] Immunotherapy includes antibody-based targeted therapies, T-cell-based therapies, immune system modulators, vaccine therapy, oncolytic virus therapies and other combinatorial strategies.[104–110] Antibody-based therapies, such as monoclonal antibodies, may target B-lymphocyte antigens, growth factor receptors, ligands, and other cell surface receptors.[104–110] T-cell-based therapies involve extracting T-cells from the patient's blood or tumor tissue, modifying, and reinfusing them to eliminate cancer cells.[104–111] Immunotherapy may also include immune system modulators, such as immune checkpoint inhibitors, cytokines, immunomodulatory drugs, and Bacillus Calmette-Guerin (BCG), and cancer vaccines.[104–110] These treatments generally work by stimulating the immune system to attack cancer cells.[104–110] Oncolytic virus therapy, where a virus infects and destroys cancer cells, also exists.[104–110] Even though improved cancer therapies are being developed and used, the number of people diagnosed with cancer continues to increase due to population growth and aging.[102,103]

With the increasing burden of cancer, there has been an increase in popularity of self-medication, including natural health product (NHP) use in patients with cancer.[16] NHPs include vitamins, minerals, herbal medicines, homeopathic remedies, traditional medicines, probiotics, amino acids, and essential fatty acids, and in Canada, are easily purchased by patients in community pharmacies.[1,3,4] Patients with cancer commonly take more than one NHP concomitantly, which may also be in combination with prescription and anticancer drugs.[10,112,113] The complex pharmacology and unique side-effect profile of immunotherapy anticancer medications potentially leaves patients at high risk of NHP-anticancer medication interactions.[40,42,114,115]

There are numerous mechanisms by which NHP-drug interactions may occur.[39,40] Pharmacokinetic interactions involve the absorption, distribution, metabolism, and/or elimination of medications.[39,54,55] Pharmacodynamic interactions however, affect the physiological response of a medication, often at the drug receptor level; they may be synergistic, additive or

antagonistic.[39,55] Interactions may be viewed as either positive or negative depending on their effect on conventional therapy and patient outcome.[39,40,116] There is an interest in positive interactions that may improve anticancer treatment effectiveness, or reduce the side effects or cancer symptoms experienced by patients.[39] Highly concerning is the potential for negative interactions, which could lead to treatment failure or enhanced toxicity and adverse events (AEs).[39]

Most of the summarized literature on NHP-anticancer medication interactions comes from preclinical studies.[39,40,116] Translating *in vitro* studies to clinical effects is often unreliable due to variations in NHP solubility and bioavailability in physiological conditions.[40,43] Clinical data are required for the evaluation of potentially clinically relevant interactions.[43] We are undertaking this systematic review to summarize existing evidence regarding the efficacy and safety of concurrent use of NHPs and anticancer immunotherapy.

Methods

This systematic review was registered with PROSPERO: ID CRD42019124758 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[100,117] was followed for reporting.

Inclusion criteria

We included human studies of patients with cancer of any age, gender, or ethnicity, taking NHPs and anticancer immunotherapy concurrently. There was no restriction on stage or type of cancer or setting. Observational studies were included to enhance the assessment of potential harms.[70,72,118] Reviews and commentaries were excluded.

There was no restriction on dose, frequency, or duration of either NHP or anticancer regimen, as long as the use of NHP and immunotherapy was concomitant. Although single product use simplifies causality assessment of interactions, we included studies where patients are taking more than one anticancer medication and/or more than one NHP, which includes both multi-ingredient products and multiple individual products. This enhances generalizability as polypharmacy is common in patients with cancer.[119]

We developed a clinically relevant list of NHPs for inclusion, including garlic, ginseng, milk thistle, mistletoe, probiotics, turmeric, vitamin C, vitamin D, and vitamin E, following a similar process that has been previously published by our research team.[120,121] MEDLINE and

EMBASE were searched to identify Canadian population data on commonly used NHPs by patients with cancer. Given the lack of available population data on this topic, experts in the field, including naturopaths, oncologists, and those working in integrative oncology, were also contacted to provide a list of NHPs relevant to their practice. The NHPs collected from literature and expert responses were listed and ranked by frequency. Collaborators and clinical experts discussed the NHPs for inclusion until consensus was reached based on frequency of use, likelihood of interaction with anticancer medications, and clinical relevance for cancer patients. Cannabis was not included in this list as it not considered an NHP in Canada; cannabis is regulated separately by Health Canada through the Cannabis Regulations.[2]

Search methods

A database search was conducted using MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms were related to the population, interventions, and outcomes of interest; the full MEDLINE search strategy is available in Appendix 2.1. There was no restriction on publication date. Only studies in English were included.

Hand searches were completed of bibliographies of pertinent review articles as well as Natural Medicines™, About Herbs™ and Lexicomp® Online™ databases. Unpublished data and conference abstracts were searched using clinicaltrials.gov, WHO International Clinical Trials Registry Platform and the American Society of Clinical Oncology conference abstract library. Authors were contacted to provide any data not readily available online.

Data collection and analysis

RefWorks™ was used to merge search results and remove duplicates. The reviewers involved had expertise in NHP-related research including a doctoral student (MB), two medical students (RS and ES), and a doctoral supervisor (SV). Two reviewers (MB and RS) independently screened titles and abstracts and subsequently full-text articles for inclusion. Disagreements were discussed until consensus was reached, or where required, a third reviewer (SV) was consulted.

Data extraction was completed using a pre-piloted spreadsheet. Data were extracted by one reviewer (MB) and a second reviewer (ES) verified and examined for errors. Discrepancies were discussed until consensus was reached.

For individually-randomized, parallel-group trials the Cochrane RoB 2 tool[122] was used to assess for risk of bias. This tool assessed bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.[122] For non-randomized studies that compare harms or benefits of two or more interventions we used the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.[123] Here we assessed bias due to confounding, participant selection, intervention, missing data, measurement of outcomes and selection of reported result.[123] Risk of bias assessments were conducted by one reviewer (MB) and verified by a second (ES). Discrepancies were discussed until consensus was reached, or where required, a third reviewer (SV) was consulted.

The findings are presented as a narrative synthesis with summary tables. The heterogeneous study designs, interventions, comparators, and outcomes of included studies precluded us from pooling data for meta-analysis.

Results

Search Results

Database searches identified 625 records. An additional seven were identified through hand searches, leaving a total of 608 articles after duplicates were removed (Figure 2.1). After title and abstract screening, 440 records were excluded, and 168 full-text articles were assessed for eligibility. A total of 16 human studies were included in the final synthesis (Tables 2.1, 2.2 and 2.3), including one recent full-text publication identified after contacting the authors of a conference abstract identified in our search.[124] The majority (9) of the studies included were non-randomized studies, six of which were phase I and II clinical trials. There were also three randomized studies, three case reports, and one case series included.

The number of participants in the randomized and non-randomized studies ranged from 3 to 332. All papers involved adult patients with heterogeneous cancer diagnoses, including breast, blood, pancreatic, liver, head/neck, bladder, renal, and colorectal cancers. Five papers did not restrict participants to a single type of cancer.[125–129] Patients with cancer-related conditions, such as cachexia and fatigue were the focus of two studies.[125,129] Participants were often middle-aged, with reported mean or median ages between 52 and 70 years. One paper did not include information on patient sex,[130] but the remainder of randomized and non-randomized studies

included both male and female patients, where males represented the majority of participants in most studies.

We identified clinical data involving monoclonal antibodies (bevacizumab, catumaxomab, cetuximab, ofatumumab, panitumumab, rituximab, trastuzumab), immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab), cytokines (interferon), immunomodulatory drugs (thalidomide, lenalidomide), and BCG (Figure 2.2). Three of the included non-randomized studies evaluated concurrent NHP use with any anticancer agent; in these cases, the number of patients included in the study receiving immunotherapy was very low, making extrapolation difficult.[126,129,131] Often immunotherapy was taken concurrently with other prescription medications and anticancer agents, mimicking real-world clinical practice. However, the level of detail provided on the co-interventions varied greatly between studies. In terms of NHPs included, we identified studies with vitamin C (5), mistletoe (4), vitamin D (4), vitamin E (2), ginseng (1) and probiotics (1). No papers were identified with garlic, milk thistle or turmeric and concurrent immunotherapy.

The types of outcomes analyzed were heterogeneous and included various efficacy (treatment response, disease recurrence, survival, cachexia, fatigue) and safety (toxicity, tolerability, AEs) measurements. Of the randomized studies, all had primary outcomes focused on efficacy of concurrent anticancer medications and NHPs, with one[132] also incorporating safety. Four of the nine non-randomized studies had safety included as part of the primary outcome.[126–129] Most commonly, versions of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[133] were used to determine severity of reported AEs. Often no information or inadequate detail was provided on the ascertainment of AEs. In some prospective studies, AE ascertainment was through patient or healthcare professional report as well as laboratory evaluations.[124–126,129,130,132,134] In retrospective studies, this was done through cancer registries which extracted AE information from patient files.[127,128] There was no direct mention of causality assessment tools or how causality was determined in the included studies. Despite this, a number of studies stated whether they believed there was a causal relationship between AE reported and the NHP.[124,127,129,132,135,136]

Risk of bias

The randomized studies ranged from low to high risk of bias (Figure 2.3). In two of the three randomized studies, the lack of allocation concealment and blinding were major sources of

bias (Figures 2.4). Four non-randomized studies compared two or more interventions and were appropriate for evaluation via the ROBINS-I tool.[123] All of these studies were either at overall serious or critical risk of bias, which was influenced by the presence of baseline confounding, lack of adjustment for confounding variables, and selection biases (Figure 2.5, 2.6). The remaining papers were inherently at high risk of bias as they were phase I and II clinical studies lacking a comparison group, case series, and case reports.

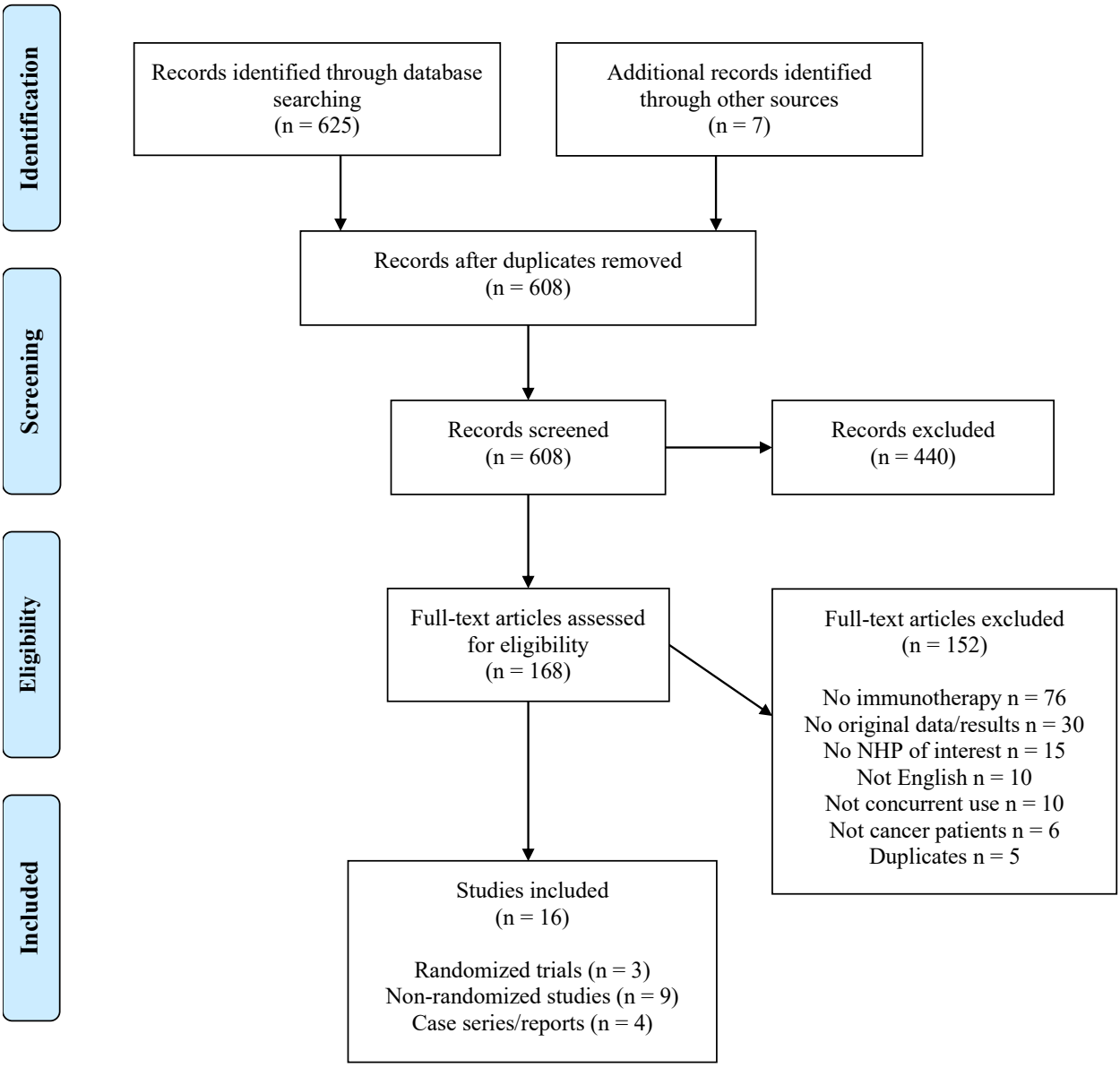
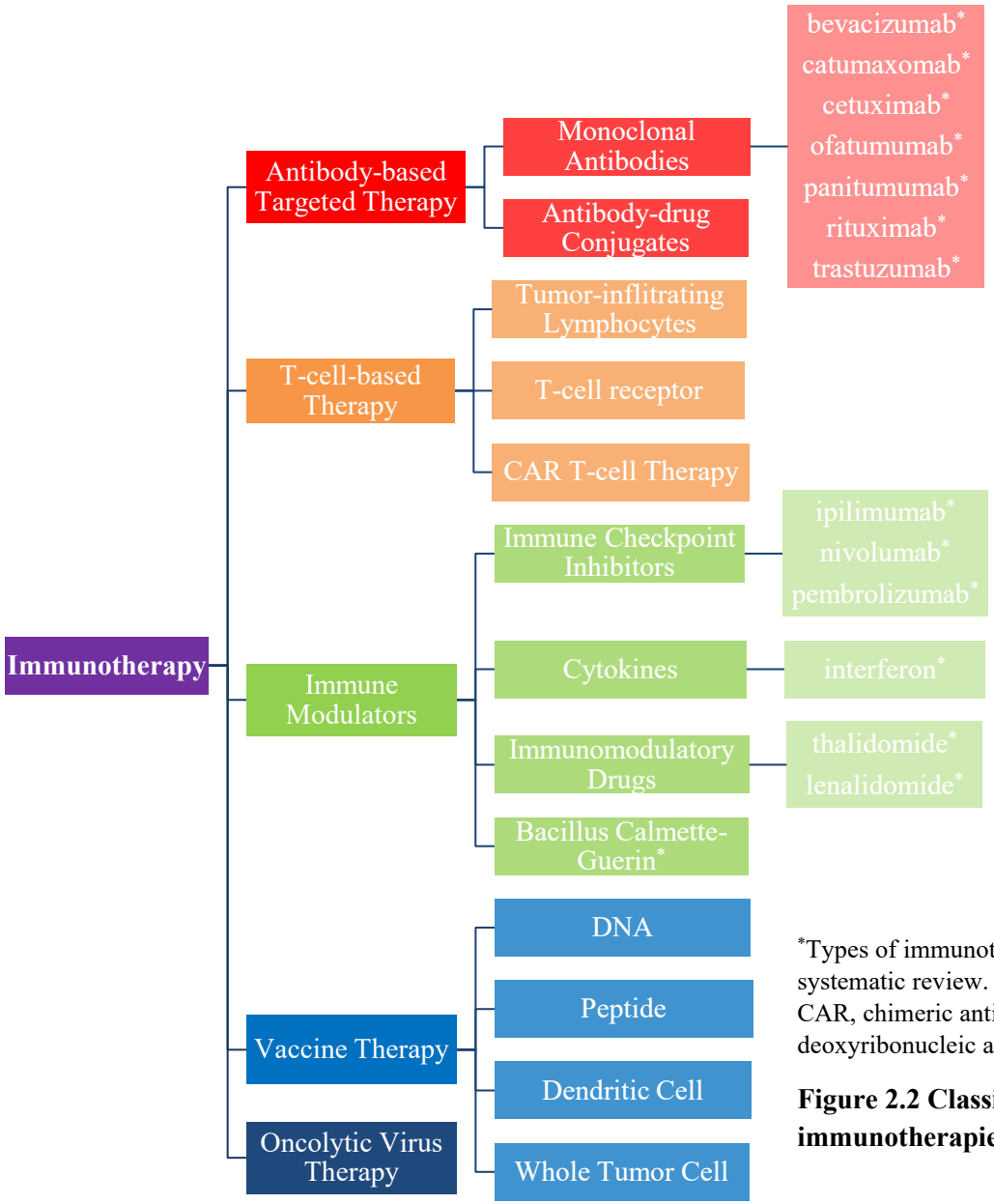


Figure 2.1 PRISMA Flow Diagram[117]



*Types of immunotherapies identified in this systematic review.
CAR, chimeric antigen receptor; DNA, deoxyribonucleic acid

Figure 2.2 Classification of immunotherapies[104–110]

Table 2.1 Concurrent NHPs and Immunotherapy in Randomized Studies

Paper Name	NHP(s)	Immunotherapy Drug(s)	Study Type	Setting	N	Participants	Intervention(s) & Comparison(s)	Primary Outcome(s)	Efficacy	Safety
Hellstrom 1988[132]	vitamin D	interferon	RCT	Sweden	81	Adults with myelodysplastic syndrome or acute myelogenous leukemia Median age = 70y Males = 56%	IDR: α-interferon + oral vitamin D3 + retinoic acid C: cytosine arabinoside Concurrent therapy up to 36 mo	Treatment response, survival, toxicity	NSS difference in treatment response (IDR 50% vs. C 43%) NSS difference in survival	Reversible hypercalcemia (corrected serum calcium > 2.90 mmol/L) in 6/30 patients on vitamin D IDR: fatal intestinal bleeding, dry skin, conjunctivitis, cheilitis, muscular pain, bone marrow hypoplasia, thrombocytopenia, leukopenia, fatigue, and flu-like symptoms Frequency of side-effects IDR > C
Ng 2019[124]	vitamin D	bevacizumab	Phase II	USA	139	Adults with advanced or metastatic colorectal cancer Median age = intervention 54y; comparison 56y Males = intervention 59%; comparison 54%	All participants: mFOLFOX6 (leucovorin, 5-fluorouracil, oxaliplatin) + bevacizumab Intervention: oral high-dose vitamin D3 Comparison: oral standard-dose vitamin D3 Median # cycles with concurrent vitamin D + bevacizumab ~13 (each cycle is 14 days)	Progression free survival (PFS)	Median PFS 13 mo. high-dose vs. 11 mo. standard-dose (p = 0.07) PFS HR 0.64 (1-sided 95% CI 0-0.9; p = 0.02)	Reported as "possibly related" to vitamin D: hyperphosphatemia (1 patient in high-dose), kidney stones (1 patient in standard-dose) Hypercalcemia not observed Fewer episodes of grade ≥3 diarrhea in high-dose (1% vs. 12%)
Mantovani 2010[125]	vitamin E, vitamin C	thalidomide	Phase III	Italy	332	Adults with advanced stage tumor at any site + clinical cachexia Mean age = arm 1 62y; arm 2 61y; arm 3 63y; arm 4 62y; arm 5 62y Males = arm 1 57%; arm 2 60%; arm 3 53%; arm 4 55%; arm 5 52%	All: polyphenols + lipoic acid + carbocysteine + vitamin E + vitamin A + vitamin C (all orally) Arm 1: medroxyprogesterone acetate or megestrol acetate Arm 2: eicosapentaenoic acid-enriched nutritional supplement Arm 3: L-carnitine Arm 4: thalidomide Arm 5: all combined Concurrent therapy x 4 mo	↑ lean body mass (LBM), ↓ resting energy expenditure (REE), ↓ fatigue	Significant difference between arms for ↑ LBM, ↓ REE and ↓ fatigue; post hoc analysis: Arm 5 superior vs. other arms	Toxicity was comparable among arms Arm 4: 2 patients - grade 1/2 somnolence Arm 5: 3 patients - grade 1/2 diarrhea; 2 patients - grade 3/4 diarrhea; 1 patient - grade 1/2 epigastralgia; 1 patient - grade 1/2 thromboembolism

NSS, not statistically significant

Table 2.2 Concurrent NHPs and Immunotherapy in Non-Randomized Studies

Paper Name	NHP(s)	Immunotherapy Drug(s)	Study Type	Setting	N	Participants	Intervention(s) & Comparison(s)	Primary Outcome(s)	Efficacy	Safety
Kountouras 1995[136]	vitamin C	interferon	Phase II	Greece	12	Adults with inoperable hepatocellular carcinoma Median age = treated 64y; untreated 62y Males = treated 71%; untreated 80%	Treated: recombinant α-interferon (IFN) + doxorubicin + tamoxifen + desferrioxamine + oral ascorbic acid Untreated: No antitumor therapy Concurrent therapy up to 76 wks	Survival, clinical response, immunological response	Mean survival 42.7 ± 19.5 wks treated vs. 8.4 ± 1.8 wks untreated ($p < 0.001$) ↑ % tumor regression & stable disease in treated group; ↓ progressing tumors in treated group (within 2 mo: $p<0.02$) Treated: maintained a sufficient immune status	Treated: all patients - "flu-like" syndrome 2-4 h after IFN dose; 1 patient - wheezing 8h after 1st IFN dose; 1 patient - mental confusion 13h after 1st IFN dose; 5 patients - transient nausea/emesis attributed to doxorubicin; 2 patients - transient fatigue; 1 patient - bone marrow suppression
Bejanyan 2012[130]	vitamin C	thalidomide	Phase II	USA	28	Adults with myelodysplastic syndromes, myeloproliferative neoplasms, or primary myelofibrosis Median age = 67y	thalidomide + arsenic trioxide + dexamethasone + oral ascorbic acid Concurrent therapy x 12 wks	Overall response rate (ORR), progression free survival (PFS), overall survival (OS)	ORR: 21.4% (3.6% partial remission, 17.9% clinical improvement, 50% stable disease) Median PFS: 14.4 mo Median OS: 21.4 mo	25% grade ≥ 3 hematologic toxicities (thrombocytopenia, neutropenia, leukocytosis) Other grade ≥3 AE: dyspnea (18%) and infections (14%) 82% fatigue (29% grade ≥3)
Kawada 2014[135]	vitamin C	rituximab	Phase I	Japan	3	Adults with relapsed CD20-positive B-cell non-Hodgkin's lymphoma 60y female; 72y male; 57y male	rituximab + cyclophosphamide + cytarabine + etoposide + dexamethasone + IV L-ascorbic acid (AA) AA during 2nd 3 wk cycle	Dose finding	All patients reached target plasma AA concentration with a 75g dose	Grade 3 hematologic toxicities in all patients (neutropenia, anemia, thrombocytopenia) No adverse reactions attributed to AA
Hoffer 2015[126]	vitamin C	bevacizumab, trastuzumab	Phase I-II	Canada	14	Adults with cancer on chemotherapy that offered <33% likelihood of clinical response Patient 1: 57y male with metastatic colon cancer Patient 2: 76y male with metastatic colon cancer	All: chemotherapy + IV ascorbic acid (AA) Patient 1: irinotecan + fluorouracil + folinic acid + bevacizumab + AA x 34 days Patient 2: irinotecan+ bevacizumab + capecitabine + AA x 115 days	Safety, PK, clinical effectiveness	Patient 1: disease progression Patient 2: stable disease x 3.5 mo Patient 3: CA 125 and CA 15-3 increased further	PK: plasma AA concentration-time profile was not affected by chemotherapy but there was short-term tissue retention of AA following chemotherapy Patient 1: no side effects/toxicity Patient 2: thirst &

						Patient 3: 54y female with recurrent breast cancer	Patient 3: capecitabine + trastuzumab + AA x 46 days			unpleasant fluttering in upper abdomen during AA infusion + fatigue & mentally hazy the day after AA Patent 3: no toxicity but withdrew due to inconvenience
Shin 2001[134]	vitamin E	interferon	Phase II	USA	45	Adults with locally advanced head and neck squamous cell carcinoma Median age = 52y Males = 80%	α-interferon (IFN) + 13-cis-retinoic acid (13-cRA) + oral α-tocopherol Concurrent therapy x 12 mo	Disease recurrence, second primary tumor (SPT) development	Recurrence: 9% locoregional, 5% locoregional + metastases 2% developed SPT	Toxicity generally consistent with previous reports of IFN and 13-cRA alone or in combination Nonhematologic AE: mild-moderate mucocutaneous AE, flu-like symptoms, anorexia, weight loss, fatigue (grade 2 & 3), peripheral neuropathy (grade 2 & 3), mild-moderate hypertriglyceridemia, grade 3 vision change - 1 patient, severe strep throat infection - 1 patient Hematologic AE: mild
Axtner 2016[131]	mistletoe	catumaxomab, bevacizumab	Cohort	Germany	240	Adults with advanced pancreatic carcinoma Median age = 68y Males = 48%	Neither: no/<1 week of Viscum album (VA) + no chemotherapy Chemo: no/<1 week of VA + chemotherapy VA: >4 weeks of VA (any route) + no chemotherapy Both: >4 weeks of VA (any route) + chemotherapy *1 patient each on: catumaxomab; bevacizumab + gemcitabine*	Median survival	Survival benefit for both (12.1 mo) vs. chemo (7.3 mo); p = 0.014 Survival benefit for VA (5.4 mo) vs. neither (2.5 mo); p = 0.006	Not discussed
Thronicke 2017[127]	mistletoe	nivolumab, ipilimumab, pembrolizumab	Pilot cohort	Germany	16	Adults with advanced or metastatic cancer Median age = 64y	Intervention: immune checkpoint inhibitors (ICM) + IV or SC Viscum album (VA) Comparison: ICM	Occurrence of adverse events (AE)	Complete response: 0 Partial response: 0 ICM vs. 33.3% ICM/VA (p = 0.21)	No serious AE or adverse reactions ≥ 1 AE: ICM 71.4% vs. ICM/VA 66.7% (p > 0.99)

						Males = 44%	Duration of VA therapy x 84 days (median)		Stable disease: 28.6% ICM vs. 22.2% ICM/VA (NS) Progressive disease: ICM 71.4% vs. 44.4% ICM/VA (p = 0.36)	AE rate: OR 1.467 (95% CI 0.183 - 11.693, p = 0.720) 1 patient: moderate nausea/ vomiting attributed to VA 2 patients: immune-related AE on ICM/VA
Schad 2018[128]	mistletoe	trastuzumab, bevacizumab, cetuximab, panitumumab, rituximab	Cohort	Germany	56	Adults with cancer Median age = 65y Males = 39%	All participants: supportive therapy & chemotherapy permitted Combined: IV Viscum album (VA) + IV monoclonal antibody (mAb) on the same day VA: no mAb 1 month on either side of VA mAb: no VA 1 month on either side of mAb Combined therapy x 3.5 mo (median)	Occurrence of adverse events (AE)	Not discussed	AE rates: mAb 26.5% vs. combined 12.9% vs. VA 4.7% AE rate mAb vs. combined therapy: OR 4.97 (95% CI 1.53 - 16.14; p = 0.008) Serious AE rates: mAb 3% vs. combined 2% vs. VA 0.8% Most common AE following combined therapy: leucopenia (16%), stomatitis (14%), diarrhea (9%), malaise (9%), skin reactions, rash, acne, nausea, chills, palmar-plantar erythrodysesthesia (each 7%)
Yennuraj-alingam 2015[129]	ginseng	rituximab, lenalidamide, trastuzamab	Phase II	USA	30	Adults with cancer-related fatigue (CRF) Median age = 58y Males = 50%	chemotherapy + oral Panax ginseng *1 patient each on: rituximab + cyclophosphamide + etoposide + vincristine + prednisone; lenalidomide; trastuzamab* Concurrent therapy x 29 days	Safety, tolerability, effect on fatigue	Improvement in Functional Assessment of Chronic Illness Therapy: fatigue (p=0.0006), physical (p=0.002) Improvement in Edmonton Symptom Assessment Scale: pain (p=0.01), fatigue (p=0.0001), appetite (p=0.0097) Median improvement in Global Symptom Evaluation: 5 points	No grade ≥3 AE attributed to ginseng Most common grade ≤3 AE: pain & nausea - not attributed to ginseng

Table 2.3 Concurrent NHPs and Immunotherapy in Case Series and Reports

Paper Name	NHP(s)	Immunotherapy Drug(s)	Type of Study	Setting	Participant(s)	Conventional drug(s) & NHP(s)	Clinical Course
Fink 2011[137]	vitamin D	trastuzumab	Case Report	Germany	59y female with HER2-overexpressing breast cancer	Drugs: docetaxel 75mg/m^2 + carboplatin + trastuzumab 6mg/kg on day 1 of each cycle NHP: Vitamin D3 2000 units oral daily	Developed moderate stomatitis, dermatitis on the fingertips, marked dysgeusia and eventually a painful fissure on the right thumb, low serum vitamin D After vitamin D x 3 wks, the skin was nearly healed, no stomatitis and ↓ taste disorder, ↑ serum vitamin D
Narsana 2014[138]	vitamin D	lenalidomide	Case Report (Conference Abstract)	USA	64y female with recent diagnosis of multiple myeloma + lytic bone lesions	Drugs: bisphosphonates + bortezomib + dexamethasone + lenalidomide + denosumab 120mg subcutaneously NHPs: oral calcium 3000mg daily + calcitriol 1mcg daily + vitamin D2 150,000 units weekly + IV calcium gluconate x 5 weeks	3 weeks post bisphosphonates & 4 days post denosumab the patient presented with severe acute hypocalcaemia (total calcium 5.2mg/dl, ionized calcium 0.78 mmol/l, vitamin D 11 ng/ml) Calcium, calcitriol and vitamin D corrected the hypocalcaemia low vitamin D may have made her more prone to develop severe hypocalcaemia
von Schoen-Angerer 2015[139]	mistletoe	Bacillus Calmette-Guerin (BCG)	Retrospective Case Series	Germany	1 patient: 64y female with high-grade muscle-invasive urothelial bladder cancer	Drug: Intravesical BCG every 3 mo x ~3 yrs NHPs: Viscum album (VA) SC weekly + Thuja e summatibus D12, Argentum nitricum compositum, Staphisagria LM, Equisetum arvense Silicea cultum D3, Senecio compositum, Tendo/Allium cepa compositum (all orally)	Follow-up: 5 years tumor-free Patient reported an increase in energy on VA Local redness/itching, nausea and headache after first 2 VA injections; gross hematuria after BCG
Kopecky 2018[140]	probiotic	nivolumab	Case Report	Czech Republic	63y male with metastatic renal cell carcinoma	Drugs: nivolumab 300mg every 14 days x 6 doses + fentanyl 100mcg/h patch every 3 days + intermittent diphenoxylate hydrochloride 2.5mg NHP: intermittent probiotic (Lactobacillus acidophilus)	14 days following the last dose of nivolumab the patient developed severe chorea-like dyskinesia and paranoid hallucinatory syndrome; query immune-related encephalitis

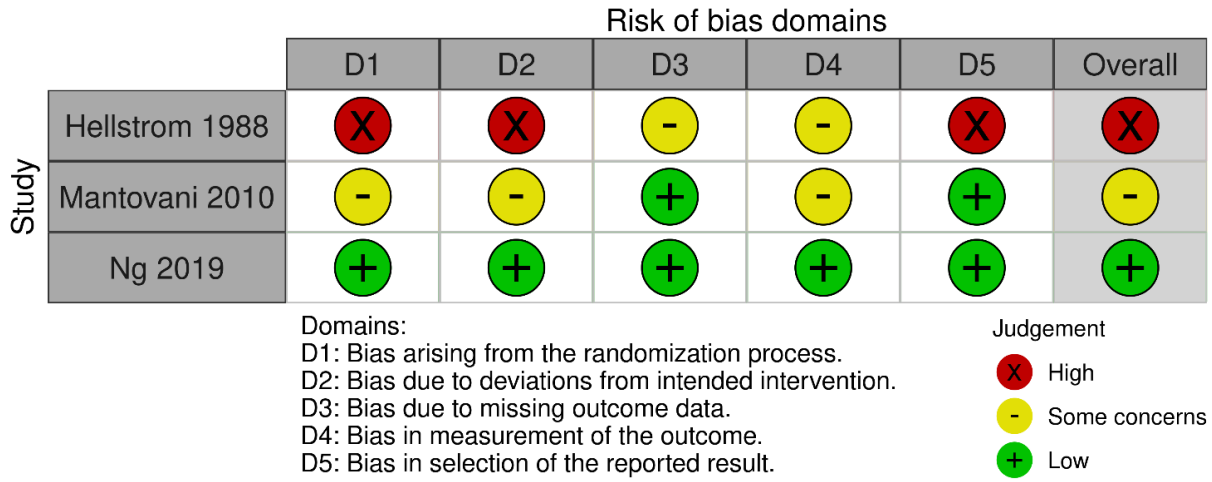


Figure 2.3 Risk of Bias Assessment of Individual Randomized Studies[141]

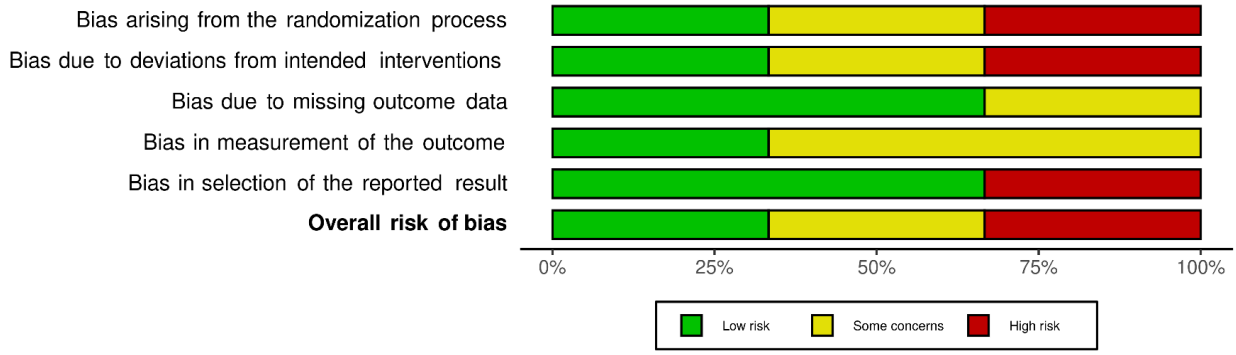


Figure 2.4 Overall Risk of Bias Assessment of Randomized Studies[141]

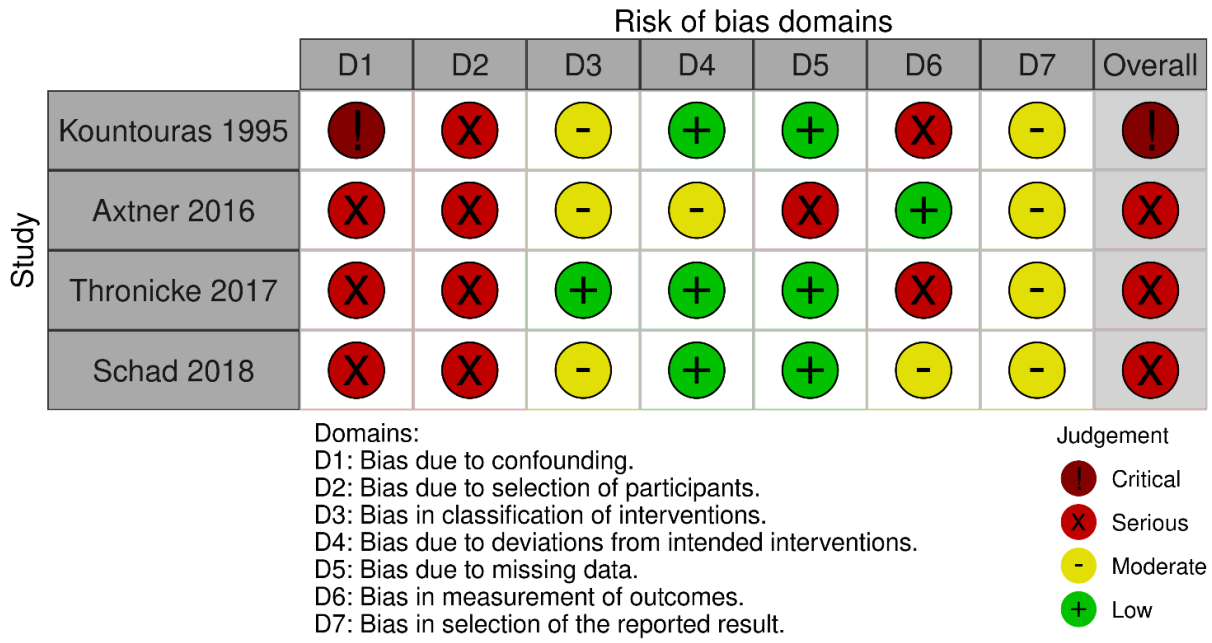


Figure 2.5 Risk of Bias Assessment of Individual Non-Randomized Studies[141]

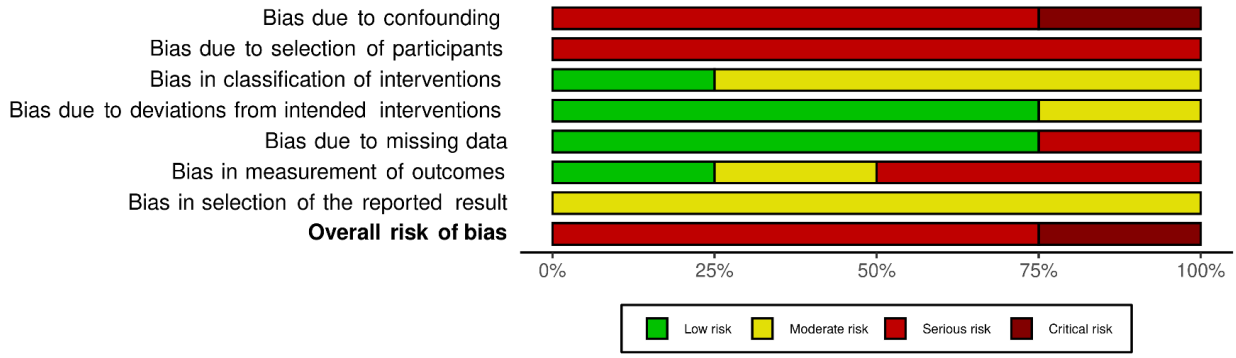


Figure 2.6 Overall Risk of Bias Assessment of Non-Randomized Studies[141]

Concurrent immunotherapy and NHPs

Monoclonal antibodies

Clinical evidence exists of concomitant use of anticancer monoclonal antibodies along with vitamin D, vitamin C, mistletoe, and ginseng.

The SUNSHINE randomized clinical trial,[124] assessed to have a low risk of bias, included 139 adults with advanced or metastatic colorectal cancer on leucovorin, 5-fluorouracil, oxaliplatin (mFOLFOX6) and bevacizumab. This trial compared progression free survival of those on high-dose oral vitamin D3 (8000 IU/day x cycle 1, then 4000 IU/day) to standard-dose oral vitamin D3 (400 IU/day). The median progression free survival was not statistically significantly different ($p = 0.07$); however, the supporting hazard ratio did show a statistically significant reduction in risk of cancer progression or death with high-dose oral vitamin D3 (HR 0.64, 95% CI 0 – 0.90; $p = 0.02$).[124] Hyperphosphatemia and nephrolithiasis were reported as possibly related to vitamin D supplementation; however, fewer episodes of grade 3 or higher diarrhea were observed in the high-dose vitamin D group.[124] Trastuzumab was also taken concurrently with vitamin D in a case report.[137] This patient developed moderate stomatitis, finger-tip dermatitis and dysgeusia after docetaxel, carboplatin, and trastuzumab therapy, which improved after oral vitamin D3 supplementation.[137]

Vitamin C was used concurrently with monoclonal antibodies in two small phase I/II clinical trials. The first, was a vitamin C dose-finding study involving three patients with non-Hodgkin's lymphoma on a regimen of rituximab, cyclophosphamide, cytarabine, etoposide, and dexamethasone.[135] While all patients reached their target plasma ascorbic acid concentration with a 75g intravenous (IV) dose, no AEs were attributed to the vitamin C.[135] Hoffer *et al.*[126] assessed the effect of high-dose IV vitamin C in 14 patients on chemotherapy which offered a low likelihood of clinical response. Three of these patients were on monoclonal antibodies, bevacizumab or trastuzumab, as part of various chemotherapy regimens.[126] While one patient reported no side effects, another reported thirst and unpleasant fluttering in their upper abdomen during vitamin C infusion and mental haziness the day following influsion.[126] The third patient did not report any toxic effects but withdrew due to the inconvenience of the vitamin C infusions.[126] A pharmacokinetic effect of chemotherapy on short-term tissue retention of ascorbic acid was also reported.[126]

In a cohort of 240 patients with advanced pancreatic cancer, a statistically significant ($p = 0.014$) benefit on median survival was observed for mistletoe combined with chemotherapy (12.1 months) compared to chemotherapy alone (7.3 months).[131] AEs were not measured.[131] This study included patients on heterogeneous chemotherapy regimens; only one patient each were on therapy that included catumaxomab or bevacizumab, making interpretation challenging.[131] A cohort of 56 adults with cancer evaluated AEs in patients on monoclonal antibodies (trastuzumab, bevacizumab, cetuximab, panitumumab, or rituximab) in combination with IV mistletoe compared to each therapy alone; all groups were permitted other supportive therapy and chemotherapy.[128] The AE rate was higher in the monoclonal antibody group versus combined therapy (OR 4.97, 95% CI 1.53-16.14; $p = 0.008$), and serious AE rates were similar (monoclonal antibodies 3% vs. combined 2%).[128]

When ginseng was taken along with chemotherapy (one patient each on rituximab or trastuzamab), cancer-related fatigue was reduced, and no AEs were attributed to ginseng.[129]

Immune checkpoint inhibitors

We identified articles that involved concurrent mistletoe or probiotics with immune checkpoint inhibitors. In a pilot cohort study of 16 adults with advanced or metastatic cancer, rates of AEs were not statistically significantly different in those on immune checkpoint inhibitors (nivolumab, ipilimumab pembrolizumab) with mistletoe in comparison to immune checkpoint inhibitors alone.[127] One patient on combination therapy reported moderate nausea and vomiting, which resolved with the discontinuation of mistletoe.[127] No serious AEs were identified over the duration of treatment (median 84 days).[127] The secondary exploratory outcome of disease response rate was not adequately powered to detect statistically significant differences.[127]

A case report was identified in which nivolumab was used concurrently with intermittent *Lactobacillus acidophilus* probiotics, along with fentanyl and intermittent diphenoxylate hydrochloride.[140] This patient, with metastatic renal cancer, developed severe chorea-like dyskinesia and paranoid hallucinatory syndrome 14 days following their 6th dose of nivolumab; this was queried as immune-related encephalitis secondary to immune checkpoint inhibitors.[140]

Other immune system modulators

Vitamins C, D, E, ginseng, and mistletoe have been used alongside anticancer cytokines, immunomodulatory drugs, and BCG in available clinical evidence.

A randomized trial of 81 patients with myelodysplastic syndrome or acute myelogenous leukemia compared α-interferon, oral vitamin D3 and retinoid acid with cytosine arabinoside.[132] There was no statistically significant difference in treatment response or survival, but authors hypothesized an additive or synergistic effect of interferon, vitamin D and retinoid acid as the individual components generally give lower response rates.[132] There was a higher frequency of side effects in the interferon, vitamin D, and retinoid acid group, and reversible hypercalcemia was noted in 20% of patients on vitamin D.[132] Vitamin D was also taken concurrently with another immunomodulator, lenalidomide, in a case report.[138] This patient experienced severe acute hypocalcaemia post bisphosphonate and denosumab therapy, which was treated with calcium, calcitriol, and vitamin D2.[138] While low serum vitamin D may have made this patient susceptible to hypocalcaemia, it is unclear whether concurrent lenalidomide had an effect on this AE.[138]

Vitamins C and E have been used in combination with vitamin A, polyphenols, lipoid acid, carbocysteine, and several conventional medications, including thalidomide, for the treatment of clinical cachexia.[125] Different combinations appeared to have differing effects on lean body mass, resting energy expenditure, and fatigue, but toxicity was comparable.[125] Forty-five adults with head and neck cancer were treated with α-interferon, 13-cis-retinoic acid, and oral vitamin E.[134] Nine percent of patient experienced locoregional recurrence, 5% metastasis, and 2% developed second primary tumors.[134] Toxicity was consistent with what would be expected of α-interferon and 13-cis-retinoic acid, taken alone or together, with patients experiencing mild to moderate non-hematological AEs, and mild hematologic AEs.[134]

Kountouras *et al.*[136] predicted an additive or synergistic effect of the combination of recombinant α-interferon, doxorubicin, tamoxifen, desferrioxamine and oral ascorbic acid. However, this study was determined to be at critical risk of bias.[136] While the mixture increased mean survival, tumor regression and stable disease, this was in comparison to patients on no antitumor therapy, suggesting a significant risk of residual confounding.[136] Toxicities observed were attributed primarily to interferon and doxorubicin.[136] A single arm study of thalidomide, arsenic trioxide, dexamethasone, and oral ascorbic acid had an overall response rate of 21% and

median progression free survival of 14.4 months in 28 patients with myelodysplastic syndrome, myeloproliferative neoplasms or primary myelofibrosis.[130] Grade ≥3 AEs included hematological toxicities, dyspnea, and infections, and 82% of patients experienced fatigue.[130]

Ginseng was taken in combination with rituximab and lenalidomide, one patient on each, with some benefit on cancer-related fatigue and without notable side effects attributed to the NHP.[129] In addition, one patient in the literature took BCG and mistletoe concurrently for the treatment of bladder cancer.[139] Local redness and itching, nausea, and headache were reported after the first two mistletoe injections, however the patient did report a feeling of increased energy on this therapy.[139] Authors also indicated that mistletoe may have had a "possible beneficial effect" on the patient's cancer as they were tumor-free for 5 years; however, there are many other clinical factors to consider, including that the patient underwent other treatments, such as tumor resection.[139]

Discussion

To our knowledge, this is the first systematic review to synthesize existing clinical evidence on concurrent anticancer immunotherapies and NHPs. In terms of the effect on efficacy, the studies included in this review generally trended towards a beneficial effect of concurrent therapy. However, there is very high level of uncertainty in this result due to the lack of, or poor choice of comparison group, heterogeneity, and overall poor internal validity of studies. Conflicting results of efficacy were also reported by the study with the lowest risk of bias.[124] Patients often take NHPs for their perceived benefits throughout cancer treatment, but we did not find sufficient evidence to support this practice during immunotherapy.[20,39] The small benefits seen in a few studies on treatment response, survival, and fatigue are, at most, hypothesis-generating and indicate the need for large, rigorous randomized controlled trials to confirm these findings.

The evidence in this review did not highlight any clear safety signals of the included NHPs taken concurrently with immunotherapy. In general, the addition of NHPs to an anticancer regimen containing immunotherapy resulted in comparable toxicity to what was observed or expected to be observed with single agents and/or the toxicity was not attributed to the NHP. Although very few AEs were reported for NHPs, often therapies were taken in heterogeneous combinations. In three papers, patients on any type of chemotherapy were included and this meant that only two of 240, three of 30, and three of 14 participants were taking

immunotherapy.[126,129,131] In addition, studies frequently lacked an adequate comparator; combined immunotherapy and NHPs were compared to a completely separate anticancer regimen[132] or no anticancer treatment at all,[136] and many others were single-arm studies. These factors make assessing causality of AEs problematic, particularly as no methods for estimating causal relationships were reported in the studies.[142] AEs may also be underestimated due to the high risk of type 2 errors in phase I and II clinical trials, as they are not designed to detect harms that are less common or delayed.[143] In half of the included studies, safety was a secondary outcome and one study[131] did not measure any safety outcome. Given the methodological limitations of the included papers, the paucity of harms reported in this review does not allow us to disregard their potential existence, but it helps provide a direction for future research.

AEs attributed to NHPs included thirst, abdominal discomfort, and mental haziness with vitamin C;[126] hyperphosphatemia, hypercalcemia and nephrolithiasis with vitamin D;[124,132] and local redness and itching, nausea, vomiting, and headache with mistletoe.[127,139] In a few studies, improved rates of AEs, such as diarrhea and mucocutaneous toxicity with vitamin D,[124,137] were seen with concurrent therapy; confirmatory studies are required. A lack of discussion on NHP use between patients and conventional oncology healthcare professionals is common.[9,11–13] Reasons for nondisclosure of NHP use include lack of clinician inquiry and patients' anticipation of clinician disapproval, disinterest, or lack of knowledge on NHPs.[9,12,126] Additionally, there is a perception that NHP use may be irrelevant or innocuous to conventional treatment.[9,11,12] The results of this systematic review reaffirm that NHPs are not without physiological effects and ongoing clinician-facilitated discussion and monitoring is required for fluctuations in anticancer efficacy and mitigation of toxicity.[11,12,28]

There are several strengths of this review. We utilized a number of productive databases with high quality, peer-reviewed articles,[71,144,145] conducted hand searching of NHP-based resources, and incorporated numerous synonyms in our search terms.[73] This allowed us to reduce some of the barriers in locating NHP-related publications, such as publication biases and inconsistent indexing.[70,71,73] In addition, we were comprehensive in our inclusion of observational studies in addition to interventional studies, to ensure that safety was adequately addressed.[70,72,100] Two independent reviewers screened titles and abstracts, and subsequently the full text articles for inclusion and Cochrane risk of bias tools[122,123] were used to assess validity issues within the studies included in our review.

Systematic reviews of complementary medicine, including NHPs, pose many unique challenges.[70,71,73,144] There is some evidence that language-related publication bias exists in complementary medicine literature,[70] thus restricting to English only text was a potential limitation this review. It is likely that language-related publication bias results in more conservative results, as more often negative complementary medicine findings are present in English-language journals in comparison to non-English-language journals.[70] As anticipated, we identified a low number of randomized controlled trials, only one of which was blinded,[124] and the interventions, controls, and outcomes were heterogeneous and not appropriate for meta-analysis.[71,72] Generalizability of the results is affected by the variations in formulations, consistency, and quality of available NHPs,[39,40,65,70] and complexity and variability of anticancer regimens utilized in the papers and in practice.

The existence of theoretical NHP-anticancer medication interactions, and the lack of sufficient supportive clinical data, is apparent in the literature.[21,40,43,58] Proposed mechanisms for NHP-anticancer medication interactions exist from *in vitro* and animal studies, focusing primarily on the induction and inhibition of the CYP enzymes, impacts on drug transporters and efflux proteins, and various pharmacodynamic effects.[18,54,58,146] Drug interactions with monoclonal antibodies, including those between two drugs, have not yet been fully elucidated in the research and therefore are often absent from previous reviews on NHP-anticancer medication.[18,54,58,147,148] It is understood that monoclonal antibodies may have a lower susceptibility to drug-drug interactions due to differences in clearance pathways; they are commonly eliminated via catabolic processes compared to hepatic metabolism, renal excretion, and biliary excretion commonly used by other medications.[115] However, NHPs' effect on immunotherapy pharmacodynamics is still a primary interest for future research, particularly as some NHPs may have immunomodulatory effects themselves as observed in *in vitro* and animal models.[115,149] Similarly, other immune system modulators in this review have few known drug-drug interactions, which could be related to their primarily non-enzymatic metabolism, or in the case of Bacillus Calmette-Guerin, absence of systemic absorption.[150] While this may provide one potential explanation for the scarcity of interactions detected in our review, it is also clear that this topic has inadequate research focus, and this would be required to determine interaction mechanisms.

This systematic review highlights that NHPs have pharmacologic actions and cannot be ignored throughout patient care, particularly in patients taking concomitant immunotherapy. To further supplement conversations and monitoring of NHP use during anticancer treatments, additional clarity is required on the positive and negative impacts. There are opportunities to improve research in this area by: 1) consistent documentation of NHP use by healthcare providers, 2) enhanced researcher reporting of AEs in clinical studies, including assessment of causality, and 3) effective sharing and dissemination of NHP-drug interaction data. Despite the "bench-to-bed-side" approach to evaluation NHP-drug interactions suggested by Awortwe *et al.,*[142] the ability to adequately study clinically relevant NHP-anticancer drug interactions requires simultaneous research that starts at the bedside. Given NHP use is already common in current practice,[20,22] if NHP use is documented in clinical electronic health records or included in cancer registries, there is great potential to use this for more robust pharmacoepidemiologic research.[151] This approach has been adopted in Germany by Network Oncology, a registry that includes complementary therapies in addition to conventional medicine, and was utilized in all mistletoe cohort studies in this review.[127,128,131] Another important step forward is to improve reporting of AEs. The Consolidated Standards of Reporting Trials (CONSORT) group has recommendations for reporting harms in randomized trials.[152] Like the findings of this review, other papers have described sub-optimal AE reporting in oncology publications[72] and following the use of herbal medicine.[101] The CONSORT recommendations[152] need to be applied consistently to cancer research focused on both conventional and complementary medicine. In addition to improvements needed in randomized trials, enhanced pharmacovigilance and post-marketing AE reporting is required for NHP use in oncology, including consistent causality assessment with existing tools.[96,99,142] Lastly, this information needs to be shared; as evidence builds with enhanced NHP and AE reporting, an accessible database of NHP-anticancer medication interactions is required for knowledge translation.[116]

Conclusion

There are limited clinical data that exist on concurrent use of immunotherapy and vitamins C, D, E, mistletoe, ginseng, and probiotics. Current evidence can be considered as hypothesis-generating, largely involving phase I and II clinical trials, which are heterogeneous in patients, interventions, and outcomes, and case series or reports. Larger scale clinical studies

with two or more comparison groups are needed to further assist clinicians in shared decision making regarding the efficacy and safety of combining NHPs and anticancer immunotherapy.

CHAPTER 3: Natural health product use with antimicrotubule anticancer medications: A systematic review

Introduction

Cancer is common and affects people of all demographics.[102,103] It is suggested that about half of Canadians will develop cancer in their lifetime and new cases are expected to rise worldwide, predicted at over 27 million new cases in 2040.[102,103] The aging and growing population, compounded by multiple environmental and health-related risk factors contribute to the increasing human and economic burden of cancer.[102,103]

In comparison to healthy adults, individuals with cancer report higher natural health product (NHP) use.[17] Health Canada defines NHPs as vitamins, minerals, herbal medicines, homeopathic remedies, traditional medicines, probiotics, amino acids, and essential fatty acids.[76] Comparable definitions are used internationally, with the addition of enzymes,[153] aromatherapy,[154] and plants.[155] Use of complementary therapies, including NHPs, is increasing.[16,26] In women with breast cancer, complementary health approaches increased approximately 15% over a 7-year span.[16] Decision-making related to NHP use in patients with cancer is a complex and dynamic process, shaped by a number of sociodemographic, disease-related, and psychological factors.[20,23–26] Patients may choose NHPs to improve their general condition, provide symptom relief, and/or support conventional therapy.[23,30,34] Many patients become first time NHP users after the diagnosis of cancer which may be related to the sense of losing control;[24,156] making self-care choices can empower patients.[24] NHP use is often revisited throughout cancer therapy in relation to changes in health status or other treatment landmarks.[20,24,25]

The widespread use of NHPs in patients with cancer, including concurrent use with prescription medications, puts them at risk of NHP-drug interactions.[10,112,113] Antimicrotubule, or microtubule-targeting drugs, are anticancer medications that target part of the cytoskeleton that helps maintain the shape of a cell, and are involved in chromosome separation during cell replication.[105,107,157] These medications include taxanes (e.g., paclitaxel, docetaxel, cabazitaxel), vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinorelbine), eribulin, ixabepilone, and estramustine.[105,107,157–159] Paclitaxel and docetaxel are commonly used to treat a wide range of solid tumors such as breast, lung and ovarian cancers.[105,150,158] Prostate cancer may also be treated by taxanes, docetaxel or cabazitaxel.[105,150,158] Vinca alkaloids are used to treat several

types of cancers as well. [88,131,13] Vincristine is used in the treatment of leukemia, lymphoma, and other childhood cancers.[88,131,13] Vinblastine treats lymphoma and testicular cancer, and vinorelbine is used to treat breast and non-small cell lung cancer. [88,131,13] Eribulin and ixabepilone also have a role in the treatment of breast cancer. [88,131,13]

NHP interactions with antimicrotubule anticancer agents may have major clinical consequences by impacting treatment efficacy, toxicity, or quality of life.[40,42,146] NHP-drug interactions are viewed as positive or negative contingent on their clinical impact and influence on anticancer therapy.[39,40,116] Positive interactions could involve increasing the sensitivity of cancer cells to chemotherapy, improving survival, response rates or quality of life, and reducing chemotherapy-related side effects.[39,61,116] The mechanism by which interactions occur may be pharmacokinetic, impacting drug absorption, distribution, metabolism and/or elimination, or pharmacodynamic, resulting in synergistic, additive, or antagonistic drug effects.[39,54,55] Negative pharmacokinetic interactions are possible by altering plasma concentrations of chemotherapy; metabolic enzyme induction could result in treatment failure and enzyme inhibition could increase toxicity.[39,40,54,61,116] Anticancer medications are especially sensitive to these types of interactions due to their narrow therapeutic index.[40] Potentiating chemotherapy adverse events (AEs) or countering their anticancer action may also occur via pharmacodynamic NHP interactions.[39,54,61,116,146]

Concerns that exist regarding NHP-antimicrotubule drug interactions are primarily based on *in vitro* and animal studies.[39,40,43,61,112] Often these studies have focused on interactions involving the induction and inhibition of cytochrome P450 (CYP) enzymes, drug transporters, and efflux proteins.[39,40,43,54,56–58] Antagonistic effects on anticancer cytotoxicity and therapeutic efficacy have also been found.[39,61–63] NHP solubility, bioavailability, and product variation frequently make preclinical prediction of clinical outcomes challenging, and *in vitro* data often do not translate to what is seen in clinical research or practice.[39,40,43,61,116] With the surge in self-care and NHP use in patients with cancer,[16,26] it is necessary to determine whether these theoretical interactions are established in human studies. The purpose of this review is to summarize available clinical evidence on the efficacy and safety of concurrent use of NHP and antimicrotubule anticancer medications.

Methods

This systematic review was registered with PROSPERO: ID CRD42019124757. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[100,117] was followed.

Inclusion criteria

All English language human studies, both observational and interventional, were eligible for inclusion. Participants with any stage or type of cancer were included. There was no restriction on participant age, gender, or ethnicity.

Studies were included if concurrent use of antimicrotubule agents and NHPs was present. Anticancer regimens could include additional anticancer medications in other pharmacological classes as long as an antimicrotubule agent was also present; there was no restriction on dose, frequency or duration. A clinically relevant list of NHPs was developed for inclusion, containing garlic, ginseng, milk thistle, mistletoe, probiotics, turmeric, vitamin C, vitamin D, and vitamin E. The NHP selection process, previously published by our research team,[121] involved identification of Canadian population-based data using MEDLINE and EMBASE in addition to expert consensus. Frequency of use, interaction potential, and clinical relevance for cancer patients were used as selection criteria. Cannabis was not included in this systematic review because it regulated by Health Canada differently than NHPs.[2] NHPs of any dose, frequency, or duration were included; this involved patients taking more than one NHP, either multi-ingredient or multiple single-ingredient products.

We expected that many studies retrieved in our search would have heterogeneous outcomes; therefore, both efficacy and safety of combined therapy was reviewed.

Search methods

MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception. Terms related to the population, interventions, and outcomes of interest were used. The MEDLINE search strategy (Appendix 3.1) was translated using appropriate subject headings for each database. Handsearching was completed of reference lists, drug databases (Natural Medicines™, About Herbs™ and Lexicomp® Online™), clinicaltrials.gov, WHO International Clinical Trials Registry Platform, and the American Society of Clinical Oncology conference abstract library.

Data collection and analysis

Search results were exported to RefWorks™ and duplicates were removed. Reviewers included a doctoral student, of which this systematic review is part of their thesis (MB), the doctoral student's supervisor (SV), and two medical students with research experience in NHP interactions and AEs (RS and ES). Titles and abstracts were screened independently by two reviewers (MB and RS). Two reviewers (MB and ES) then independently examined full-text reports to determine eligibility for inclusion. Disagreements were discussed until consensus was reached, or if required, a third reviewer (SV) was consulted. Data extraction was completed by one reviewer (MB) using a pre-piloted spreadsheet. A second reviewer (ES) verified and examined for errors; any discrepancies were discussed.

Cochrane risk of bias assessment tools were used. The RoB 2 tool[122] was used for individually-randomized, parallel-group trials and the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool[123] for non-randomized studies. Risk of bias assessments were conducted by one reviewer (MB) and checked by a second (ES). Discrepancies were discussed until consensus was reached, or if required, a third reviewer (SV) was consulted.

Data were too heterogeneous to pool for meta-analysis. Measures of effect have been reported in summary tables as provided in original papers. Findings are also presented as a narrative synthesis.

Results

Search Results

A total of 561 records were identified after duplicates were removed. After title and abstract screening, 483 records were excluded, and an additional 39 articles were excluded after full-text articles were assessed for eligibility. Thirty-nine human studies met inclusion criteria, including 15 randomized trials and 17 non-randomized studies, most of which were phase I, phase II or pilot studies, and one of which was a conference abstract.[160] Seven case series and reports were also included. Details of each step is depicted in the PRISMA flow diagram (Figure 3.1).

Heterogenous study designs, methods and outcomes precluded a meta-analysis, but extracted data are presented in Tables 3.1, 3.2 and 3.3. Sample sizes of included studies ranged from 10 to 1225, with half recruiting less than 50 participants. Reported mean or median ages of adult patients ranged from 44 to 73 years of age. A single study focused on pediatric patients.[161]

Patients had a variety of diagnoses, including prostate, breast, lung, gynecological, and pancreatic cancers, leukemias and sarcomas; participants often had metastatic or advanced disease.

At least one paper was identified for each of the NHPs included in the search. They were taken either as monotherapy or in combination with other NHPs, either as individual or multi-ingredient products. Several phase I, II, and III clinical studies focused on vitamin D analogues, such as high-dose calcitriol. Vitamin D analogues and vitamin D containing more than 2,500 International Units (IU) per dosage form are not classified as NHPs by Health Canada,[162] but available evidence can provide important insight into concurrent vitamin D and anticancer medications, particularly regarding safety signals. NHPs were taken concurrently with antimicrotubule agents including paclitaxel, docetaxel, vincristine, vinorelbine, vindesine, and estramustine. Many studies included other anticancer and prescription medications that were taken concurrently as part of therapeutic regimens, as is common in clinical practice. Some studies included patients on any type of chemotherapy, and only select patients were taking antimicrotubule medications.[129,163–169]

Primary outcomes of the included studies were diverse. As many studies were aimed at drug development, outcomes on cancer benefits, such as survival, time to progression, and prostate-specific antigen (PSA) response were common. Others looked at NHPs' effects on chemotherapy and cancer-related side effects, including neuropathy, hepatotoxicity, immune function, fatigue, and quality of life. While a few articles focused on safety and tolerability as part of their primary outcome, AEs were often secondary outcomes, and three studies did not assess AEs at all.[170–172] Commonly, AEs in the included papers were graded by severity using versions of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[133]. How the AEs were ascertained was described in varying degrees, and often involved a brief description of whether they were clinician or patient reported. Some studies described the likelihood that an AE occurred from NHP or drug exposure, indicating that some form of causality assessment was performed.[160,161,164,166,168,173–183] While it appears that expert judgement was the most common approach taken to determine causality, there was no information on the exact processes used.[184] Only one case report described using the Roussel Uclaf Causality Assessment Method (RUCAM) / Council for International Organizations of

Medical Sciences (CIOMS) scale, an algorithmic approach, to determine a causal relationship.[177,184,185]

Risk of bias

For the randomized trials, they were judged to raise some concerns or have a high risk of bias (Figures 3.2, 3.3). Bias arising from the randomization process and due to deviations from intended interventions was of primary concern. The lack of allocation concealment and blinding were major contributors to these areas of bias. Three non-randomized studies were appropriate for assessment using the ROBINS-I tool[123] and were determined to be at serious or critical risk of bias (Figures 3.4, 3.5). Residual confounding and information biases were concerning in these papers. The remaining non-randomized studies lacked a comparison group. These articles, primarily phase I and II clinical trials, are important for drug discovery and approval, but they have inherent limitations and biases;[186] only a small number of subjects are studied, often with strict inclusion criteria and for a short duration.

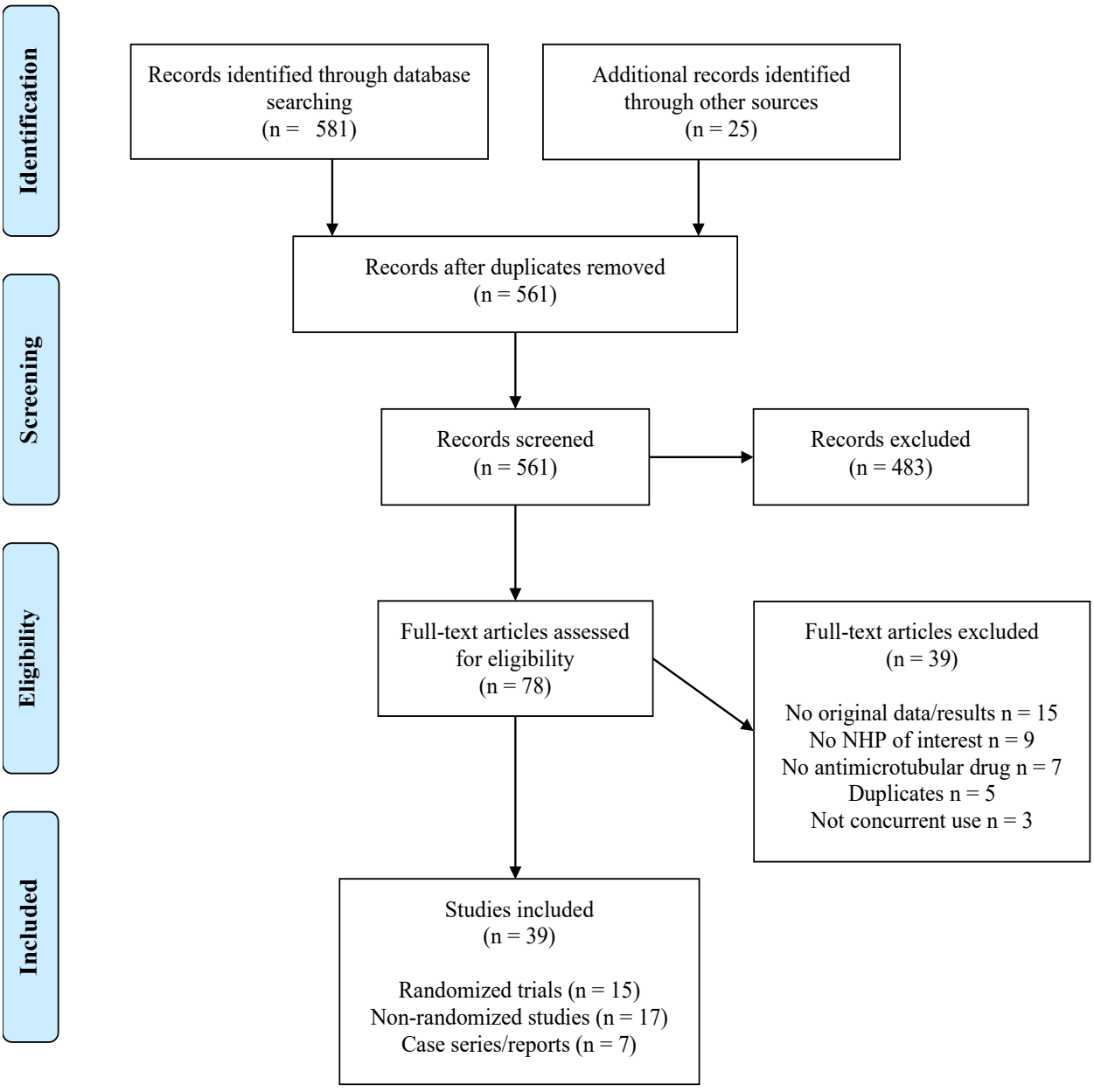


Figure 3.1 PRISMA Flow Diagram[117]

Table 3.1 Concurrent NHPs and Anticancer Antimicrotubule Drugs in Randomized Studies

Paper Name	NHP(s)	Antimicrotubule Drug(s)	Study Type	Setting	N	Participants	Intervention(s) & Comparison(s)	Primary Outcome(s)	Efficacy	Safety
Ma 2014[187]	vitamin C	paclitaxel	Phase I-IIa	USA	27	Females with stage III/IV ovarian cancer	Intervention: paclitaxel + carboplatin + high-dose IV ascorbate Control: paclitaxel + carboplatin Concurrent x 6 mo	Safety	Survival: NSS trend towards improvement Median time to progression: NSS ↑	Grade 3 or 4 AE: NSS different Grade 1 or 2 AE: statistically significant ↓ with ascorbate ↓ neurotoxicity, infection, bone marrow, hepatobiliary/ pancreatic, renal/ genitourinary, pulmonary, GI and dermatology toxicities
Beer 2006[188]	vitamin D analogue	docetaxel	Exploratory analysis of ASCENT	USA, Canada	250	Adult males with metastatic, androgen-independent prostate cancer Median age = Intervention: 68y; Control: 70y	Intervention: docetaxel weekly + high-dose oral calcitriol Control: docetaxel weekly + placebo Concurrent x 3 weeks of a 4 week cycle; continued until disease progression, unacceptable toxicity or patient request	≥ 50% Prostate-specific antigen (PSA) reduction within 6 months, confirmed ≥ 4 weeks later	Published elsewhere	Exploratory analysis of safety: ↓ incidence of serious AEs (27% vs. 41%, p = 0.05) ↓ incidence of serious AEs due to thrombosis (1.6% vs. 7.2%, p = 0.04) ↓ grade 3 and 4 thrombosis (1.6% vs. 8.0% p = 0.03) and any grade thrombosis (1.6% vs. 8.8%, p = 0.02)
Beer 2007[180] (ASCENT-1)	vitamin D analogue	docetaxel	Phase II	USA, Canada	250	Adult males with metastatic, androgen-independent prostate cancer Median age = Intervention: 68y; Control: 70y	Intervention: docetaxel weekly + high-dose oral calcitriol Control: docetaxel weekly + placebo Concurrent x 3 weeks of a 4 week cycle; continued until disease progression, unacceptable toxicity or patient request	≥ 50% PSA reduction within 6 months, confirmed ≥ 4 weeks later	PSA response NSS: 49% placebo vs. 58% calcitriol (p = 0.065) 2° endpoint: overall survival improved HR 0.67 (95% CI 0.45-0.97; p = 0.04)	Incidence of grade 3 or 4 AE: 70% placebo vs. 58% calcitriol (p = 0.065) Transient hypercalcemia: 8% placebo vs. 33% calcitriol (no grade 3 or 4) Creatinine elevation: 6% placebo vs. 7% calcitriol (no grade 3 or 4) 1 patient on calcitriol had a symptomatic renal calculi

Attia 2008[181]	vitamin D analogue	docetaxel	Phase II	USA	70	Adult males with metastatic, androgen-independent prostate cancer Median age = Intervention: 72y; Control: 70y	Intervention: docetaxel + oral doxercalciferol (DC) Control: docetaxel + placebo Concurrent x median 6, 28 day cycles	PSA response	No difference in the rate of PSA response: 46.7% DC vs. 39.4% placebo (p = 0.560)	Rate of grade ≥3 toxicity: 46% DC vs. 42% placebo (p = 0.785) Increased rates of grade 3 diarrhea in DC group (p=0.025) DC group increased 24h urinary calcium DC dose reduction needed for grade 2 (2 patients) and grade 4 (1 patient) hypercalcemia
Scher 2011[189] (ASCENT-2)	vitamin D analogue	docetaxel	Phase III	USA, Canada, Germany, Hungary, Czech Republic, Romania, Slovakia, Serbia	953	Adult males with metastatic, castration-resistant prostate cancer Mean age = Intervention: 70y; Control: 71y	Intervention: docetaxel weekly + high-dose oral calcitriol + dexamethasone Control: prednisone + docetaxel every 3 weeks + dexamethasone Concurrent x 30 wks or until unacceptable toxicity or disease progression	Overall survival (OS)	Trial stopped early for ↑ death: 10.1% control vs. 17.0% calcitriol Median OS: 20.2 mo control vs. 17.8 mo calcitriol (p = 0.002)	Similar rates of overall and serious AE Similar thromboembolic events Hypercalcemia: 0.6% control vs. 5.9% calcitriol (p <0.001) Calcitriol group: ↑ anemia (p = 0.003), nausea (p = 0.031), vomiting (p <0.001), anorexia (p <0.001), dyspnea (p = 0.003), epistaxis (p <0.001), grade ≥ 3 fatigue (p = 0.040)
Hines 2009[163]	vitamin D	taxanes	Phase III	North America	216	Premenopausal females with breast cancer (stages I to IIIB) Mean age = 44y	All participants: oral calcium + oral vitamin D Intervention: chemotherapy + risedronate Control: chemotherapy + placebo Concurrent therapy ≤1 year *Taxane-based chemotherapy 3% of patients; anthracycline +*	Change in lumbar spine bone mineral density (BMD) from baseline to 1 year	Lumbar spine BMD: NSS 4.3% loss risedronate vs. 5.4% loss placebo (p = 0.18)	Grade 4 AE: 9 patients on risedronate vs. 5 patients on placebo *Of note, both groups were on vitamin D*

							taxane-based 55% of patients			
Argyriou 2005[164]	vitamin E	paclitaxel	Pilot	Greece	40	Adults with nonmyeloid malignancies Mean age = 59y Males = 58%	Intervention: chemotherapy (13/20 patients on paclitaxel) + oral α-tocopherol Control: chemotherapy alone (12/20 patients on paclitaxel) Concurrent x 6 courses of chemotherapy + ≤ 3 months post	Incidence of neurotoxicity	Incidence of neurotoxicity: intervention 25% vs. control 73.3% (p = 0.019; ITT population p = 0.023) Neurotoxicity RR = 0.34 (95% CI 0.14- 0.84)	Similar AE rates between groups Most common: GI toxicity (nausea and vomiting), alopecia and myelosuppression (leukopenia, neutropenia or thrombocytopenia) No AEs attributed to vitamin E
Argyriou 2006[182]	vitamin E	paclitaxel	Phase II	Greece	37	Adults with solid or nonmyeloid malignancy Mean age = Intervention: 57y; Control: 57y Males = Intervention: 44%; Control: 32%	Intervention: paclitaxel + oral α-tocopherol Control: paclitaxel alone Concurrent x 6 courses of paclitaxel + ≤ 3 months post	Incidence of paclitaxel-induced peripheral neuropathy (PIPN)	Incidence of PIPN: intervention 18.7% vs. control 62.5% (p = 0.03; ITT population p= 0.032) Neurotoxicity RR = 0.3, (95% CI 0.1-0.9)	Similar AE rates between groups (p = 0.96) Most common: nausea, vomiting and alopecia No AEs attributed to vitamin E
Kottschade 2011[165]	vitamin E	taxanes	Phase III	USA	207	Adults with gross cancer removed + curative-intent chemotherapy Age >50y = 61% Males = 18%	Intervention: chemotherapy + oral α-tocopherol Control: chemotherapy + placebo *58% were on taxanes* Concurrent x chemotherapy duration + 1 mo	Incidence of grade 2+ sensory neuropathy (SN)	No difference in incidence of grade 2+ SN; vitamin E 34% vs. placebo 29% (p=0.43)	No difference in toxicity between groups Intervention group: two grade 3 AE (thrombocytopenia & hypersensitivity); deemed likely related to chemotherapy
Anoushirvani 2018[170]	vitamin E	paclitaxel	RCT	Iran	63	Adults with a solid tumour Mean age = omega 52y; vitamin E 51y; control 52y Males = omega 29%; vitamin E 24%; control 29%	Omega: oral omega-3 + paclitaxel Vitamin E: oral vitamin E + paclitaxel Control: placebo + paclitaxel NHP use started with paclitaxel & continued 3 mo after discontinuation	Presence of neuropathy	Without neuropathy: 71.4% omega vs. 66.7% vitamin E vs. 28.6 placebo; intervention groups vs. control p=0.0001; NS difference between	Not discussed

									intervention groups	
Chen 2009[190]	ginseng	vinorelbine	RCT	China	63	Adults with advanced non-small cell lung cancer Mean age = intervention 65y; control 58y Males = intervention 55%; control 50%	Intervention: vinorelbine + cisplatin + IV Shengmai Injection (red ginseng, lilyturf root, magnolia vine fruit) + oral Gujin Granule (milkvetch root, asiabell root, mulberry bark, lilyturf root, balloonflower root, magnolia vine fruit, licorice root) Control: vinorelbine + cisplatin Concurrent x median 2.94 cycles of chemotherapy	Response rate, 1 year survival rate, median survival time and median time to progression (TTP)	Response rate: 48.5% intervention vs. 32.2% control ($p = 0.0373$); Median survival time: 13 mo intervention vs. 9 mo control ($p = 0.014$); 1 year survival rate: NSS ($p = 0.4042$) Median TTP: NSS ($p = 0.4142$)	Grade 3/4 hematological toxicity: 33.3% intervention vs. 39.3% control ($p = 0.31$) No other severe AE found
Fang 2018[191]	ginseng	paclitaxel	RCT	China	150	Adults with advanced small cell lung cancer Mean age = Intervention 67y; Control 65y Males = Intervention 69%; Control 69%	Intervention: paclitaxel + cisplatin + oral herbal therapy (astragalus, ginseng, glossy privet fruit, radix glehniae, notoginseng powder, rhizoma atractylodis macrocephalae, radix ophiopogonis, safflower, semen coicis, ultrapure water) Control: paclitaxel + cisplatin Concurrent x 3 mo	Peripheral blood T cell and ratio test, serum inflammatory factors	CD_4^+ T cell, CD_8^+ T cell and CD_4^+/CD_8^+ T cell were statistically significantly ↑ in intervention group after 1 mo, 2 mo and 3 mo IL-2, IL-6 and TNF-α statistically significant ↑ in intervention group after 1 mo, 2 mo and 3 mo	↓ GI AE ($p = 0.031$), serious hair loss ($p = 0.004$) and liver/kidney toxicity ($p = 0.025$) in intervention group
Ladas 2010[161]	milk thistle	vincristine	Pilot	USA, Canada	50	Children 1-19 yo with acute lymphoblastic leukemia in maintenance phase chemotherapy with ≥ grade 2 hepatotoxicity Median age = Intervention 8y; Control 6y Males = 58%	Intervention: chemotherapy (vincristine, prednisone or dexamethasone, mercaptopurine or thioguanine, methotrexate) + oral milk thistle Control: chemotherapy + placebo	Hepatotoxicity (AST, ALT, total bilirubin) at day 28 and 56	NSS differences in mean levels of AST, ALT or total bilirubin at day 28 ↓ AST at day 56 ($p = 0.04$) with milk thistle NSS differences in mean reduction in AST	Similar grade 3 or 4 toxicities Side effects in milk thistle group included diarrhea, flatulence, irritability and stomach-ache Adherence: 68% milk thistle group vs. 96% placebo

							Concurrent therapy x 28 days		or ALT from baseline to day 28 ↑ mean reduction in AST from baseline to day 56 (p = 0.05)	
Piao 2004[166]	mistletoe	vinorelbine, vindesine	RCT	China	233	Adult patients with breast, ovarian and non-small cell lung cancer Median age = 51y Males = 22%	Intervention: chemotherapy + subcutaneous mistletoe Control: chemotherapy + phytopharmacon Lentinan *Those with non-small cell lung cancer (94 patients): vinorelbine + cisplatin or mitomycin + vindesine + cisplatin* Concurrent > 4 wks ≤ 12 wks	Quality of life, safety	Statistically significant improvement of quality of life with mistletoe	Total number of AE: 52 intervention vs. 90 control Serious number of AE: 5 intervention vs. 10 control 1 serious AE attributed to mistletoe: angioedema and urticaria Other AE attributed to mistletoe: fever (4 patients), rubor/pruritis at injection site (7 patients)
Marschalek 2017[167]	probiotic	paclitaxel, docetaxel	Pilot	Austria	27	Postmenopausal females with breast cancer Median age = Intervention 59y ; Control 62y	Intervention: chemotherapy + oral probiotic (*Lactobacillus: L. crispatus, L. rhamnosus, L. jensenii, L. gasseri*) Control: chemotherapy + placebo *Paclitaxel 27.3% of patients; epirubicin, cyclophosphamide followed by docetaxel 45.5% of patients* Concurrent x 2 wks	Vaginal microbiota (Nugent score)	Positive influence on vaginal microbiotia (towards normal) in 63% intervention vs. 36% control	No AEs reported by patients

NSS, not statistically significant; ITT, intention to treat

Table 3.2 Concurrent NHPs and Anticancer Antimicrotubule Drugs in Non-Randomized Studies

Paper Name	NHP(s)	Antimicrotubule Drug(s)	Study Type	Setting	N	Participants	Intervention(s) & Comparison(s)	Primary Outcome(s)	Efficacy	Safety
Hoffer 2015[126]	vitamin C, vitamin D	docetaxel, paclitaxel	Phase I-II	Canada	14	Adults with cancer on chemotherapy that offered <33% likelihood of clinical response Patient 1: 73y female with stage IV lung cancer Patient 2: 47y female with stage IIB cervical cancer Patient 3: 63y male with metastatic tonsil cancer Patient 4: 58y male with metastatic, small cell lung cancer	All: chemotherapy + IV ascorbic acid (AA) Patient 1: carboplatin + docetaxel + AA x 85 days Patient 2: paclitaxel + vitamin D + AA x 2 mo Patient 3: carboplatin + docetaxel + AA x 178 days Patient 4: paclitaxel + AA x 11 days	Safety, PK, clinical effectiveness	Patient 1: transient stable disease x 46 days Patient 2: transient stable disease x 84 days; ↑ energy level Patient 3: transient stable disease x 112 days; improved well-being Patient 4: disease progression	PK: plasma AA concentration-time profile was not affected by chemotherapy but there was short-term tissue retention of AA following chemotherapy Patient 1: no AE attributed to vitamin C Patient 2: chilliness, thirst, headache, rumbling feelings and shakiness during infusion (↓ by slowing infusion rate) Patent 3: no AE discussed Patient 4: no AE discussed
Beer 2001[192]	vitamin D analogue	docetaxel	Phase II pilot	USA	11	Adult males with androgen-independent prostate cancer Median age = 73y	docetaxel + dexamethasone + oral high-dose calcitriol Concurrent ≤8 weeks	50% PSA reduction x 2 consecutive evaluations ≥4 weeks apart	All patients: ↓ serum PSA 5 patients completed 8 weeks and all had ≥50% PSA reduction, 2 patients had confirmatory PSA & met PSA response criteria	Grade 1 AE: 2 episodes of allergic reaction, 1 episode of aminotransferase elevation Grade 2 AE: 1 patient each - neutropenia, leukopenia, diarrhea, fatigue Grade 3 AE: 1 patient catheter-related infection
Beer 2003[193]	vitamin D analogue	docetaxel	Phase II	USA	37	Adult males with metastatic, androgen-independent prostate cancer Median age = 73y	docetaxel + dexamethasone + oral high-dose calcitriol Concurrent x median 43 weeks	50% PSA reduction x 2 consecutive evaluations ≥4 weeks apart	PSA response: 81% (95% CI 68%-95%)	Grade ≥3 AE: 41% leukopenia, 24% neutropenia, 3% anemia Non-hematologic toxicity: 24% hyperglycemia, 11% peptic ulcer, 8% pneumonia (1 death) Hypercalcemia: 2 patients grade 1 + 1

										patient grade 2 (took ↑ dose in error); resolved without intervention No symptomatic urinary calculi Transient creatinine elevations (grade 1): 6 patients Similar AUC and half-life of docetaxel with and without calcitriol
Muindi 2002[183]	vitamin D analogue	paclitaxel	Phase I	USA	36	Adult patients with advanced solid tumors Median age = 64y Males = 72%	paclitaxel + pre-medications (dexamethasone, diphenhydramine, ranitidine or famotidine, prochlorperazine) + oral high-dose calcitriol Concurrent x 3-38 days	PK analysis, dose limiting toxicity	Substantial interpatient variation in peak serum calcitriol concentration, time to reach maximum concentration and area under the curve (AUC) Serum calcitriol AUC was not proportional to dose ($p = 0.0014$)	No dose-limiting hypercalcemia or toxicity observed
Blanke 2009[173]	vitamin D analogue	docetaxel	Phase II	North America	25	Adults with previously untreated metastatic or locally advanced pancreatic cancer Median age = 63y Male = 68%	docetaxel + dexamethasone + oral high-dose calcitriol Concurrent x median 2 cycles	Time-to-progression	Median time-to-progression: 3.6 mo (95% CI 1.9-5.6 mo) Overall survival: 5.6 mo (95% CI 4.1-9.8 mo)	Grade 3 AE: 52% of patients; hyperglycemia (13%) – attributed to dexamethasone; fatigue (9%) No significant hypercalcemia seen
Medioni 2014[174]	vitamin D analogue	docetaxel	Phase I	France	56	Adult males with naïve, metastatic, castrate-resistant prostate cancer Median age = 71y	docetaxel + prednisone + oral inecalcitol Concurrent ≤6 cycles	Dose-limiting toxicity (DLT)	PSA response: 85% had ≥30% PSA decline within 3 mo	DLT in 2 of 4 patients receiving 8,000 µg/day; maximum tolerated dose = 4,000µg daily Hypercalcemia: 3 patients experienced grades 2 and 3 at two highest doses; 31.5% reported at least 1 case of grade 1

										Higher than expected frequency of neutropenia Mean PTH levels ↓
Lacouture 2017[160]	vitamin D analogue	taxanes	Phase I (conference abstract)	USA	21	Adult females with breast, gynecologic cancers and sarcomas	taxane-based chemotherapy+ topical calcitriol Concurrent ≥3 mo	Maximum tolerated dose (MTD)	Inter-individual PK variability Clinical response observed at each dose level	Treatment-related AE (probably/possibly): mild-moderate scalp pain, ↑ vitamin D levels, passage of renal calculus MTD not detected No dose limiting toxicities or severe treatment-related AEs
Petrioli 2007[175]	vitamin D analogue	docetaxel	Phase II	Italy	26	Adult males with metastatic, hormone-refractory prostate cancer Median age = 68y	docetaxel + dexamethasone + ondansetron + oral high-dose calcitriol Concurrent ≤24 cycles	PSA response: ≥50% PSA reduction for ≥3 weeks, tolerability	PSA response: 27% of patients, median duration of 3.8 mo	Most frequent AE: neutropenia, anemia, thrombocytopenia, fatigue Grade 3 AE: neutropenia (2 patients), anemia (2 patients), thrombocytopenia (1 patient), vomiting (1 patient), fatigue (1 patient) Hypercalcemia: grade 1 = 16 patients, grade 2 = 1 patient Hypophosphatemia in most patients
Tiffany 2005[178]	vitamin D analogue	docetaxel, estramustine	Phase I-II	USA	24	Adult males with metastatic, androgen-independent prostate cancer Median age = 67y	Estramustine + docetaxel + dexamethasone + oral high-dose calcitriol + aspirin + warfarin Concurrent x median 5 cycles	Safety	PSA response (↓ ≥50%): 32% Measurable disease: 13% partial response, 20% stable disease Median time to progression: 17 wks Median overall survival: 54 wks	Most common grade 2, 3 or 4 AEs: hyperglycemia, hypophosphatemia, anemia, neutropenia, fatigue, nausea, constipation Hypercalcaemia: grade 1 - 12.5%, grade 2 - 4.2%

										Grade 1 ↑ creatinine: 42% 1 patient had dose-limiting toxicity: grade 3 ↑ liver function test
Siewinski 2004[171]	vitamin E	paclitaxel	Non-randomized	Poland	22	Adult females with stage III/IV ovarian cancer Age range = 23 - 64y	Intervention: vitamin E + cisplatin + paclitaxel Control: cisplatin + paclitaxel Concurrent x 3 wks	Serum cysteine peptidases, cysteine peptidase inhibitor activity	↓ cysteine peptidase activity with vitamin E ↑ cysteine peptidase inhibitor activity with vitamin E	Not discussed
Zirpoli 2017[172] (DELCaP)	vitamin C, vitamin D, vitamin E	paclitaxel	Secondary Analysis of Phase III RCT	USA	1225	Adult females with stage I-III breast cancer < 40y = 32%; 40 – 59y = 56%; > 60y = 12%	All participants: doxorubicin + cyclophosphamide + paclitaxel Interventions: supplement use (including vitamin C, D and E) Control: Non-users of selected supplements Concurrent use (duration not assessed)	Chemotherapy -induced peripheral neuropathy (CIPN)	Vitamin C, D and E were not statistically significantly associated with likelihood of grade 3/4 neuropathy	Not discussed
Cox 2006[194]	garlic	docetaxel	PK study	USA	10	Adult females with metastatic or incurable, localized, breast cancer Median age = 53y	docetaxel + dexamethasone + pre-medication (ondansetron, ranitidine, diphenhydramine) + oral garlic Concurrent x 12 days	Docetaxel PK	Not discussed	Mean clearance ($L/h/m^2$): ↓ from 30.8 on docetaxel alone to 23.7 on garlic x 4 days to 20.0 on garlic x 12 days; NSS (p = 0.17) Patients carrying a CYP3A5*1A allele may be more susceptible to ↓ clearance NSS: change in peak concentration (p = 0.79), area under the curve (p = 0.36), volume of distribution at steady state

										(p=0.84), half life (0.36)
Wang 2014[195]	ginseng	docetaxel	Cohort	China	78	Adults with breast cancer Median age = Arm 1 48y; Arm 2 52y; Arm 3 49y; Control 46y	All participants: docetaxel, epirubicin, cyclophosphamide Arm 1: cantharidin sodium injection Arm 2: IV Shenmai injection (ginsenosides + ophiopogonis) Arm 3: cantharidin sodium + IV Shenmai injection Control: chemotherapy only Concurrent ≥3 cycles of chemotherapy	Efficacy, toxicity	No disease progression in any arms	↓ incidence of nausea, vomiting, fatigue and bone marrow suppression compared to control
Yennuraj-alingam 2015[129]	ginseng	paclitaxel, docetaxel, vincristine	Phase II	USA	30	Adults with cancer-related fatigue (CRF) Median age = 58y Males = 50%	chemotherapy + oral Panax ginseng *1 patient each on: carboplatin + docetaxel + 5-fluorouracil, rituxamab + cyclophosphamide + etoposide + vincristine + prednisone, gemcitabine + docetaxel; 3 patients: carboplatin + paclitaxel* Concurrent therapy x 29 days	Safety, tolerability, effect on fatigue	Improvement in Functional Assessment of Chronic Illness Therapy: fatigue (p=0.0006), physical (p=0.002) Improvement in Edmonton Symptom Assessment Scale: pain (p=0.01), fatigue (p=0.0001), appetite (p=0.0097) Median improvement in Global Symptom Evaluation: 5 points	No grade ≥3 AE attributed to ginseng Most common grade ≤3 AE: pain & nausea - not attributed to ginseng
Eisenbraun 2011[168]	mistletoe	paclitaxel	Prospective single-arm	Germany	270	Adults with stage I-III breast cancer Mean age = 55y	chemotherapy + subcutaneous mistletoe paclitaxel was part of 7.4% of regimens Concurrent x mean 20 weeks	Health related quality of life	Quality of life function and symptom scales initially ↓ during chemotherapy, then remained stable and ↑ compared to baseline 4 weeks after chemotherapy (p<0.0001)	Local reactions at injection site: 87% of patients Expected side effects: lassitude (33%), headache (24.1%) and unspecified malaise (18.9%), 1 case of

										dizziness, 1 case of dermatitis Severe AE: necrotizing colitis - deemed unlikely related to mistletoe 40.4% indicated occasional limitations, 8.5% indicated confinements and 6.3% stopped mistletoe
Schad 2014[169]	mistletoe	paclitaxel	Retrospective single-arm	Germany	39	Adults with pancreatic cancer Median age = 61y Males = 56%	chemotherapy + intratumoral mistletoe *1 patient on paclitaxel + cisplatin*	Safety, efficacy	Median overall survival: 11 mo	Most common AE: ↑ body temperature ≤38°C AEs: fever >38°C, pain, nausea, generalized skin irritation, changes in blood count, circulatory problems and headaches During 223 applications, 6 procedure-related difficulties and 2 errors occurred
Mahammedi 2016[176]	turmeric	docetaxel	Phase II pilot	France	30	Adult males with metastatic, castration-resistant prostate cancer Median age = 69y	docetaxel + prednisone + oral curcumin Concurrent ≤6 cycles of chemotherapy	Objective response rate (ORR) of target lesions, ↓ PSA by ≥50%	ORR: 40% partial response, 60% stable disease PSA response: 59% of patients	Death: 1 cerebral hemorrhage, 1 respiratory desaturation Grade 3 or 4 AE: neutropenia (63%), ungual toxicity, anorexia No AEs were attributed to curcumin by investigators

Table 3.3 Concurrent NHPs and Anticancer Antimicrotubule Drugs in Case Series and Reports

Paper Name	NHP(s)	Antimicrotubule Drug(s)	Study Type	Setting	Participant(s)	Conventional drug(s) and NHP(s)	Clinical Course
Carr 2014[196]	vitamin C	paclitaxel	Case Report	New Zealand	45y female with invasive ductal carcinoma of the left breast (grade 2, ER+, PR+, HER2-)	Drug: paclitaxel once weekly NHP: vitamin C 50g IV twice weekly, 2 days either side of each chemotherapy session	↓ fatigue, pain, appetite loss, nausea/vomiting and insomnia + ↑ physical, emotional, cognitive, social functioning and global health status following 4 weeks of vitamin C administration No AE observed by the patient or physician
Madison 2002[197]	vitamin D	estramustine	Case Report (Letter to the Editor)	USA	88y male with prostate cancer and bone metastases	Drug: estramustine 2000 mg/m^2 IV weekly x 2 doses NHPs: calcium carbonate 3900 mg per day + calcitriol 0.5 µg per day, cholecalciferol 50,000 units per week after diagnosis of deficiency	After 2 doses of estramustine developed severe hypocalcemia (5.4 mg/dL; ionized 0.73 mmol/L), hypophosphatemia, low 24h urine calcium, severe vitamin D deficiency (8 ng/mL). Improvement after supplementation initiated (not resolved as patient died of respiratory failure) Vitamin D deficiency predisposed patient to severe hypocalcemia with IV estramustine AEs not discussed
Watthanasuntorn 2018[198]	vitamin D	docetaxel	Case Report	USA	71y male with metastatic prostate cancer	Drugs: docetaxel + amlodipine + gemfibrozil + furosemide + metoprolol + denosumab NHPs: initially taking vitamin D_2; IV then oral calcium + oral ergocalciferol 50,000 units weekly + calcitriol 25 µg daily	20 days after first dose of denosumab and cycle 3 of docetaxel developed severe hypocalcemia; serum vitamin D also low Stable calcium with calcium and additional vitamin D supplementation Vitamin D deficiency likely contributed to the development of hypocalcemia
Fink 2011[137]	vitamin D	docetaxel	Case Report	Germany	59y female with HER2-overexpressing breast cancer	Drugs: docetaxel 75mg/m^2 + carboplatin + trastuzumab 6mg/kg on day 1 of each cycle NHP: Vitamin D3 2000 units oral daily	Developed moderate stomatitis, dermatitis on the fingertips, marked dysgeusia and eventually a painful fissure on the right thumb, low serum vitamin D After vitamin D x 3 wks, the skin was nearly healed, no stomatitis and ↓ taste disorder, ↑ serum vitamin D
Koizumi 2005[199]	vitamin E, vitamin C	paclitaxel	Case Series	India	Patient 1: 56y female with recurrent breast cancer Patient 2: 31y female with uterine and cervical cancer Patient 3: 61y female with breast cancer	Patient 1: Drug: paclitaxel 3 times per month NHP: oral α-tocopherol monoglucoside 50mg after chemotherapy infusion x 6 mo Patient 2: Drugs: paclitaxel + carboplatin 3 times per month NHP: oral α-tocopherol monoglucoside 1.0g/kg after chemotherapy infusion x 8 mo Patient 3: Drug: paclitaxel NHP: oral ascorbic acid glucoside 200mg/kg 2 hours before chemotherapy x 11 doses	Patient 1: α-tocopherol monoglucoside reduced nausea, loss of appetite and insomnia Patient 2: no nausea, insomnia or lack of appetite on combination therapy Patient 3: ascorbic acid glucoside resolved nausea No AEs observed

Legnani 2008[200]	mistletoe	paclitaxel, vinorelbine	Case Series	Italy	Patient 1: 68y female with metastatic tubal cancer Patient 2: 65y female with metastatic breast cancer	Patient 1: Drugs: carboplatin + paclitaxel NHPs: Viscum album fermentatum Mali injection 20 days prior to start of the chemotherapy and x 6 cycles + Aurum metallicum praeparatum trit. D30 + Argentum metallicum praeparatum dil. D20 + Hypericum Auro cultum + Levico mineral water Patient 2: Drug: vinorelbine day 1, 8 then repeated in 21 days NHPs: Viscum album fermentatum Pini injection + Quarz trit. D6 + Argentum metallicum trit. D10	Patient 1: ↓ chemotherapy side effects (anemia, nausea, vomiting), improved quality of life; AE: local flushing Patient 2: stable disease, no infection; AE: skin flushing and warmth
Costa 2018[177]	turmeric, milk thistle, vitamin E, vitamin C	paclitaxel	Case Report	Portugal	67y male with lung cancer	Drugs: paclitaxel 165mg/m^2 + carboplatin 275mg/m^2 every 2 weeks + metformin + sitagliptin + alfuzosin + atorvastatin + budesonide + formoterol + tiotropium bromide NHPs: 4 days after first cycle of chemotherapy started turmeric 15g/day, milk thistle 300mg with 1.5% silymarin three times daily 30 minutes before meals, vitamin C 60mg, vitamin E 20mg, vitamin A 1.5mg, zinc sulfate 5.5mg, selenium 50µg; 6 days after first cycle of chemotherapy started Chlorella 520mg/day x 14 days, colostrum 650mg/day x 1 week; two weeks after the 2nd cycle of chemotherapy Chlorella restarted and stopped day before 3rd cycle	Patient developed asthenia, anorexia, jaundice and choluria, elevated liver function tests (acute toxic hepatitis); once all drugs and dietary supplements stopped, the patient had a rapid recovery Potential ↑ of plasma paclitaxel due to CYP2C8 and CYP3A4 inhibition by milk thistle and turmeric respectively and Chlorella contaminated with Oscillatoriales cyanobacteria and cyanotoxin Microcystin-LR may have contributed to hepatotoxicity

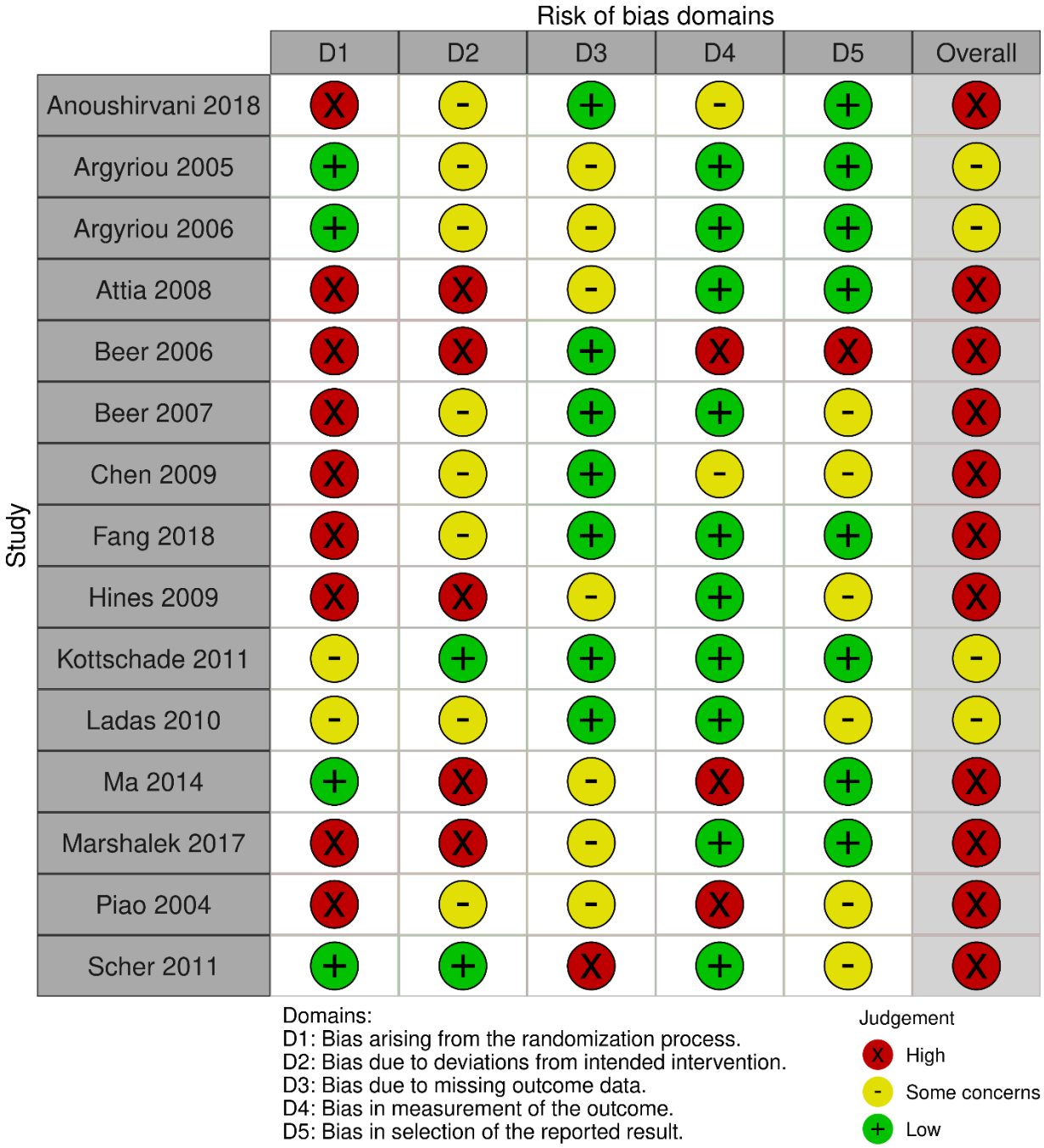


Figure 3.2 Risk of Bias Assessment of Individual Randomized Studies[141]

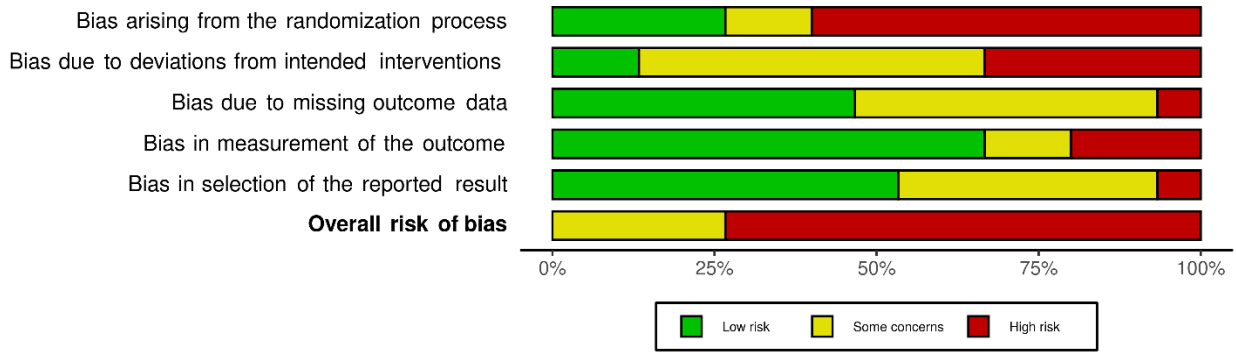


Figure 3.3 Overall Risk of Bias Assessment of Randomized Studies[141]

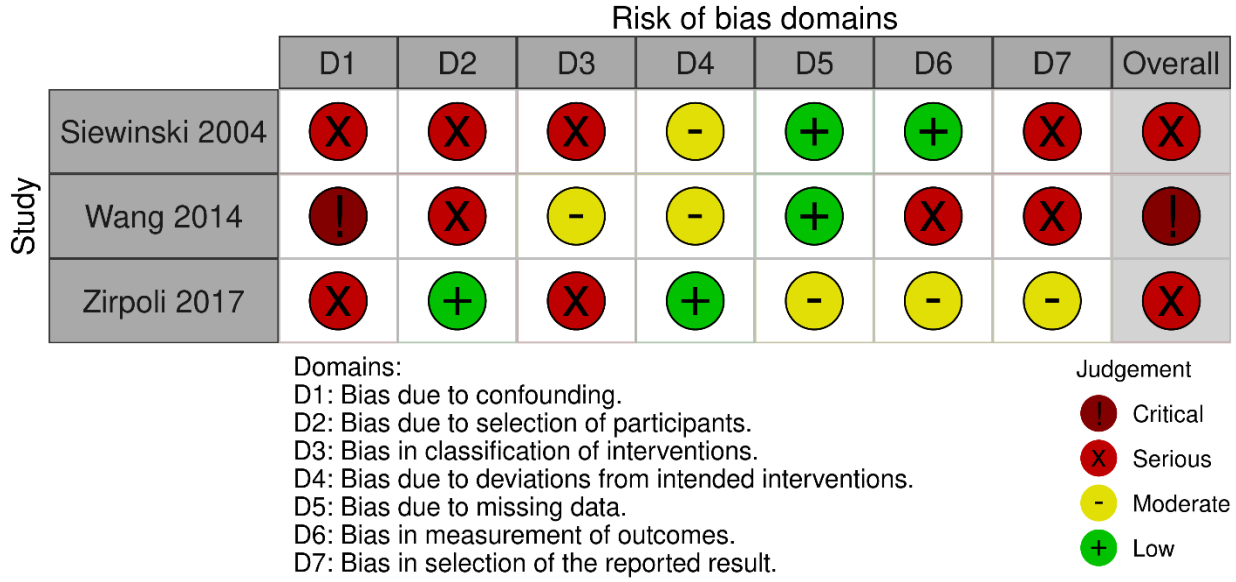


Figure 3.4 Risk of Bias Assessment of Individual Non-Randomized Studies[141]

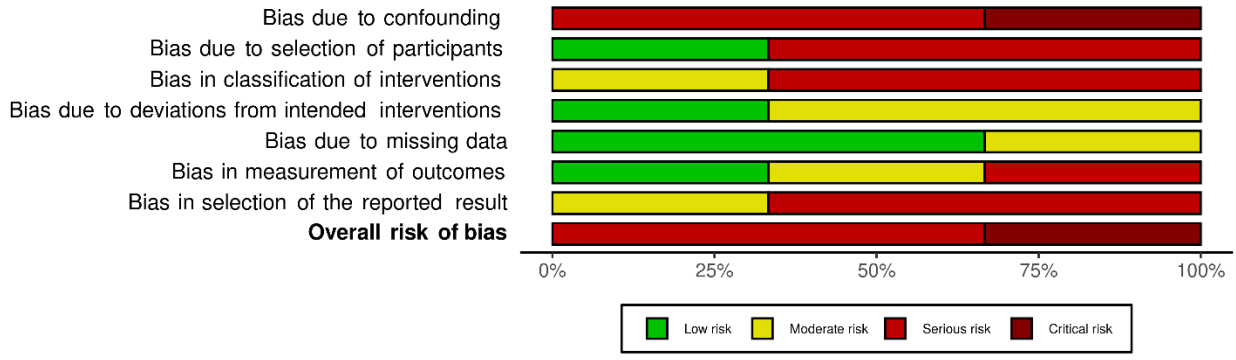


Figure 3.5 Overall Risk of Bias Assessment of Non-Randomized Studies[141]

Concurrent antimicrotubule anticancer medications and NHPs

Vitamin C

Vitamin C has been used along with taxanes, paclitaxel and docetaxel, in available clinical evidence. In a phase I/IIa randomized study of 27 women with advanced ovarian cancer, the combination of paclitaxel, carboplatin, and high-dose intravenous (IV) ascorbic acid resulted in a decrease in grade 1 and 2 AEs and similar rates of grade 3 and 4 AEs compared to chemotherapy alone.[187] There was a trend towards improved survival and increased time to progression, but as secondary outcomes they were underpowered and not statistically significant.[187] Hoffer *et al.* noted transient stable disease and improved energy in four patients on taxane-based chemotherapy and IV ascorbic acid, but no comparison group was used.[126] Similarly, two case reports, one using IV and one using oral vitamin C, noted a reduction in cancer and chemotherapy-related side effects such as fatigue, pain, appetite loss, nausea, vomiting, and insomnia, along with an improvement in functioning.[196,199] In terms of the pharmacokinetics of vitamin C, the concentration-time profile was not affected by chemotherapy, but there was short-term tissue retention following anticancer medications.[126] Side effects of chilliness, thirst, headache, and shakiness during vitamin C infusion occurred which were reduced by slowing the infusion rate.[126]

In the Diet, Exercise, Lifestyle, and Cancer Prognosis (DELCaP) study, an observational study adjunct to a phase III randomized trial, NHPs' effect on chemotherapy-induced peripheral neuropathy was evaluated in patients with breast cancer.[172] During the randomized trial, which assessed varying regimens of doxorubicin, cyclophosphamide, and paclitaxel, participants were surveyed on their supplement use before and during chemotherapy.[172] Although multivitamin use was marginally associated with reduced peripheral neuropathy, other NHP use, including vitamin C, D, and E were not.[172] Concerning is that in a companion paper published after this review's literature search, a non-statistically significant increase in cancer recurrence and death was found with the use of any antioxidant (vitamins A, C, and E, carotenoids, coenzyme Q10) before and during chemotherapy.[201] Vitamin C, D, E and acidophilus probiotic use on their own also trended towards harm, but the result was imprecise and insufficiently powered to detect a statistically significant difference.[201]

Vitamin D

Vitamin D, particularly vitamin D analogue use with antimicrotubule chemotherapy was identified most frequently in the literature. In phase I and II non-randomized studies lacking a comparison group, docetaxel was tested with oral vitamin D analogues, calcitriol or inecalcitol, and produced varying PSA responses in patients with advanced castrate-resistant prostate cancer.[174,175,178,192,193] One study also included estramustine.[178] These findings were further evaluated in randomized controlled trials. The phase II Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT)-1 trial found no statistically significant difference in PSA response ($p = 0.16$) between docetaxel with oral calcitriol 45µg, and docetaxel with placebo.[180] Similarly, no benefit was found with the addition of doxercalciferol to docetaxel on PSA response.[181] However, in the ASCENT-1 trial, there was an improvement observed in the secondary outcome of survival, which was then evaluated in the phase III trial, ASCENT-2.[180,189] This trial was stopped early for increased death in the calcitriol group (17.0%) compared to control (10.1%).[189] It is possible that differing docetaxel dosing between arms (weekly vs. every 3 weeks) may have had some effect on survival, however, the concern still remains regarding the effect of calcitriol on shorter patient survival.[189]

Vitamin D analogues were also used with taxanes in patients with advanced solid tumors, sarcomas, and pancreatic, breast, and gynecological cancers; however, clinical response is unclear in these phase I/II studies since no comparator was used.[160,173,183] In both oral and topical formulation, it appears that calcitriol has substantial interpatient variation in its pharmacokinetics; serum calcitriol area under the curve was also not proportional to dose.[160,183]

Patterns of AEs during concurrent use of taxanes and vitamin D analogues are present. The most frequently reported AEs attributed to vitamin D were hypercalcemia,[174,175,178,180,189,193] renal calculi,[160,180] and creatinine elevation.[178,180,193] Studies often prohibited the use of calcium supplements with vitamin D analogues[174,178,180,181,189,193] and some also restricted dietary calcium and encouraged increased oral hydration.[178,193] Other side effects reported included increased liver function tests, and diarrhea.[178,181] In one study that looked at topical calcitriol during taxane-based chemotherapy for the prevention of alopecia, mild to moderate scalp pain occurred in addition to increased serum vitamin D levels.[160] The preliminary decrease in incidence of serious AEs and thrombosis seen in the ASCENT-1 trial with calcitriol was not confirmed in ASCENT-2, as similar rates were seen in each group.[180,188,189]

Oral vitamin D supplementation was used in a phase III randomized controlled trial of premenopausal women with breast cancer; over half of patients were on taxane-based chemotherapy.[163] This trial was designed to assess the effect of risedronate on chemotherapy-induced bone loss.[163] While no vitamin D related AEs were noted, little else can be gleaned from this study as both arms had identical vitamin D supplementation.[163] Three case reports also involved vitamin D supplementation during chemotherapy.[137,197,198] Severe hypocalcaemia was experienced by patients with metastatic prostate cancer.[197,198] One patient experienced this after estramustine administration and the other following docetaxel and denosumab.[197,198] Both patients were found to have vitamin D deficiency and required calcium and vitamin D supplementation.[197,198] Another patient with breast cancer on docetaxel, carboplatin, and trastuzumab developed stomatitis, dermatitis, and dysgeusia.[137] Vitamin D was initiated for a low serum vitamin D level, and after 3 weeks symptoms were improved.[137]

Vitamin E

Oral vitamin E has been evaluated for its use in taxane-induced peripheral neuropathy in four randomized controlled trials.[164,165,170,182] In a pilot study and then a phase II trial, Argyriou and colleagues found that the addition of α-tocopherol to chemotherapy reduced the incidence of neurotoxicity;[164,182] a similar benefit was found by Anoushirvani *et al.*[170] In a phase III study with 207 patients on curative-intent chemotherapy, of which 58% were on taxanes, there was no statistically significant difference in incidence of grade 2 or higher sensory neuropathy.[165] The effect of vitamin E on neuropathy was also not significant in the DELCaP observational study.[172] Enzymatic changes from vitamin E supplementation were assessed in patients on paclitaxel and cisplatin for ovarian cancer.[171] Vitamin E supplementation had an effect on cysteine peptidases and their inhibitors, indicating a theoretical risk of NHP-anticancer drug interaction, which could be either beneficial or harmful.[171] AE rates between chemotherapy and vitamin E compared to chemotherapy alone or with placebo were similar.[164,165,182] Common side effects included nausea, vomiting, alopecia, and myelosuppression, but none were attributed to vitamin E.[164,165,182,199] A 2020 observational study did find that antioxidant use, including vitamin E, before and during paclitaxel-containing chemotherapy trended towards increased breast cancer recurrence and mortality.[201]

Ginseng

Ginseng, often in combination with other NHPs, has been used in patients with cancer on antimicrotubule medications. In three included studies, ginseng was one ingredient as part of Traditional Chinese Medicine, making extrapolation to other ginseng products very challenging.[190,191,195] In one randomized trial, Shengmai Injection, a combination of red ginseng, lilyturf root and magnolia vine fruit, was taken with vinorelbine and cisplatin.[190] Another Chinese medicine, Gujin Granule, was also taken.[190] Some benefit was seen in response rate and median survival, but there was no difference in 1 year survival rate or time to progression compared to anticancer agents alone.[190] Similar grade 3 or 4 toxicities were seen between groups.[190] A treatment of strengthening and consolidating body resistance, a Chinese medicine with multiple herbs including ginseng, was used in patients with advanced small-cell lung cancer on paclitaxel and cisplatin.[191] An increase in the surrogate endpoints of peripheral blood T-cells and serum inflammatory markers indicated a theoretical effect of this herbal remedy on immune function.[191] A decrease in gastrointestinal side effects, hair loss, liver toxicity, and kidney toxicity was also noted in comparison to chemotherapy alone.[191] Shenmai injection, ginsenosides, and ophiopogonis was used along with docetaxel, epirubicin and cyclophosphamide, and in one arm, with cantharidin sodium injection.[195] While a decline in chemotherapy-related AEs were noted with the addition of the Shenmai injection, this study was determined to have a critical risk of bias, and so these findings must be confirmed.[195] Improvement in fatigue, appetite and pain, without additional AEs, was found with the use of oral Panax ginseng and chemotherapy in patients with cancer-related fatigue.[129] However, only six of the included 30 participants were on antimicrotubule drugs.[129]

Mistletoe

There is weak evidence of improved quality of life with subcutaneous mistletoe when used with vinca alkaloids and paclitaxel.[166,168,200] However, AEs such as fever and injection site reactions were common.[166,168,200] Allergic reactions, including angioedema and urticaria, have also been reported with mistletoe treatment.[166] Similar AEs, such as increased body temperature, fever, skin irritation, and headaches have been seen with mistletoe given intratumorally.[169] Procedure-related difficulties and errors also occurred with this administration.[169] The discomfort of local reactions and frequent injections of mistletoe was highlighted by Eisenbraun *et al.* as

40% of participants indicated occasional limitations with administration, 9% indicated confinements, and 6% stopped therapy altogether.[168]

Other NHPs

Garlic, probiotics, milk thistle, and turmeric were less commonly reported in the literature with concurrent antimicrotubule agents. In a pharmacokinetic study, a short 12 day course of garlic decreased the mean clearance of docetaxel in patients with advanced breast cancer.[194] This was not statistically significant; however, it was suggested that CYP polymorphisms may play a role on the susceptibility to this effect.[194] Oral Lactobacillus probiotic use in postmenopausal women with breast cancer had a positive effect on vaginal microbiota without any reported AEs.[167] Patients included in this pilot study were on several chemotherapy regimens; 27% were on paclitaxel and 45% were on docetaxel.[167] Oral curcumin was used in a single arm study along with docetaxel and prednisone for advanced prostate cancer and no AEs were attributed to its use.[176] In pediatric patients with acute lymphoblastic leukemia and hepatotoxicity, the addition of milk thistle to a vincristine-containing chemotherapy regimen did not improve aspartate aminotransferase, alanine aminotransferase, or bilirubin at day 28, but significantly reduced aspartate aminotransferase levels at day 56.[161] In a case report of a male with lung cancer, milk thistle and large doses of turmeric may have contributed to the development of hepatoxicity with concurrent paclitaxel use.[177]

Discussion

Clinical evidence of concurrent NHP and antimicrotubule anticancer medications exists but is largely limited to phase I, phase II, or pilot studies, and case series or reports. Language-related publication bias may exist; however, excluding non-English-language articles was likely to provide more conservative results as negative findings for complementary approaches are more common in English-language journals.[70] Generally, findings were more positive in small phase I or II studies. This may be partly due to inherent limitations of early clinical trials; they often lack the statistical power to detect uncommon harms, have strict exclusion criteria, and because of their short study duration, there is also a risk to underestimate harms and overestimate benefits.[143] Additionally, many of these studies lacked a comparison group. In studies with increased power and rigor, a lack of efficacy and notable safety signals were identified. For example, while case reports and phase I/II studies highlighted a trend towards improved cancer

outcomes with vitamin C, and reduced chemotherapy side effects with vitamin C or E,[126,164,182,187,196,199] this was not confirmed in a phase III study or large analysis of a phase III randomized trial.[165,172,201] In fact, there was no benefit of vitamin C or E on chemotherapy-induced peripheral neuropathy, and a trend towards increased cancer recurrence and death with antioxidant use (vitamins A, C, and E, carotenoids, coenzyme Q10).[165,172,201] Similarly, vitamin D analogue use along with antimicrotubule agents showed some promise for prostate cancer in non-randomized phase I and II studies,[174,175,178,192] but this PSA response was not found to be significantly different when compared to chemotherapy alone in larger phase II randomized trials.[180,181] Most concerning is that a phase III trial was stopped early for increased death with the addition of high-dose calcitriol to docetaxel.[189]

NHPs' actions in the body can be similar to pharmaceutical products; some drugs have been developed from herbs and plants, including vinca alkaloids and taxanes themselves.[39,202] The active components of NHPs have important implications for drug discovery, but also on the potential for clinically significant interactions with medications.[39] Antioxidants, such as vitamin C and E, can reduce free radicals, and therefore reduce oxidative tissue damage.[39,61,203] This could work against chemotherapy drugs that generate free radicals as part of their mechanism of action including anthracyclines, platinum analogs, alkylating agents, and anticancer antibiotics.[203] This pharmacodynamic interaction could lead to treatment failure and provides a potential explanation for the findings of increased cancer recurrence and lower survival by Ambrosone *et al.*[39,61,201,203] It is also possible that the potential NHP-drug interaction is between antioxidants and doxorubicin and/or cyclophosphamide versus paclitaxel, given these agents' differing cytotoxic mechanisms.[39,61,201,203] A trend towards worsened disease-free survival was similarly found in breast cancer patients taking a combination of three to six of the antioxidants high-dose beta-carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc in addition to chemotherapy; the types of chemotherapy used were not reported.[204] Vitamin D, in the form of calcitriol, also showed lower survival when taken with docetaxel in ASCENT-2.[189] The difficulty in interpreting this result is that differing dosing of docetaxel were used in each arm: docetaxel weekly in the intervention, and every 3 weeks along with twice daily prednisone in the control group.[189] During the time between the phase II ASCENT-1 and phase III ASCENT-2 trials, docetaxel every 3 weeks was established as the new standard of care for advanced prostate cancer. Despite this, ASCENT-2 progressed with the calcitriol and docetaxel weekly regimen as

studied in ASCENT-1.[189] Therefore, the impact that calcitriol had on the increased risk of death remains unclear. Vitamin D has also been shown to significantly reduce atorvastatin and its active metabolites, indicating that it may induce CYP3A4 enzymes.[57] As docetaxel is primarily metabolized by CYP3A4, there is a potential for a pharmacokinetic interaction with vitamin D.[150] A pharmacokinetic interaction may have also occurred between milk thistle, turmeric and paclitaxel.[177] Acute toxic hepatitis experienced by a 67-year-old male with lung cancer was initially attributed to paclitaxel.[177] However due to greater than expected severity of the AE, it was thought that inhibition of CYP2C8 and CYP3A4 by milk thistle and turmeric, and therefore, increase in plasma concentration of paclitaxel, may have contributed.[177,205] The effect of milk thistle was less clear, given its potential hepatoprotective activity,[177,206] however the turmeric was assessed as probably related to the AE.[177] Complicating this interaction was that the patient was also found to be taking a chlorella supplement that was contaminated with cyanobacteria and cyanotoxin, which was also deemed to have a probable relationship with the hepatotoxicity experienced.[177]

Evidence on NHP use presents unique challenges with regards to external validity. Due to inconsistency in quality control, NHPs may be contaminated and adulterated with dust, pollens, insects, rodents, parasites, microbes, fungi, mold, toxins, pesticides, toxic heavy metals, or prescription drugs.[65] Likewise, a lack of standardization in growing, handling and/or manufacturing can lead to significant variation in the composition of the products, varying by batch and manufacturer.[39,40,65,69,70,207] It is crucial that generalization and extrapolation from clinical evidence to commercially available NHPs is done with caution, and that the complexity and differences in NHP formulations are considered. Although recommendations on reporting of herbal interventions in randomized controlled trials do exist,[208,209] challenges still exist in the application of these studies due to discrepancies between the product being studied, and the product being used in practice. Polypharmacy is also common in patients with cancer, particularly at advanced stages.[45,46] This is related to anticancer regimens, which generally involve multiple agents being co-administered, as well as other prescription medications managing comorbidities.[45,46] Chronic medications used for comorbidities were often not mentioned in the studies of this review, but frequently participants were on more than one anticancer medication and additional prescription medications to prevent and manage chemotherapy-related side effects. Further complicating this is that multiple NHPs or NHPs with

multiple ingredients may be used. In the four included studies on ginseng, each intervention involved a vastly different formulation of ginseng.[129,190,191,195] Three of these studies combined ginseng with at least one additional NHP ingredient.[190,191,195] Generalization of these findings to other forms of ginseng becomes problematic and it also presents an obstacle for causality assessment.

Numerous methods and tools exist for the assessment of causality of AEs, some specifically developed for drug interactions and NHPs.[47,94,96,184,210–213] Causality assessment is recognized as essential when reporting and reviewing harms,[100,152] but the information provided on the ascertainment of AEs and causality assessment was very limited in the papers of this systematic review. Much of the AE data in this review are from secondary outcomes, single-arm studies, and case reports, which makes determining whether causal relationship exists difficult, particularly with the aforementioned polypharmacy and inconsistencies of quality, content, and formulation of NHPs. Despite this, some studies reported on the likelihood that an AE was related to a NHP, anticancer medication or other prescription medication.[160,161,178–183,164,166,168,173–177] It appeared that this was primarily based on clinician judgement, but no information was provided on the specific method used. Where this becomes most concerning is when AEs are not attributed to the NHP without clear explanation on why or how this was determined,[160,164,168,176] or when AEs are not discussed at all.[170–172,197,201] This indicates that there is a risk that harms may be underestimated.

Nonetheless, in both efficacy and safety evaluations of available evidence, the addition of NHPs to anticancer antimicrotubule medications is not benign. Beyond potential harmful implications on cancer recurrence and survival, some notable AEs occurred. Negative effects of administration occurred, such as IV infusion reactions with vitamin C,[126] local injection site reactions and discomfort, as well as procedure-related difficulties with mistletoe.[166,168,169,200] Increased body temperature, fever and headaches were also associated with mistletoe use.[166,168,169,200] Hypercalcemia, renal calculi, creatinine elevation, increased liver function tests, and diarrhea were attributed to vitamin D use during anticancer therapy.[160,174,175,178,180,181,189,193] It is important for clinicians to be aware of potential benefits and risks of combined therapy, as lack of knowledge is a threat to effective communication between health care providers and patients.[9,12,207] Non-judgmental dialogue about NHPs between provider and patient is critical to maximize benefit and avoid potential AEs.[9,11,28,61] Evidence suggests that patients want to

collaborate with their conventional healthcare providers on NHP decision-making, even if this involves clinicians admitting that uncertainty exists.[9,214]

This review has summarized existing evidence suggesting there are clinical consequences of taking certain NHPs along with taxanes, vinca alkaloids, or estramustine. Difficulties in current evidence do exist with lack of consistent clinical efficacy, heterogeneity, methodological limitations, and low number of study participants, as well as challenges with application to clinical practice. With this evidence alone, we are unable to provide specific clinical recommendations on the use of NHPs concurrently with microtubule-targeting anticancer medications, but it provides groundwork for future investigation. A rigorous and standardized approach to research is necessary to improve generalizability for front-line clinicians. The Consolidated Standards of Reporting Trials (CONSORT) statement has extensions that provide recommendations for improved reporting of randomized trials of herbal medicine interventions and harms data.[152,208,209] Clear descriptions of NHP interventions including characteristics, dosage, regimen, and quality testing should be reported, as well as details on the ascertainment and causality assessment of harms outcomes.[96,152,208,209] Consideration should also be given to the types of NHP formulations used in clinical research. Although individually isolated active compounds makes characterizing biological effects, aggregating data, and assessing causality simpler, it does not necessarily aid in our understanding of NHP formulations that are available over-the-counter.[39,61] Many NHPs have a long history of use as traditional medicines, despite the paucity of clinical studies.[212] Given that the use of NHPs is already high, post-marketing pharmacovigilance and pharmacoepidemiologic research can provide critical real-world evidence.[143,186,212,215] Structured patient interviews regarding NHP use have been developed and implemented.[47,50,94,95] This active surveillance method uses a systematic approach to ascertain NHP use and related AEs to complement ongoing passive pharmacovigilance processes.[47,50,83,85,94,95,99] Several patient care settings have incorporated this method as part of their clinical practice.[47,50,94,95] If documentation of NHP usage improves with clinician-initiated communication, real-world data sources, such as electronic medical records and population-based databases or registries can be utilized.[186,215,216] Approaches to dialogue about NHPs also include establishing trust, exploring patients' attitudes, values and lived experiences, discussing the evidence, and collaborating with patients to form a treatment and monitoring plan.[28,61,217]. Given the complexity of NHPs and the evidence about them, an individualized approach to care

is necessary. This approach could involve pharmacists; as the most accessible healthcare professional in Canada and as medication management experts,[218] pharmacists are well-positioned to play a role in the discussion and monitoring of patients' NHP use alongside other members of the healthcare team.

Conclusion

This systematic review has summarized clinical outcomes on taking NHPs concurrently with antimicrotubule anticancer medications. While human studies on this topic are primarily limited to phase I/II and pilot studies with methodological weaknesses, and case series/reports, safety concerns on the use of vitamins C, D, and E, milk thistle, and turmeric have been identified. Current literature is insufficient to provide strong direction on efficacy of combined use; however, it is important that clinicians are aware of the existing evidence and its limitations. To improve this body of evidence, consistent and enhanced reporting on NHP interventions and harms data in clinical studies is required, in addition to ongoing efforts in post-marketing surveillance. Clinician-initiated discussion, monitoring, and documentation of NHP use is required to supplement real-world data sources and provide an individualized, patient-centered approach to cancer care.

CHAPTER 4: Study of natural health product adverse reactions (SONAR) in adult patients with cancer: a cross-sectional study

Introduction

Natural health products (NHPs), named dietary supplements and ingredients in the US,[219] are defined by Health Canada as vitamins, minerals, herbal medicines, homeopathic remedies, traditional medicines, probiotics, amino acids and essential fatty acids.[76] Self-treatment with NHPs, and visits to complementary health practitioners by patients with cancer has significantly increased over the years, and it appears that patients with cancer report higher NHP use as compared to healthy adults.[16,17] Patients may choose to use NHPs to improve their quality of life, ability to cope with their cancer diagnosis, and/or to support their conventional anticancer treatment by improving effectiveness or reducing side effects.[23,30,34] While the use of NHPs during cancer treatment is often perceived by patients as positive,[23,34,156] little is known about the potential harms of concurrent use.

Anticancer medications generally have a narrow therapeutic index, with small differences between therapeutic and toxic doses; slight changes in plasma concentrations can result in adverse events (AEs) or treatment failure.[40–42] Polypharmacy involving prescribed medications for cancer and other chronic diseases in addition to NHP use, further adds to the complexity and interaction potential.[45,46] NHPs may modulate the activity of drug-metabolizing enzymes and drug transporters or influence the pharmacodynamic effects of medications.[18,40,43,54,58] Therefore, patients with cancer are potentially vulnerable to clinically important NHP-drug interactions and serious AEs.[10,27,112,113,220] However, these theoretical effects have not been well-documented clinically, and further investigation is needed.[39,54,221]

Early clinical trials for approval of medications and NHPs are often limited by their highly controlled environment, small number of highly selected patients, and short trial duration.[222,223] Pre-marketing investigation of NHPs may be further limited, sometimes relying only on pilot studies and textbook references for evidence of efficacy and safety.[75–78] A lack of standardization in the manufacturing and quality control of NHPs also exists, which increases the risk of contamination, adulteration, or variation in the composition of the product.[39,40,65] Given their prevalence of use, monitoring NHPs after their approval and sale is necessary to extend safety monitoring and improve our understanding of NHP adverse events and interactions.[75]

A common method of post-marketing surveillance is passive surveillance, also known as spontaneous reporting, that relies on unsolicited reports of AEs by healthcare professionals and more recently, patients themselves.[77,83–85] Spontaneous reporting is often limited by underreporting, poor quality reports, and the inability to quantify the risks.[87,90–92,224] Unfortunately, passive surveillance of NHP AEs is further obstructed by the infrequent disclosure of NHP use or NHP-related AEs to healthcare providers.[89,224,225] Nondisclosure is common due to lack of inquiry by healthcare professionals, patients' fear of healthcare professionals' disapproval, and the perception that NHPs are inherently safe and irrelevant to their conventional care.[11,12,225]

Active surveillance methods aim to overcome the barriers of spontaneous reporting by soliciting AEs in a pre-organized, systematic process.[83,85,99] To date, our team has developed an approach to the active surveillance of NHPs, which has been used in community pharmacies and ambulatory mental health and HIV clinics.[47–50,94,95] More data are urgently needed on other high-risk populations, including patients with cancer. We hypothesize that adults with cancer who take NHPs concurrently with prescription medications are at a higher risk of experiencing AEs compared to those taking prescription medications alone. The purpose of this cross-sectional study was to identify and characterize NHP use, and associated AEs experienced by adult medical oncology patients.

Methods

Ethics approval was obtained from the Health Research Ethics Board at the University of Alberta (Pro00025387) and University of Calgary (HREBA.CC-16-0245). Site-specific operational approval was also obtained.

Active surveillance

Active surveillance methods were conducted as previously published by our research team, with minor modifications.[47–50,94,95] Using a one-page screening form (Appendix 4.1), adults at outpatient oncology clinics were screened to investigate the use of prescription medications and NHPs. The screening form prompted patients for their gender, and although this was self-defined, it likely captured patients' biological sex. Patients were asked about any undesirable effects, and what actions, if any, were taken to treat them. Clinic staff received initial training on the screening process. A site principal investigator was identified at each cancer centre to act as a

primary contact for those centres. Ongoing follow-up and support occurred with the site principal investigators via phone and email. Screening questions included:

(1) In the last month, have you taken any anticancer or prescription medications? *If Yes, list the medications and for how long they have been taken. If unsure, please ask your healthcare team.*

(2) In the last month, have you taken any natural health products (NHPs) e.g. vitamins, minerals, herbals, homeopathic remedies, traditional Chinese medicines, probiotics etc.? *If Yes, list the NHP and for how long they have been taken. Please try to be as specific as possible.*

(3) In the last month, have you experienced any undesirable effects? *If Yes, describe these effects.*

(4) What did you do about it? A) Nothing/treated it myself; B) Phoned for information; C) Saw doctor about it; D) Doctor treated it; E) I was hospitalized because of it

Clinicians at participating clinics were asked to review the completed screening forms and describe whether the patient-reported AE(s) were serious and unexpected or caused a delay or change in treatment. They were also asked to report any additional serious and unexpected AEs they observed.

If the patient reported NHP use in question 2 and indicated 4D or 4E, or the healthcare provider indicated that a serious and unexpected AE occurred, an information package outlining the study and a consent form for a follow-up telephone interview was provided to the patient. If consent was obtained, a telephone interview was conducted by the study pharmacist. This interview gathered details relating to the AE (duration, treatment, seriousness), NHPs and prescription drugs used (name, strength, dose, duration of use, indication), demographic information, and medical history, including both social and family history. This information was utilized for causality assessment.

Causality assessment

What separates an AE from a suspected or actual adverse reaction (AR) is a causal relationship between product and the AE.[179,226] Currently, there is no universally accepted gold standard for causality assessment of AEs.[212,213] A stepwise approach was used as previously executed by our research team utilizing algorithmic assessment tools and expert judement.[47,94,96] Data collected from the telephone interviews was summarized and submitted to two adjudicators,

clinical NHP experts, that independently assessed each case. Three tools, slightly modified for specific analysis of NHP-associated AE, were used: 1) World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) system[227] 2) Naranjo Causality Scale[228] 3) Horn Drug Interaction Probability Scale (DIPS)[229]. The WHO-UMC system[227] was completed for each case and the Naranjo Causality Scale[228] was used if there was at least a possible NHP-related AE, and the Horn DIPS[229] if there was at least a possible NHP-drug or NHP-NHP interaction. Disagreements between experts were discussed until consensus and final decision was reached, or another expert was consulted. Laboratory analysis, if deemed necessary by adjudicators (e.g., high likelihood of contamination or adulteration, probable or possible causality), was available to support causality interpretation.

Participants

Consecutive adult patients attending either new or follow-up appointments at participating outpatient oncology clinics were screened as part of the clinic's routine patient assessment. Informed consent was the only inclusion criteria for initial screening. There was no restriction on stage or type of cancer. Inclusion criteria for detailed patient follow-up interview included: 1) the use of NHPs in the last month 2) an undesirable effect was experienced in the last month and was deemed serious by the patient (medically treated or required hospitalization) and/or serious and unexpected by a healthcare provider 3) written consent from the patient.

Interventions

A patient was classified as using a prescription medication in the last month if they answered "yes" to question 1 and/or they listed at least one medication that had a drug identification number. A patient was classified as using a NHP in the last month if they "yes" to question 2 and/or they listed at least one NHP as defined by Health Canada.[76]

Outcomes

Using active surveillance, the following outcomes were assessed: 1) prevalence of product/drug use in adult oncology patients including prescription medication use alone, NHP use alone and concurrent NHP and prescription drug use; 2) description of common NHPs used by patients with cancer; 3) prevalence of AEs in patients using NHPs alone, prescription drugs alone and concurrent NHP and prescription drug use; 4) comparison of prevalence of AEs

between patient groups 1, 2, and 3; 5) description of the types of AEs reported in patient groups 1, 2, and 3. Causality assessment was used to describe potential mechanisms and causality of serious AEs occurring while patients with cancer were taking at least one NHP.

A patient was considered as having an AE if they answered "yes" to question 3 and/or the patient or healthcare provider listed at least one undesirable effect. AEs were coded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[230] and System Organ Class of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy.[231] The patient was considered to have had a serious AE if the patient reported that the AE resulted in medical treatment or hospitalization, and/or if a healthcare provider deemed an AE to be serious and unexpected, or cause a delay or change in treatment. Healthcare providers were prompted to deem a grade 3 or higher AE as defined by the NCI CTCAE as serious.[230] The NCI CTCAE[230] is a severity scale, and while seriousness and severity are not synonymous,[232] this scale was used due to its familiarity with oncologists. NCI CTCAE grade $\geq$3 describes AEs that involve hospitalization, prolongation of hospitalization, life-threatening consequences, or death, which mimic the definition of a serious AE as defined by Health Canada.[233]

Sample size

With a sample size of 821 patients, assuming an AE prevalence of 20% for patients taking prescription medications alone and an α of 0.05, we calculated 80% power to detect a minimum clinically significant difference in mean AE prevalence of 5% (effect size: 0.125) in those taking prescription medications and NHPs concurrently. The sample size was inflated by 10% to 904 patients to account for potential losses to follow-up and missing data. The Chi-square test was used to calculate the sample size using G*Power 3.1.[234] Similar work in patients attending Canadian community pharmacies identified an AE prevalence on concurrent prescription medications and NHPs of approximately 7%.[47,94,235] Based on pilot data we assumed that AE prevalence would be higher in patients with cancer.

Data management

Study data were managed using REDCap electronic data capture tools[236] hosted and supported by the Women and Children's Health Research Institute at the University of Alberta.

Data analysis

Patient demographic information, NHP use, and prescription medication use was examined with descriptive statistics, using frequencies and percentages. AE prevalence was calculated and compared between patients who used prescription medications alone, NHPs alone, and both concurrently using the Chi-square test and, when small frequencies were present, the Fisher exact test. Multivariate logistic regression was used to calculate the odds ratio and associated 95% confidence interval (CI) for AE prevalence comparing patients using NHPs and prescription medications concurrently to prescription drug use alone while controlling for cancer centre. STATA Version 15.1[237] was used for analyses.

Results

A total of 996 adult oncology patients were screened between 2012 and 2017. Patients were screened at cancer centres in Alberta and Ontario. Patients screened at participating clinics were primarily female (70.3%) which did not differ significantly between patients using prescription medications alone, NHPs alone, both concurrently and neither. The most common cancer diagnoses were breast (29.2%), colorectal (17.6%), and lung cancer (15.3%) (Table 4.1).

Natural health product use

Of the 996 patients, 274 (27.5%) were taking prescription medications alone, 123 (12.4%) were taking NHPs alone, 498 (50.0%) were taking prescription medications and NHPs concurrently, and 101 (10.1%) were taking neither prescriptions nor NHPs in the last month (Figure 4.1). The most frequently reported NHPs that were taken by medical oncology patients are listed in Table 4.2, with vitamin D and multivitamins being most common. The median number of NHPs that patients were taking concurrently was two (interquartile range (IQR) 1-4); the maximum was 20 concurrent NHPs, which was the case for one participant.

Adverse events

The most common AEs reported were gastrointestinal disorders, general disorders and administration site conditions (e.g., chills, fatigue, fever, generalized pain, injection site reactions), nervous system disorders (e.g., headache, paresthesia, peripheral neuropathy), and skin disorders (e.g., alopecia, nail changes, rash). Table 4.3 lists the frequencies of AEs, of any severity, classified by MedDRA System Organ Class and stratified by product and drug use. The

median number of AEs reported by each patient was two for both those taking NHPs and prescription drugs concurrently (IQR 1-3; range 1-7) and those taking prescription drugs only (IQR 1-2.5; range 1-7). Patient sex was not significantly associated with AE prevalence.

A significantly higher ($p < 0.0001$) number of patients taking prescriptions alone reported an AE in the last month (N = 121; 44.2%) compared to those taking NHPs alone (N = 14; 11.4%). Of the 121 patients on prescription medications alone reporting at least one AE, 83 were taking at least one anticancer medication, 21 did not report taking an anticancer medication, and 17 did not list their medications. AEs were experienced by 39.6% (N = 197) of patients taking prescription drugs and NHPs concurrently. Of these 197 patients, 146 were taking at least one anticancer medication, 44 did not report taking an anticancer medication, and seven did not list their medications. The prevalence of AEs in patients taking prescription drugs and NHPs concurrently was not significantly different from those taking prescriptions alone (OR 0.85, 95% CI 0.62–1.16; $p = 0.298$). These results remained consistent when analysis was conducted with only participants reporting the use of at least one anticancer medication.

Seventy-six patients that were taking at least one prescription drug or NHP were excluded from the analysis of serious AEs due to missing information. Serious AEs were reported in 2.5% of patients on NHPs alone (N = 3), 8.0% on prescriptions alone (N = 19) and 6.9% on both (N = 32) (Figure 4.1). The proportions of patients reporting serious AEs were not statistically significantly different (Table 4.4). Further details on the serious AEs reported can be found in Appendix 4.3.

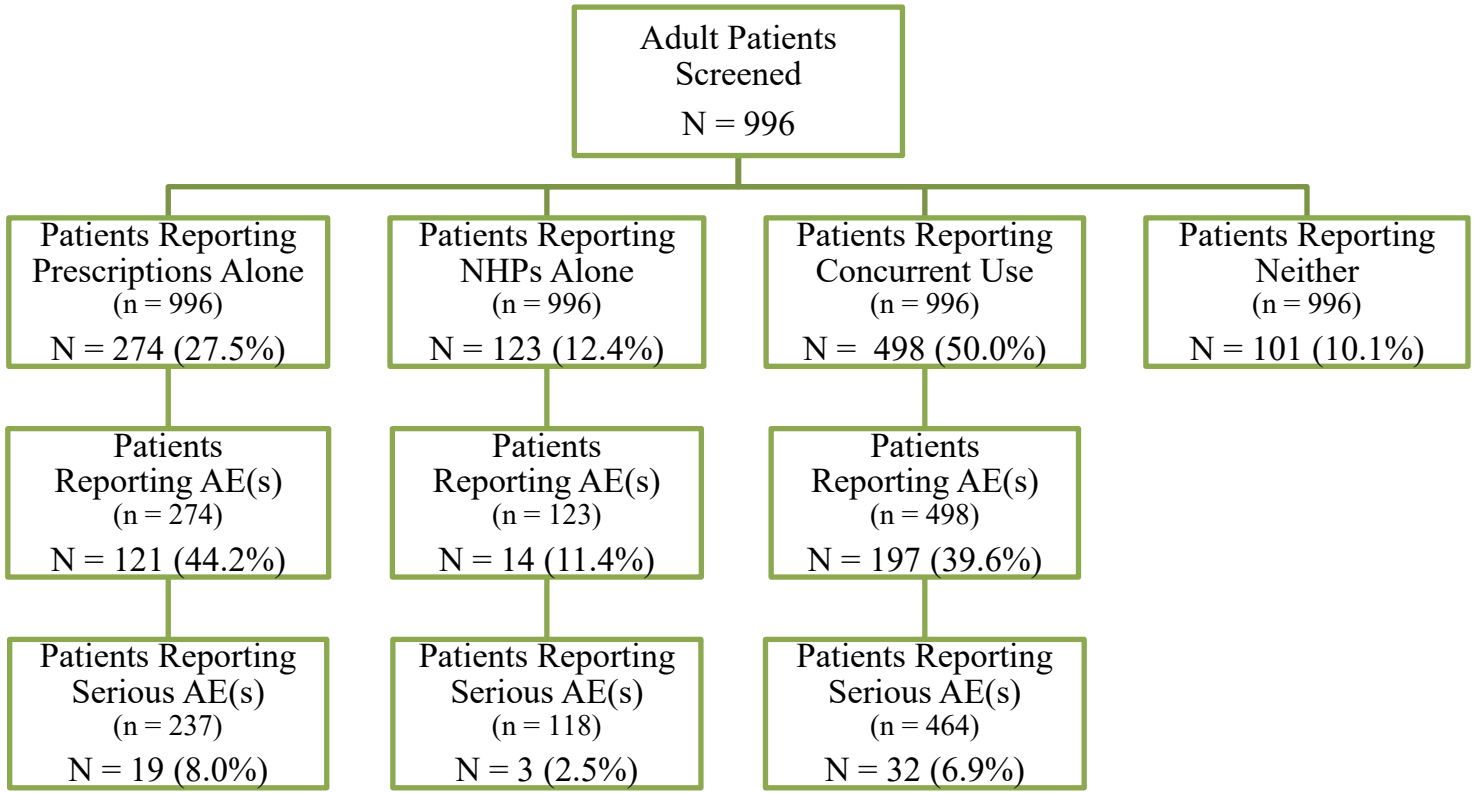
Causality assessment

Thirty-five participants qualified for a follow-up telephone interview, five of which consented to be contacted. Of those, one participant was successfully contacted, and a telephone interview was completed. At the time of initial screening a 72-year-old female with breast cancer was taking eribulin chemotherapy and a course of cephalexin along with a multivitamin, calcium supplement, and halibut liver oil. The patient had reported blurred vision, loss of appetite, weight loss, nail changes, skin dryness, numbness in fingers and toes as well as a hospitalization for pneumonia and pleural effusion. Both adjudicators determined that these AEs were unlikely related to the NHPs as per the WHO-UMC causality assessment system.[227] No further assessment was required.

Table 4.1 Demographic information stratified by prescription medication use alone, NHP use alone, concurrent prescription medication and NHP use, and the use of neither

		Total (n = 996)	Prescriptions Alone (n = 274)	NHPs Alone (n = 123)	Concurrent (n = 498)	Neither (n = 101)
		N (%)	N (%)	N (%)	N (%)	N (%)
Sex[a]	Female	588 (70.3)	148 (66.4)	78 (74.3)	304 (70.7)	58 (73.4)
	Male	249 (29.7)	75 (33.6)	27 (25.7)	126 (29.3)	21 (26.6)
Cancer Centre	Centre 1	572 (57.4)	171 (62.4)	47 (38.2)	281 (56.4)	73 (72.3)
	Centre 2	223 (22.4)	75 (27.4)	27 (22.0)	104 (20.9)	17 (16.8)
	Centre 3	113 (11.4)	26 (9.5)	12 (9.8)	66 (13.3)	9 (8.9)
	Centre 4	88 (8.8)	2 (0.7)	37 (30.1)	47 (9.4)	2 (2.0)
Cancer Diagnosis[b]	Breast	179 (29.2)	54 (30.9)	17 (28.8)	86 (26.9)	22 (37.3)
	Colorectal	108 (17.6)	34 (19.4)	11 (18.6)	56 (17.5)	7 (11.9)
	Lung	94 (15.3)	27 (15.4)	2 (3.4)	56 (17.5)	9 (15.3)
	Melanoma	70 (11.4)	22 (12.6)	5 (8.5)	39 (12.2)	4 (6.8)
	Ovarian	44 (7.2)	5 (2.9)	7 (11.9)	23 (7.2)	9 (15.3)
	Uterine	29 (4.7)	6 (3.4)	9 (15.3)	12 (3.8)	2 (3.4)
	Pancreatic	14 (2.3)	4 (2.3)	0 (0.0)	10 (3.1)	0 (0.0)
	Liver	11 (1.8)	8 (4.6)	1 (1.7)	2 (0.6)	0 (0.0)
	Esophageal	10 (1.6)	1 (0.6)	0 (0.0)	9 (2.8)	0 (0.0)
	Gastric	10 (1.6)	1 (0.6)	2 (3.4)	7 (2.2)	0 (0.0)
	Peritoneal	7 (1.1)	1 (0.6)	0 (0.0)	3 (0.9)	3 (5.1)
	Cervical	6 (1.0)	1 (0.6)	2 (3.4)	1 (0.3)	2 (3.4)
	Prostate	6 (1.0)	3 (1.7)	0 (0.0)	3 (0.9)	0 (0.0)
	Other	25 (4.1)	8 (4.6)	3 (5.1)	13 (4.1)	1 (1.7)

[a]159 participants had missing data: total, n = 837; prescriptions alone, n = 223; NHPs alone, n = 105; concurrent, n = 430; neither, n = 79
[b]383 participants had missing data: total, n = 613; prescriptions alone, n = 175; NHPs alone, n = 59; concurrent, n = 320; neither, n = 59
NHPs, natural health products



Note: 76 patients were excluded from the final row as they did not have information on the seriousness of the AE (see n = sample size).
AE, adverse event; NHPs, natural health products

Figure 4.1 The proportion of adult oncology patients using prescription medications alone, NHPs alone, prescription medications and NHPs concurrently and the proportion of patients reporting any AE(s) and serious AE(s) for each patient group

Table 4.2 Most common natural health products reported

NHPs Reported (n = 1908)	N (%)
Vitamin D	328 (17.2)
Multivitamin	183 (9.6)
Vitamin B	166 (8.7)
Calcium	150 (7.9)
Vitamin C	125 (6.6)
Omega-3 fatty acids/Fish oils	111 (5.8)
Turmeric/Curcumin	75 (3.9)
Probiotics	70 (3.7)
Magnesium	67 (3.5)
Mushrooms (e.g., Turkey Tail, Reishi, Chaga, Maitake)	43 (2.3)
Melatonin	37 (1.9)
Glucosamine	24 (1.3)
Iron	24 (1.3)
Vitamin E	23 (1.2)
Coenzyme Q10	22 (1.2)
Green tea	22 (1.2)
Folic acid	17 (0.9)
Mistletoe	13 (0.7)
Chinese herbs (unspecified)	12 (0.6)
Zinc	12 (0.6)
Senna	11 (0.6)
Potassium	11 (0.6)
Essiac	10 (0.5)
Ginseng	8 (0.4)

NHPs, natural health products

Table 4.3 Classification of adverse events by MedDRA System Organ Class stratified by prescription medication use alone, NHP use alone and concurrent prescription medication and NHP use

Adverse Event by MedDRA System Organ Class	Prescriptions Alone (n = 227)	NHP Alone (n = 16)	Concurrent (n = 401)	Total (n = 644)
	N (%)	N (%)	N (%)	N (%)
Gastrointestinal disorders	61 (26.87)	2 (12.50)	123 (30.67)	186 (28.88)
General disorders and administration site conditions	51 (22.47)	2 (12.50)	70 (17.46)	123 (19.10)
Nervous system disorders	36 (15.86)	2 (12.50)	42 (10.47)	80 (12.42)
Skin and subcutaneous tissue disorders	20 (8.81)	2 (12.50)	36 (8.98)	58 (9.01)
Musculoskeletal and connective tissue disorders	13 (5.73)	4 (25.00)	33 (8.23)	50 (7.76)
Respiratory, thoracic and mediastinal disorders	6 (2.64)	0 (0.00)	14 (3.49)	20 (3.11)
Metabolism and nutrition disorders	5 (2.20)	0 (0.00)	15 (3.74)	20 (3.11)
Infection and infestations	2 (0.88)	2 (12.50)	12 (2.99)	16 (2.48)
Psychiatric disorders	4 (1.76)	1 (6.25)	10 (2.49)	15 (2.33)
Eye disorders	1 (0.44)	1 (6.25)	12 (2.99)	14 (2.17)
Vascular disorders	8 (3.52)	0 (0.00)	7 (1.75)	15 (2.33)
Blood and lymphatic system disorders	5 (2.20)	0 (0.00)	7 (1.75)	12 (1.86)
Reproductive system and breast disorders	3 (1.32)	0 (0.00)	6 (1.50)	9 (1.40)
Investigations	1 (0.44)	0 (0.00)	7 (1.75)	8 (1.24)
Renal and urinary disorders	4 (1.76)	0 (0.00)	2 (0.50)	6 (0.93)
Ear and labyrinth disorders	2 (0.88)	0 (0.00)	1 (0.25)	3 (0.47)
Endocrine disorders	2 (0.88)	0 (0.00)	1 (0.25)	3 (0.47)
Immune system disorders	1 (0.44)	0 (0.00)	1 (0.25)	2 (0.31)
Injury, poisoning and procedural complications	2 (0.88)	0 (0.00)	0 (0.00)	2 (0.31)
Hepatobiliary disorders	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Cardiac disorders	0 (0.00)	0 (0.00)	1 (0.25)	1 (0.16)
Neoplasms benign, malignant and unspecified	0 (0.00)	0 (0.00)	1 (0.25)	1 (0.16)

MedDRA, The Medical Dictionary for Regulatory Activities; NHPs, natural health products

Table 4.4 Comparison of the proportions of patients reporting AEs between those using prescription medications alone, NHPs alone and prescription medications and NHPs concurrently using Chi-square test and Fisher exact test[*]

		Prescriptions Alone (n = 274)	NHPs Alone (n = 123)	P-value[#]	Concurrent (n = 498)	P-value[^]	P-value[$]	Total (n = 895)	P-value[~]
		N (%)	N (%)		N (%)			N (%)	
Reporting AE(s)	Yes	121 (44.2)	14 (11.4)	<0.0001	197 (39.6)	0.214	<0.0001	332 (37.1)	<0.0001
Reporting Serious AE(s)[a]	Yes	19 (8.0)	3 (2.5)	0.059[*]	32 (6.9)	0.589	0.084[*]	54 (6.6)	0.119[*]

[#]P-value of comparison between Prescriptions Alone vs. NHPs Alone;
[^]P-value of comparison between Prescriptions Alone vs. Concurrent;
[$]P-value of comparison between NHPs Alone vs. Concurrent;
[~]P-value of comparison between three groups
[a]76 participants had missing data: prescriptions alone, n = 237; NHPs alone, n = 118; concurrent, n = 464; total, n = 819
AE, adverse event; NHPs, natural health products

Discussion

Half of the adults screened at outpatient oncology clinics were taking NHPs concurrently with prescription medications. The proportion of patients taking NHPs increases to over 60% when including patients who were taking NHPs alone. This is consistent to previous reports of prevalence of NHP use in patients with cancer ranging from 13 to 63%.[18] While our prevalence of concurrent use is slightly higher than what was seen by Engdal *et al.* (38%), we included all prescription medications, whereas they considered herbal remedies that were taken concurrently with anticancer agents only.[21] Similarly, Jermini *et al*. found that 45% of patients were using complementary approaches at the time of cancer treatment.[22] The use of more than one NHP at a time is also consistent with previous findings.[21] The high prevalence of NHP use in Canadian oncology clinics highlights the need for clinician inquiry on this subject. Up to 77% of patients with cancer may not disclose their use of complementary approaches to their conventional healthcare provider.[11] One significant barrier in disclosure of NHP use is healthcare providers' lack of inquiry.[11] Unlike passive surveillance and other types of patient surveys, this active surveillance approach was integrated into clinical workflow as part of patient history taking. Screening was feasible and served to open the discussion regarding NHP use. Clinician-led discussion also has the potential to enhance the provider-patient relationship, improve patient satisfaction, and is the first step to risk mitigation.[11,13,28]

To our knowledge, this is the first surveillance study investigating AE prevalence associated with NHP use in adults with cancer. In a cross-sectional study conducted in France, the overall prevalence of experiencing at least one AE in patients with advanced and recurrent ovarian cancer was 74.8%.[238] Serious AEs were experienced by 12.6% of patients.[238] While the overall AE prevalence for patients taking at least one prescription medication or NHP was much lower in our study at 37.1% and 6.6% for serious AEs, we captured this data over a one-month recall period versus 12 months of follow-up, making comparison challenging. Another potential explanation for this discrepancy is the presence of recall bias. We aimed to limit recall bias by using a narrow screening timeframe of one month; however, some evidence suggests that a one-week timeframe might be optimal to avoid substantial loss of information for patient-reported outcomes.[239,240] Differing from some of the previous screening procedures utilized by our research team,[47,94] healthcare provider reported AEs were additionally incorporated to enhance detection of AEs, particularly those that a patient may be unaware of, such as laboratory-based

events, or treatment changes or delays. Despite these efforts to increase reporting of AEs, it is possible that our overall AE prevalence is lower compared to previous reports[238,241–244] due to the screening of patients healthy enough to attend outpatient oncology clinics. Additionally, if the screening form was filled out, but questions about AEs were left blank, the assumption was made that no AE occurred in the last month; this may have underestimated AE prevalence.

No significant difference in overall AE prevalence in adult oncology patients on prescription medications and NHPs compared to prescription medications alone was seen. This is in contrast to community pharmacies, HIV clinics, and mental health clinics where patients were 6.4, 3.2 and 2.1 times more likely to experience an AE with concurrent use compared to prescription drug use alone, respectively.[47–49] It is possible that the addition of NHPs to prescription medications in patients with cancer does not increase the risk of experiencing an AE. Given the heterogeneity among products included in Health Canada's classification of NHPs,[1] it is also possible that some combinations of products increase the risk of AEs, while others lower or have no effect on the risk. This could occur through pharmacokinetic or pharmacodynamic NHP-drug interactions.[18,40,43,54,58] The prevalence of AEs in those taking prescription medications alone was much higher than has been observed in other SONAR studies with different populations.[47–50,95] This is not surprising as the risk of AEs is generally high for patients taking anticancer medications.[238] However, if patients are very sick already on prescription medications, it may make it more difficult to discern AEs that occur when NHPs are taken concurrently. As more data are systematically gathered, further evaluation of patterns and the identification of safety signals can (and should) occur.[245] Important limitations exist and need to be considered in the interpretation of AE prevalence in this study. Prognostic variations between patients could influence our results as only cancer centre was adjusted for in the multivariate analysis. It is likely several unmeasured or unknown confounders still exist. For example, patients were screened when attending new or follow-up visits at an outpatient cancer clinic. Included patients may have been seeking care when they were newly diagnosed, initiating cancer treatment, or at other treatment milestones. This is further highlighted in that some patients were not on anticancer medications and 10% were on no prescription medications or NHPs during the one-month screening timeframe. Information was not gathered on the patient's current phase of care or health status and differences in this may have impacted our results. It may be helpful to restrict the screening inclusion criteria to those who have been on anticancer

medications in the last one month to reduce heterogeneity and improve detection of potential NHP-anticancer medication interactions. Information biases such as social desirability bias may have also impacted AE prevalence.[246] Since this screening form was used as part of clinical care, it is possible that those who were taking NHPs may not want to disclose that they had a negative effect to their oncologist or healthcare team. Anticipation of disapproval or fear of judgement is a known barrier to patient-clinician discussion of complementary approaches.[11,12,225] Cancer care is complex in that medications fluctuate frequently and inter- and intra-patient variability of treatment effects is common.[40,42] Patients may experience fluctuating symptoms and symptom severity over time, which may not be accurately captured in a one-month recall.[240] Daily symptom diaries may be better suited for capturing this variability, however they add considerably to patient burden.[240] Another consideration is that our study may have incompletely detected AEs that caused a reduced treatment response or indirect harms such as a delay in treatment. We tried to capture these types of AEs by including a checkbox for healthcare providers on the screening form for "caused a delay or change in treatment." However, these occurrences may be infrequently thought of as an AE, and lack of reporting on this does not rule out that they exist.[21]

Due to the observational study design, we are only able to look at associations and not causality of most of the AE data. This means that we are not able to distinguish between AEs caused by anticancer medications, other prescription medication, NHPs, or other factors such as the underlying condition. Additionally, we are unable to determine the direction of the association due to the collection of exposure and outcome data at a single time point. Reverse causality could exist, in which patients are taking a particular NHP to treat a side effect. Due to these inherent limitations, a detailed causality adjudication procedure was in place for serious AEs occurring while patients were taking NHPs. However, there was a large loss to follow-up on those eligible for a telephone interview, severely limiting causality assessment. Only 14% of eligible participants consented to be contacted, and just one (3%) was successfully contacted. The initial screening forms were anonymous, so we were unable to report on why consent was not obtained for some eligible participants. Some logistical challenges were reported by clinic staff when eligible patients were mistakenly not provided the consent form to participate in the telephone interview, despite ongoing support offered by SONAR investigators. Beliefs regarding

the relationship between AE experienced and NHP, fear of judgement, or perceived burden of a follow-up interview may have also contributed to losses to follow-up.

This high rate of losses to follow-up also occurred during active surveillance completed previously by our research team.[47,94] Therefore, the screening form was adapted for this study to provide data regarding the seriousness of the AE on initial screening by asking patients to identify what actions they took regarding the AE. This was an important first step in providing meaningful data on the clinical relevance of reported AEs, though further standardization of patient reported AEs could enrich this data. Recently, a measurement system was developed for patient reporting of symptomatic AEs in cancer clinical trials.[239] The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement System allows for direct patient reports of AEs by utilizing plain-language symptom terms and prompts that reflect the frequency, severity and interference of the symptom.[239] While this AE measurement system alone does not investigate the use of NHPs or prescription medications, it may be beneficial to merge with our existing active surveillance screening questions to allow for enhanced AE description at initial patient contact. Additionally, since cancer care is complex and may involve frequent fluctuations in health status and cancer treatments, challenges exist when delaying patient follow-up and causality assessment. Gathering sufficient information on initial screening for causality assessment or conducting causality assessment as part of initial contact should be considered in future research. Ongoing collection of comprehensive data on NHP AEs in adults with cancer is necessary to facilitate the development of a database for information sharing and to support the identification of safety signals, complementing existing vigilance programs.

It is known that improved communication about NHP use is urgently needed between conventional healthcare providers and patients.[11,13,28] This active surveillance method was integrated successfully into clinical care and NHP use was reviewed and discussed at cancer clinic visits. Canada has made significant progress over the past 10 years regarding the use of electronic medical records (EMRs).[247] Electronic health record data is available for 94% of Canadians, and 85% of Canadian primary care physicians use EMRs.[247] Additionally, these electronic systems are improving the ability to communicate and share health information; in some EMRs, patients can document and contribute their own health information.[248] Incorporating the screening and documentation of NHP use and AEs as presented in this paper as

part of documentation in EMRs has immense potential for linking to other important prognostic factors and following patients over time.

Conclusion

Active surveillance was successfully implemented in cancer centres to detect NHP use and associated AEs. The majority of adults with cancer are taking NHPs and half are taking NHPs along with prescription medications. Adults with cancer frequently experience AEs while taking prescription drugs and NHPs concurrently, as well as from prescription medications alone. Prevalence of AEs appear similar between these groups, but further research is required to determine the causality of these AEs and the impact on patients over the continuum of cancer care. Incorporating questions about NHP use and AEs is feasible in outpatient cancer clinics as part of best practice and there is potential to integrate this approach into EMRs to enhance data linkage, surveillance, and patient safety.

CHAPTER 5: Study of natural health product adverse reactions (SONAR) in children with cancer: a cross-sectional study

Introduction

Complementary health approaches, outside of what would be considered conventional medical care, are used commonly by children.[249] These include nutritional approaches, such as dietary supplements and herbs, psychological approaches, such as meditation, and physical approaches, such as massage or acupuncture.[249] A national survey in the US reported that approximately 12% of children aged 4 to 17 years use complementary health approaches.[31] It appears that use is even higher in children with chronic, recurrent, or incurable conditions.[32,95] In pediatric patients with cancer, prevalence of complementary health use ranges from 6% up to 91%.[30]

Approximately 1,000 children aged ≤14 years are diagnosed with cancer each year in Canada.[250] The most common cancers in children are leukemias, tumors of the central nervous system, and lymphomas.[251] Survival of childhood cancer continues to increase, likely due to improved treatment protocols, supportive care, and the development of new therapies.[250] Despite these advances, in Canada, cancer is still the leading cause of disease-related mortality in children over one month of age, and chronic disabilities caused by cancer treatments are common.[251] Children with cancer and their families often use complementary approaches to help treat cancer, provide symptomatic relief, or reduce side effects from conventional therapy.[30,34] Complementary therapy is often thought of as more "natural" and is therefore, perceived as safe.[33] Three quarters of pediatric patients and families surveyed at a pediatric outpatient clinic in Quebec did not believe that complementary approaches could cause adverse events (AEs) or interact with medications.[33]

Natural health products (NHPs), known as dietary supplements in the US,[219] are of the most common complementary approaches used by pediatric patients.[30–32] NHPs are classified by Health Canada as vitamins and minerals, herbal medicines, probiotics, amino acids, essential fatty acids, homeopathic remedies, and traditional medicines.[1] Complementary approaches are commonly used with conventional medical care, including prescription medications.[32] Like conventional medicine, NHPs are potentially biologically active and have the possibility to cause AEs.[39] When taken with prescription drugs, there is also a risk of NHP-drug interactions.[40,43]

This is particularly concerning for anticancer agents, which often have a narrow window between plasma concentrations that cause serious toxicities and those that have a lack of therapeutic response.[40] Although pediatric patients with cancer are vulnerable to these theoretical risks, very limited clinical evidence exists on AEs associated with NHP use in this population.

Assessing for potential AEs was recently identified as a top priority internationally in pediatric complementary medicine research.[252] Due to inconsistent and limited pre-marketing requirements, as well as the potential for variations in composition and quality of NHPs, there is a need for rigorous post-marketing surveillance to assess AEs.[75,78,224] Several passive surveillance systems exist, where AEs are spontaneously reported by healthcare professionals and patients; however, they are severely limited by under-reporting.[83,85,87] This is intensified for NHPs because patient disclosure of their use to healthcare providers is very low.[32,33] Although it is well known that a systematic method of soliciting AEs is needed, very few of these active surveillance methods exist, particularly for children.[33,83,85,93] AE reporting rates are increased with the use of active surveillance as compared to routine passive methods.[47,97,98] This has been observed in general pediatric primary care and more recently, in pediatric chiropractic care.[97,98]

To address some of the limitations of passive surveillance, our research team has developed an active surveillance system for the reporting of NHP-related AEs.[47,48,50,94,95] This has been modeled in community pharmacies,[47,94] HIV clinics[49] and both adult and pediatric mental health clinics.[48,50,95] We hypothesize that children with cancer are at a higher risk of experiencing AEs while concurrently using NHPs and prescription medications compared to those using prescription medications alone. The purpose of this cross-sectional study was to implement this NHP active surveillance method in outpatient pediatric oncology clinics to: 1) determine the prevalence of NHP and/or prescription drug use in pediatric oncology patients 2) describe common NHPs used by pediatric patients with cancer; 3) determine the prevalence of AEs in those using NHPs alone, prescription medications alone, and concurrent NHP and prescription medications; 4) compare the prevalence of AEs between groups 1, 2, and 3; 5) describe of the types of AEs occurring; and 6) determine the likelihood of NHPs causing a serious AE.

Methods

Ethics approval was obtained from the Health Research Ethics Board at the University of Alberta (Pro00025387). Site-specific operational approval was also obtained.

Active surveillance

Active surveillance methods previously published by our research team were adapted and used at pediatric oncology centers.[47,48,50,94,95] Patients up to 18 years old and their guardians attending appointments at participating outpatient cancer clinics were provided a one-page screening form to fill out (Appendix 5.1) as part of history taking. Clinic staff received training on the screening process to assure consistency in the process and enhance feasibility within clinical workflow. Ongoing phone and email follow-up was provided to a site principal investigator, who acted as a primary contact for each participating centre. The surveys were completed anonymously, and the only inclusion criterion was informed consent. Questions on the survey asked about the child's prescription medication use, NHP use, and any AEs experienced over the last month.

(1) In the last month, has your child taken any anticancer or prescription medications? *If Yes, list the medications and for how long they have been taken. If unsure, please ask your healthcare team.*

(2) In the last month, has your child taken any natural health products (NHPs) e.g. vitamins, minerals, herbals, homeopathic remedies, traditional Chinese medicines, probiotics etc.? *If Yes, list the NHP and for how long they have been taken. Please try to be as specific as possible.*

(3) In the last month, has your child experienced any undesirable effects? *If Yes, describe these effects.*

(4) What did you do about it? A) Nothing/treated it myself; B) Phoned for information; C) Saw doctor about it; D) Doctor treated it; E) Was hospitalized because of it

The healthcare providers at the clinic were then asked to review the screening form. If the patient/guardian had reported an undesirable effect in question 3, healthcare providers were asked to describe whether it was serious or caused a delay or change in treatment. Additionally, they were asked to report any other serious and unexpected AE.

(5) For healthcare provider: In the last month, has the patient had any other serious and unexpected adverse effect? *If Yes, describe the effect.* Please identify if serious and unexpected or caused a delay or change in treatment.

If the patient/guardian responded that the patient had taken an NHP in the last month (question 2), had an undesirable effect (question 3) which required medical intervention (question 4D) or hospitalization (question 4E), or the healthcare provider indicated that a serious and unexpected AE occurred (question 5), they were provided an information package and consent form for a follow-up interview. A telephone interview was conducted if consent was obtained to gather additional details on the patient's medical history, NHP and prescription drug history and the AE(s) experienced to assist with causality assessment.

Prescription medication use was defined as responding "yes" to question 1 and/or listing at least one medication with a drug identification number. NHP use was defined as responding "yes" to question 2 and/or listing at least on NHP as defined by Health Canada.[76] Concurrent use was defined as reporting both prescription medication use and NHP use.

A patient was considered to have had an AE if the patient/guardian responded "yes" to question 3 and/or the patient/guardian or healthcare provider reported at least one undesirable effect. If question 3, 4 and 5 were left empty and other portions of the form were filled out, the assumption was that no AE occurred in the last month. A serious AE was defined as the patient/guardian report of an undesirable effect resulting in medical treatment or hospitalization and/or the healthcare provider indicated an AE was serious and unexpected or resulted in a delay/change in treatment. Healthcare providers were guided to classify ≥ grade 3 AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[230] as serious. The NCI CTCAE and System Organ Class of the Medical Dictionary for Regulatory Activities (MedDRA) and were used to code AEs.[230,231]

Causality assessment

Causality assessment was conducted for consenting participants if the child/guardian had reported NHP use and a serious AE in the last month. This was done to determine whether a suspected or actual NHP adverse reaction had occurred.[179,226] After the follow-up interview, data was summarized for two adjudicators. The adjudication was done using methods previously published by our research team.[47,94,96] Each adjudicator independently assessed each case using

the World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) system, modified to consider all health products (vs. drugs only).[227] If there was at least a possible causal relationship between NHP(s) and AE(s), a modified Naranjo Causality Scale[228] was then conducted. The modified Horn Drug Interaction Probability Scale (DIPS)[229] was also used if there was at least a possible NHP-drug or NHP-NHP interaction. Inconsistency in NHP content and quality, including potential adulteration and contamination, complicates causality assessment.[253–257] Therefore, laboratory analysis was available, if deemed necessary by adjudicators. Disagreements were discussed until consensus was reached, or if required, a third adjudicator was consulted.

Sample size

Previous NHP active surveillance work in patients seeking care at Canadian community pharmacies determined AE prevalence in patients on concurrent prescription medications and NHPs to be approximately 7%.[47,94,235] We anticipated that the prevalence of AEs will be higher in pediatric patients with cancer. With a sample size of 206 patients, assuming an AE prevalence of 20% for patients taking prescription medications alone and an α of 0.05, we calculated 80% power to detect a minimum clinically significant difference in mean AE prevalence of 10% (effect size: 0.25) in those taking prescription medications and NHPs concurrently. To account for potential losses to follow-up and missing data, the sample size was inflated by 10% to 227 patients. Sample size was calculated with the Chi-square test using G*Power 3.1.[234]

Data management

Study data were managed using REDCap electronic data capture tools[236] hosted and supported by the Women and Children's Health Research Institute at the University of Alberta.

Data analysis

Descriptive statistics were used to summarize patient demographic information and determine the frequencies and percentages of NHP use, prescription medication use, and AEs. The Chi-square test and Fisher exact test, when small frequencies were present, were used to compare the prevalence of AEs in each patient group. The odds ratio and associated 95% confidence interval (CI) for AE prevalence in patients using NHPs and prescription medications concurrently compared to prescription medication use alone was calculated using multivariate

logistic regression controlling for cancer centre. Data analysis was performed using STATA Version 15.1.[237]

Results

Three cancer centres in two Canadian provinces participated. A total of 282 patients under the age of 18 were screened between 2014 and 2018. Male patients represented 54.4% of those included, which did not vary significantly between patient groups. Leukemia (49.2%), central nervous system cancers (15.1%), and lymphoma (11.0%) were the most frequent cancer diagnoses reported (Table 5.1).

Natural health product use

Of the 282 patients included, 104 (36.9%) were taking prescription medication alone, 39 (13.8%) were taking NHPs alone, 111 (39.4%) were taking NHPs and prescription medication concurrently, and 28 (9.9%) were taking neither NHPs nor prescription medications in the last month. In those taking NHPs, the median number of NHPs used was 1 (interquartile range (IQR) 1-2; range 1-13). Vitamin D and multivitamins were, by far, the most frequently reported NHPs used. The most common NHPs reported are presented in Table 5.2.

Adverse events

Figure 5.1 shows the proportion of patients reporting any AEs and serious AEs for each patient group. Only two (5.1%) patients taking NHPs alone reported AEs; one indicated that the AEs were not serious and the other had missing information on seriousness. Thirty-six percent (N = 40) of patients taking NHPs and prescription drugs concurrently reported at least one AE compared to 34.6% (N = 36) taking prescription drugs alone. After controlling for cancer centre, there was no significant difference in the odds of experiencing an AE between these two groups (OR 0.99, 95% CI 0.56–1.77; p = 0.981). Of the 40 patients experiencing an AE on concurrent therapy, 31 were taking at least one anticancer medication, eight were taking prescription medication(s) other than anticancer medications, and one did not list their medications. Of the 36 patients experiencing an AE on prescription drugs alone, 30 were taking an anticancer medication, five were taking other prescription medication(s), and one did not list their medications. Patient sex was not significantly associated with the prevalence of AEs. Gastrointestinal disorders were of the most frequently reported class of AEs, followed by general

disorders and administration site conditions, and nervous system disorders. Table 5.3 provides further details on types of AEs, of any severity, reported in each patient group. A median of two AEs (IQR 1-3; range 1-7) were reported by each patient in both those taking NHPs and prescription drugs concurrently and those taking only prescription drugs. The proportion of patients reporting serious AEs were also similar between groups with 10.1% (N = 11) with concurrent therapy and 10.0% (N = 10) with prescription medications alone (p = 0.982) (Table 5.4). Further information on the serious AEs can be found in Appendix 5.3 including patient sex, diagnosis, prescription medications, NHPs, CTCAE terms, and actions taken.

Table 5.1 Demographic information stratified by prescription medication use alone, NHP use alone, concurrent use, and the use of neither

		Total (n = 282)	Prescriptions Alone (n = 104)	NHPs Alone (n = 39)	Concurrent (n = 111)	Neither (n = 28)
		N (%)	N (%)	N (%)	N (%)	N (%)
Sex[a]	Male	153 (54.4)	59 (56.7)	19 (48.7)	61 (55.5)	14 (50.0)
	Female	128 (45.6)	45 (43.3)	20 (51.3)	49 (44.5)	14 (50.0)
Cancer Centre	Centre 1	173 (61.4)	51 (49.0)	38 (97.4)	60 (54.1)	24 (85.7)
	Centre 2	77 (27.3)	42 (40.4)	1 (2.6)	32 (28.8)	2 (7.1)
	Centre 3	32 (11.4)	11 (10.6)	0 (0.0)	19 (17.1)	2 (7.1)
Cancer Diagnosis[b]	Leukemia	130 (49.2)	53 (53.5)	10 (32.3)	59 (54.6)	8 (30.8)
	CNS	40 (15.1)	13 (13.1)	5 (16.1)	15 (13.9)	7 (26.9)
	Lymphoma	29 (11.0)	10 (10.1)	2 (6.5)	13 (12.0)	4 (15.4)
	Sarcoma	18 (6.8)	8 (8.1)	1 (3.2)	6 (5.6)	3 (11.5)
	Neuroblastoma	15 (5.7)	5 (5.1)	4 (12.9)	4 (3.7)	2 (7.7)
	Wilms tumor	12 (4.6)	7 (7.1)	3 (9.7)	2 (1.9)	0 (0.0)
	Hepatoblastoma	5 (1.9)	0 (0.0)	1 (3.2)	3 (2.8)	1 (3.9)
	Other	15 (5.7)	3 (3.0)	5 (16.1)	6 (5.6)	1 (3.9)

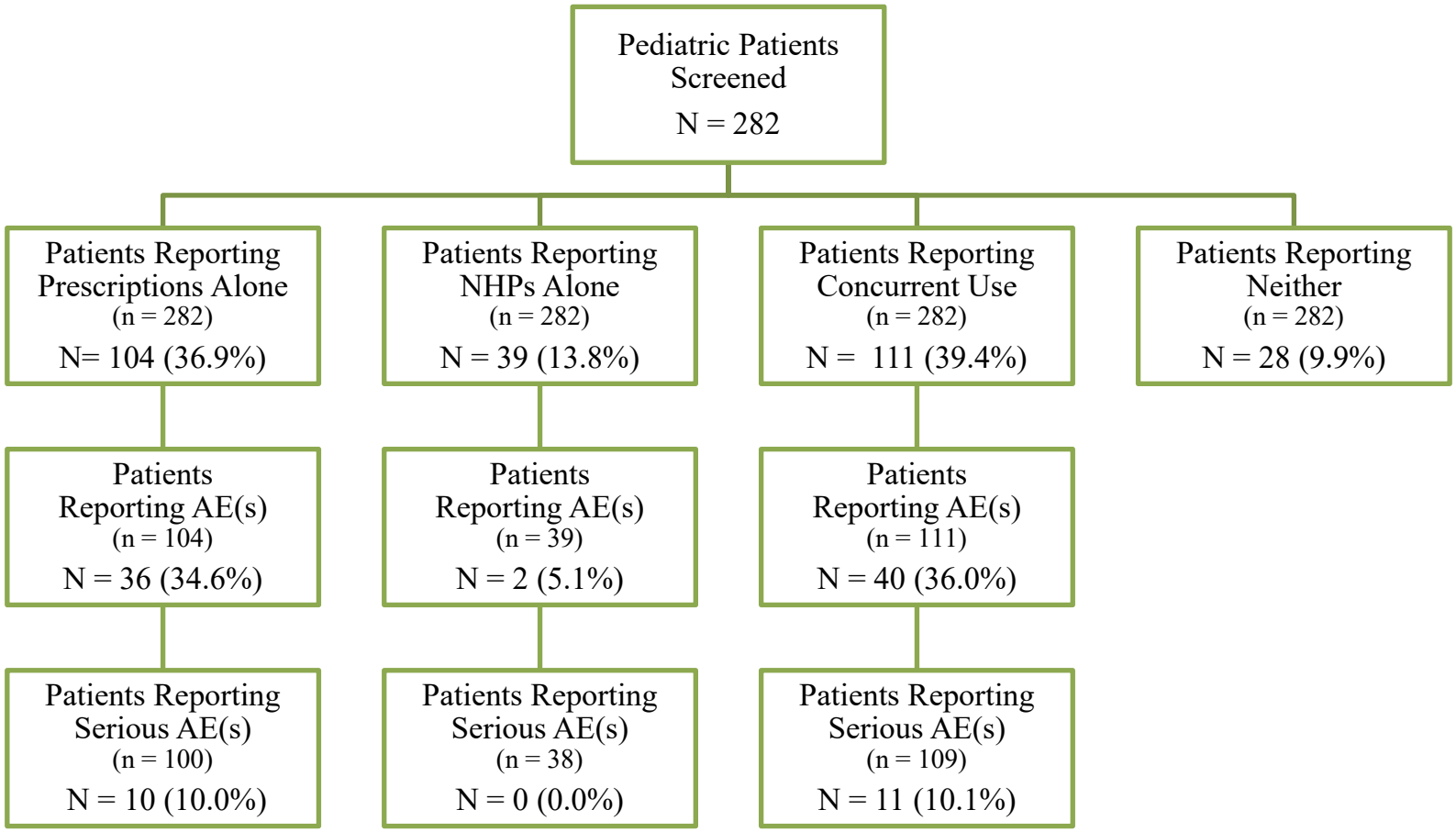
[a]1 participant had missing data: total, n = 281; concurrent, n = 110

[b]18 participants had missing data: total, n = 264; prescriptions alone, n = 99; NHPs alone, n = 31; concurrent, n = 108; neither, n = 26

NHPs, natural health products; CNS, central nervous system

Table 5.2 Most common natural health products reported

NHPs Reported (n = 254)	**N (%)**
Vitamin D	79 (31.1)
Multivitamin	47 (18.5)
Omega-3 fatty acids/Fish oils	16 (6.3)
Vitamin C	12 (4.7)
Probiotics	10 (3.9)
Essential oils (unspecified)	9 (3.5)
Iron	6 (2.4)
Vitamin B (unspecified, B_6, B_{12})	6 (2.4)
Melatonin	6 (2.4)
Magnesium	5 (2.0)
Calcium	4 (1.6)
Astragalus	4 (1.6)
Coenzyme Q10	3 (1.2)
Antioxidants (unspecified)	3 (1.2)



AE, adverse event; NHPs, natural health products
Note: 7 patients were excluded from the final row as they did not have information on the seriousness of the adverse event (see n = sample size).

Figure 5.1 The proportion of pediatric oncology patients using prescription medications alone, NHPs alone, prescription medications and NHPs concurrently and the proportion of patients reporting any AE(s) and serious AE(s) for each patient group

Table 5.3 Classification of adverse events by MedDRA System Organ Class stratified by prescription medication use alone, NHP use alone and concurrent prescription drug and NHP use

Adverse Events by MedDRA System Organ Classes	Prescriptions Alone (n = 80)	NHP Alone (n = 4)	Concurrent (n = 95)	Total (n = 179)
	N (%)	N (%)	N (%)	N (%)
Gastrointestinal disorders	38 (47.50)	0 (0.00)	38 (40.00)	76 (42.46)
General disorders and administration site conditions	8 (10.00)	0 (0.00)	16 (20.00)	24 (13.41)
Nervous system disorders	10 (12.50)	0 (0.00)	12 (12.63)	22 (12.29)
Skin and subcutaneous tissue disorders	7 (8.75)	1 (2.50)	6 (6.32)	14 (7.82)
Metabolism and nutrition disorders	5 (6.25)	0 (0.00)	6 (6.32)	11 (6.15)
Psychiatric disorders	2 (2.50)	1 (2.50)	8 (8.42)	11 (6.15)
Musculoskeletal and connective tissue disorders	2 (2.50)	1 (2.50)	4 (4.21)	7 (3.91)
Blood and lymphatic system disorders	3 (3.75)	0 (0.00)	2 (2.11)	5 (2.79)
Investigations	2 (2.50)	0 (0.00)	2 (2.11)	4 (2.23)
Eye disorders	1 (1.25)	1 (2.50)	1 (1.05)	3 (1.68)
Infection and infestations	1 (1.25)	0 (0.00)	0 (0.00)	1 (0.56)
Renal and urinary disorders	1 (1.25)	0 (0.00)	0 (0.00)	1 (0.56)

MedDRA, The Medical Dictionary for Regulatory Activities; NHPs, natural health products

Table 5.4 Comparison of the proportions of patients reporting AEs between those using prescription medications alone, NHPs alone and prescription medications and NHPs concurrently using Chi-square test and Fisher exact test[*]

		Prescriptions Alone (n = 104)	NHPs Alone (n = 39)	P-value[#]	Concurrent (n = 111)	P-value[^]	P-value[$]	Total (n = 254)	P-value[~]
		N (%)	N (%)		N (%)			N (%)	
Reporting AE(s)	Yes	36 (34.6)	2 (5.1)	<0.0001[*]	40 (36.0)	0.828	<0.0001[*]	78 (30.7)	<0.0001[*]
Reporting Serious AE(s)[a]	Yes	10 (10.0)	0 (0.0)	0.062[*]	11 (10.1)	0.982	0.067[*]	21 (8.5)	0.093[*]

[#]P-value of comparison between Prescriptions Alone vs. NHPs Alone;
[^]P-value of comparison between Prescriptions Alone vs. Concurrent;
[$]P-value of comparison between NHPs Alone vs. Concurrent;
[~]P-value of comparison between three groups
[a]7 participants had missing data: prescriptions alone, n = 100; NHPs alone, n = 38; concurrent, n = 109; total, n = 247
AE, adverse event; NHPs, natural health products

Causality assessment

After initial screening, 11 patients qualified for a follow-up telephone interview. Of these, two guardians consented to be contacted, and one was successfully contacted. A 6-year-old male patient with acute lymphoblastic leukemia was receiving vincristine, methotrexate, 6-mercaptopurine and asparaginase and developed ptosis and foot drop. At this point the NHPs alpha lipoic acid, vitamin B6, and coenzyme Q10 were initiated for neuropathy support. Since it was determined at the follow-up interview that the NHPs were initiated after the AEs developed, both adjudicators agreed that there was no causal relationship between NHPs and AEs.

Discussion

In this study, we identified that just over half of the children with cancer were taking NHPs, and 2 in 5 patients took both NHPs and prescription drugs concurrently. A 2010 systematic review on the prevalence of complementary medicine use in pediatric cancer had similar findings with the use of herbal remedies ranging from 2% to 45% of those surveyed and dietary and nutritional interventions ranging from 3% to 47%.[30] Studies published after this systematic review also reported similar proportions of NHP use.[32,34,37] Valji *et al.* surveyed pediatric oncology clinics and found that 60.5% of patients used complementary approaches.[37] They observed that 40.8% of participants used NHPs along with prescriptions drugs, with multivitamins being the most commonly used product.[37] Multivitamin use was also high in our study, second only to vitamin D. Although we did not ask patients and guardians why they chose to use NHPs, reasons suggested in the literature include treating or helping with the treatment of cancer, strengthening the immune system, or reducing side effects of conventional cancer treatment.[30,34] Some families use NHPs prior to their child's diagnosis and continue them afterwards, and some start therapies at diagnosis.[34] Decision making regarding NHP use at initial diagnosis or recurrence of cancer is often characterized by feelings of fear and loss of control.[24] However, this decision making process does not happen at any one time point, it continues throughout cancer care.[24]

Of patients taking at least one NHP or prescription drug, 31% reported experiencing an AE, and 9% reported a serious AE. These proportions are higher than has been seen by our research team's surveillance in other patient populations;[47,48,50,94,95] however, given the high rate of side effects commonly experienced with anticancer medications[244], this is not unexpected.

There was no significant difference between the prevalence of AEs in those who reported taking both NHPs and prescription drugs compared to those taking prescription drugs alone. This is also in contrast to what has been seen in patients attending community pharmacies, HIV clinics, and mental health clinics, which reported a significant increase in risk of AEs with concurrent use of NHP and prescription drugs.[47–50] Much of what is known about interactions between NHPs and anticancer medications comes from the results of *in vitro* studies and challenges often exist in extrapolating this to what is experienced clinically.[40,43] This may be due to the poor bioavailability of NHPs and/or the variation in doses and content of products used in clinical practice.[40,43] These factors may have contributed to the lack of significant impact that the addition of NHPs to prescription medications had on the risk of experiencing an AE. Health Canada's definition of NHPs is broad and it is likely that inter-product variation on the risk of AEs exists.[40] Some NHPs or combinations of NHPs and prescription medications may have resulted in a reduction in AEs, some may have increased AEs, and some may have had no effect.[61] However, due to substantial loss to follow-up for the telephone interview, we can only report on associations and not causality for nearly all AEs; we are unable to report on the likelihood that the AEs reported were caused by prescription medications, NHPs or other factors.[179] Further complicating this association is the potential for residual confounding, given that very few patient characteristics were measured, and consequently were not controlled for.

Small differences between the types of AEs reported in each patient group were observed. A slight decrease in frequency of gastrointestinal disorders was noted in the patient group using NHPs and prescription drugs concurrently. Children with cancer and their families use NHPs to reduce chemotherapy side effects[30,34] and NHPs are commonly trialed for pediatric gastrointestinal complaints.[258] Limited, low quality evidence exists on the benefits of some NHPs for gastrointestinal side effects in patients with cancer. In a case report, the addition of oral vitamin D to chemotherapy improved the patient's stomatitis and dysgeusia.[137] A reduction in chemotherapy induced nausea and vomiting has been seen with vitamin C in case reports and a phase I/IIa clinical study.[187,196,199] Probiotics may decrease the incidence of diarrhea when given with chemotherapy or radiation.[61] Confirmatory studies are needed to explore the potential association between the use of NHPs and a decrease in gastrointestinal AEs. On the other hand, there was an increase in frequency of general disorders and administration site conditions, as

well as psychiatric disorders in the concurrent therapy group. The impact of NHPs on the increase of these types of AEs also warrants further investigation.

The cross-sectional design of this study means that a temporal relationship between NHPs and AEs cannot be directly assessed.[86] Protopathic bias, also referred to as reverse causation, may be present where the use of an NHP is the result of the AE or early sign of the AE.[259] This concept is highlighted when looking at our patient who was successfully reached for telephone follow-up. This patient qualified for interview since they reported taking an NHP and experiencing a serious AE in the last month. Upon further investigation during the interview, it was determined that the NHPs were initiated after the AE occurred, to treat the AE. One of the first steps of causality assessment is establishing a temporal relationship.[83,227] While this is effectively captured in our causality assessment methods,[47,94] it was reserved for patients experiencing a serious AE who consented for a follow-up interview. Therefore, we do not know the temporal relationship of other NHPs and AEs.

This study has several key strengths. An active surveillance pharmacovigilance method was implemented to systematically ascertain AEs in children with cancer. Active surveillance systems are quite rare worldwide,[93] particularly in children.[85] Very little is known about NHP-related AEs in children with cancer[97,101] and to our knowledge, no other active pharmacovigilance system currently exists to assess them. Active surveillance systems that do exist have been shown to significantly increase the number of AE reports in children, including those that are serious and life-threatening.[97,260] Often the quality of information reported is also improved.[86,260] Another strength is that our method was integrated into routine clinical care. Lack of discussion about NHP use between patients and conventional oncology care providers is common,[9,11–13] so including questions regarding NHP use as part of history taking in children with cancer is a step towards enhanced practice. Our study confirms that NHPs are taken by many children during cancer care, emphasizing the need for inquiry and discussion about NHPs at each patient visit. At an individual health level, collaborating with patients and their families is needed to form a shared treatment and monitoring plan.[28,61] These discussions about NHPs and the documentation of NHP use can also impact efficacy and safety at a population health level by increasing available real world data.

Some potential limitations exist with this study. Patients and families were asked to recall product use and AEs over a one-month period. Although this timeframe is relatively narrow,

some suggest that a one-week period may be best to reduce recall bias.[239,240] As mentioned previously, a drawback of cross-sectional studies is that they examine prevalence at a single timepoint.[86] Cancer treatment is complex and may involve changes to therapies over time. For example, some patients screened at participating clinics did not report taking any anticancer medications in the last one month. It also appears that NHP use may also be dynamic and depend on the phase of cancer care.[24] Including only patients actively being treated with anticancer medications could limit heterogeneity and enhance detection of NHP-anticancer medication interactions. Since exposures may also change over time, a longitudinal study could provide a deeper understanding of AEs throughout cancer care.[86] Another weakness is that the screening form did not gather extensive data on patient characteristics and it is likely that residual confounding exists. However, adding to the screening form must be balanced with participation and reporting rates. In other active surveillance programs, the top barriers impacting reporting include heavy workload and time to complete detailed questionnaires.[260] These barriers may be overcome by linking to other types of data sources, such as registries and electronic medical records.[85,86,93,261,262] One major limitation that we have identified in our surveillance method is the high rate of loss to follow-up in securing a telephone interview with participants. Only one of the 11 qualified participants was successfully contacted and able to provide adequate information for causality adjudication. Since losses to follow-up were noted as being high in previous work by our research team,[47,94] patients/guardians in this study were asked to identify what action they took regarding the AE on initial screening (question 4). This was to provide meaningful information regarding the seriousness of the AE without the need of an additional follow-up interview. A further consideration may be to conduct causality assessment during initial screening, particularly for serious AEs. As healthcare providers were asked to review the screening form and report AEs themselves, they could also be asked to conduct a brief causality assessment. Yet this may not be feasible because lack of time, lack of knowledge about NHPs, and difficulty in determining whether an AE is associated with a product or a disease have been noted as significant barriers in adverse reaction reporting.[260,263]

There are several opportunities for future work in this area. First, it is important that the discussion and documentation of NHP use and AEs in pediatric cancer clinics continues. It is necessary for this to be part of routine care. Our screening questions may serve as a helpful guide for clinicians to integrate inquiry and documentation of NHP use and AEs as part of their best

possible medication history.[264] Though the priority with NHPs is to "first do no harm"[252] this is not possible without a complete history of what the patient is taking; only then can clinicians make informed and shared decisions with patients and families.[264] This also needs to be done consistently across phases and transitions of care.[264] Not only does this have the potential to reduce the risk of AEs, it facilitates accurate monitoring of all medication use, including NHPs.[264,265] Electronic medical records are increasingly common, and it is possible that completing and documenting a best possible medication history, including the screening of NHP use, can occur electronically.[265,266] This can allow for enhanced tracking of outcome measures, such as AEs, and may provide valuable real world data for ongoing pharmacovigilance efforts.[85,265] There is also an opportunity to develop a patient registry on NHP use or add this information to existing cancer registries, and again this requires continual inquiry by healthcare providers.[151] Longitudinal studies looking at the use of NHPs and AEs experienced throughout the cancer trajectory would also add value to this area of study. Until real world data sources on NHP use improve, prospective studies involving primary data collection could be developed. Though there is a clear need for clinical practice change regarding discussion, documentation, and monitoring of NHP use, these changes will take time. Ongoing active surveillance of NHP-related AEs in children with cancer is necessary for enhanced patient safety. Active surveillance can increase reporting and the quality of AE reports in an area with sparse information.[86,97,260] Due to the large losses to follow-up in completing causality assessment, it may be helpful to conduct this at initial screening or continue with a stepwise approach but assess every AE experienced while on an NHP. Intensive monitoring supported by additional resources at a sample of sentinel sites may improve feasibility of continued active surveillance by reducing the burden on clinicians. This could supplement ongoing efforts to improve discussion and documentation in the clinical setting. Lastly, as more data is gathered on NHPs and potential AEs, it can be used to support existing vigilance programs in the development a population-based database that facilitates sharing of information and identification of safety signals.

Conclusion

More than half of children with cancer take NHPs, and many take them along with prescription medications. AEs were frequently reported using an active surveillance system at pediatric cancer centers across Canada. Thirty-one percent of patients taking at least one NHP or

prescription drug reported AE(s), and 9% reported a serious AE. While no significant differences were noted in the prevalence of overall or serious AEs between those using NHPs and prescription medication concurrently, and those using only prescription medications, this preliminary quantification requires further investigation. A focus on causality assessment is required to improve our understanding of NHP adverse reactions in this population. Ongoing inquiry and documentation of NHP use and AEs in routine clinical practice, supplemented by intensive active surveillance systems will improve our ability to identify important safety signals.

CHAPTER 6: Conclusion

Summary

This thesis was undertaken to enhance our understanding of clinically important natural health product (NHP)-associated adverse events (AEs), including NHP-drug interactions in patients with cancer. Two systematic reviews were conducted to synthesize the existing clinical evidence on the efficacy and safety of concurrent use of NHPs and two classes of anticancer medications, immunotherapies and antimicrotubule anticancer agents. Available evidence is heterogeneous and primarily consists of phase I and II clinical trials and pilot studies with methodological limitations, as well as case series and reports. Several AEs associated with NHPs were identified in the reviews. In particular, safety signals with the use of vitamins C, D, and E, milk thistle, and turmeric alongside antimicrotubule agents were identified. The efficacy and safety data on concurrent anticancer medication and NHP use identified in the systematic reviews are best considered hypothesis-generating, as opposed to hypothesis-proving. This thesis has identified important gaps in the literature and has several implications for future research.

Active surveillance was implemented in adult and pediatric cancer centres across Canada as part of routine clinical workflow to detect NHP use and associated AEs. The majority of patients with cancer, both adults and children, take NHPs and many take them along with prescription medications. The prevalence of AEs during prescription drug use and concurrent NHP and prescription drug use was high, but similar between groups. This is in contrast to active surveillance conducted by our research team in community pharmacies as well as mental health and HIV clinics, all of which saw an increase in the proportion of patients reporting AEs if they were taking both NHPs and prescription medications as compared to prescriptions alone.[47–50] Since a cross-sectional study design was used and a high loss to follow-up occurred prior to causality adjudication, we were only able to report on potential associations and not causal relationships between NHPs and AEs. With careful examination of this limitation and others, there are a few important next steps for further work in this area.

Limitations

<u>Systematic reviews</u>

1. **Internal validity of available evidence & reporting of harms:** The available evidence on concurrent NHPs and anticancer antimicrotubule agents and immunotherapies had

several limitations. In most of the papers included in the systematic reviews, harms were secondary outcomes, and in a few papers, they were not reported at all. Where harms were reported, variable detail was provided on how harms-related data was collected. This information was generally limited to whether AEs were clinician or patient reported, without adequate detail on the mode of data collection (e.g., questionnaires, interviews, tests), the timing of data collection, or how attribution of the AE to the NHP or other intervention was performed.[101,152] There is no universally accepted method for attribution of the event to an intervention, or causality assessment.[212] However, a number of methods do exist, and some are specifically developed for NHPs.[47,94,96,184,210–213] Exact methods used were often not described in the papers included in the systematic reviews, making it difficult to determine the true likelihood that the AE(s) were caused by the NHP of interest. Additionally, since many studies were designed to determine whether the addition of an NHP increased the effectiveness of anticancer medications or reduced their side effects, the high risk of bias present in most studies with a comparison group may have biased the results away from the null hypothesis. Therefore, these studies were more likely to show an increase in beneficial effects and decrease in harmful effects. The remaining papers were primarily phase I/II clinical studies without a comparison group. Phase I and II studies are important for drug development, but they often lack sufficient power to detect uncommon AEs and have a short duration, which may also overestimate benefits and underestimate harms.[143,186]

2. **External validity of available evidence:** There are challenges in the generalizability of the systematic review findings. The heterogeneity in the available research prevented meta-analysis and the ability to provide concrete direction on clinical guidance. Study participants had a range of cancer diagnoses and cancer-related conditions, and outcomes for both safety and efficacy varied substantially among studies. Also limiting the generalizability of the systematic reviews is the complexity and variability of anticancer regimens, often involving multiple agents administered concurrently. Although the use of multiple agents mimics usual practice,[45,46] it is challenging to extrapolate findings in which the doses, frequencies, and concurrent therapies vary among studies and may also differ from the regimens being used in practice, which may also vary between sites.

Despite this, we were able to summarize the findings for several commonly used anticancer agents. Unique obstacles also exist in generalizing the results based on NHP use, and this must be done with caution. Frequently, the NHPs studied do not match the products being used in a clinical setting. We aimed to overcome these limitations by focusing on a clinically relevant list of NHPs selected based on Canadian population data and clinical expertise. Commercially available formulations of NHPs may vary from the product studied, and many NHPs are available in combination products over the counter.[39,40,65,70,207] Additionally, even products with the same single ingredient can have significant variation in their content, varying between brands but also within brands between batches.[39,40,65,70,207] This highlights the importance of using real world data, such as that used in SONAR active surveillance.

3. **Gaps in studied NHPs and anticancer medications:** Of the NHPs included in the search (garlic, ginseng, milk thistle, mistletoe, probiotics, turmeric, vitamin C, vitamin D, and vitamin E) there was evidence of each one of them being used concurrently with antimicrotubule agents in at least one paper. For concurrent use with immunotherapy, no clinical data were identified for garlic, milk thistle, or turmeric. There were not studies that focused on each of the available antimicrotubule medications or immunotherapies. These systematic reviews aimed to focus on a list of NHPs that were relevant to cancer care in terms of their frequency of use, and potential for interaction with anticancer medications. However, this list was not all-inclusive, and as data are continued to be collected in this area and NHP use changes over time, other relevant NHPs are likely to be identified. Additionally, while cannabis falls outside Health Canada's definition of NHPs, it is often considered a complementary therapy and has clinical relevance for patients with cancer, particularly since the recent legalization of recreational use in Canada.[1,2,267] It is also important to note that a total of eight groups of anticancer agents were identified by our research team as necessary to review NHP-drug interactions; this thesis focused on only two of those drug categories for feasibility reasons. Further assessment of all relevant classes of anticancer agents would be worthwhile.

Active surveillance

1. **Information bias:** As a cross-sectional study design was used for active surveillance, information bias is possible. Frequently, NHP use is discouraged during chemotherapy, radiation therapy or cancer surgery.[268] Therefore, social desirability bias may have been present.[246] It is possible that some patients using NHPs did not want to disclose AEs to their healthcare team due to fear of judgement.[11,12,225]

2. **Selection bias:** Only seven cancer centres across Canada participated in these active-surveillance studies. Additionally, only some clinics and clinicians within these centres participated. Therefore, it is possible that selection bias exists where patients screened at participating clinics were not representative of the overall population of patients with cancer.[269] This is particularly relevant among adult patients as clinics were often diagnosis-based, meaning that some cancer diagnoses are likely over-represented in the sample. This likely contributed to the distribution of sex in our adult data, as several clinics seeing female-predominate cancers participated. It is also possible that selection bias exists because patients were screened at ambulatory clinics, and this requires patients to be healthy enough to attend; those with more severe illness may have been excluded.[269] Although staff and clinicians that were involved in the screening process were instructed to screen consecutive patients, it is possible that those selected or willing to participate also contributed to potential bias.

3. **Confounding:** Confounding may have occurred in which a variable associated with NHP and/or prescription drug use influenced the likelihood of experiencing an AE.[269] Limited data were gathered on patient characteristics beyond the exposures and outcome of interest. As a result, only cancer centre was adjusted for in the multivariate analysis. Likely several unmeasured and unknown confounders still exist and were not controlled for, leading to residual confounding. Further exacerbating this is the potential heterogeneity in patients as they were attending both new and follow-up visits. This means that patients may have accessed care at various phases within the cancer care trajectory, including at diagnosis or relapse and during or after cancer treatment. The decision to use NHPs is often reevaluated based on changes in health status or other

treatment landmarks[20,24,25] so the patient's phase of care may have had an impact on NHP use. Health status and the use of varying non-drug cancer treatments (e.g., radiation, surgery) at different phases of care could have also impacted the AEs experienced.

4. **Causality:** It is not possible for us to make causal inferences due to the cross-sectional design of these studies. Therefore, we were only able to report on the associations between drug or product taken and AE(s) experienced. Interpreting the associations is challenging because we were unable to investigate the temporal relationship since both exposure and outcome data are collected simultaneously. Reverse causation may exist where the use of an NHP is the result of an AE, rather than its cause.[259] A causality assessment procedure was planned for patients taking an NHP and reporting a serious AE. Substantial loss to follow-up occurred prior to this step, and therefore, for most cases we were unable to report on whether the AEs reported were caused by prescription medications, NHPs, or other factors.[179]

5. **AEs in oncology:** The proportion of patients on prescription medications alone reporting AEs was much higher in patients with cancer as compared to what was seen in SONAR studies in community pharmacies, mental health clinics and HIV clinics.[47–50,94,95] It was also common for patients with cancer to report more than one AE in the last one month. This is likely due to the toxicity of anticancer drugs, which include a wide range of side effects.[270] Symptoms of cancer may also have contributed to reported AEs.[270] Since the toxicity of anticancer medications may be perceived as "normal" by patients with cancer,[270] it may be more difficult to detect differences in AEs that occur with the addition of NHPs, particularly if the symptoms and/or symptom severity fluctuate over time. Accurate determination of the severity of each AE reported is required.[270] Moreover, it is likely that our cross-sectional studies incompletely detected potential reduction in cancer treatment effectiveness. Although healthcare providers were asked to report AEs that "caused a delay or change in treatment," cancer treatment failure is likely best evaluated using other study designs.[86]

6. **NHP definition:** The Health Canada definition of NHPs[1] was used for classifying patient groups in active surveillance as used in previous SONAR studies.[47–50,94,95] While these NHPs share the same regulations, it is important to consider the diversity of products included in this definition and also what is not included, such as cannabis and drugs which require a prescription that are derived from natural sources.[1,76] Given the inherent differences that exist between products such as vitamins and minerals as compared to herbal medicines,[39] there may also be variations in their influence on drug interactions and AEs. A large proportion of patients screened were using vitamins and minerals, which may have had an impact on the AE prevalence observed. By adopting active surveillance of NHP-related AEs in patients with cancer more widely, the development of a population-based database would be possible to look further at potential differences among products.

7. **Reported medications:** Some patients that were screened at participating clinics who were taking prescription medications did not report any anticancer medications. It is possible that patients were screened prior to or more than one month post chemotherapy treatment. It is also possible that patients did not completely report this as they assumed the clinic already had this information or they were uncertain about these medications. However, the screening form did specify that patients report anticancer medications and other prescription medications and prompted patients to ask their healthcare team if uncertain of their medications. There were also several patients that did not record the specific medications they were taking, and therefore these data were missing.

Implications for Research

Harms Reporting in Primary Research on NHPs

The systematic reviews in this thesis identified that clinical studies determining the effects of concurrent NHP and anticancer medications are limited, particularly on immunotherapies. Ongoing clinical research in this area, particularly when safety signals are identified, will facilitate evidence-based clinical practice and support decision making. With this research, it is likely that challenges will always exist in extrapolating NHPs studied to those used by patients seen in clinic.[39,40,65,70,207] However, the consolidated standards of reporting trials (CONSORT) statement for herbal interventions provides a number of recommendations for

complete and accurate reporting.[271] Reproducibility and clinical applicability of the study is enhanced by providing precise details of NHPs used, including product name, characteristics, dosage regimen, and any chemical and purity testing conducted.[271] Similar recommendations exist for published case reports on AEs following NHP use.[101] Clear reporting will assist clinicians in determining whether results apply to the clinical context, including whether variations in NHP content or contaminants had a role in outcome.

Enhanced reporting on harms data is also required in studies on the use of NHPs in patients with cancer, as it is currently suboptimal. In particular, improvements are required in describing how harms-related information was collected, and presenting the absolute risk of each AE as per the harms extension of the CONSORT statement.[152] How harms data were collected, when it was collected, and the rules around stopping the trial for harms should be included.[152] The grade and seriousness of AEs should also be described.[152] Causality assessment of AEs should be performed using available tools.[96,99,142]

Additional Syntheses

The synthesis of clinical evidence on the efficacy and safety of concurrent use of NHPs with other classes of anticancer medications is needed, including antimetabolites, alkylating agents, endocrine therapies, platinum analogs, small molecule inhibitors, and topoisomerase inhibitors. This is a current priority of our research team. Furthermore, future efforts could look at expanding the list of NHPs reviewed. While having consistency among NHPs reviewed in our systematic reviews may be beneficial for the development of an NHP-drug interaction tool,[272] selection of NHPs with the strongest preclinical evidence of interaction or AE potential with each class of anticancer medication should be considered moving forward. Our active surveillance results can further contribute to NHP utilization data by identifying NHPs commonly used by patients with cancer. With careful consideration of cannabis-specific research challenges,[273,274] it would be also be meaningful to evaluate the effects of concurrent cannabis and anticancer medications.

SONAR Active Surveillance Methods

Based on the experiences and limitations identified with the active surveillance studies, several opportunities have been identified. Seeking further information on patient characteristics as part of screening is suggested. This could include health status or phase of cancer care, and

other patient demographic information (e.g., age, comorbidities, other concurrent treatments – surgeries, radiation). There is also an opportunity for linking screening data with existing electronic medical records, disease registries, or laboratory test result repositories to collect additional patient information.[143] It is recommended that at least one additional source of information is used to verify patient reported medication use as part of a Best Possible Medication History (BPMH).[264] Therefore, linking to existing data sources may also improve the accuracy and completeness of the patients' anticancer and prescription medication history.

Our study team aimed to address the high rate of losses to follow-up prior to the telephone interview by asking patients to identify what actions they took regarding the AE on the initial screening form. This was to narrow the focus of follow-up to those who may have experienced the most clinically relevant AEs. This also allowed for the collection of meaningful information regarding the seriousness of the AEs without additional follow-up. However, there is still opportunity to enhance our understanding of serious AEs and their causation. The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement System could be incorporated into the questionnaire.[239] It utilizes plain-language symptom terms and prompts to indicate the frequency, severity, and interference of the symptom.[239] This is suggested because although the actions patients take as a result of an AE provide us some insight into seriousness, it may not always accurately reflect this. For example, if a patient experienced moderate dyspepsia requiring medical intervention, this would be classified as grade 2, or not severe, by the CTCAE version 5.0;[133] however, we would have classified this as serious, based on our methods. CTCAE grade 3 or higher describes an AE that involves hospitalization, prolongation of hospitalization, life-threatening consequences or death, which matches the definition of a serious AE as defined by Health Canada.[233] Although our method was likely conservative in classifying AEs more serious than they were, utilizing PRO-CTCAE[239] as part of our screening may reduce the risk of such discrepancies. Accurately grading each AE reported would be useful in determining the clinical relevance of AEs, particularly as it was found that this patient population commonly reported more than one AE at a time.

The use of an electronic screening form, versus the paper-based form used in these studies, would be helpful, particularly if adding in screening questions. Electronic questionnaires have shown to decrease the amount of missing information compared to paper-based.[275] For

example, information on the duration of use of each medication or NHP was included on our screening form, but patient report of this information was often partially or completely missing. The use of an electronic form may improve the report of this information at initial screening, and therefore, valuable information on temporal relationships.

The NHP utilization data gleaned from our active surveillance studies can be used to design future studies with an ample sample size to evaluate separate categories of NHPs, such as vitamins/minerals, herbal medicines, and fatty acid supplements. This would allow for the determination of differences, if any, that may exist in AE prevalence amongst some NHPs. However, due to the variety of NHPs available, it is essential that active surveillance is adopted more widely to facilitate the development of a population-based database. Consideration should also be given to narrowing the inclusion criteria for screening to patients who are actively being treated with anticancer medications to reduce heterogeneity and enhance the ability to detect potential NHP-anticancer medication interactions.

Longitudinal Studies

There is also an opportunity to utilize a longitudinal study design to capture NHP and prescription medication use, and AEs experienced over time. The choice to use NHPs does not happen at one time point during cancer care, it is revisited throughout, meaning that the use of NHPs is likely to fluctuate in this patient population;[24] cancer treatments also commonly change over time. Since exposures are expected to shift throughout phases of care, longitudinal studies may be helpful to observe patients over a period of time and allow for the calculation of incidence.[86] This may also be particularly valuable for time-dependent outcomes, such as time to cancer progression or survival, which may be influenced by changes in anticancer medication effectiveness. Such studies may be prospective, relying on the generation of primary data to conduct this research.[276] If improved clinical documentation of NHP use occurs, secondary data could be used to conduct retrospective longitudinal studies.[276]

Implications for Clinical Practice

Clinical Care

Active screening for NHP use and AEs was successfully integrated into routine care at several cancer centres. Patient disclosure of NHP use to conventional healthcare providers' is historically very low, often due to a lack of inquiry by the provider.[9–15] Our screening methods

can serve as a guide for clinician-initiated discussion by directly asking about NHP use and AEs experienced as part of best possible medication histories during ambulatory cancer care visits and across transitions of care.[11,264] Not only does this have opportunity to enhance rapport between provider and patient, facilitate shared-decision making and increase patient satisfaction, it allows for close monitoring of efficacy and safety.[11,13,28]

Electronic medical records are increasingly part of standard care in Canada.[247,265] This provides a great opportunity for the documentation of patient NHP use by healthcare providers and the tracking of this use. Various outcome measures, such as AEs, can also be studied through routine electronic healthcare data.[85] Over time, electronic medical records can become a valuable real world data source for use in longitudinal studies and other pharmacovigilance efforts for NHPs.[85,265,276]

Knowledge Translation

A number of pharmacist responsibilities around NHPs have been identified in the literature, including being knowledgeable about, providing education on, and ensuring safe and appropriate use of NHPs.[3–5] Pharmacists, as drug experts, are well-positioned to lead conversations with patients about NHP use.[12] The role of a pharmacist involves assessing the indication, efficacy, safety, and adherence of medications.[12,277] This role also involves the understanding and awareness of potential drug interactions.[12,277] However, it appears that a perceived lack of knowledge about NHPs contributes to pharmacist reluctance to counsel on NHPs or report NHP-associated AEs.[3,278] Similarly, lack of training and limited knowledge about NHPs appear to prevent physician engagement in discussions about NHPs.[279] Patient disappointment with the lack of information or support provided by conventional health practitioners is also apparent.[11]

This thesis has major implications for knowledge translation. First, all available clinical research has been synthesized on concomitant use of NHPs relevant for cancer care and immunotherapy and antimicrotubule anticancer medications. These systematic reviews will be published in high impact, open access journals and presented at relevant conferences. Additionally, we plan to use the results of these systematic reviews to supplement ongoing work by our research team to develop clinician tools.[272] A quick-reference, oncology-specific NHP-drug interaction tool is planned to provide an evidence-based resource for frontline clinicians. The systematic reviews can also be incorporated into existing web tools, such as Knowledge in

Integrative Oncology Website (KNOW), which provides a summary of human studies on natural agents in cancer care.[280]

Implications for Policy

Pharmacovigilance

Completing my thesis during the COVID-19 pandemic has been a unique experience. Two key policy opportunities, related to this thesis, have also been highlighted by the pandemic: 1) the need to address misleading claims and misinformation of health products,[281] and 2) establishing robust safety surveillance systems.[282] The spread of misinformation, including that of NHPs, has been amplified by the COVID-19 pandemic.[282] The first step identified to address and manage an infodemic, "too much information including false or misleading information", is to identify, collate, review, and appraise available evidence.[282,283] While this ongoing effort is important as it relates to COVID-19, the momentum should continue to combat misinformation and enhance safety of NHPs used for other conditions, such as cancer. The systematic reviews of this thesis have begun taking steps to identify and synthesize clinical evidence on the use of NHPs during cancer treatment, and there is an opportunity to work with health authorities, such as Health Canada, to communicate and translate this information to the public, as well as continue the synthesis of this information in a coordinated manner.[282]

Countries have been recommended to strengthen their surveillance systems for the detection of AEs following COVID-19 immunization, and it is important that these efforts are sustained in the monitoring of other health products.[282] With the completion of this work on active surveillance of NHP use and AEs in cancer centres coinciding with an international call for enhanced pharmacovigilance, there is great opportunity to capitalize on the focus on safety surveillance and collaborate with health authorities.[282] Ongoing active surveillance of NHP-related AEs in patients with cancer is necessary for patient safety. Our active surveillance method, utilizing structured patient interviews regarding NHP use, can be used to complement existing passive surveillance processes.[47,50,83,85,94,95,99] Active surveillance has been shown to increase the number of AE reports and the quality of reported information, allowing for causality assessment.[47,86,94,97,98] By working with Health Canada to implement ongoing intensive monitoring, it will be possible to collect more data on NHPs and associated AEs. Systematic data collection efforts can facilitate the development of a population-based database that can be used for information sharing and the identification of safety signals.[116,186,215,216,245]

Conclusion

This work has expanded our understanding on the safety of NHP use in patients with cancer. Contrary to our hypothesis, and to our surprise, active surveillance did not demonstrate that patients with cancer who take NHPs are at a higher risk of experiencing clinically important AEs. Critical considerations of this work include that each type of NHP may have differing impacts on AEs, and it is not possible to determine NHP causation of harm using these studies alone. Several NHP-associated AEs and NHP-drug interactions were identified in our systematic reviews. Although these safety signals are hypothesis generating, as opposed to hypothesis-proving, they are a reminder that NHP use cannot be ignored throughout patient care. Until important research gaps are addressed, recommendations on the use of NHPs in patients with cancer must be individualized; given the seriousness of the condition being treated, continued caution about polypharmacy appears prudent.

There is a continued need for clinical research on the use of NHPs with anticancer medications, particularly when safety signals are detected. Causality assessment is crucial to improve our understanding of the NHP-associated AEs in this population. Clinical studies should also be designed in a way to minimize bias and improve the reporting of the NHP interventions used and harms-related outcomes. An increase in primary studies in this area will facilitate ongoing efforts to synthesize and disseminate evidence-based information on the use of NHPs in patients with cancer and support clinicians in shared-decision making.

Active screening for NHP use and AEs was successfully integrated into clinical workflow. There are opportunities for enhancement of our active surveillance method by screening only patients being actively treated with anticancer medications, utilizing an electronic screening form, incorporating validated patient-reported AE measurement systems and additional demographic questions, and linking to healthcare databases. Our active surveillance methods can be adopted more widely to be used as a framework for improved inquiry and documentation of NHP use and AEs in routine oncology practice, and to augment pharmacovigilance of NHPs to enhance safety signal detection through the development of a population-based database.

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APPENDICES

Appendix 2.1 MEDLINE Search Strategy (Immunotherapy)

1. exp Neoplasms/
2. exp CARCINOMA/
3. cancer.mp.
4. exp INTEGRATIVE ONCOLOGY/
5. oncology.mp.
6. or/1-5
7. exp IMMUNOTHERAPY/
8. exp Biological Products/
9. exp Antibodies, Monoclonal/
10. exp RITUXIMAB/
11. ofatumumab.mp.
12. Obinutuzumab.mp.
13. Ibritumomab.mp.
14. Tositumomab.mp.
15. exp ALEMTUZUMAB/
16. Blinatumomab.mp.
17. Brentuximab.mp.
18. Daratumumab.mp.
19. Dinutuximab.mp.
20. Gemtuzumab.mp.
21. Inotuzumab.mp.
22. exp IPILIMUMAB/
23. Nivolumab.mp.
24. Pembrolizumab.mp.
25. Cemiplimab.mp.
26. exp DENOSUMAB/
27. Elotuzumab.mp.
28. Siltuximab.mp.
29. Avelumab.mp.
30. Durvalumab.mp.
31. Atezolizumab.mp.
32. exp CETUXIMAB/
33. Panitumumab.mp.
34. Necitumumab.mp.
35. exp TRASTUZUMAB/
36. pertuzumab.mp.
37. exp BEVACIZUMAB/
38. ramucirumab.mp.
39. olaratumab.mp.
40. exp Interferons/
41. exp Interleukins/
42. exp Interleukin-2/
43. exp Interferon-alpha/
44. tisagenlecleucel.mp.
45. axicabtagene.mp.
46. Denileukin.mp.
47. Aflibercept.mp.
48. exp Cancer Vaccines/
49. Talimogene Laherparepvec.mp.
50. exp BCG Vaccine/
51. exp THALIDOMIDE/
52. lenalidomide.mp.
53. pomalidomide.mp.
54. or/7-53
55. exp GARLIC/
56. Sativum allium.mp.
57. Allium sativum.mp.
58. exp PANAX/
59. ginseng.mp.
60. american ginseng.mp.
61. exp Milk Thistle/
62. milk thistle.mp.
63. exp Ascorbic Acid/
64. vitamin c.mp.
65. Vitamin D.ti,ab.
66. exp Vitamin E/
67. Vitamin E.ti,ab.
68. exp Curcuma/
69. turmeric.mp.
70. exp MISTLETOE/
71. mistletoe.mp.
72. exp PROBIOTICS/
73. exp LACTOBACILLUS ACIDOPHILUS/
74. exp Lactobacillus/
75. exp BIFIDOBACTERIUM/
76. exp SACCHAROMYCES BOULARDII/
77. vsl3.mp.
78. or/55-77
79. exp Drug Interactions/
80. exp Herb-Drug Interactions/
81. exp "Drug-Related Side Effects and Adverse Reactions"/
82. drug toxicity.mp.
83. exp Drug Monitoring/
84. exp Adverse Drug Reaction Reporting Systems/
85. side effect$.mp.
86. adverse drug reaction.mp.
87. drug interaction$.mp.
88. adverse effect.mp.
89. adverse event.mp.
90. drug safety.mp.
91. drug complication.mp.
92. harm.mp.
93. drug harm.mp.
94. drug intolerance.mp.
95. exp Disease Progression/
96. exp SURVIVAL/
97. exp "Quality of Life"/
98. common terminology criteria for adverse events.mp.
99. or/79-98
100. 6 and 54 and 78 and 99

Appendix 3.1 MEDLINE Search Strategy (Antimicrotubule)

1. exp Neoplasms/
2. exp CARCINOMA/
3. cancer.mp.
4. exp INTEGRATIVE ONCOLOGY/
5. oncology.mp.
6. or/1-5
7. exp Tubulin Modulators/
8. exp Taxoids/
9. antimicrotubular.mp.
10. exp Antimitotic Agents/
11. taxane.mp.
12. exp Paclitaxel/
13. exp Docetaxel/
14. cabazitaxel.mp.
15. exp Vinca Alkaloids/
16. exp Vincristine/
17. exp Vinblastine/
18. exp Vinorelbine/
19. exp Vindesine/
20. eribulin.mp.
21. exp Estramustine/
22. Ixabepilone.mp.
23. or/7-22
24. exp GARLIC/
25. Sativum allium.mp.
26. Allium sativum.mp.
27. exp PANAX/
28. ginseng.mp.
29. american ginseng.mp.
30. exp Milk Thistle/
31. milk thistle.mp.
32. exp Ascorbic Acid/
33. vitamin c.mp.
34. Vitamin D.ti,ab.
35. exp Vitamin E/
36. Vitamin E.ti,ab.
37. exp Curcuma/
38. turmeric.mp.
39. exp MISTLETOE/
40. mistletoe.mp.
41. exp PROBIOTICS/
42. exp LACTOBACILLUS ACIDOPHILUS/
43. exp Lactobacillus/
44. exp BIFIDOBACTERIUM/
45. exp SACCHAROMYCES BOULARDII/
46. vsl3.mp.
47. or/24-46
48. exp Drug Interactions/
49. exp Herb-Drug Interactions/
50. exp "Drug-Related Side Effects and Adverse Reactions"/
51. drug toxicity.mp.
52. exp Drug Monitoring/
53. exp Adverse Drug Reaction Reporting Systems/
54. side effect$.mp.
55. adverse drug reaction.mp.
56. drug interaction$.mp.
57. adverse effect.mp.
58. adverse event.mp.
59. drug safety.mp.
60. drug complication.mp.
61. harm.mp.
62. drug harm.mp.
63. drug intolerance.mp.
64. exp Disease Progression/
65. exp SURVIVAL/
66. exp "Quality of Life"/
67. common terminology criteria for adverse events.mp.
68. or/48-67
69. 6 and 23 and 47 and 68

Appendix 4.1 Adult screening form

Date: D D / M M / Y Y Y Y [Insert Institute Name]: [Insert Oncologist Name],[Insert Clinic Name]

Natural Health Product – Drug Assessment

Please note this form is ONLY to be completed by patients or their legal guardians

Our goal is to help our patients maintain and improve their health. Your health care team needs to know about all the products you take in order to provide you with the best care possible.

FOR PATIENT Gender: ○ Male ○ Female Cancer Diagnosis: _____

① In the last month, have you taken any anticancer or prescription medications? ○ Yes ○ No
*If **Yes**, list the medications and for how long they have been taken. If unsure, please ask your healthcare team.*

② In the last month, have you taken any natural health products (NHPs) e.g. vitamins, minerals, herbals, homeopathic remedies, traditional Chinese medicines, probiotics etc.? ● Yes ○ No
*If **Yes**, list the NHP and for how long have they been taken. Please try to be as specific as possible.*

③ In the last 1 month, have you experienced any undesirable effects? ○ Yes ○ No
*If **Yes**, describe these effects.*

④ What did you do about it?
A ○ Nothing/treated it myself
B ○ Phoned for information
C ○ Saw doctor about it
D ● Doctor treated it
E ● I was hospitalized because of it

FOR HEALTH CARE PROVIDER USE ONLY

Please describe if the adverse effect was:
● * Serious (≥3 grade CTCAE) and unexpected
OR
● Caused a delay or change in treatment

FOR HEALTH CARE PROVIDER USE ONLY

⑤ In the last month, has the patient had any other serious and unexpected adverse effect? ● Yes ○ No
*If **Yes**, describe the effect*

Please identify if:
○ * Serious (≥3 grade CTCAE) and unexpected
OR
○ Caused a delay or change in treatment

PATIENT CONSENT FOR CONTACT

IF ANSWERED ● Yes To Q2, and any one of Q4D, Q4E or Q5, please give SONAR information sheet to the patient and seek consent to participate.

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Form Version June 29, 2015

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Appendix 4.2 Adult multivariate logistic regression

Table A4.2.1 Comparison of the proportion of patients reporting adverse events between prescription medication use alone, NHP use alone and concurrent prescription drug and NHP use adjusted for cancer centre

Variable		OR (95% CI)	P-value
Product use	Prescriptions alone	Reference	
	NHP alone	0.16 (0.09 – 0.30)	<0.0001
	Concurrent	0.85 (0.62 – 1.16)	0.298
Cancer centre	Centre 1	Reference	
	Centre 2	0.68 (0.48 – 0.95)	0.026
	Centre 3	0.27 (0.16 – 0.46)	<0.0001
	Centre 4	0.86 (0.50 – 1.48)	0.587

Appendix 4.3 Adult serious adverse event details

Table A4.3.1 Serious adverse events reported by patients on prescription medications only

Sex	Diagnosis	Prescription Drug(s)	Adverse Event(s) Classified by CTCAE	Result of Adverse Event(s)
--	--	**capecitabine**	thromboembolic event	phoned for information saw or asked doctor about it doctor treated it caused a delay or change in treatment (healthcare provider report)
--	--	hydromorphone lorazepam oxycodone	pain	doctor treated it
F	--	pegfilgrastim	fever	was hospitalized
--	--	beta blocker blood pressure medication warfarin	renal calculi	doctor treated it
F	--	**letrozole**	hot flashes tremor	saw or asked doctor about it unexpected (healthcare provider report)
F	--	**doxorubicin** dexamethasone fluticasone metoclopramide	anorexia	nothing/treated it themselves doctor treated it

		salmeterol tinzaparin tiotropium		
F	--	**chemotherapy** anti-emetic dexamethasone diphenhydramine filgrastim mometasone nitrofurantoin ondansetron	rash	doctor treated it
F	breast cancer	**capecitabine**	diarrhea hypokalemia rash	phoned for information doctor treated it
F	metastatic breast cancer	**capecitabine** antibiotics clodronate lorazepam metoclopramide morphine	fatigue fever nausea pain vomiting	doctor treated it was hospitalized
F	breast cancer	**letrozole** candesartan citalopram gabapentin hydrochlorothiazide insulin aspart insulin glargine lansoprazole metformin naproxen ondansetron tramadol	cognitive disturbance confusion peripheral sensory neuropathy	doctor treated it
F	lung cancer	**gefitinib** amlodipine celecoxib domperidone irbesartan levothyroxine metoprolol nitrofurantoin	diarrhea fatigue nausea rash	doctor treated it

		omeprazole paroxetine sucralfate zopiclone		
M	melanoma	**pembrolizumab** codeine metoclopramide	anorexia dyspnea fatigue	doctor treated it
F	melanoma	**dabrafenib** **trametinib** hydrocortisone lidocaine nystatin pilocarpine	arthritis nausea vomiting	doctor treated it
M	melanoma	**nivolumab** gabapentin hydrocortisone insulin aspart insulin glargine lansoprazole levothyroxine oxycodone	adrenal insufficiency arthritis hyperglycemia hypopituitarism	doctor treated it
M	pancreatic cancer	**gemcitabine** **paclitaxel** sitagliptin	unspecified bleeding unspecified infection	doctor treated it
F	peritoneal cancer	**bevacizumab** hydromorphone levothyroxine lorazepam metoclopramide pantoprazole perindopril zopiclone	abdominal pain fever	was hospitalized

Table A4.3.2 Serious adverse events reported by patients on natural health products only

Sex	Diagnosis	Natural Health Product(s)	Adverse Event(s) Classified by CTCAE	Result of Adverse Event(s)
F	breast cancer	astragalus curcumin melatonin modified citrus pectin probiotic vitamin d zinc	thrush	doctor treated it
F	liver cancer	calcium multivitamin vitamin c vitamin d vitamin e	unspecified surgical complications	doctor treated it

Table A4.3.3 Serious adverse events reported by patients on both prescription medications and natural health products

Sex	Diagnosis	Prescription Drug(s)	Natural Health Product(s)	Adverse Event(s) Classified by CTCAE	Result of Adverse Event(s)
--	--	**pertuzumab** **trastuzumab** allergy medication denosumab diuretic etanercept hydroxychloroquine zopiclone	calcium iron omega 3 probiotic stinging nettle seeds vitamin b17 vitamin c vitamin d vitamin e	rash maculo-papular	nothing/treated it themselves doctor treated it
--	--	fluticasone salbutamol salmeterol tiotropium zopiclone	vitamin b vitamin d	dyspnea	doctor treated it
--	--	**capecitabine** **lapatinib** denosumab pantoprazole steroid	probiotic (type 1) probiotic (type 2)	diarrhea dysarthria headache nausea vomiting	doctor treated it
--	--	**goserelin**	vitamin b	back pain	saw or asked doctor about it

		tamoxifen	vitamin c vitamin d		doctor treated it
--	--	**exemestane**	calcium vitamin d	lung infection	doctor treated it
F	--	**clinical trial drug** **goserelin** **letrozole** hydromorphone ipratropium lorazepam naproxen ondansetron pamidronate pantoprazole pregabalin ranitidine salbutamol tramadol zopiclone	melatonin	fatigue nausea pain premature menopause	nothing/treated it themselves saw or asked doctor about it doctor treated it
M	--	**carboplatin** **pemetrexed**	curcumin EGCG melatonin omega vitamin d	small intestinal obstruction	was hospitalized
--	--	anti-emetic beta blocker bladder medication morphine morphine long acting	magnesium potassium	urinary retention	phoned for information saw or asked doctor about it was hospitalized
F	--	**carboplatin** **gemcitabine** amitriptyline antibiotics codeine filgrastim gabapentin morphine ondansetron oxycodone	comprehensive immune support greens probiotic	anemia fatigue myalgia nausea neutropenia platelet count decreased vomiting	saw or asked doctor about it doctor treated it

M	--	**enzalutamide** **leuprolide** amlodipine bisoprolol gabapentin lansoprazole levodopa/carbidopa	cranberry vitalux vitamin b12 vitamin d	anaphylaxis rash	doctor treated it was hospitalized serious, unexpected and caused a delay or change in treatment (healthcare provider report)
M	--	mouthwash	multivitamin vitamin	generalized edema mucositis oral tremor	doctor treated it
F	--	dalteparin esomeprazole oxycodone pregabalin	ginger	diarrhea vomiting	doctor treated it
M	--	carvedilol fluticasone glycopyrrolate hydrocortisone rosuvastatin salbutamol salmeterol spironolactone	olive oil omega vitamin c vitamin d	dyspnea fatigue	doctor treated it
F	breast cancer	**capecitabine** **lapatinib** atorvastatin levothyroxine risedronate	multivitamin probiotic	eye infection otitis media	doctor treated it
F	breast cancer	**tamoxifen** **trastuzumab**	magnesium omega 3 vitamin b12 vitamin d	bladder infection	doctor treated it
F	breast cancer	**capecitabine** budesonide formoterol pantoprazole	dandelion root	colonic obstruction	doctor treated it
F	breast cancer	**carboplatin** **docetaxel** **trastuzumab** fluticasone	calcium multivitamin	diarrhea hypotension	was hospitalized

		levothyroxine rosuvastatin telmisartan			
F	metastatic breast cancer	**paclitaxel** **trastuzumab** dexamethasone	probiotic vitamins	pharyngitis	doctor treated it
F	stage 4 colon cancer	**fluorouracil** **leucovorin** **oxaliplatin** dexamethasone hydrocortisone lidocaine nystatin ondansetron	broccoli calcium magnesium mushroom vitamin d	cold sensitivity mucositis oral peripheral sensory neuropathy	doctor treated it
M	colorectal cancer	**capecitabine** dexamethasone ranitidine	AHCC curcumin essiac grape seed green tea magnesium melatonin milk thistle omega 3 (type 1) omega 3 (type 2) vitamin c vitamin d vitamin k vitox zinc	fatigue pelvic pain	nothing/treated it themselves doctor treated it
M	rectal cancer (T3N2)	**capecitabine** codeine	alkaline water ginger melatonin turmeric vitamin d	colitis diarrhea fatigue pain	saw or asked doctor about it doctor treated it
M	small cell lung cancer	dexamethasone lansoprazole metoclopramide tenofovir unknown	omega 3 vitamin b vitamin b12 vitamin d	dizziness gastrointestinal pain headache nausea	nothing/treated it myself doctor treated it caused a delay or change in treatment (healthcare provider report)

F	lung cancer	**ceritinib** naproxen PEG 3350	probiotic	constipation ECG changes	saw or asked doctor about it doctor treated it
F	small cell lung cancer	**carboplatin** **vinorelbine** inhaler piperacillin/tazobactam	calcium glucosamine potassium	diarrhea lung infection nausea vomiting weight loss	doctor treated it
M	lung cancer	**chemotherapy** allopurinol aspirin lansoprazole levodopa/carbidopa	folic acid multivitamin senna vitamin b12 vitamin d	mucositis oral	caused a delay or change in treatment (healthcare provider report)
F	lung cancer	**gefitinib** clobetasol betamethasone minocycline valsartan	aloe vera asparagus puree cayenne pepper juice protein powder wheat grass	dyspnea edema limbs generalized muscle weakness	nothing/treated it myself doctor treated it
M	lung cancer	**pembrolizumab** antibiotic aspirin/dipyridamole pantoprazole prednisone	grape seed	pneumonitis	serious (healthcare provider report)
M	metastatic melanoma	**dabrafenib** **trametinib** tinzaparin	multivitamin	headache nausea	doctor treated it
F	ovarian cancer	bladder medication ciprofloxacin levothyroxine solifenacin	multivitamin	nausea	doctor treated it

Table A4.3.4 Serious adverse event causality assessment

Age	Sex	Diagnosis	Prescription Drugs	NHPs	AE Description	WHO-UMC Causality Assessment Scale
72	F	breast cancer	1. cephalexin 500mg orally four times daily for 7 days 2. eribulin 1.4 mg/m2 (2.25mg) IV on days 1 and 8 of a 21-day treatment cycle which was then reduced to 1.75mg for the remaining 7 cycles	1. calcium 600mg orally daily 2. halibut liver oil 1000mg orally daily 3. multivitamin 1 tablet orally daily	anorexia bladder infection blurred vision dry skin (feet) lung infection nail changes paresthesia (fingers & toes) pleural effusion weight loss	unlikely

Appendix 5.1 Pediatric screening form

Date: D D / M M / Y Y Y Y [Insert Institute Name]: [Insert Oncologist Name],[Insert Clinic Name]

Natural Health Product – Drug Assessment

Please note this form is ONLY to be completed by patients or their legal guardians

Our goal is to help our patients maintain and improve their health. Your health care team needs to know about all the products your child takes in order to provide the best care possible.

FOR PATIENT Gender: ○ Male ○ Female Cancer Diagnosis: _____

① In the last month, has your child taken any anticancer or prescription medications? ○ Yes ○ No
*If **Yes**, list the medications and for how long they have been taken. If unsure, please ask your healthcare team.*

② In the last month, has your child taken any natural health products (NHPs) e.g. vitamins, minerals, herbals, homeopathic remedies, traditional Chinese medicines, probiotics etc.? ○ Yes ○ No
*If **Yes**, list the NHP and for how long have they been taken. Please try to be as specific as possible.*

③ In the last 1 month, has your child experienced any undesirable effects? ○ Yes ○ No
*If **Yes**, describe these effects.*

④ What did you do about it?
A ○ Nothing/treated it myself
B ○ Phoned for information
C ○ Saw doctor about it
D ○ Doctor treated it
E ○ I was hospitalized because of it

FOR HEALTH CARE PROVIDER USE ONLY

Please describe if the adverse effect was:
○ * Serious (≥3 grade CTCAE) and unexpected
OR
○ Caused a delay or change in treatment

FOR HEALTH CARE PROVIDER USE ONLY

⑤ In the last month, has the patient had any other serious and unexpected adverse effect? ○ Yes ○ No
*If **Yes**, describe the effect*

Please identify if:
○ * Serious (≥3 grade CTCAE) and unexpected
OR
○ Caused a delay or change in treatment

PATIENT CONSENT FOR CONTACT

IF ANSWERED ○ Yes To Q2, and any one of Q4D, Q4E or Q5, please give SONAR information sheet to the patient's guardian and seek consent to participate.

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Form Version June 29, 2015

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Appendix 5.2 Pediatric multivariate logistic regression

Table A5.2.1 Comparison of the proportion of patients reporting adverse events between prescription medication use alone, NHP use alone and concurrent prescription drug and NHP use adjusted for cancer centre

Variable		OR (95% CI)	P-value
Product use	Prescriptions alone	Reference	
	NHP alone	0.07 (0.01 – 0.30)	<0.0001
	Concurrent	0.99 (0.56 – 1.77)	0.981
Cancer centre	Centre 1	Reference	
	Centre 2	0.36 (0.19 – 0.70)	0.003
	Centre 3	0.52 (0.22 – 1.24)	0.143

Appendix 5.3 Pediatric serious adverse event details

Table A5.3.1 Serious adverse events reported by patients on prescription medications only

Sex	Diagnosis	Prescription Drug(s)	Adverse Event(s) Classified by CTCAE	Result of Adverse Event(s)
F	ALL	**mercaptopurine** **vincristine** allopurinol ganciclovir pentamidine prednisone	anemia muscle cramps neutropenia	nothing/treated it themselves doctor treated it
M	Wilms tumor	**dactinomycin** **vincristine** pantoprazole sulfamethoxazole/trimethoprim	vomiting	was hospitalized
F	Hodgkins lymphoma	**bleomycin** **cyclophosphamide** **doxorubicin** **etoposide** **vincristine**	constipation	doctor treated it
F	ALL	**methotrexate** **vincristine** hydrocortisone lidocaine morphine nystatin	anorexia constipation fatigue mucositis oral nausea vomiting	phoned for information saw or asked doctor about it was hospitalized

		ondansetron PEG 3350 sulfamethoxazole/trimethoprim		
M	ALL B-cell	**asparaginase** **cyclophosphamide** **cytarabine** **methotrexate** **mercaptopurine** **vincristine**	appendicitis typhlitis	was hospitalized
M	ALL	**methotrexate** **mercaptopurine** prednisone sulfamethoxazole/trimethoprim	anxiety dry skin dyspepsia headache mucositis oral vomiting	saw or asked doctor about it doctor treated it
M	lymphoma	**asparaginase** **daunorubicin** **doxorubicin** **methotrexate** **mercaptopurine** **thioguanine** **vincristine** citalopram ondansetron sulfamethoxazole/trimethoprim	alopecia anorexia gait disturbance mucositis oral	waw or asked doctor about it caused a delay or change in treatment (healthcare provider report)
M	ALL	**vincristine** dexamethasone gabapentin	migraine pain in extremity	doctor treated it was hospitalized
F	Anaplastic ependymoma grade 3	**chemotherapy** **vincristine**	alopecia anemia weight loss	saw or asked doctor about it was hospitalized caused a delay or change in treatment (healthcare provider report)
M	--	**methotrexate** ondansetron	unspecified skin erythema vomiting	doctor treated it

Table A5.3.2 Serious adverse events reported by patients on both prescription medications and natural health products

Sex	Diagnosis	Prescription Drug(s)	Natural Health Product(s)	Adverse Event(s) Classified by CTCAE	Result of Adverse Event(s)
F	--	**mercaptopurine** **methotrexate** **vincristine** ondansetron pantoprazole prednisone sulfamethoxazole/trimethoprim	basil leaves ginger omega 3 vitamin c vitamin d	anorexia fever malaise pain	doctor treated it
M	ALL	**mercaptopurine** dexamethasone sulfamethoxazole/trimethoprim	vitamin d	constipation diarrhea nausea pain in extremity peripheral motor neuropathy vomiting	saw or asked doctor about it doctor treated it
M	ALL	**mercaptopurine** **methotrexate** dexamethasone	multivitamin	anorexia fatigue nausea	doctor treated it
F	ALL	**chemotherapy** anesthetic antibiotic morphine PEG 3350	multivitamin	agitation mucositis oral	doctor treated it
M	ALL	**mercaptopurine** **methotrexate** prednisone sulfamethoxazole/trimethoprim	omega 3 vitamin d	dyspepsia generalized edema weight gain	doctor treated it
F	ALL Ph+	**imatinib** ondansetron PEG 3350 omeprazole nabilone olanzapine tinzaparin citalopram sulfamethoxazole/trimethoprim	essential oils magnesium potassium	constipation growth suppression insomnia vomiting weight loss	phoned for information was hospitalized
F	medulloblastoma	**leuprolide** hydrocortisone	magnesium multivitamin	fatigue headache	nothing/treated it themselves saw or asked doctor about it

		lansoprazole levothyroxine somatropin		nausea pain	doctor treated it
F	neuroblastoma	**cisplatin** **cyclophosphamide** **topotecan** amlodipine captopril methadone morphine ondansetron sulfamethoxazole/trimethoprim	vegetable/fruit juice vitamin d	alopecia nausea constipation diarrhea insomnia pruritus unspecified blood disorder vomiting	saw or asked doctor about it doctor treated it
F	PNET	filgrastim ondansetron sulfamethoxazole/trimethoprim	vitamin d	rash	doctor treated it

Table A5.3.3 Serious adverse event causality assessment

Age	**Sex**	**Diagnosis**	**Drug**	**NHP**	**AE Description**	**WHO-UMC Causality Assessment Scale**
6	M	ALL	1. Vincristine (varying doses) 2. Methotrexate (varying doses) 3. 6-Mercaptopurine 4. Asparaginase 5. Dexamethasone	1. Alpha lipoic acid 100mg orally daily 2. Vitamin B6 50mg orally daily 3. Coenzyme Q10 200mg orally daily	Neuropathy (ptosis and foot drop) NHPs were started after the development of neuropathy as potential treatment.	Unlikely