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The use of vitamins, minerals, herbal supplements, and other dietary supplements as complementary and alternative therapies in cancer care: A literature review

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Abstract

Complementary and alternative medicines have become increasingly popular among cancer patients over the past 45 to 55 years. Among the various types of complementary and alternative therapies, vitamins, minerals, and supplements appear to be most commonly used. This literature review aims to identify evidence related to the efficacy and safety of vitamins, minerals, herbal supplements, and any other dietary supplements (VMHD) as complementary and alternative therapies in the treatment of cancer. Methods: A literature search was conducted using Ovid MEDLINE, Embase, and Cochrane Central databases to identify any trials assessing the efficacy and safety of VMHD over the past 5 years. Results: Twenty studies were included in this review. Included studies investigated the use of VMHD as treatments for traditional medicine side effects, or as potential treatments for cancer. Goshajinkigan was reported to significantly reduce peripheral neurotoxicity in two independent studies. However, outcomes for other VHMD therapies were not reported across multiple studies, making comparison of findings challenging. Conclusions: Limited evidence supporting VHMD therapies for disease management and remedying the side-effects of traditional treatments is available from the past five years. Comparisons using recent trial evidence are challenging due to limited cases where multiple studies evaluate the same VHMD therapies for the same outcomes, and quality of evidence is limited by small sample sizes and drawbacks in study design. Future syntheses may benefit from inclusion of other study designs and peer-reviewed literature published prior to the year 2011.

Keywords: Complementary, alternative, vitamins, minerals, herbal supplements, dietary supplements

Introduction

The National Center for Complementary and Integrative Health defines an alternative medicine or

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therapy as "a non-mainstream practice used in place of conventional medicine," while, a complementary medicine or therapy is defined as "a non-mainstream practice used together with conventional medicine" (1).

Typical complementary health approaches among adults in the United States include natural products (herbs, vitamins, minerals, and probiotics), mind and body practices (yoga, chiropractic and osteopathic manipulation, meditation, massage therapy, acupuncture, relaxation techniques, tai chi, healing touch, hypnotherapy, movement therapies and qi gong), and other approaches including traditional Chinese medicine, homeopathy, naturopathy, ayurvedic medicine, and traditional healers (1). Some forms of alternative medicine, such as traditional Chinese medicine, date back over 3,000 years ago. Despite this, it was in the 1960s and 1970s that complementary and alternative medicine (CAM) first rose in visibility and availability (2-4). Since then, the use of CAM for diseases and disorders, including cancer, has increased significantly. A recent systematic review and meta-analysis of articles from 15 countries found the average proportion of cancer patients using CAM in the 1970s and 1980s to be 25% (5). This proportion increased significantly to 49% for investigations completed after the year 2000 (5).

Among types of complementary and alternative therapies, vitamins, minerals, and supplements seem to be most commonly used among cancer patients (6, 7). The 2007 National Health Interview Survey conducted in the United States found that among 1,785 respondents, vitamin/mineral supplementation were used by nearly 77% (7).

The purpose of this literature review is to discuss the efficacy and safety of vitamins, minerals, herbal supplements, and any other dietary supplements (VMHD) as complementary and alternative therapies in the treatment of cancer.

Methods

A literature search was conducted using Ovid MEDLINE (2011 – August Week 31 2016), Embase (2011 – 2016 Week 31) and Cochrane Central (2011 – 2016 Week 31) databases. Search terms included: "vitamins," "minerals," "supplements," "herbs," "cancer or neoplasm," "integrative therapy," "alternative therapy" and "complementary therapy."

Eligibility criteria

Articles were considered eligible if they: a) involved an experimental study design; b) involved a cancer patient population; and c) evaluated the effectiveness of orally-ingested VMHD therapies on cancer symptom outcomes. Other study designs, studies examining other patient populations, and studies evaluating VMHD therapies administered through other routes were excluded.

Selection process, data abstraction and analysis

Titles and abstracts from the literature search were screened for eligibility by a single reviewer. Potentially eligible titles and abstracts were retrieved as full-text articles and screened using the same *a priori* eligibility criteria by the reviewer. Data extraction was subsequently completed by the reviewer for studies deemed eligible for inclusion, and checked for accuracy by a second reviewer, with discrepancies resolved via discussion. Results were subsequently summarized qualitatively.

Results

One hundred and eighteen articles were identified by the literature search using the three electronic databases. Following the removal of duplicates, titles and abstract screening yielded 40 potentially eligible hits, of which 20 were finally deemed eligible following full-text review (see Figure 1).

Of the 20 eligible studies, 15 evaluated herbal supplements (8-22), 4 evaluated dietary supplements (23-26), 2 evaluated vitamins (8, 27), and two evaluated minerals (in combination with herbal supplements) (13, 14) (see Table 1). Four enrolled patients from the United States of America (9, 10, 18, 23), 4 from Japan (8, 17, 20, 21), 3 from Iran (24-26), 2 from China (15, 22), 2 from Taiwan (12, 16) 1 from Egypt (14), 1 from Germany (27), 1 from India (13), 1 from Israel (19), and 1 from Malaysia (11).

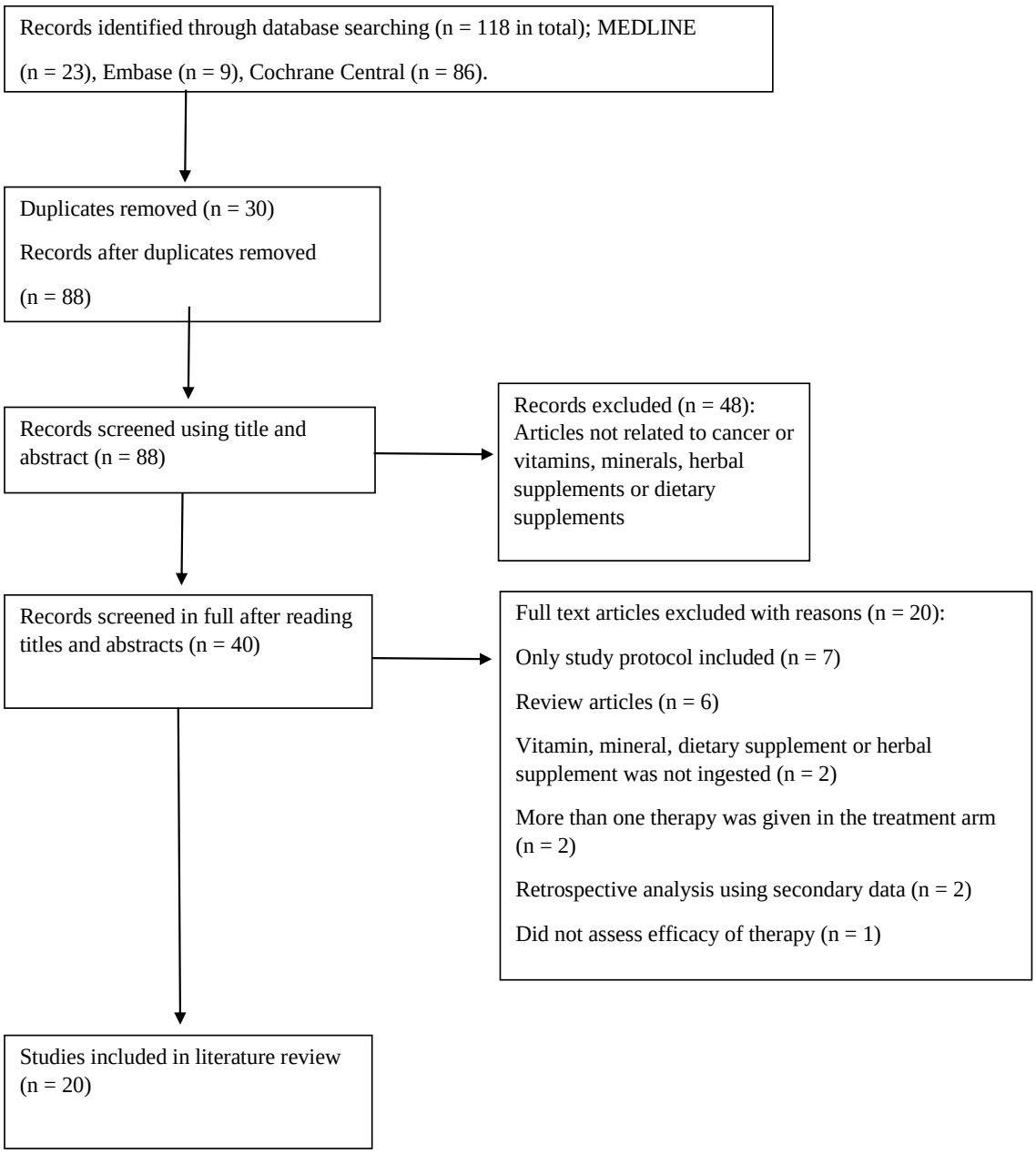

Figure 1. Identification of studies on vitamins, minerals, herbal supplements or dietary supplements as complementary or alternative therapies used in cancer patients.

Therapies treating side-effects

Two independent studies investigated the efficacy of Goshajinkigan (GJG), a traditional Japanese medicine, in treating chemotherapy-induced neurotoxicity and found promising results. Abe and colleagues compared GJG with Mecobalamin (vitamin B12) as treatments for peripheral neurotoxicity associated with docetaxel in breast cancer patients (8). It was found that there were significantly fewer incidences of neurotoxicity ($p < 0.01$) in patients given GJG compared to vitamin B12. In a study by Nishioka and colleagues, colorectal patients received the FOLFOX6

chemotherapy treatment regimen and received GJG or no therapy (17). Those given GJG experienced significantly less grade 3 peripheral neuropathy than those in the control group given placebo ($p < 0.01$). No significant differences were found between the two treatment arms in number of adverse events or tumor response to the FOLFOX regimen (17). Another study by El-Ghiaty and colleagues examined the ability of cystone to reduce cisplatin-induced nephrotoxicity (14). Clearance and serum creatinine was found to be significantly better in those receiving cystone compared to baseline ($p < 0.05$), indicating some potential protective effects of cystone with regard to nephrotoxicity (14). Rostock and colleagues also investigated the efficacy of vitamin B1/B6 in treating chemotherapy-induced peripheral neuropathy, but found no significant difference across any assessment measures when compared to placebo (27).

Other studies have focused on chemotherapy-induced side effects and quality of life (QoL), and have discovered potential benefits for specific outcomes. Deshmukh and colleagues found the use of ayurvedic drugs MPP and MKD significantly increased patient Karnofsky Performance Status (KPS) ($p < 0.0001$) and decreased Eastern Cooperation Oncology Group (ECOG) scores ($p = 0.0022$) compared to placebo, when used for 6 months after treatment (13). Ryan and colleagues found significant reduction in average nausea ($p = 0.013$) and nausea at its worst ($p = 0.003$) when comparing ginger to control (18). However, no difference in QoL or vomiting symptoms were found (18). Some gastrointestinal adverse events were reported, including grade 2 heartburn, bruising/flushing and rashes (18). Yaal-Hahoshen and colleagues found significantly less severe anemia ($p < 0.01$), leukopenia ($p < 0.03$) and neutropenia ($p < 0.04$) in breast cancer patients treated with botanical compound mixture LCS101 (19).

The use of oral Fructus bruceae oil for radiotherapy-induced side effects in esophageal cancer patients was assessed by Shan and colleagues (15). The rate of complete and partial remission was reported to be significantly higher in the treatment arm compared to the control group with no treatment ($p < 0.05$) (15). A significant improvement in KPS, nausea and vomiting, and radiation esophagitis and pneumonitis was also seen ($p < 0.05$ for all) (15).

In addition to chemotherapy and radiotherapy, three studies investigated the use of herbal supplements on postoperative adverse effects and recovery. Yoshikawa and colleagues investigated the use of daikenchuto on gastrectomy and laparoscopic colectomy side effects and complications (20, 21). For those undergoing gastrectomy who were randomized to receive daikenchuto, the median time until first defecation and incidence of bowel movement disorder was significantly lower ($p = 0.05$ for both outcomes). No daikenchuto-related serious advese events occurred. For those undergoing laparoscopic colorectal resection who received daikenchuto, a significantly shorter time until first flatus was seen when compared to control ($p = 0.02$) (20, 21). Zhong and colleagues administered Jianpi Huayu, a mixture of herbal extracts, to patients after hepatectomy (22). Significant differences favoring the treatment arm were seen in length of stay ($p = 0.034$), postoperative alanine aminotransferase (ALT) levels ($p = 0.042$), disease recurrence, number of singular recurrent lesions, and disease-free survival and overall survival at 1, 3 and 5 years follow-up (22).

Three studies assessed the efficacy of therapies on sleep and fatigue. Cruciani and colleagues found no significant difference between L-carnitine and placebo for the treatment of fatigue (23). Barton and colleagues did not provide data to support the efficacy of Valeriana officinalis on improving sleep, but an exploratory analysis found that use for fatigue may warrant further study (10). Biswal and colleagues found that the treatment arm given herbal supplement Withania somnifera produced significantly lower scores on the Piper's Fatigue Scale (PFS), Schwartz's Cancer Fatigue Scale (SCFS-6) and the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 quality of life questionnaire fatigue scale ($p < 0.001$, $p = 0.003$ and $p < 0.001$, respectively) (11).

Lastly, Madhavi and colleagues investigated conjugated linoleic acid (CLA) supplementation as a therapy for improving nutritional status, and symptoms of eating problems and dietary intake in patients with rectal cancer (24). In those receiving CLA, a significant decrease was seen in appetite loss, nausea, diarrhea, pain, and significant increase in dietary intake ($p<0.05$ for all) (24).

Table 1. Overview of articles included in literature review, including author, complementary and alternative medicine (CAM) type, CAM, sample size, cancer type, current treatment being received, and the symptoms, diseases or conditions intended to be treated

Author	CAM Type	CAM	Sample Size (n)	Cancer Type	Current Treatment of patients enrolled	Dependent variable/Intent to treat
Abe H et al. (2013), Japan	Herbal supplement and Vitamin	Goshajinkigan, Vitamin B12	60	Breast cancer (stage I, IIA, IIB, or III)	Chemotherapy (Docetaxel)	Peripheral neuropathy/neurotoxicity
Azrad M et al. (2013), USA	Herbal supplement	Flaxseed	147	Prostate cancer	Awaiting Prostectomy	Tumor cell proliferation
Barton DL et al. (2011), USA	Herbal supplement	Valeriana Officinalis	119	Any	Chemotherapy, Radiotherapy, Oral anti-tumor agents, or Endocrine therapy	Sleep
Biswal BM et al. (2012), Malaysia	Herbal supplement	Withania somnifera	100	Breast cancer	Chemotherapy	Chemotherapy-induced fatigue and Quality of Life
Chen WT-L et al.(2014), Taiwan	Herbal supplement	MB-6	72	Metastatic colorectal cancer	Chemotherapy (FOLFOX4)	Chemotherapy effectiveness
Cruciani RA et al. (2012), USA	Dietary supplement	L-cartinine	376	Any (invasive malignancies)	Any	Fatigue
Deshmukhq V et al. (2014), India	Herbal supplement and Mineral	Ayurvedic drugs (MPP, MKD)	67	Any	Chemotherapy	Chemotherapy side effects and toxicity
El-Ghiaty MA et al. (2014), Egypt	Herbal supplement and Mineral	Cystone	49	Any	Chemotherapy (Cisplatin)	Cisplatin-induced nephrotoxity, cytotoxic activity of cisplatin.
Kuo W-H et al. (2012), Taiwan	Herbal supplement	Tien-hsein	44	Metastatic Breast cancer	None	Breast cancer
Mahdavi R et al. (2013), Iran	Dietary supplement	Linoleic acid	31	Rectal cancer (stage II or III)	Chemotherapy and Radiotherapy	Nutritional status, eating problems, and dietary intake
Mohammadzadeh M et al. (2013), Iran	Dietary supplement	Linoleic acid	32	Rectal cancer (stage II or III)	Chemotherapy and Radiotherapy	Inflammatory factors and matrix metalloproteinase (MMP) enzymes
Nishioka M et al. (2011), Japan	Herbal supplement	Goshajinkigan	45	Colorectal cancer	Chemotherapy (FOLFOX6)	Peripheral neuropathy
Ostradrahimi A et al. (2014), Iran	Dietary supplement	Beta glucan	30	Breast cancer (stage II or III)	Chemotherapy	White blood cell counts and serum levels of IL-4 and IL-12
Rostock M et al. (2013), Germany	Vitamin	Vitamin B1/B6	32	Any cancer (in remission)	Completed chemotherapy	Chemotherapy-induced peripheral neuropathy
Ryan JL et al. (2012), USA	Herbal supplement	Ginger	576	Any	Chemotherapy	Chemotherapy-induced nausea
Shan GY et al. (2011), China	Herbal supplement	Fructus bruceae Oil	80	Esophageal cancer (grade II or III)	Radiotherapy	Radiotherapy side effects
Yaal-Hahoshen N et al. (2011), Israel	Herbal supplement	LCS101	65	Breast cancer	Chemotherapy	Chemotherapy-induced Hematological toxicity
Yoshikawa K et al. (2015), Japan	Herbal supplement	Daikenchuto	195	Gastric cancer	Gastrectomy	Gastrectomy side effects
Yoshikawa K et al. (2012), Japan	Herbal supplement	Daikenchuto	30	Colorectal cancer	Laparoscopic Colectomy	Inflammatory response
Zhong C et al. (2014), China	Herbal supplement	Jianpi Huayu	120	Hepatocellular carcinoma	Hepatectomy	Postoperative recovery

CAM= Complementary and Alternative Medicine; MKD= Mauktikyukta Kamdudha; MPP=Mauktikyukta Praval Panchmrut

Therapies for disease management

A total of 5 studies primarily assessed the efficacy of complementary and alternative therapies on disease management (9, 12, 16, 25, 26).

Three studies used biomarkers to assess the efficacy of treatment in patients. Mohammadzadeh and colleagues assessed the effect of CLA on inflammatory factors and enzymes in rectal cancer patients (25). When compared to placebo, significantly lower concentrations of TNF-α ($p = 0.04$), hsCRP ($p = 0.03$), and MMP-9 ($p = 0.04$) were observed in the treatment group (25). Ostradrahimi and colleagues assessed the effect of beta-glucan on white blood cell (WBC) counts, and serum interleuken (IL)-4 and IL-12 concentrations (26). No significant difference was found between treatment and control groups with regards to WBC counts, but a significant increase was seen in IL-4 concentration ($p = 0.001$). A significant increase in IL-12 level was seen from baseline ($p = 0.03$), but not in control (26). Azrad and colleagues examined the effect of flaxseed lignans, enterolactone and enterodiol on tumor proliferation (9). Urinary enterlignans and enterolactone were found to be significantly and inversely related with Ki67, a tumor cell proliferation marker ($p = 0.011$ and $p = 0.007$, respectively). However, no significant relationship was found with other markers. No adverse effects were reported (9).

MB-6, a botanical compound made from a combination of plant extracts, was investigated by Chen and colleagues for its potential ability to increasing chemotherapy effectiveness in colorectal cancer patients undergoing the FOLFOX4 chemotherapy regimen (12). No significant difference in overall response, progression free survival, mortality rate, or overall status was found with MB-6 administration. However, those in the treatment arm experienced significantly lower disease progression rate ($p = 0.026$) compared to placebo. A significantly higher incidence of adverse events of at least grade 4 were reported in the placebo arm compared to the treatment arm ($p = 0.004$) (12)

One study examined the use of a VMHD without additional traditional treatment regimen. Kuo and colleagues randomized breast cancer patients with no satisfactory response in conventional treatment, to receive tien-hsein or placebo (16). Significant improvements were seen in QoL, and specifically physical, role, emotional, cognitive, and fatigue functions from baseline, in the treatment group ($p < 0.001$), but not for control group. Significantly fewer side effects were reported on the EORTC-QLQ-BR23 in the treatment arm compared to the placebo arm ($p < 0.05$) (16).

Discussion

The majority of articles included in this review assessed efficacy of VHMD therapies where a traditional treatment regimen is combined with an alternative therapy in combating disease or traditional treatment side-effects. Our findings suggest that VHMD interventions may be effective in disease management, addressing side-effects of alternate treatments, and improving QoL.

Overall, it is difficult to draw conclusions using the results of studies included in this literature review. In the majority of cases, only one study was found investigating the effect of a given VHMD therapy, making comparison of findings across studies challenging and limiting both the generalizability and strength of the conclusions. Only one VHMD intervention had evidence that was comparable across studies: the effect of GJG on peripheral neurotoxicity (8, 17). In this case, similar results were found between the studies although treatment regimens and control groups were different. Significantly fewer grade 3 neurotoxicity events were found in the treatment groups when compared to placebo and vitamin B12 (standard treatment for peripheral neuropathy in Japan) (8, 17). The majority of studies reviewed also did not report any adverse events with regards to the therapy being investigated. One exception is the study by Ryan and colleagues, which reported adverse events that caused a number of patients to withdraw from the study, primarily related to ginger-induced gastrointestinal symptoms (heartburn, bruising/flushing, rash) (18).

Study findings were also limited by the design of the included studies. Several studies did not use a placebo in their control arms, and thus did not incorporate blinding of patients (9, 11, 13-15, 21, 22). The results of these open-label studies must be used carefully as participant bias may influence their

findings, especially where self-reported tools are used to measure outcomes such as QoL or self-reported adverse events (28).

Finally, the findings of our scoping review are limited by the relatively limited number of studies included, their small sample sizes, and the inclusion of trials only published since the year 2011.

Conclusion

The use of VMHD in the treatment of cancer and traditional treatment side effects appears potentially promising. Many of the studies included in our scoping review were unique in their treatment condition and reported otucomes, making comparisons across studies challenging. However, GJG was found to significantly reduce peripheral neurotoxicity in two independent studies. Results from these studies and other included studies should be interpreted recognizing their limitations.

Future studies may benefit from the inclusion of larger samples, the inclusion of a placebo arm consistently, and study designs that involve randomization to study arms while minimizing risk of bias. Syntheses of all available evidence, not limited by year of publication and study design, might be more effective in evaluating these therapies.

Conflict of interest

None.

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None.

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